Full evidence review

Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients

Evidence review
Search strategies
Health economics evidence review
Health economics plan

Developed for NICE by the National Collaborating Centre for Cancer

Contents

Definition of Neutropenic Sepsis: guideline chapter two.

1. How do neutrophil count and temperature relate to the risk of complications of sepsis, in cancer patients with suspected neutropenic sepsis? (Topic D1)

Guideline subgroup members

Anne Davidson (lead), Jeanette Hawkins, Paul Wallman, Mark Holland, Wendy King and Barry Hancock

Review question

How do neutrophil count and temperature relate to the risk of complications of sepsis, in cancer patients with suspected neutropenic sepsis?

Rationale

The risk of life threatening infection in patients receiving treatment for cancer is related to the absolute neutrophil count and a fever is a strong, but not the only indicator, of infection. Patients (or their carers) are educated to seek advice promptly if they develop a fever and will usually be advised to attend hospital. The neutrophil count at the time of presentation influences the decision on whether hospital inpatient admission is necessary and subsequent neutrophil counts will influence the duration of any hospital stay.

Standard protocols for empiric treatment of suspected neutropenic sepsis require the resolution of fever and neutropenia prior to discharge, but around 40% patients treated according to current standard protocols are not found to have either clinical or microbiologically proven infection.

Whilst the risk of mortality and other adverse clinical outcomes including intensive care admission are known to be highest when the absolute neutrophil count is less than $0.1x10^9$/l it has been believed necessary to set the thresholds for empiric treatment higher to ensure appropriate treatment for patients at potential risk. Febrile neutropenia protocols usually define neutropenia as an absolute neutrophil count of less than 0.5 $x10^9$/l, or less than $1.0x10^9$/l and "falling", the interpretation of which requires some knowledge of chemotherapy regimens and expected patterns of myelosuppression. A clinically significant fever has been defined variously as 37.5°C, 38.0°C or 38.5°C over different time points. There is also inconsistency between protocols on advice on how and where to measure body temperature, and to confuse matters further some protocols also use absolute monocyte counts.

An evaluation of the risk of mortality or other adverse outcome specifically related to infection, the absolute neutrophil count and the degree of fever would help determine the appropriate threshold for empiric treatment and in the development of evidence based guidelines for risk stratification. This may in turn reduce unnecessary hospitalisation of those without serious clinical infection. An additional benefit for patient would be more consistent advice from health care professionals working in different health care settings

Question in PICO (PFO) format

Patients/population	Factors	Outcome
Patients with suspected neutropenic sepsis	• Neutrophil count • Temperature	• Mortality • Critical care • Serious infection • Clinically documented infection • Complications • Length of stay

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central.

On the advice of the guideline group we restricted the search to studies published from 2000 onwards, because without a search term for an intervention the strategy was returning too many results. The search was done on the 30th of November 2010 and updated on 7th November 2011.

Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

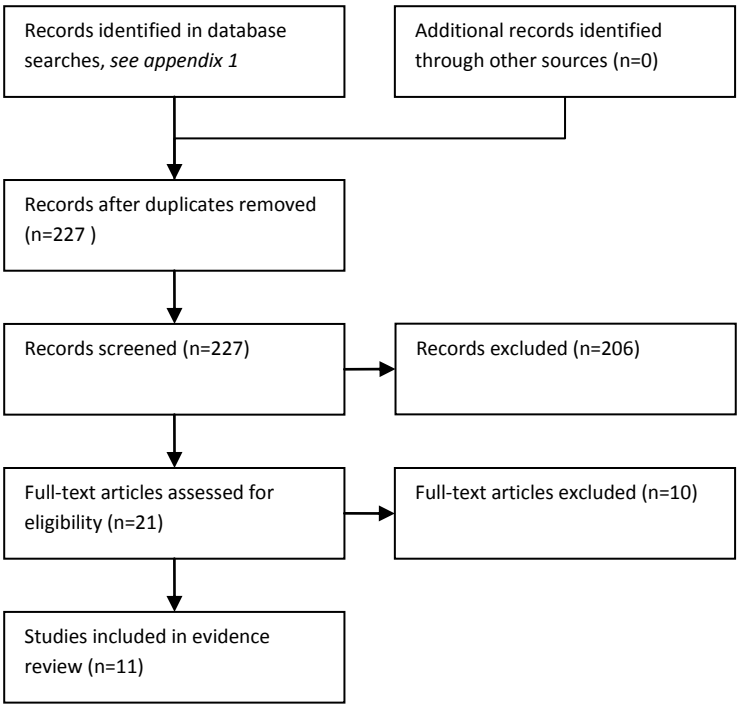
Data synthesis

We looked for evidence about the association between the two prognostic factors (neutrophil count and temperature) and the outcomes listed in the PICO. The odds of outcomes associated with the different cut-off levels of ANC or temperature were recorded from both univariate and multivariate analysis if reported. If studies reported the rates of outcomes according to ANC or temperature level, these were included in meta-analysis of univariate odds ratios. The positive and negative predictive values of the various neutropenia and fever definitions for each outcome were calculated wherever possible.

RESULTS

Results of the literature searches

Figure 1.1 Study flow diagram



Description of included studies

The literature searches identified 227 potentially relevant studies, and eleven of these were included as evidence.

There were no studies designed to test different definitions of neutropenia and fever in cancer patients with possible neutropenic sepsis. A single study (Apostolopoulou, 2010) was not restricted to patients with neutropenia or fever. The ten other studies had inclusion criteria of both neutropenia and fever, thus patients at very low risk of bacterial infection would be excluded. These studies probably underestimate the usefulness of neutropenia and fever as predictive factors for neutropenic sepsis because they are limited to a restricted range of ANC and temperature values.

Six studies included only children and adolescents : Hakim et al (2010), Santolaya et al (2001), Klaassen et al (2000), Ammann (2003), Ammann (2010), Tezcan et al (2006). Four studies included adults only: Apostolopoulou et al (2010), Ha et al (2010), Moon et al (2006) and Klastersky et al (2000). One study (Apostolopoulou et al, 2010) was limited to patients with haematological cancers. One study (Ha et al, 2010) was limited to patients at low risk of adverse events, defined as MASCC score greater than 20.

Most studies treated temperature and ANC as dichotomous variables by choosing a cut-point and putting each patient into either of two groups. ANC and temperature would be analysed more effectively by treating them as continuous variables but only one study (West et al, 2004) treated temperature in this way.

Some studies in children used axillary temperature measurements (Klaassen et al, 2000; Santolaya et al, 2001; Ammann et al, 2010). Klaassen et al (2000) reported converting axillary temperatures to their oral equivalent by adding 1.0°C.

Study quality

No evidence comparing definitions of neutropenia or fever in cancer patients with possible neutropenic sepsis were found.

Eleven observational studies about temperature and neutrophil count as prognostic factors in patients receiving treatment for fever and neutropenia. Seven studies involved paediatric patients and ten included only patients with fever (definitions ranged from a single temperature measurement greater than 38.0°C to 38.0°C for at least four hours) and neutropenia (ANC < 0.5 $X10^9$/litre or 1.0 $X10^9$/litre and falling). These studies probably underestimate the usefulness of neutropenia and fever as prognostic factors in neutropenic sepsis because they are limited to a restricted range of ANC and temperature values, excluding patients with low risk of neutropenic sepsis. The evidence is therefore of low quality.

Literature searches identified no evidence about the relationship between mortality or length of stay and definitions of neutropenia and fever.

Summary of evidence

Positive and negative predictive values of fever and neutropenia definitions

The predictive values of the various definitions of neutropenia and fever are listed in tables 1.1 to 1.3.

Positive predictive value is the proportion of patients meeting the definition of neutropenia and fever who experienced the outcome. High positive predictive value is desirable if there are harms associated with subsequent treatment or tests and you want to avoid over treating or over investigating patients who will not benefit.

Negative predictive value is the proportion of patients who don't meet the definition of neutropenia and fever who didn't experience the outcome. High negative predictive value is desirable if there are harms associated with not treating or investigating patients: for example not treating a patient with neutropenic sepsis could be fatal.

Although tables 1.1 to 1.3 contain definitions of neutropenia as ANC <100/mm^3 and fever as temperature >39°C, these were not used in clinical practice in any of the studies. Some studies presented enough data, however, to calculate the positive predictive values of these definitions in theory.

Negative predictive values were not estimable in studies restricted to patients with both fever and neutropenia – because these studies contained only patients who met the both the neutropenia and fever criteria.

Defining fever as temperature>39.0°C (instead of >38.0°C) increased the positive predictive value (PPV) of neutropenia and fever for bacteraemia (Ha et al, 2010), severe infection (Santolaya et al, 2001; Ammann et al, 2003 and Klaassen et al, 2000) and adverse events (Klastersky et al, 2010).

Although the negative predictive value of this definition was not estimable it would probably decrease (relative to >38.0°C) meaning more patients with severe infection would be missed.

Defining neutropenia as ANC < 100/mm^3 increased the PPV of neutropenia and fever for bacteraemia (Ha et al, 2010), severe infection (Santolaya et al, 2001) and adverse events (Klastersky et al, 2010 and Moon et al, 2009). Again the effect of this change on NPV was not estimable but would probably decrease NPV.

ANC, temperature and mortality

Table 1.4 summarizes evidence about the association between ANC and outcome. The association between ANC or temperature and mortality was not reported separately, except in one study (Tezcan et al, 2006). In this study of children with fever and neutropenia there was no significant association between severe neutropenia (ANC <100/mm^3) and mortality: OR=0.57 (95% C.I. 0.23 to 1.43).

The lack of prognostic factor analyses for mortality may in part be due to the relatively low mortality rates in the included studies. Large patient numbers would be required to perform multivariate analysis of prognostic studies for mortality. Some studies, however, included mortality as part of their definition of severe bacterial infection.

ANC and bacteraemia

In a prospective study of 102 hospitalised patients with haematological malignancies (Apostolopoulou et al, 2010) absolute neutrophil count of less than 500/mm3 was associated with an increased odds of bacteraemia, OR = 27.87 (95% C.I. 3.52 to 220.43). Sixteen of the seventeen patients with bacteraemia had neutropenia, but 31 of the 47 patients with neutropenia did not develop bacteraemia. This definition of neutropenia had a sensitivity of 94% for the development of bacteraemia, with specificity of 64%. As a consequence this definition of neutropenia had a negative predictive value of 98%, meaning that only 2% of patients without neutropenia developed bacteraemia.

In a series of 802 low risk patients (MASCC score > 20) with both neutropenia and fever, Ha et al (2010) reported that profound neutropenia (absolute neutrophil count < 50/ mm^3) was significantly associated with bacteraemia: OR = 2.26 [95% C.I. 1.50 to 3.51].

Bacteraemia was included as part of the definition of serious infection in five studies. Figure 1.2 shows the odd ratio for bacteraemia or severe bacterial infection at different absolute neutrophil count cut off values.

ANC and severe/significant/invasive/documented infection

Severe (also referred to as significant, invasive or documented) infection was a composite outcome defined as culture positive for bacteria or clinical/laboratory evidence of sepsis in the absence of a positive culture. Some studies (for example Amman et al 2003; Klaassen et al 2000) also included death from infection in their definition.

In patients with both neutropenia and fever, severe neutropenia (defined as absolute neutrophil count < 100/mm^3) was associated with increased odds of severe infection: OR=1.80 (95% C.I. 1.43 to 2.26) (Ammann et al 2003; Hakim et al, 2010; Santolaya et al 2001 and Tezcan et al 2006 ; see figure

1). However there was significant heterogeneity between studies: one of the studies (Ammann et al 2003) did not observe a significant association between severe neutropenia and the odds of severe infection.

ANC and complications

Three studies examined the relationship between severe neutropenia and the odds of complications in patients with neutropenia and fever. Ammann et al (2010) observed increased odds of adverse events in patients with profound neutropenia, OR=3.3 (95% C.I. 1.7 to 6.1). Similarly Klastersky et al 2000 reported increased odds of adverse events in patients with severe neutropenia, OR=1.76 (95% C.I. 1.14 to 2.72). Moon et al (2009) did not observe significantly increased odds of adverse events in patients with severe neutropenia, OR=1.18 (C.I. 0.57 to 2.44) in their series of cancer patients presenting to the emergency department with neutropenia and fever.

ANC and critical care or length of stay

None of the included studies reported on the relationship between ANC and the length of stay or the requirement for critical care.

Temperature and bacteraemia

Table 1.5 summarizes evidence about the association between temperature and outcome. In Ha et al (2010) temperature of 39°C or more was associated with increased odds of bacteraemia in both univariate (OR= 2.05; 95% C.I. 1.06 to 3.98) and multivariate analyses (OR= 2.91; 95% C.I. 1.30 to 6.49) , when compared to temperature between 38°C and 39°C. . Figure 1.3 shows the odd ratio for bacteraemia or severe bacterial infection at different temperature cut off values.

Temperature and Critical care

West et al (2004) analyzed temperature as a continuous variable in children with neutropenia and fever. An increase of one degree in temperature was associated with a relative increase of 1.74 (95% 1.25 to 2.43) in the odds of receiving critical care within 24 hours of presentation.

Temperature and severe/significant/invasive/documented infection

In four studies of patients with both neutropenia and fever, temperature greater than 39°C was associated with a significantly increased odds of severe infection: OR= 1.82 (95% C.I. 1.36 to 2.42) when compared with temperature between 38°C and 39°C.

Temperature and complications

In children with both neutropenia and fever Ammann et al (2010) reported a significant increase in the odds of an adverse event when temperature was greater than 39°C (OR=2.8, 95% C.I. 1.2 to 6.4). In adults with neutropenia and fever Klastersky et al (2000) found temperature greater than 39°C was associated with more adverse events (OR=2.02, 95% C.I. 1.34 to 3.04).

Temperature and length of stay

None of the included studies reported on the relationship between temperature and the length of stay.

Evidence statements

There was sparse evidence from a single study in 102 patients (Apostolopoulou, et al., 2010) that ANC < 0.5 $X10^9$/litre has high negative predictive value for bacteraemia. All other evidence came

from studies of patients with both neutropenia and fever and thus has limited value due to the restricted range of possible temperature and ANC values.

Low quality evidence suggests that defining fever as temperature >39.0°C (instead of >38.0°C) increases the positive predictive value (PPV) of neutropenia and fever for bacteraemia, severe infection and adverse events (Ammann, et al., 2003, Ha, et al., 2010, Hakim et al., 2010, Klassen et al., 2000 and Santolaya, et al.,). Although the negative predictive value (NPV) of this definition was not estimable, using the >39.0°C definition would probably decrease NPV (relative to >38.0°C).

Low quality evidence suggests that defining neutropenia as ANC < 0.1 $X10^9$/litre (instead of < 0.5 $X10^9$/litre or 1.0 $X10^9$/litre and falling) increases the PPV of neutropenia and fever for bacteraemia, severe infection and adverse events (Apostolopoulou, et al., 2010, Ha et al., 2010, Hakim, et al., 2010, Klassen, et al., 2000, Santolaya et al., 2001 and Tezcan, et al., 2006). Again the effect of this change on NPV was not estimable but would probably decrease NPV.

There was low quality evidence from one paediatric study (West, et al., 2004), that each additional degree in temperature above 38.0°C was associated with a relative increase of 1.74 (95% 1.25 to 2.43) in the odds of receiving critical care within 24 hours of presentation.

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Table 1.1. Positive and negative predictive values of definitions of febrile neutropenia for bacteraemia

Definition	**Positive predictive value**	**Negative predictive value**
ANC <500/mm^3 any temperature	34% (Apostolopoulou 2010)	98% (Apostolopoulou 2010)
ANC <500/mm^3 or <1000/mm^3 expected to fall to <500/mm^3 and temperature ≥38.3°C or ≥38.0°C for ≥1 hour.	10% (Ha 2010 – low risk patients)	Not estimable
ANC <50/mm^3 and temperature ≥38.3°C or ≥38.0°C for ≥1 hour.	15% (Ha 2010– low risk patients)	Not estimable
ANC <500/mm^3 or <1000/mm^3 expected to fall to <500/mm^3 and temperature ≥39.0°C	16% (Ha 2010– low risk patients)	Not estimable

Table 1.2. Positive and negative predictive values of definitions of febrile neutropenia for severe infection

Definition	Positive predictive value	Negative predictive value
ANC ≤500/mm^3 and temperature ≥38.5 °C or >38.0°C for at least 2 hours	40% (Santolaya, 2001)	Not estimable
ANC <100/mm^3 and temperature ≥38.5 °C or >38.0°C for at least 2 hours	47% (Santolaya, 2001)	Not estimable
ANC ≤500/mm^3 and temperature ≥39.0°C	52% (Santolaya, 2001)	Not estimable
ANC <500/mm^3 or <1000/mm3 expected to fall to <500/mm^3 and temperature ≥39.0 °C or ≥38.5°C for at least 2 hours.	37% (Ammann. 2003)	Not estimable
ANC <500/mm^3 or <1000/mm^3 expected to fall to <500/mm^3 and temperature ≥39.0 °C	43% (Ammann. 2003)	Not estimable
ANC <500/mm^3 or <1000/mm^3 and falling and temperature ≥38.5°C or ≥38.0°C for at least 2 hours.	38% (Klaassen, 2000)	Not estimable
ANC <500/mm^3 or <1000/mm^3 and falling and temperature ≥39.0°C	53% (Klaassen, 2000)	Not estimable
ANC <500/mm^3 or <1000/mm^3 expected to fall to <500/mm^3 and temperature ≥38.3 °C or ≥38.0°C for at least 4 hours.	56% (Tezcan 2006)	Not estimable
ANC <100/mm^3 and temperature ≥38.3 °C or ≥38.0°C for at least 4 hours.	62% (Tezcan 2006)	Not estimable

Table 1.3. Positive and negative predictive values of definitions of febrile neutropenia for any adverse event

Definition of neutropenia and fever	Positive predictive value	Negative predictive value
ANC <500/mm^3 and temperature ≥38.5 °C or >38.0°C for at least two hours	29% (Ammann 2010)	Not estimable
ANC <500/mm^3 and temperature >38.0°C	15% (Klastersky 2010)	Not estimable
ANC <100/mm^3 and temperature >38.0°C	17% (Klastersky 2010)	Not estimable
ANC <500/mm^3 and temperature ≥39.0°C	21% (Klastersky 2010)	Not estimable
ANC <500/mm^3 and temperature ≥38.3 °C or >38.0°C for at least an hour	20% (Moon 2009)	Not estimable
ANC <100/mm^3 and temperature ≥38.3 °C or >38.0°C for at least an hour	21% (Moon 2009)	Not estimable

Figure 1.2. Bacteraemia or severe bacterial infection according to absolute neutrophil count

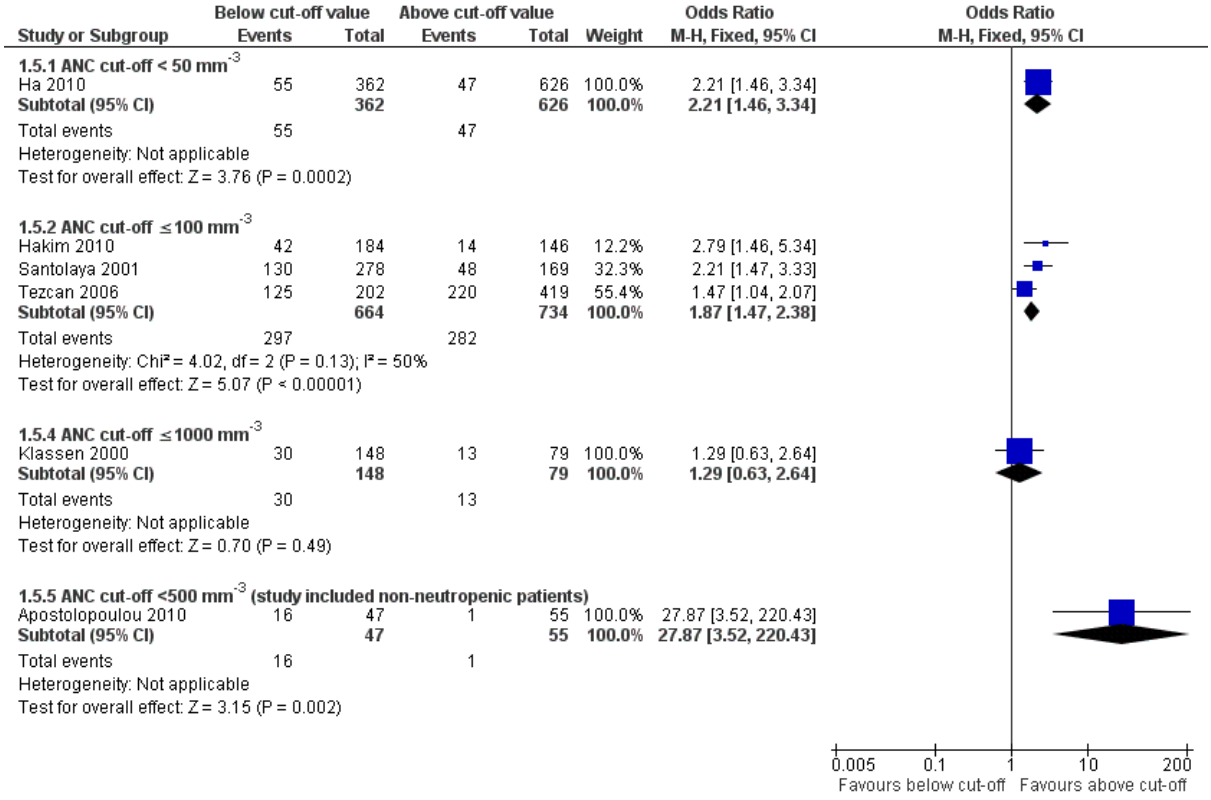
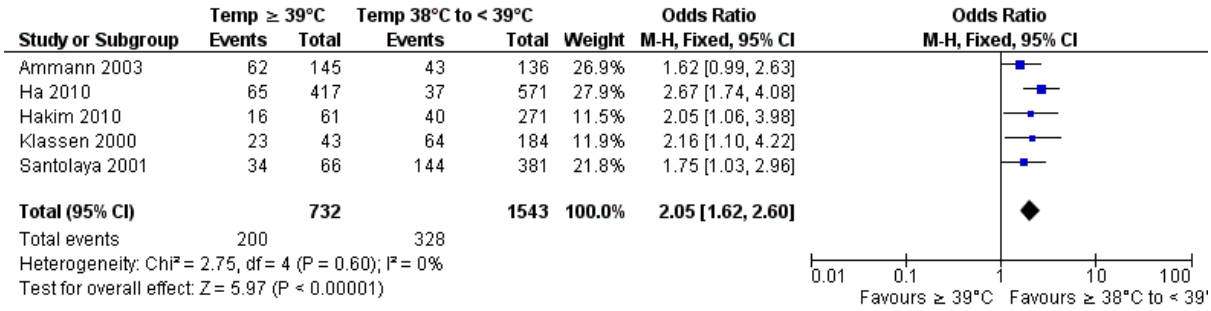


Figure 1.3. Bacteraemia or severe bacterial infection according to temperature



1 ***Table 1.4. Absolute neutrophil count as a predictive factor for outcome***

Study (years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Outcome	Outcome according to ANC cut-off	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
Apostolopoulou 2010 (2007) Cyprus	102 (47 had neutropenia: ANC <500/mm^3)	Adult patients (>17 years) with haematological cancer hospitalized for more than 48 hours in a haematological oncology unit		Bacteraemia (culture positive plus signs or symptoms)	< 500/mm^3: n 16, N 47 ≥ 500/mm^3: n 1, N 55	27.87 [3.52 to 220.43]	Used IPS and APACHE II scores.	
Ha 2010 (1995 to 2007) Korea	802 (988)	Adult patients (>18 years) after anticancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to be <500/mm^3 within 48 hours), fever (≥38.3°C or ≥38.0°C for ≥1 hour) at low risk of complications (MASCC ≥ 21)		Bacteraemia (positive cultures with signs and symptoms of infection)	<50/mm^3: n 55, N 362 ≥50 to 1000/mm^3: n 47, N 626	2.29 [1.50 to 3.51]	1.92 [1.16 to 3.19]	Clinical sites of infection, hypotension, central line, body temperature, ANC < 50/mm3 and CRP ≥ 10 mg/dL
Hakim 2010 (2004 to 2005) USA	332 (332)	Paediatric cancer patients (up to 22 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours)	Febrile neutropenic episodes in inpatients	Invasive bacterial infection (bacteraemia, positive urine culture or culture negative sepsis)	< 100/mm^3: n 42, N 184 ≥100 to 1000/mm^3: n 14, N 146 2 missing values	2.79 [1.46 to 5.34]	2.68 [1.25 to 5.76]	Cancer type, temperature, ANC and clinical appearance

Study (years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Outcome	Outcome according to ANC cut-off	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
Santolaya 2001 (1996 to 1997) Chile	257 (447)	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC ≤500/mm^3) and fever (≥38.5°C or ≥38.0°C for two separate measurements separated by 1 hour.)		Invasive bacterial infection (bacteraemia, positive culture from a usually sterile site) Probable IBI was defined as the absence of a positive culture plus clinical or lab findings suggestive of sepsis or focal organ involvement in defined cases.	<100/mm^3: n 130, N 278; ≥100 to 500/mm^3: n 48, N 169	2.21 [1.47 to 3.33]	ANC was not included in the final multivariate model (P N.R.)	
Klaassen 2000 (1996 to 1997) Canada	140 (227)	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall) and fever (≥38.5°C or multiple readings ≥38.0°C in a 12 hour period).	New diagnosis of cancer, bone marrow or stem cell transplantation within the last 6 months. Comorbidity or abnormal CXR at presentation.	Significant bacterial infection (culture positive for bacteria, interstitial or lobar consolidation on CXR, or death from infection).	≤1000/mm^3: n 30, N 148; >1000/mm^3: n 13, N 79 Protocol specifies ANC <1000/mm3, however some children appear to have had higher ANC than this	1.04 [0.50 to 2.14]	ANC was not included in the final multivariate model (P N.R.)	

Study (years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Outcome	Outcome according to ANC cut-off	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
Amman 2003 (1993 to 2001) Switzerland	111 (285)	Paediatric cancer patients (up to 17 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after nonmyeloablative chemotherapy.	Patients with severe bacterial infection at presentation.	Severe bacterial infection (bacteraemia, positive urine culture or pneumonia).	<100/mm^3: n 21, N 80; ≥100 to 1000/mm^3: n 14, N 60 155 missing values – exclude from meta-analysis	1.17 [0.54 to 2.55]	ANC was not included in the final multivariate model (P>0.05)	
					<500/mm^3: n 33, N 128; ≥500 to 1000/mm^3: n 2, N 12 155 missing values– exclude from meta-analysis	1.74 [0.36 to 8.34]	ANC was not included in the final multivariate model (P>0.05)	
Tezcan 2006 (1996 to 2002) Turkey	240 (621)	Paediatric cancer patients (up to 17 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and predicted to fall to <500) and fever (≥38.3°C or ≥38.0°C for ≥4 hours)	Fever occurring after transfusion or G-CSF administration.	Microbiologically documented infection (bacteraemia or positive culture from a usually sterile site)	<100/mm^3: n 134, N 358; ≥100 to 1000/mm^3: n 91, N 263 NOTE: The total number of patients with profound neutropenia does not agree with that reported for the other outcomes in this study.	1.13 [0.81 to 1.58]	ANC was not included in the multivariate model	
				Documented infection (microbiologically documented infection or	<100/mm^3: n 125, N 202; ≥100 to 1000/mm^3: n 220, N 419	1.47 [1.04 to 2.07]	ANC was not included in the multivariate model	

<table>
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<tr><td></td><td></td><td></td><td></td><td>Death</td><td><table><tr><td colspan="2"><100/mm^3</td><td colspan="2">≥100 to 1000/mm^3</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>6</td><td>205</td><td>21</td><td>416</td></tr></table></td><td>0.57 [0.23 to 1.43]</td><td>ANC was not included in the multivariate model</td><td></td></tr>
<tr><td>Amman 2010 (2004 to 2007)

Switzerland & Germany</td><td>206 (423)</td><td>Paediatric cancer patients (1 to 18 years) with neutropenia (ANC <500/mm^3) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after nonmyeloablative chemotherapy.</td><td></td><td>Any adverse event</td><td>For episodes with no known adverse events at presentation (N=393, 101 missing values)
<table><tr><td colspan="2"><100/mm^3</td><td colspan="2">≥100 to 500/mm^3</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>N.R.</td><td>182</td><td>N.R.</td><td>110</td></tr></table></td><td>3.3 [1.7 to 6.1] using mixed logistic regression to account for multiple episodes per patient.</td><td>ANC was not included in the final multivariate model (P>0.10)</td><td></td></tr>
<tr><td>Klastersky 2000 (1994 to 1997)

USA</td><td>Derivation set 756 (756)</td><td>Patients with malignancy treated with chemotherapy and neutropenia (ANC <500/mm^3) and fever (>38.0°C). Age > 16 years. Appropriate</td><td></td><td>Any adverse event</td><td><table><tr><td colspan="2"><100/mm^3</td><td colspan="2">≥100 to 500/mm^3</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>89</td><td>523</td><td>23</td><td>233</td></tr></table></td><td>1.76 [1.14, 2.72]</td><td>ANC was not included in the final multivariate model (P>0.05)</td><td></td></tr>
</table>

<table>
<tr><th>Study (years) and country</th><th>N patients (N FN episodes)</th><th>Inclusion criteria</th><th>Exclusion criteria</th><th>Outcome</th><th>Outcome according to ANC cut-off</th><th>Univariate OR [95% C.I.]</th><th>Multivariate OR [95% C.I.]</th><th>Variables included in multivariate analysis</th></tr>
<tr><td></td><td></td><td>empirical antibiotic treatment</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Moon 2009 (2004 to 2007)

Korea</td><td>168 (192)</td><td>Adult patients (>18 years) with malignancy presenting to the emergency department with neutropenia (ANC <500/mm^3) and fever (≥38.3°C or ≥38.0°C for ≥1 hours). Blood pressure > 90 mm Hg at presentation.</td><td>Radiotherapy before or during the episode, altered mental state, patients transferred to other hospitals and FN as initial presentation of cancer.</td><td>Any adverse event</td><td><table><tr><td colspan="2"><100/mm^3</td><td colspan="2">≥100 to 500/mm^3</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>24</td><td>115</td><td>14</td><td>77</td></tr></table></td><td>1.18 [0.57, 2.44]</td><td>ANC was not included in the final multivariate model (P>0.05)</td><td></td></tr>
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2 ***Table 1.5. Temperature as a predictive factor for outcome***

Study (study years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Method of temperature measurement	Outcome	Outcome according to temperature group	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
Hakim 2010 (2004 to 2005) USA	332(332)	Paediatric cancer patients (up to 22 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours)	Febrile neutropenic episodes in inpatients	Oral temperature at presentation	Invasive bacterial infection (bacteraemia, positive urine culture or culture negative sepsis).	≥39.0°C: n 16, N 61 < 39.0°C: n 40, N 271	2.05 [1.06 to 3.98]	2.91 [1.3 to 6.49]	Cancer type, temperature, ANC and clinical appearance
Ha 2010 (1995 to 2007) Korea	802 (988)	Adult patients (>18 years) after anticancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to be <500/mm3 within 48 hours), fever (≥38.3°C or ≥38.0°C for ≥1 hour) at low risk of complications (MASCC ≥ 21)		Not reported	Bacteraemia (positive cultures with signs and symptoms of infection).	≥39.0°C: n 65, N 417 38.0°C to < 39.0°: n 37, N 571	2.67 [1.76 to 4.05]	1.86 [1.12 to 3.11]	Clinical sites of infection, hypotension, central line, body temperature, ANC < 50/mm3 and CRP ≥ 10 mg/dL
Amman 2003 (1993 to 2001)	111 (285)	Paediatric cancer patients (up to 17 years) with neutropenia (ANC	Patients with severe bacterial infection at presentation.	Maximal axillary temperature at	Severe bacterial infection (bacteraemia,	>39.0°C: n 62, N 145 38.5°C to ≤ 39.0°: n 43, N 136	1.62 [0.99 to 2.63]	Temperature was not included in the final	

Study (study years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Method of temperature measurement	Outcome	Outcome according to temperature group	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
Switzerland		<500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after nonmyleoablative chemotherapy.		presentation	positive urine culture, pneumonia or death from infection).	4 missing values		multivariate model (P>0.05)	
Santolaya 2001 (1996 to 1997) Chile	257 (447)	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC ≤500/mm^3) and fever (≥38.5°C or ≥38.0°C for ≥2 hours)		Axillary temperature at enrolment into the study	Invasive bacterial infection (bacteraemia, positive culture from a usually sterile site). Probable IBI was defined as the absence of a positive culture plus clinical or lab findings suggestive of sepsis or focal organ involvement in defined cases.	≥39.0°C: n 34, N 66 38.0°C to < 39.0°: n 144, N 381	1.75 [1.03 to 2.96]	Temperature was not included in the final multivariate model (P N.R.)	
Klaassen	140 (227)	Paediatric cancer	New diagnosis	Oral or	Significant	>39.0°C 38.0°C to	2.16 [1.10	2.2 [1.1 to	AML versus

Study (study years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Method of temperature measurement	Outcome	Outcome according to temperature group	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
2000 (1996 to 1997) Canada		patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall) and fever (≥38.5°C or ≥38.0°C for ≥12 hours).	of cancer, bone marrow or stem cell transplantation within the last 6 months. Comorbidity or abnormal CXR at presentation.	equivalent temperature	bacterial infection (culture positive for bacteria, interstitial or lobar consolidation on CXR, or death from infection).	<table><tr><td></td><td></td><td colspan="2">≤ 39.0°</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>23</td><td>43</td><td>64</td><td>184</td></tr></table>	to 4.22]	4.6]	NHL, bone marrow disease, general appearance unwell at presentation, monocyte count <$0.1X10^9$ L^{-1}, peak temperature >39.0°C
Amman 2010 (2004 to 2007) Switzerland & Germany	206 (423)	Paediatric cancer patients (1 to 18 years) with neutropenia (ANC <500/mm^3) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after nonmyeloablative chemotherapy.		Axillary temperature	Any adverse event	For episodes with no known adverse events at presentation (N=393, 15 missing values) <table><tr><td colspan="2">≥39.5°C</td><td colspan="2">38.0°C to < 39.5°</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>N.R.</td><td>24</td><td>N.R.</td><td>354</td></tr></table>	2.8 [1.2 to 6.4] using mixed logistic regression to account for multiple episodes per patient.	Temperature was not included in the final multivariate model (P>0.10)	
Klastersky 2000 (1994 to 1997) USA	756 (756)	Patients with malignancy treated with chemotherapy and neutropenia (ANC >500/mm^3) and fever (>38.0°C). Age >		Measured orally by patient or medical staff.	Any adverse event	<table><tr><td colspan="2">≥39.0°C</td><td colspan="2">38.0°C to < 39.0°</td></tr><tr><td>n</td><td>N</td><td>n</td><td>N</td></tr><tr><td>52</td><td>248</td><td>61</td><td>508</td></tr></table>	2.02 [1.34 to 3.04]	Temperature was not included in the final multivariate model (P>0.05)	

Study (study years) and country	N patients (N FN episodes)	Inclusion criteria	Exclusion criteria	Method of temperature measurement	Outcome	Outcome according to temperature group	Univariate OR [95% C.I.]	Multivariate OR [95% C.I.]	Variables included in multivariate analysis
		16 years. Appropriate empirical antibiotic treatment							
West 2004 (1994 to 1998) USA	143 (303)	Paediatric cancer patients (<18 years) admitted for treatment induced neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall to <500/mm^3), and fever (≥38.5°C or ≥38.0°C for ≥1 hour).	Patients with uncontrolled cancer refractory to treatment. Newly diagnosed patients undergoing induction chemotherapy. Events where patients required critical care within one hour of presentation	Not specified, although patient/parent reported temperatures were accepted.	Critical care within 24hrs of presentation (fluid resuscitation ≥ mL/kg body weight, mechanical ventilation or use of vasoactive agents).	Peak temperature was analysed as a continuous variable. Critical care was administered in 36/303 episodes.	N.R.	1.74 [1.25 to 2.43]	Height of fever, capillary filling time >3s, mucositis present, and DBP z score < -2 S.D.

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Information, Support and Training: Guideline chapter three

2. What types of information and support have patients with neutropenic sepsis (and their carers) found useful or requested? (Topic I).

Guideline subgroup members for this question

Miranda Holmes (Lead), Catherine Oakley, Janie Thomas and Nicola Perry

Review question*:*

What types of information and support have patients with neutropenic sepsis (and their carers) found useful or requested?

Rationale

Neutropenic sepsis is a life threatening blood infection which can occur if patients develop a low white blood cell count following chemotherapy. The Chemotherapy Services in England: Ensuring quality and safety report (August 2009) advises that "all patients should be given both verbal and written information about their treatment, likely side effects and whom they should contact if problems arise". It has been suggested that variation in the provision of neutropenic sepsis information and support for patients (and their carer) currently exists. The type of information patients and carers need is to be reviewed, as part of the 'patient/carer information topic'. This review question has been included, with the purpose of researching the patient/carer perspective as to what types of information and support they have found useful or requested.

We wanted to analyse the research that explores which support and information strategies are most effective in prompting patients to attend hospital early if they experience symptoms of neutropenic sepsis, as a delay in antibiotic treatment can increase the risk of death. Research where hospitals have measured the length of delay in time or/and identified a reduction in the delay (between time patient develops signs and symptoms to the time patient seeks medical help /treatment/presents to Hospital), would be of particular interest.

Information and support may include structured pre-treatment information (verbal, written, internet, audio, DVD's, etc) education sessions (may include PC based training), DVD's, nurse led clinics, 24 hour Chemotherapy Helpline, alert cards, home nursing, pro-active telephone monitoring and patient mobile technology to log symptoms.

Neutropenic sepsis information and support may include the following topic areas; prevention, risks of infection, signs and symptoms, who to contact, when to contact and how to access treatment.

The research findings will be used to inform the NICE Neutropenic Sepsis Guideline recommendations to help ensure that chemotherapy patients at risk of neutropenic sepsis (and their carers) are given the appropriate information and support.

METHODS

Information sources and eligibility criteria

A search was undertaken for qualitative studies, articles, reports, questionnaires, structured interviews and focus groups where patients with neutropenic sepsis or their carers have directly reported their experience of support and information (e.g., What information and support have the patients/carers found useful? What information and support have patients/carers requested? Is there any research to indicate patients/carers medium preference?) and all such studies were included.

The search was done on the 18th of January 2011 and updated on the 2nd of November 2011

Review Strategy

Qualitative research is frequently carried out using diverse techniques. Therefore, it was anticipated that the research material would be reviewed, analysed and summarised by theme. The thematic analysis includes quotes from patients or their carers, as supporting evidence.

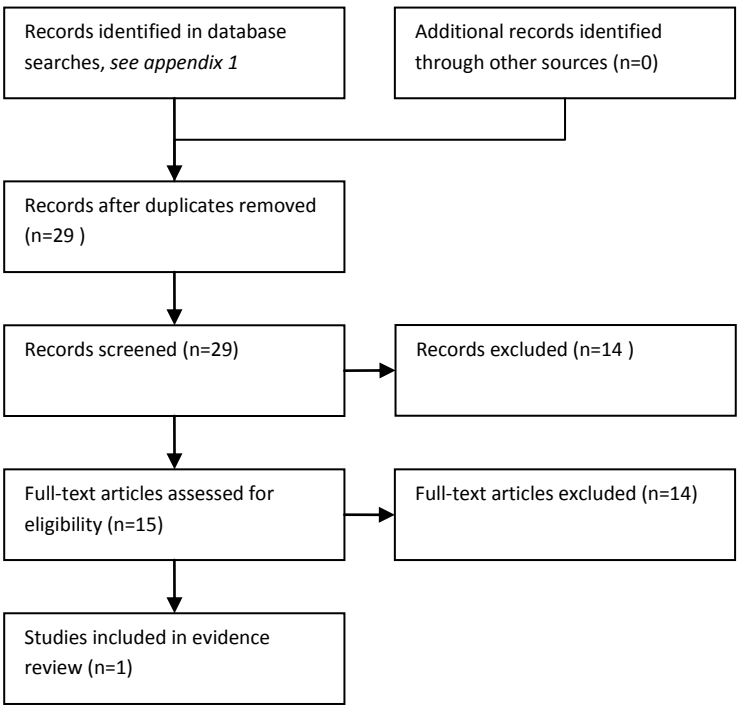
The information specialist (SA) performed an initial screening of the literature search results. One reviewer (MSH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria outlined above.

RESULTS

Results of the literature searches

29 studies were identified in the literature searches (Figure 2.1). Of these, 28 were excluded because they were narrative reviews (N = 6), not in PICO (N = 18), protocol (N = 1), intervention not specified (N = 1), in Japanese (N = 1) or a letter (N = 1).

Figure 2.1 Study flow diagram



Study quality

The literature search identified one qualitative study (Higgins, et al., 2008) designed to evaluate an alert card containing information for patients and healthcare professionals.

The overall quality of evidence was low, because it only included a single study of one intervention. This study was not designed to explore which types of information and support patients with neutropenic sepsis (and their carers) find useful.

Evidence statements

Higgins, et al., (2008) reported recurring themes from patient responses to their alert card intervention. These included 'Made me feel safe', 'Gave me assurance that if I needed help there was someone to give it to me at the earliest possible moment', 'Symptoms clearly explained', 'Great to have contact numbers'. The authors state that "Overall, the results showed a high level of patient satisfaction."

EVIDENCE TABLES

Citation: Higgins A. Raising awareness of neutropenic sepsis risk in ambulatory patients. Cancer Nursing Practice 2008 Nov;9(7):34-8.
Design: (Description of) qualitative study **Country**: South West London Cancer Network (which comprises 3 district general hospitals, 1 specialist cancer hospital and a teaching hospital) **Aim**: To measure the satisfaction of patients on cytotoxic medication with an alert card containing information for patients and healthcare professionals about the risks for myelosuppressed patients and about the need for patients to seek treatment promptly.
Inclusion criteria Patients of a South West London Cancer Network hospital on cytotoxic medication.
Exclusion criteria
Population Patients of a South West London Cancer Network hospital on cytotoxic medication.
Intervention Implementation of alert card: The alert card contains information for both patients (on one side) and healthcare professionals (on the other side) and states that the patient is on cytotoxic chemotherapy. The side that contains information for patients instructs them to contact their hospital team urgently if they feel unwell or develop any of the following symptoms: Chest pain or difficulty breathing, temperature > 38°C, shivering episodes, flu-like symptoms, gum/nose bleeds or unusual bruising, mouth ulcers that stop them eating or drinking, vomiting, 4 or more bowel movements or diarrhoea. The side of the card that contains information for healthcare professionals instructs them that the patient is at risk of neutropenic sepsis, and for them to take full blood count and cultures, that febrile neutropenic patient require urgent inpatient treatment with IV antibiotics according to local clinical guidelines and fluid replacement, and that even if afebrile, unwell neutropenic patients should be admitted and treated as above. This side of the card also contain two phone numbers (office hours/out of hours) that the healthcare professionals can use for further advice and to keep the patient's oncologist, haematologist, or healthcare worker informed.
Outcomes Patient satisfaction as measured by a questionnaire containing 9 multiple-choice questions and 3 open-ended

questions inviting the patients to describe the most helpful aspects of the alert card, features they did not like about the alert card and any other comments they might like to make about the card.
Results Patient satisfaction was measured 6 months after the full implementation of the card in the South West London Cancer Network using the survey described in the 'Outcomes' section over a 3-month period. 57 questionnaires were returned from 3 (of of 5 possible) hospitals. 2 (of the 5 possible) hospitals did not participate in the survey due to staff shortages: - 89% of the respondents indicated that they had received the card - 82% of the respondents indicated that they carried it at all times; a further 8 % of the respondents indicated that they did so some of the time. Recurring themes from the analysis: - 'Made me feel safe.' - 'Gave me assurance that if I needed help there was someone to give it to me at the earliest possible moment'. - 'Symptoms clearly explained'. - 'Great to have contact numbers'. The authors state that "Overall, the results showed a high level of patient satisfaction." (page 38).
General comments It is difficult to evaluate the quality of this study because a lot of information is not fully reported. It is unclear what the response rate is as it is not stated how many patients were approached for and included in the survey in terms of the number of questionnaires distributed. Moreover, responses were not broken down by the individual questions, rather it appears that the paper is only reporting a summary overview of the responses. It must, of course, also be borne in mind that this study does not provide any evidence on whether the alert card makes any difference to any clinical outcomes (e.g., door-to-needle, treatment time or -outcomes) of these patients.
References of Included Studies (For systematic reviews): NA

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3. Training of all healthcare professionals on the identification and management of neutropenic sepsis. (Topic J)

Guideline subgroup members for this question

Catherine Oakley (lead), Mark Holland, Anne Higgins, Miranda Holmes and Nicola Perry

Review question

Does training healthcare professionals on the identification and management of neutropenic sepsis improve outcomes for patients receiving anti-cancer treatment?

Rationale

Cancer chemotherapy can cause a low white blood cell count which sometimes results in a life threatening blood infection called neutropenic sepsis. We want to analyse the research that explores the benefits of training for healthcare professionals about neutropenic sepsis. Training could be basic or more involved to include the use of teaching aids such as DVDs or simulators which allow healthcare professionals to role-play the practical treatment of patients with neutropenic sepsis. We want to establish if education for healthcare professionals about neutropenic sepsis results in prompt, appropriate treatment should neutropenic sepsis occur.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients receiving anti-cancer treatment	Enhanced extra training for healthcare professionals on the identification and management of neutropenic sepsis in addition to standard training	Standard training for healthcare professionals	• Mortality, • ICU admissions • Door to needle time • Length of stay • Patient satisfaction • Healthcare professionals knowledge of neutropenic sepsis management

METHODS

Information sources and eligibility criteria

The search strategy will be available in the full guideline. Although this is an intervention question, the search was not restricted to randomised trials and systematic reviews of such trials as limited evidence on this topic area was expected. The search was conducted on the 2nd of February 2011 and on 2nd November 2011.

Selection of studies and data synthesis

It was anticipated that studies comparing enhanced training to standard training (regardless of the type of enhancement) would be grouped and, if possible, their results be pooled. If the data lent itself to it, subgroup analyses would also be undertaken on the basis of the different types of training interventions employed in the included studies.

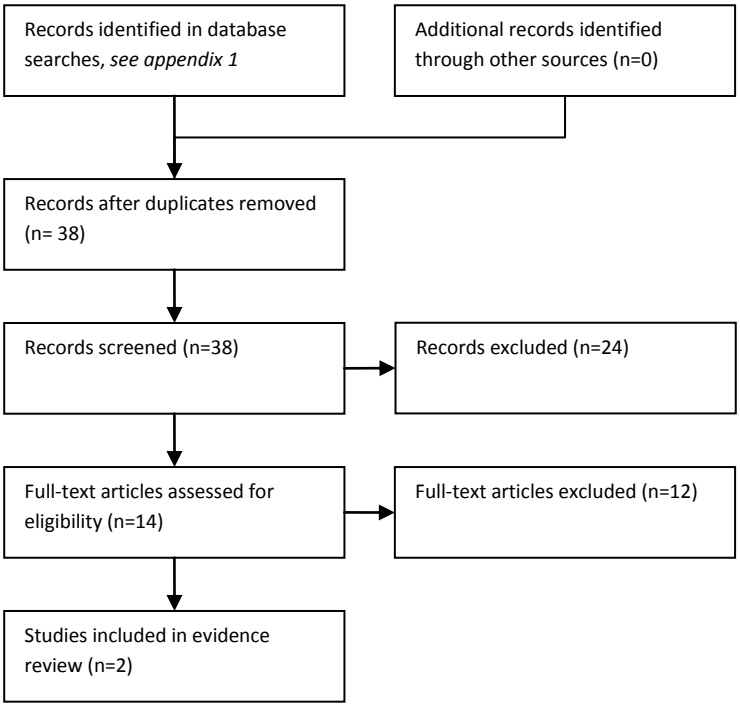
The information specialist (SA) performed an initial screening of the literature search results. One reviewer (MSH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria outlined above.

RESULTS

Results of literature searches

38 studies were identified in the literature searches (Figure 3.1). Of these, 36 were excluded because they did not meeting the PICO criteria (N = 35) or were a narrative review (N = 1). Two studies were included in the evidence review of which one was a retrospective study (Lim et al., 2010) while the other was an audit reported only in abstract form (Sastry et al., 2009).

Figure 3.1 Study flow diagram



Lim et al. (2010) retrospectively evaluated the clinical impact of implementing an electronic clinical practice guideline on the management and outcomes of patients presenting with febrile neutropenia at four urban emergency departments, one of which was designated as the intervention hospital (because the practice guideline was developed and had most penetration there) while the remaining three hospitals were considered controls.

Lim et al. reported that ECG and blood culture, but not chest X-ray were more often performed in patients presenting to the intervention hospital (N = 128), and that times from triage to room placement and from triage to physician assessment did not differ significantly between the control (N = 73) and intervention hospitals, but that time from triage to first consultation was shorter at the intervention hospital than at the control hospitals and so was time from triage to first antibiotic. However, the median times from triage to first antibiotic of the subgroup of physicians at the intervention hospital who elected to use the electronic clinical practice guideline did not differ statistically significantly from that of the subgroup of physicians not using the eCPG. The proportion

of patients admitted/transferred and the time from triage to admission/transfer or to discharge did not differ significantly between the intervention and control hospitals. However, patients presenting to control hospitals were more likely to be discharged home than patients presenting to the intervention hospital (See also the Grade and Evidence tables below for details on evidence quality of this study).

Sastry et al. (2009) in an audit/re-audit study assessed compliance with the local febrile neutropenia protocol after heightened policy awareness and re-education of staff and found that a higher proportion of febrile episodes (26/35) had medical assessment within 15 min after re-education of the medical and nursing staff on the local febrile neutropenia protocol compared to before the re-education (15/31). However, the proportions of patients receiving antibiotics within 30 min did not differ before and after re-education (See also the Grade and Evidence tables below for details on evidence quality of this study).

Study quality and results

Two studies were included in the evidence review for this topic. Lim et al. (2010) retrospectively evaluated the clinical impact of implementing an electronic clinical practice guideline on the management and outcomes of patients presenting with febrile neutropenia at four urban emergency departments. Sastry et al. (2009) in an audit/re-audit study assessed compliance with the local febrile neutropenia protocol after heightened policy awareness and re-education of staff. Both studies are subject to severe limitations and constitute an evidence body of very low quality.

Evidence Statements

Door to needle time

There was very low quality evidence from two observational studies about the effect of training on door to needle time. Lim et al (2010) reported a shorter time from triage to first antibiotic in hospitals which used an electronic clinical practice guideline for febrile neutropenia. Sastry et al (2009) study evaluated staff re-education about febrile neutropenia and found that the proportion of patients receiving antibiotics within 30 minutes of their first assessment did not differ significantly before and after re-education.

Mortality, ICU admissions, length of stay, patient satisfaction and healthcare professionals' knowledge of neutropenic sepsis management

Literature searches identified no evidence about the impact of training of healthcare professionals on the identification and management of neutropenic sepsis on these outcomes.

Table 3.1 Grade evidence profile for training of healthcare professionals on the identification and management of neutropenic sepsis

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced training of healthcare professionals on the identification and management of neutropenic sepsis	standard training of healthcare professionals on the identification and management of neutropenic sepsis	Relative (95% CI)	Absolute	
Door-to-needle time (Better indicated by lower values)											
2	observational studies	very serious[1]	serious[2]	serious[3]	serious[4]	none	163	104	Not pooled		VERY LOW

[1] One study is a retrospective study with a high risk of bias and the other study, which is an audit, is only reported in abstract form and can therefore not be comprehensively evaluated.
[2] The studies report different results, both statistically and numerically.
[3] The interventions are under-specified in the studies.
[4] The sample sizes were small in both studies.

1 EVIDENCE TABLES

Citation: Lim,C.; Bawden,J.; Wing,A.; Villa-Roel,C.; Meurer,D.P.; Bullard,M.J.; Rowe,B.H. (2010). Febrile neutropenia in EDs: the role of an electronic clinical practice guideline. American Journal of Emergency Medicine.

Design: Retrospective study

Country: Canada

Aim: To evaluate the clinical impact of implementing an electronic clinical practice guideline on the management and outcomes of patients presenting with febrile neutropenia at four urban emergency departments.

Inclusion criteria

Adult patients with an absolute white blood cell (WBC) count < 1000 cells/mm^3 or a neutrophil count < 500 cells/mm^3, a fever > 38.0°C at home or in the ED, and for whom an ED physician made a final primary or secondary diagnosis of febrile neutropenia.

One of the four hospitals was designated as the intervention hospital and all eligible visits during the 3-year study period were screened. A random sample (N = 40) from each of the other three hospitals, which were designated control hospitals, were selected.

Exclusion criteria

Patients not seen by an ED physician because they were directly admitted to an inpatient ward, or patients who left without being seen by an ED physician or without completing their treatment, or patients whose medical records were not found.

Population

Intervention hospital: N = 128; median age = 51 (IQR = 40-65); N = 56 were females; N = 50 had allergy to any medications;
Features at ED presentation: Median pulse (/min) = 109 (IQR = 96-122), median respiratory rate (/min) = 20 (IQR = 18-22), median systolic blood pressure (mmHg) = 118 (IQR = 107-135), median diastolic blood pressure (mmHg) = 72 (IQR = 63-84), median absolute WBC count (×10^3 cells/mm^3) = 0.8 (IQR = 0.4-1.3), median absolute neutrophil count (×10^3 cells/mm^3) = 0.1 (IQR = 0-0.3), median temperature (°C) = 38.2 (IQR = 37.2-38.8).
Control hospital: N = 73; median age = 57 (IQR = 47-68); N = 28 were females; N = 29 had allergy to any medications;
Features at ED presentation: Median pulse (/min) = 112 (IQR = 96-122), median respiratory rate (/min) = 18 (IQR = 18-20), median systolic blood pressure (mmHg) = 117 (IQR = 108-132), median diastolic blood pressure (mmHg) = 70 (IQR = 64-81), median absolute WBC count (×10^3 cells/mm^3) = 0.9 (IQR = 0.6-1.2), median absolute neutrophil count (×10^3 cells/mm^3) = 0.1 (IQR = 0-0.3), median temperature (°C) = 38.0 (IQR = 37.1-38.5).

The groups did not differ statistically significantly on any of these variables (all ps ≥ .09).

Intervention

The febrile neutropenia electronic clinical practice guideline FN eCPG) was developed and implemented at the designated intervention hospital in 2001 by a team of clinicians and health informatics specialists and was subject to ongoing review and modification to ensure that the recommended therapies are consistent with up-to-date clinical evidence. Physicians at all 4 hospitals can access the FN eCPG via an Intranet web browser portal. The use of the FN eCPG was not mandatory and patient management practice remained at the discretion of the most responsible physician.

The intervention hospital was chosen as such because the FN eCPG was primarily developed and had the greatest clinical penetration at that site. The authors report that "The methods for knowledge dissemination at this site have included educational sessions, survey and feedback from the clinicians, and iterative changes approved by representatives of the participating clinical groups. The remaining 3 hospitals were designated as

control hospitals as they were not developers and had less experience with the eCPG application." (p .2)

Outcomes

Informatics component outcomes: The proportion of patient visits in which the eCPG was used, changes in eCPG use over time and time flow related to ED management of FN patients, particularly the time interval from triage to the initial administration of antibiotics.
Clinical component outcomes: Change in patient outcomes (length of ED stay, disposition), investigations (cultures, imaging) and treatments (antibiotics, granulocyte colony-stimulating factor (GCF)) used in management.

Results

eCPG use:
-The FN eCPG was used for 76 of 201 patients.
-There was no evidence of eCPG use at 2 control hospitals and at the third control hospital the eCPG was used for 19% of the patients.
-57% of the patients at the intervention hospital were treated using the eCPG and this level appeared to be constant over the 3-year study period.

Emergency department management
-ECG (46.9% v 31.5%, p = .03) and blood culture (96.1% v 93.1%, p = .04) were more often performed in patients presenting to the intervention hospital.
-The control and intervention hospitals did not differ in the proportion of patients who received a chest X-ray (87.5% v 84.9%, p = .77)
-The percentage of patients receiving G-CSF did not differ between intervention and control sites (28.9% v 21.9%, p = .27). The authors note that "the FN eCPG prompts the EP to order G-CSF after consultation with the hematologist or infectious diseases physician. The FN eCPG also provides access to specific GCSF information to the EP at the point of ordering." (p 5).
- A higher proportion of patients at the intervention hospital received piperacillin-tazobactam than patients at the control hospital (65.6% v 13.7%, p < .001).
- A higher proportion of patients at the control hospital received ceftazidime than patients at the intervention hospital (60.3% v 16.4%, p < .001).
-Times from triage to room placement and from triage to physician assessment did not differ significantly between the control and intervention hospitals.
-Time from triage to first consultation was shorter at the intervention hospital than at the control hospitals (3.8 v 5.0 hours, p = .001).
-Time from triage to first antibiotic was also shorter at the intervention than at the control hospitals (3.9 v 4.9 hours, p = .02).
- The median times from triage to first antibiotic of the subgroup of physicians at the intervention hospital who elected to use the eCPG (3.8 hours) did not differ statistically significantly from that of the subgroup of physicians not using the eCPG (4.2 hours, p = .31).
-The proportion of patients admitted/transferred did not differ significantly between the intervention and control hospitals.
-Time from triage to admission/transfer did not differ significantly between the intervention and control hospitals.
-Time from triage to discharge did not differ significantly between the intervention and control hospitals.
-Patients presenting to control hospitals (15.1%) were more likely to be discharged home than patients presenting to the intervention hospital (7%, p = .04).

General comments

The authors of this retrospective study have employed rigorous data extraction methods ensuring the integrity of the extracted data. However, not much precise detail is provided about (1) the intervention itself (the FN eCPG) and (2) the implementation of the intervention. What detail is provided about both points suggests that this study seriously lacks control and there is a high risk that the findings are explicable in terms of other factors than the intervention. The evidence provided by this study can only be considered of low quality (because it is subject to a high risk of bias).

References of Included Studies (For systematic reviews): NA

1

Citation: Sastry,J.; Harrison,D.; Taylor,J.; Ronghe,M.; Gibson,B.; Murphy,D.; McIntosh,D. (2009). Re-education works! re-audit shows improved compliance to febrile neutropenia protocol in a principle treatment centre. Pediatric Blood and Cancer, 53, 866.
Design: Audit and re-audit **Country**: UK **Aim**: To assess compliance with the local febrile neutropenia protocol after heightened policy awareness and re-education of staff.
Inclusion criteria See **Population**
Exclusion criteria
Population Febrile episodes during a 4-week audit period (in Feb 2007): N = 31 Febrile episodes during a 4-week re-audit period (in May 2008): N = 35
Intervention Re-education of medical and nursing staff on the local febrile neutropenia protocol.
Outcomes Time of febrile episode, time taken to medical assessment, antibiotic administration, episode outcome.
Results **-15/31 audit patients and 26/35 re-audit patients had medical assessment within 15 min ($p < .05$; means = 22.5 and 14.1 min, respectively).** -12/31 audit patients and 19/35 re-audit patients received antibiotics within 30 min (non-significant; means = 57.74 and 33.7 min, respectively).
General comments The quality of this study cannot be assessed as it is only reported in abstract form. This also precludes detailed assessment of the intervention. This study has only been included because there is so little evidence for topic J. *It must be kept in mind when considering the recommendations for this topic that there has been no formal appraisal of the risk of bias that the results reported by this study are subject to.*
References of Included Studies (For systematic reviews): NA

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Identification and Assessment: guideline chapter four

4. Signs and symptoms of neutropenic sepsis (Topic A).

Guideline subgroup members

Helen Clayson (lead), Anne Davidson, Nicola Perry and Janie Thomas.

Review question

Which symptoms and/or signs experienced by patients in the community predict neutropenic sepsis?

Rationale

Neutropenic sepsis is a potentially fatal complication following anti-cancer treatments. Most people receive anti-cancer treatments as outpatients and symptoms and/or signs that might predict the development of neutropenic sepsis often occur in patients in the community. Delay in diagnosis is associated with poor outcomes, sometimes resulting in avoidable deaths. There is great variation in those symptoms and/or signs that may predict the development of neutropenic sepsis; this leads to variations in practice such as in the information given to patients and the criteria for urgent admission to hospital. Overdiagnosis results in inappropriate admissions to hospital and this may delay anti-cancer treatments; underdiagnosis or delay in diagnosis puts patients at risk of serious infections or, at worst, avoidable death due to neutropenia-related infections. Topic A addresses this variation in practice and aims to examine the evidence around several key symptoms and signs to assess their utility in the community as predictors of neutropenic sepsis.

Question in PICO format

Patients/ population	Symptoms/signs	Reference test	Target condition
Patients in the community, who have received anti-cancer treatment	• Perceived or real pyrexia • Perceived or real sub-normal temperature • Flu-like symptoms • Rigor • Malaise • Parental/carer concern • Mucositis • Diarrhoea and vomiting • Altered mental status • Symptoms or signs of a primary infection site	"Gold standard" definition of neutropenic sepsis (see topic D1) or accept whatever reference standard was used in the original studies	• Neutropenic sepsis (within a specified time period – 1 week) • Mortality • Severe sepsis

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, BNI, Cinah, Psychinfo, Web of Science (SCI & SSCI) and ISI Proceedings.

There were no publication date limits set. The searches were conducted between the 20th April and the 3rd May 2011, and updated on 7th November 2011.

The information specialist (SB) did the first screen of the literature search results. Two reviewers (NB & KF) selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then ordered and appraised.

Data synthesis

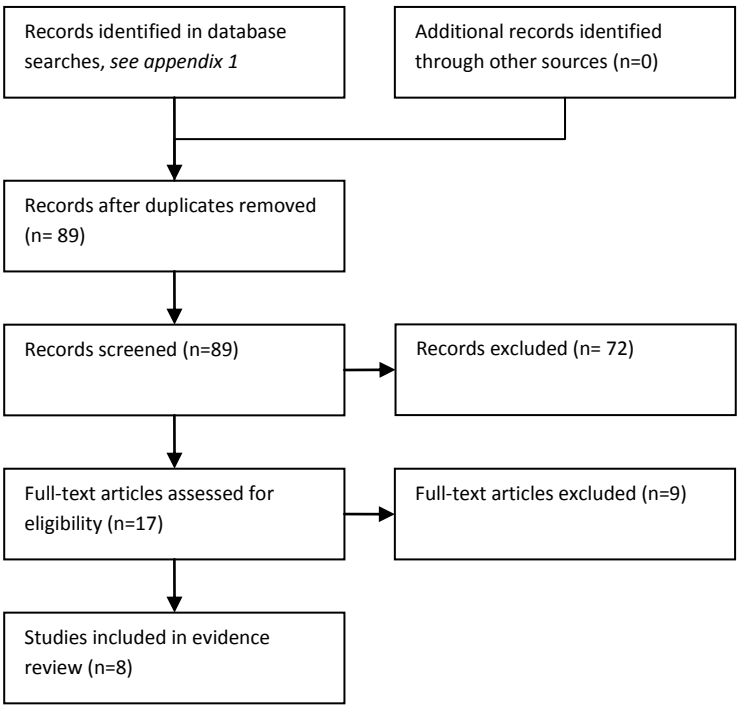
One reviewer (KF) extracted data and assessed study quality using items from the QUADAS checklist for diagnostic studies. Where possible, the sensitivity and specificity of the particular test was extracted into 2X2 tables. The heterogeneity of outcome measures precluded data pooling.

RESULTS

Results of literature searches

After de-duplication, 112 records were identified. After a preliminary sift, eighty-nine papers were reviewed. Seventeen papers were ordered and eight were included in this summary (Ammann *et al*., 2003, Ammann *et al*., 2004, Ammann *et al*., 2010, Chayakulkeeree *et al*., 2003, Hakim *et al*., 2010, Klaassen *et al*., 2000, Klastersky *et al*., 2000 and West *et al*., 2004).

Figure 4.1 Study flow diagram



Description of included studies

There was no evidence about signs and symptoms in the community that might predict severe sepsis, mortality or sepsis within a time period. Instead, the included papers reported largely retrospective data on patients who had presented at hospital with treatment induced neutropenia and fever. As part of the initial clinical assessment, some variables of interest were noted i.e. high temperature, appearance, mucositis, altered mental status, gastrointestinal upset or signs of infection.

The limited spectrum of patients in these studies means we do not have evidence about patients in the community setting. This is an important shortcoming as the sensitivity and specificity of symptoms or signs in the community might differ greatly from their sensitivity and specificity in secondary care.

The target condition in all studies was the clinical outcome for patients where an unfavourable outcome could be considered as one or more of the following: sepsis, bacteremia, serious medical complications, microbiologically documented infection, critical care, fever relapse, positive urine/blood cultures or death due to infection. Unfortunately, these variables were frequently considered in groups and hence results for each outcome could not be extracted.

Six studies recruited paediatric patients, one study recruited adults only and one had a mixed population of children and adults. The absolute proportion of haematological malignancies varied across studies, or was not documented, but was often half or more than half of the patients. Tests were typically, but not exclusively, performed on patients admitted with fever and neutropenia, before the initiation of empiric antimicrobial therapy.

Two studies presented data on a single episode of neutropenic fever per patient whilst the majority included multiple episodes in their analyses. Multiple episodes may not be independent and could introduce bias. Investigators performed univariate analyses using Mann Whitney, X^2 or Student's t-tests. Significant variables were applied to multivariate analyses using backwards or forwards stepwise logistic regression. Only univariate results are presented here since covariates were irrelevant to the question.

Blinding was rarely used. Blinding is where reference tests are interpreted without knowledge of the index test results and vice-versa. The reference test (or gold standard) is the definitive test whereas the index test is the factor under investigation (e.g. oral mucositis). For index tests in prospective studies, clearly lack of blinding is not an issue since the outcome of interest could not have been known at the time of presentation.

Table 4.1 is a summary of study quality, according to the QUADAS check list. Only three studies were prospective.

In all cases, two by two tables, sensitivity and specificity were calculated as far as possible from the data presented in each study although odds ratios and P values were as reported by the authors.

Table 4.1 Study quality according to QUADAS criteria

Study Reference	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?	Relevant clinical information?	Withdrawals explained?
Ammann 2003	N	?	?	Y	Y	Y	?	?	Y	Y
Ammann 2004	N	?	?	Y	Y	Y	?	?	?	Y
Ammann 2010	N	?	Y	Y	Y	Y	?	?	Y	Y
Chayakulkeeree 2003	N	?	?	Y	Y	Y	?	?	Y	Y
Hakim 2010	N	?	Y	Y	Y	Y	?	?	Y	Y
Klaassen 2010	N	?	Y	Y	Y	Y	Y	Y	Y	Y
Klastersky 2000	N	?	Y	Y	Y	Y	?	?	Y	Y
West 2004	N	?	Y	Y	Y	Y	?	?	Y	Y

Study quality and results

There was no direct evidence about signs and symptoms of cancer patients in the community that might predict neutropenic sepsis. The available evidence came from retrospective studies of patients who had presented at hospital with treatment induced neutropenia and fever. This evidence is summarised in Table 4.2 and in Figures 4.2 to 4.8. By including only patients with confirmed neutropenia and fever these studies are not a representative spectrum of patients in the community. The sensitivity and specificity of symptoms or signs for neutropenic sepsis in the community might differ from that in secondary care. Studies typically reported composite outcomes encompassing severe bacterial infection, death and critical care. For these reasons the evidence is of very low quality.

Table 4.2– Signs and symptoms as predictors of adverse outcome in patients with fever and neutropenia.

Sign or symptom	Number of of studies (patients)	Prevalence of adverse outcome* (range)	Sensitivity for adverse outcome (range)	Specificity for adverse outcome (range)	Positive LR (range)	Negative LR (range)	References
Mucositis	5 (1605)	12% to 56%	3% to 39%	60% to 100%	0.64 to 2.82	0.71 to 1.24	Ammann, et al., (2003, 2004, 2010), Chayakulkeeree, et al (2003) and West, et al (2004)
General appearance unwell	4 (855)	17% to 33%	31% to 75%	31% to 78%	1.08 to 1.82	0.75 to 0.90	Ammann, et al., (2003, 2004), Hakim, et al., (2010) and Klaassen, et al., (2010)
Temperature >39°C	8 (2602)	15% to 38%	12% to 58%	53% to 95%	1.17 to 2.91	0.71 to 0.92	Ammann, et al., (2003, 2004, 2010), Chayakulkeeree, et al., (2003), Hakim, et al., (2010), Klaassen, et al., (2010) and Klastersky, et al., (2000)
Clinical signs of infection	2 (677)	23% to 37%	21% to 23%	65% to 75%	0.59 to 0.90	1.03 to 1.23	Ammann, et al., (2003, 2004, 2010),
Chills	2 (586)	12% to 36%	10% to 11%	96% to 97%	2.47 to 2.91	0.93	Ammann, et al., (2003, 2004) and West, et al., (2004)
Altered mental state	2 (1023)	15% to 60%	16% to 17%	95% to 97%	3.67 to 6.09	0.86 to 0.87	Chayakulkeeree, et al., (2003) and Klastersky, et al., (2000)
No evidence found for the following symptoms or signs: flu-like symptoms, rigor, parental or carer concern, diarrhoea and vomiting							

**Adverse outcome was a composite outcome including death, critical care, unresolved fever and bacteraemia.*

Evidence statements

There was uncertainty about which signs and symptoms predict neutropenic sepsis and its complications in cancer patients in the community due to a lack of published evidence.

Chills and altered mental status were associated with adverse outcome in two secondary care studies, but most patients with neutropenic sepsis did not experience either of these symptoms.

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Ammann RA, Bodmer N, Hirt A, Niggli FK, Nadal D, Simon A, Ozsahin H, Kontny U, Kuhne T, Popovic MB, Luthy AR and Aebi C (2010). Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. *J.Clin.Oncol.* **28:** 2008-2014.

Chayakulkeeree M and Thamlikitkul V (2003). Risk index for predicting complications and prognosis in Thai patients with neutropenia and fever. *J.Med.Assoc.Thai.* **86:** 212-223.

Hakim H, Flynn PM, Srivastava DK, Knapp KM, Li C, Okuma J and Gaur AH (2010). Risk prediction in pediatric cancer patients with fever and neutropenia. *Pediatr.Infect.Dis.J.* **29:** 53-59.

Klaassen RJ, Goodman TR, Pham B and Doyle JJ (2000). "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J.Clin.Oncol.* **18:** 1012-1019.

Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K and Talcott J (2000). The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J.Clin.Oncol.* **18:** 3038-3051.

West DC, Marcin JP, Mawis R, He J, Nagle A and Dimand R (2004). Children with cancer, fever, and treatment-induced neutropenia: risk factors associated with illness requiring the administration of critical care therapies. *Pediatr.Emerg.Care.* **20:** 79-84.

Figure 4.2 Temperature.

This plot suggests that about half of the patients that develop neutropenic sepsis have a temperature of > 39°C whereas about a fifth of patients that don't develop sepsis also have a similarly high temperature. Since patients were only included in these studies if they presented with a fever, defined generally as between >38°C and 39°C, these data may not be particularly informative. Data from Ammann et al. (2004 and 2010) differ from the other studies, reporting very low sensitivity and very high specificity. This may be due to the high cut-off values used by the investigators for a positive variable, respectively 39.7°C and 39.5°C.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ammann 2003	62	83	44	92	0.58 [0.49, 0.68]	0.53 [0.45, 0.60]
Ammann 2004	16	17	69	246	0.19 [0.11, 0.29]	0.94 [0.90, 0.96]
Ammann 2010	11	14	81	287	0.12 [0.06, 0.20]	0.95 [0.92, 0.97]
Chayakulkeeree 2003	83	48	76	60	0.52 [0.44, 0.60]	0.56 [0.46, 0.65]
Hakim 2010	28	91	28	183	0.50 [0.36, 0.64]	0.67 [0.61, 0.72]
Klaassen 2010	23	64	20	120	0.53 [0.38, 0.69]	0.65 [0.58, 0.72]
Klastersky 2000	52	196	61	447	0.46 [0.37, 0.56]	0.70 [0.66, 0.73]

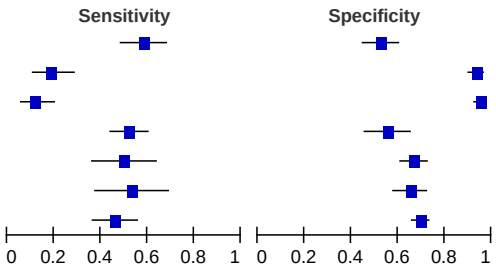


Figure 4.3 General appearance.

This outcome was measured in paediatric patients who, in the opinion of the clinician, looked unwell. The results are similar to those of temperature in that about half of the children that developed an adverse event looked unwell but also a fifth of the patients who didn't develop a complication also looked unwell. Amman et al (2003) analysed appearance in sub-groups, appearance not reduced versus slightly reduced or severely reduced. The first comparison resulted in an acceptable sensitivity and specificity compared with the other studies but there were no clear definitions of this outcome in order to differentiate between 'slightly reduced' and 'severely reduced' appearance.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ammann 2003	54	99	18	44	0.75 [0.63, 0.84]	0.31 [0.23, 0.39]
Ammann 2003	8	13	18	44	0.31 [0.14, 0.52]	0.77 [0.64, 0.87]
Hakim 2010	28	91	28	183	0.50 [0.36, 0.64]	0.67 [0.61, 0.72]
Klaassen 2010	17	40	26	144	0.40 [0.25, 0.56]	0.78 [0.72, 0.84]

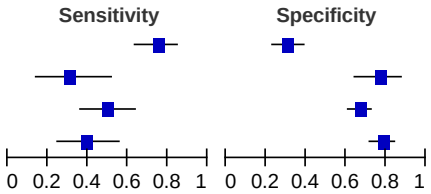


Figure 4.4 Chills.

The two sets of data available for this variable both showed very high specificity and very low sensitivity, that is to say that the majority of patients who experienced an adverse event ('severe bacterial infection' in the case of Ammann et al., 2003 and the 'need for critical care therapy' in West et al, 2004) were not considered as having, or did not have, chills on presentation. These results suggest that chills might be useful in indentifying patients at high risk of adverse events (accepting that many patients with chills will not have adverse outcome). The absence of chills, however, is not a good predictor of patients at low risk of adverse events.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ammann 2003	10	6	93	174	0.10 [0.05, 0.17]	0.97 [0.93, 0.99]
Ammann 2004	0	0	0	0	Not estimable	Not estimable
West 2004	4	12	32	255	0.11 [0.03, 0.26]	0.96 [0.92, 0.98]

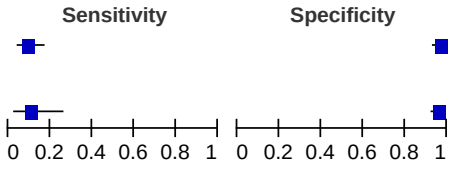


Figure 4.5 Mucositis.

The two sets of data for Ammann et al., 2010 relate respectively to 'oral mucositis to any degree' and 'other mucositis to any degree'. The observed relationship between sensitivity and specificity across the studies might suggest a threshold effect i.e. some dependence on the definition of mucositis used in the individual studies. However, the highest sensitivity was just 40% and therefore up to less than half of patients who experienced the target condition had mucositis whilst up to 40% of patients who did not develop the outcome also had mucositis.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ammann 2003	3	0	83	166	0.03 [0.01, 0.10]	1.00 [0.98, 1.00]
Ammann 2010	10	37	82	264	0.11 [0.05, 0.19]	0.88 [0.83, 0.91]
Ammann 2010	23	121	66	180	0.26 [0.17, 0.36]	0.60 [0.54, 0.65]
Chayakulkeeree 2003	57	16	92	102	0.38 [0.30, 0.47]	0.86 [0.79, 0.92]
West 2004	14	69	22	198	0.39 [0.23, 0.57]	0.74 [0.68, 0.79]

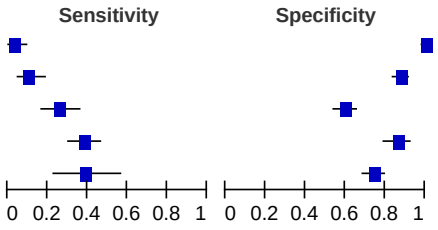


Figure 4.6 Clinical signs of an infection.

Approximately 20% of patients, regardless of outcome, had clinical signs of infection. The ROC curve (see Figure vii) suggests clinical signs of infection were slightly more common in patients with good outcomes. In these studies at least, clinical signs were not a useful predictor of adverse events.

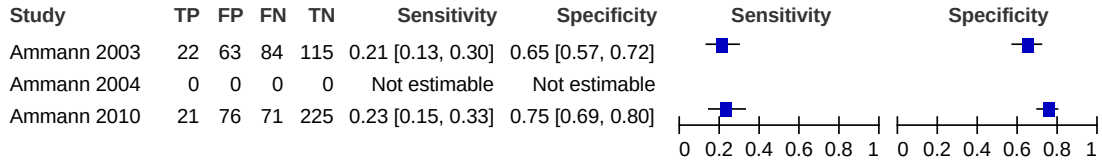


Figure 4.7 Confused mental state.

This is a similar result to those for the variable chills. It suggests that confused mental state might be useful in indentifying patients at risk of adverse events. The absence of confused mental state, however, is not a good indicator of low risk of adverse events.

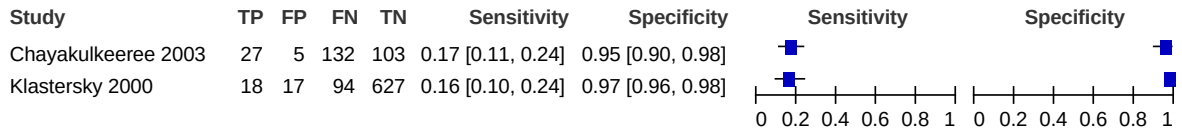
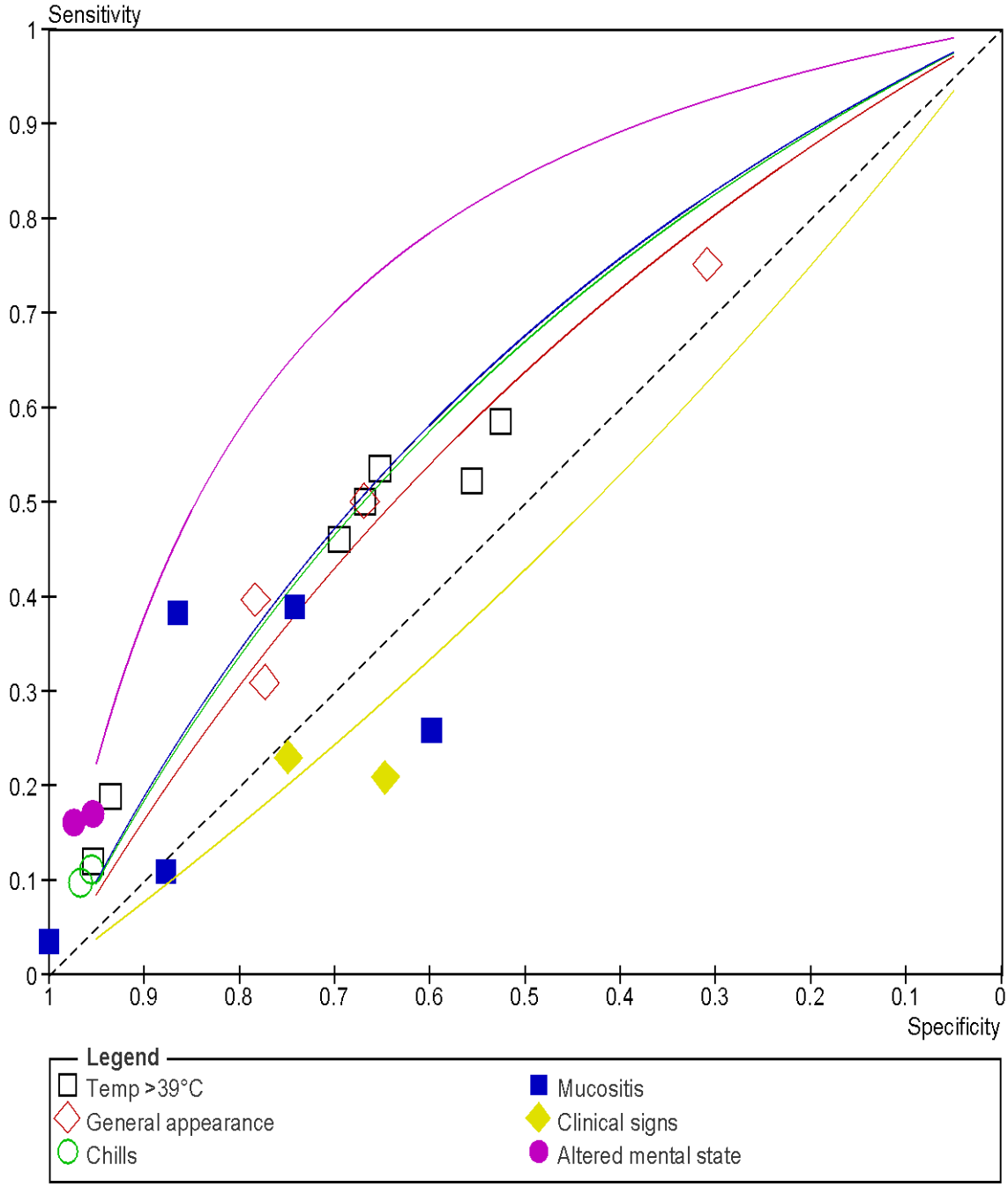


Figure 4.8 Summary ROC curve for all variables.



1 **EVIDENCE TABLES**

2

Author(s): Ammann *et al.* (2003)

Country: Switzerland

Study Design: Retrospective observational study.

Study participants: Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after myelosuppressive chemotherapy. There were 285 FN episodes in 111 children. Median age at the first FN episode was 6.3 years. The proportion with haematological cancers was not reported.

Target condition/reference standard:

Severe (significant) bacterial infection defined as: bacteraemia, positive urine culture, pneumonia, clinically unequivocal diagnosis of infection, serum CRP >150mg/L or unexpected death from infection.

Index tests and comparators:

(i) Maximum fever at presentation: ≤39°C versus >39°C

(ii) General appearance at presentation: not reduced versus slightly reduced

(iii) General appearance at presentation: not reduced versus severe reduced

(iv) Chills at presentation: no versus yes

(v) Oral mucositis at presentation: no (or slight) versus severe

(vi) Clinical signs of viral infection: no versus yes.

Follow up: Not reported.

Comments:

Patients had presented with febrile neutropenia at a single centre between January 1st 1993 and 31st December 2001. The aim of the study was to predict severe bacterial infection in young patients presenting with neutropenia and fever. Of thirty-nine covariates, six were relevant to this question. There were missing values for some covariates: fever (N=4), appearance (N=49), chills (N=2), mucositis (N=33) and signs of viral infection (N=1). The rate of severe bacterial infection was 106/285 (37%). Note that the confidence intervals were 99% to allow for multiple comparisons.

(i) OR 1.62 (99%CI: 0.83-3.18) TP(true positive) =62, FP(false positive)=83, FN (false negative)=44, TN (true negative)=92 (ii) OR 1.33 (99%CI: 0.56-3.35) TP=54 FP=99 FN=18 TN=44 (iii) OR 1.50 (99%CI: 0.32-6.51) TP=8 FP=13 FN=18 TN=44 (iv) OR 3.07 (99%CI: 0.71-15.6) TP=10 FP=6 FN=93 TN=174 (v) OR ∞ (99%CI: ∞-1.54) TP=3 FP=0 FN=83 TN=166 (vi) OR 2.05 (99%CI: 0.96-4.57) TP=22 FP=63 FN=84 TN=115

1

Author(s): Ammann *et al.* (2004) **Country:** Switzerland
Study Design: Retrospective observational study.
Study participants: Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after myelosuppressive chemotherapy. There were 364 FN episodes in 132 children.
Target condition/reference standard: Bacteremia, defined as: at least one positive blood culture using a qualitative automated culture system (BacT/ALERT by bioMérieux). The authors were particularly interested in the incidence of Gram –ve infection.
Index tests and comparators: (i) Maximum fever at presentation: <39.7°C versus >39.7°C (ii) Chills at presentation (iii) No clinical evidence of viral infection.
Follow up: Not reported.
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 1993 and 31st December 2001. The aim of the study was to predict the risk of bacteremia in young patients presenting with neutropenia and fever. Of forty-four covariates, one was relevant to this

question. The rate of bacteremia in the first episode only was 85/348 and there were 30 episodes of Gram –ve bacteremia. The majority of patients (N=285) in this study overlapped with those in Ammann *et al.*, 2003 but, in this case, the 79 patients who had presented with known serious bacterial infection are included since the outcome of interest (bacteremia) is different.

Risk of bacteremia:

(i) OR 3.2 (95%CI: 1.5-7.1) TP=16 FP=17 FN=69 TN=246

Risk of Gram –ve bacteremia:

(ii) OR 3.5 (95%CI: 1.3-9.7) Sensitivity and specificity could not be derived from the data.

(iii) OR 3.6 (95%CI: 1.1-19.0). Sensitivity and specificity could not be derived from the data.

1

Author(s): Ammann *et al.* (2010)

Country: Switzerland

Study Design: Prospective observational study. No evidence to suggest randomisation.

Study participants: Paediatric cancer patients (1 - 18 years) of median age 6.9 years (IQR: 3.8-11.6) with neutropenia (ANC <0.5 $X10^9$/l) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after non-myeloablative chemotherapy. Multiple episodes were allowed. 472 episodes were reported in 206 patients.

Target condition/reference standard:

Adverse events: defined as serious medical complications, including death or the need for critical care as a result of infection, microbiologically documented infection or radiologically confirmed pneumonia.

Index tests and comparators:

At presentation, without adverse events known:

(i) General condition severely reduced versus not

(ii) Oral mucositis present to any degree versus not

(iii) Other mucositis present to any degree versus not

(iv) Clinical signs of upper respiratory infection versus not

(v) Axillary temperature >39.5°C versus not
Follow up: Patients were assessed at presentation, then again after 8 to 24 hours of inpatient therapy. Length of follow up for adverse events was not reported.
Comments: Patients had presented with febrile neutropenia at four centres between January 2004 and December 2007. The aim of the study was to develop a score to predict the risk of adverse events in young patients with cancer and neutropenic fever, comparing performance either at presentation or on a later reassessment. The investigators analysed the results using univariate logistic regression to produce odds ratios for each predictor. There were 92 adverse events in 393 episodes. At presentation, without adverse events known (N=393): (i) OR 2.3 (95%CI: 1.2-4.7) (P=0.019)* TP=14 FP=23 FN=78 TN=278 (ii) OR 0.6 (95%CI: 0.4-1.0) (P=0.070) TP=26 FP=121 FN=66 TN=180 (iii) OR 0.9 (95%CI: 0.5-1.9) (P=0.84) TP=10 FP=37 FN=82 TN=264 (iv) OR 0.9 (95%CI: 0.5-1.6) (P=0.72) TP=21 FP=76 FN=71 TN=225 (v) OR 2.8 (95%CI: 1.2-6.4) (P=0.015)* TP=11 FP=14 FN=81 TN=287 *These characteristics were used as part of a multivariate prediction model.

1

Author(s): Chayakulkeeree *et al.* (2003) **Country:** Thailand
Study Design: Retrospective observational study.
Study participants: Adult or adolescent patients (>12 years, mean age 44.7 years) with febrile (>38°C) neutropenia (<500/mm^3). Nearly half (45%) the patients were male. There were 267 episodes in 220 patients. 158/220 (72%) patients had a haematological malignancy. Episodes were: clinically documented infection (N=38), microbiologically documented infection (N=90) or fever of unknown origin (N=139).
Target condition/reference standard: Favourable outcome: fever resolved in 5 days of starting treatment and without complications Unfavourable outcome: Death, serious complications, modification of initial therapy, relapse of

resolved fever or fever longer than 5 days. The reference standard was clinical follow up as reported in patients' medical records.
Index tests and comparators: (i) Temperature ≥39°C versus <39°C (ii) Altered mental state versus not (iii) Mucositis versus not (iv) Diarrhoea versus not (v) Abdominal pain versus not (vi) Nausea and vomiting versus not
Follow up: Five days
Comments: Patients had presented with febrile neutropenia at a single centre between January 1999 and December 2000. The aim of the study was to identify types of infection and the causative organisms; also to validate a risk score. (i) OR 1.37 (95%CI: 0.84-2.23) (P=0.263) TP=83 FP=48 FN=76 TN=60 (ii) OR 4.21 (95%CI: 1.62-10.94) (P=0.004) TP=27 FP=5 FN=132 TN=103 (iii) OR 3.21 (95%CI: 1.73-5.95) (P<0.001) TP=57 FP=16 FN=102 TN=92 (iv) OR 3.26 (95%CI: 1.65-6.43) (P=0.001) TP=46 FP=12 FN=113 TN=96 (v) OR 3.08 (95%CI: 1.32-7.18) (P=0.014) TP=28 FP=7 FN=131 TN=101 (vi) OR 1.63 (95%CI: 0.81-3.27) (P=0.232) TP=29 FP=13 FN=130 TN=95

1

Author(s): Hakim *et al.* (2010) **Country:** United States of America
Study Design: Retrospective observational study
Study participants: Paediatric cancer patients (up to 22 years) with neutropenia (ANC <500/mm^3

or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours). Median age was 6 years (2.4 months – 21.6 years). There were 332 FN episodes in 332 children (one episode per patient was selected at random from the records).
Target condition/reference standard: Invasive bacterial infection: bacteraemia, positive urine culture or culture negative sepsis
Index tests and comparators: (i) Temperature ≥39°C versus <39°C (ii) Clinical appearance: sick/toxic versus well. This variable was adjudged by the admitting physician. 'Well' was defined as 'looking well, in no distress or playful'; 'Sick if 'noted to be irritable, or looking ill' and 'toxic' if 'not breathing or noted to appear toxic, lethargic or obtunded'.
Follow up: N/A
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 2004 and 31st December 2005. (i) OR 2.05 (95%CI: 1.00-4.20) TP=28 FP=91 FN=28 TN=183 (ii) OR 3.84 (95%CI: 2.02-7.28) TP=28 FP=55 FN=29 TN=219

1

Author(s): Klaassen *et al.* (2010) **Country:** Canada.
Study Design: Prospective observational study (consecutive data)
Study participants: Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall) and fever (≥38.5°C or multiple readings ≥38.0°C in a 12 hour period). There were 227 FN episodes in 140 children (median age: 6.8 years). 57% of patients had haematological cancer. 12% had bacteraemia and 19% had significant infection.
Target condition/reference standard: Significant bacterial infection, defined as any blood or urine culture positive for bacteria,

interstitial or lobar consolidation on chest X-ray or unexpected death from infection (patient was not receiving palliative treatment) before ANC recovery.
Index tests and comparators: (i) General appearance unwell on first exam versus not (ii) Localised bacterial infection versus not (iii) Maximum temperature >39.0°C versus not
Follow up: Length of follow-up was not reported.
Comments: Patients were admitted to a single institution between 1st August 1996 and 31st July 1997. (i) OR 2.35 (95%CI: 1.17-4.73) (P=0.03) TP=17 FP=40 FN=26 TN=144 (ii) OR 0.47 (95%CI: 1.16-1.35) (P=0.24) TP=4 FP=33 FN=39 TN=151 (iii) OR 2.16 (95%CI: 1.11-4.20) (P=0.04) TP=23 FP=64 FN=20 TN=120

1

Author(s): Klastersky *et al.* 2000 **Country:** Multinational
Study Design: Prospective study. Consecutive or random sample (depending on participating institution).
Study participants: Adult patients (>16 years) with malignancy treated with chemotherapy and neutropenia (ANC >500/mm^3) and fever (>38.0°C). There were 756 FN episodes in 756 patients (derivation set). Median age was 52 years (range: 16-91). 331/756 (44%) patients had haematological cancer.
Target condition/reference standard: Adverse events, defined as fever resolution for five consecutive days with occurrence of a serious medical complication including death.
Index tests and comparators: (i) Temperature ≥39.0°C versus <39.0°C

(ii) Confusion or altered mental state versus not (iii) Symptoms: severe or moribund versus moderate (iv) Symptoms: severe or moribund versus none or mild
Follow up: Follow-up was not reported.
Comments: Patients were registered at 20 institutions (15 countries) between December 1994 and November 1997. (i) OR 2.02 (95%CI: 1.34-3.04) (P<0.001) TP=52 FP=196 FN=61 TN=447 (ii) OR 7.15 (95%CI: 3.56-14.37) (P<0.001) TP=18 FP=17 FN=94 TN=627 (iii) OR 5.77 (95%CI: 3.57-9.31) (P<0.001) TP=56 FP=74 FN=41 TN=304 (iv) OR 13.9 (95%CI: 7.3-26.3) (P<0.001) TP=56 FP=74 FN=14 TN=257

1

Author(s): West *et al.* 2004 **Country:** United States of America
Study Design: Retrospective observational study.
Study participants: Paediatric patients (<18 years) with treatment induced neutropenia (ANC >500/mm^3 or <1000/mm^3 and falling) and fever (single temperature of ≥38.5°C or at least three temperatures of >38°C an hour apart within 24h). There were 304 FN episodes in 143 patients. Mean age was 7.6 years (±SD 4.6). 57% of patients had a haematological cancer.
Target condition/reference standard: Critical care therapy, defined as fluid resuscitation of ≥60 ml/kg body weight above maintenance fluid requirements, mechanical ventilation or the use of vasoactive infusions.
Index tests and comparators: (i) Presence of chills within 24 hours of presentation versus not (ii) Oral mucositis versus not

Follow up: Not reported
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 1994 and 31st December 1998. 36/303 episodes required critical care treatment. (i) OR 2.66 (95%CI: 0.85-8.34) (P=0.10) TP=4 FP=12 FN=32 TN=255 (ii) OR 1.83 (95%CI: 0.90-3.73) (P=0.11) TP=14 FP=69 FN=22 TN=198

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2

3

5. Investigations appropriate for risk stratification and management. (Topic D2).

Guideline group members

Anne Davidson (lead), Jeanette Hawkins, Paul Wallman, Mark Holland, Wendy King and Barry Hancock

Review question

Which tests predict outcome and response to treatment in patients with suspected neutropenic sepsis?

Rationale

The majority of protocols for the management of febrile neutropenia or suspected neutropenic sepsis will recommend a number of routine laboratory investigations. Some which are an essential component of routine patient management, for example renal function tests, may also predict a more complicated course in terms of neutropenic sepsis. Other tests such as CRP and ESR are used as more specific markers of infection and may influence decisions regarding length of stay. Recent studies have suggested that investigations such as procalcitonin, IL6 and IL8 may be useful in outcome prediction, although these are not widely available in all hospitals in the United Kingdom. Lactate is routinely used in the management of patients with septic shock, but is not necessarily measured at the outset of febrile neutropenic episodes. It has been suggested that early measurement of lactate may predict the development of septic shock in patients with febrile neutropenia.

Although the absolute neutrophil count is generally used in management protocols for febrile neutropenia, monocyte count and lymphocyte count may also be useful independent prognostic factors.

It would be extremely useful to develop an evidence based guideline based on an understanding of which tests most accurately predict patients at high risk of an adverse outcome. An early prediction of patients at higher risk of an adverse outcome may prompt more aggressive management and intensive monitoring with a potential reduction in mortality rates. Tests which accurately predict patients at low, or no, risk of serious clinical infection could incorporated into risk stratification management protocols.

Question in PICO format

Patients/population	Tests	Outcomes
Patients with suspected neutropenic sepsis	• CRP • Lactate • Full blood count • Liver function tests • Kidney function tests	• Mortality • critical care (level 1,2 or 3) • Length of stay

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Psychinfo and BMI. The full strategy will be available in the full guideline. There were no publication date limits set. The date of the search was January 5th 2011, and it was updated on November 7th 2011.

Papers ordered for other topics (D1 and E1) were also checked for eligibility for this topic.

Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for and checked against the inclusion criteria.

Data synthesis

One reviewer (NB) extracted data and assessed study quality was assessed using ten items from the QUADAS checklist for diagnostic studies. Where possible the sensitivity and specificity of the particular test was extracted into 2X2 tables.

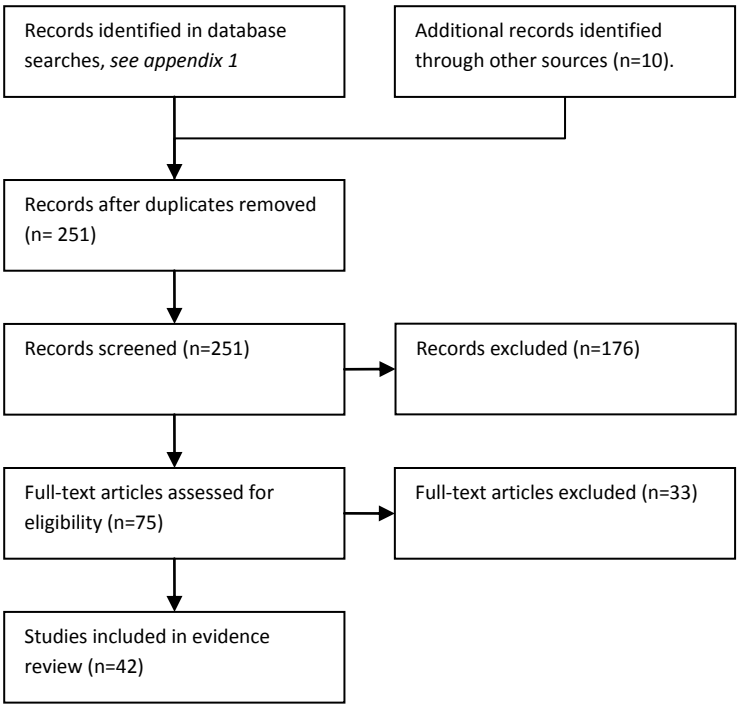
When there were sufficient studies reporting the diagnostic accuracy of a given test for a particular outcome meta-analysis was attempted. If there was no evidence of heterogeneity of both sensitivity and specificity then separate univariate meta-analyses of sensitivity and specificity were done using random effects models. If there was heterogeneity then the DiagMeta package within the R statistical computing program was used to fit a bivariate ROC model (Chappell, Raab and Wardlaw, 2009).

In some cases studies did not use a cut-off threshold but reported the mean and standard deviation of a biomarker according to outcome group. In studies where only the median and range were reported for a given biomarker, methods described by Hozo, Djulbegovic and Hozo (2005) were used to estimate the mean and standard deviation. Meta-analysis of the mean difference between outcome groups was done using RevMan 5.0.

RESULTS

Results of the literature searches

Figure 5.1 Study flow diagram



21/42 studies were done in children, 18/42 were in adults and 3 were in adults and children. Most of the febrile neutropenic episodes were experienced by patients with haematological malignancy. Twelve studies included only patients with haematological malignancy. In 25 of the 30 remaining studies more than 50% of the included patients had haematological malignancy.

Tests were typically done on admission for fever and neutropenia, before the initiation of antimicrobial therapy. Some studies repeated tests over the first few days of fever, to compare how serum levels of biomarkers changed over time in patients with and without severe infection.

Figure 5.2 is a summary of study quality, according to the QUADAS check list. 25/42 studies were prospective. It was unclear in 16/42 studies how patients were selected for inclusion (for example whether it was a consecutive or random sample of eligible patients) this is a potential source of bias.

Blinding was rarely used. Blinding is where reference tests were interpreted without knowledge of the index test results and vice-versa. The reference test (sometimes called the gold standard test) is the definitive test, whereas the index test is the one under investigation (e.g. serum CRP level). For index tests in prospective studies, lack of blinding should not be a problem as the eventual outcome of the patient would be unknown at the time of admission.

Study quality and results

There were relatively few studies of tests to predict mortality in patients admitted for fever and neutropenia. There was very limited evidence about CRP, lactate, full blood count, liver function tests or kidney function tests for the prediction of length of hospital stay. This evidence is

summarised in Table 5.1. Our searches identified no studies of tests to predict the requirement for critical care; however there was some evidence about tests to predict severe sepsis and documented infection.

Tests were typically done on admission for fever and neutropenia, before the initiation of antimicrobial therapy. Some studies repeated tests over the first few days of fever, to compare how serum levels of biomarkers changed over time in patients with and without severe infection.

25 of the 42 studies were prospective. It was unclear in 16/42 studies how patients were selected for inclusion (for example whether it was a consecutive or random sample of eligible patients) this is a potential source of bias. Blinding was explicitly used in 6/42 studies. For index tests in prospective studies, lack of blinding to the reference standard result should not be a problem as the eventual outcome of the patient would be unknown at the time of admission. Similarly lack of blinding to the index test result should not influence objective outcomes like mortality.

Table 5.1 –Diagnostic Accuracy for Investigations appropriate for risk stratification and management

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
Mortality									
Lactate	3 mmol/L	1 (110)	6%	0.43 0.82]	0.93	6.31	0.61	Not pooled	Ramzi 2007
AMC	0.1 X 10^9/L	2 (931)	4%	Range 0.37 [0.18, 1.00 [0.77,	Range 0.51 to 0.58	0.88 to 2.04	0 to 1.08	Not pooled	Santolaya 2007; Tezcan 2006
ANC	0.1 X 10^9/L	3 (1388)	4% to 8%	0.67 [0.10, 0.97]	0.71 [0.49, 0. 86]	0.66 to 3.18	0 to 1.17	Univariate random effects model	Santolaya 2007; Tezcan 2006; Wilbur 2000
CRP	90 mg/L	1 (373)	4%	0.79	0.62	2.07	0.34	Not pooled	Santolaya 2007;
Creatinine	17 mg/L	1 (393)	8%	0.53	0.89	4.92	0.53	Not pooled	Wilbur 2000
BUN	180 to 260 mg/L	2 (764)	4% to 8%	Range 0.43 to 0.69	Range 0.86 to 0.94 [	5.04 to 7.33	0.36 to 0.61	Not pooled	Santolaya 2007; Wilbur 2000
Albumin	25 g/L	1 (268)	10%	0.29	0.88 [	2.36	0.81	Not pooled	Wilbur 2000
Platelets	25,000 /mm^3	1 (394)	8%	0.44	0.76	1.82	0.74	Not pooled	Wilbur 2000
Severe sepsis									
Lactate	2 to 3 mmol/L	2 (340)	13% to 20%	Range 0.26 to 0.57	Range 0.97 to 0.98	8.00 to 27.43	0.44 to 0.76	Not pooled	Mato 2010; Ramzi 2007
CRP	60 mg/L to 100 mg/L	4 (829)	20% to 58%	0.75 [0.52, 0.89]	0.64 [0.60, 0.67]	1.47 to 2.31	0 to 0.72	Univariate random effects model	Erten 2000; Karan 2002; Moon 2009; Santolaya 2008
Creatinine	2 to 20 mg/L	3(1215)	15% to 60%	0.07 [0.03, 0.14]	0.97 [0.80, 0.99]	0.68 to 7.34	0.88 to 1.02	Univariate random effects model	Chayakulkeeree 2003; Moon 2009; Klastersky 2000
BUN	200	2(459)	26% to	Range 0.27	Range 0.88	2.25	0.96	Not	Chayakulkee

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
	mg/L		60%	to 0.44	to 0.93	to 6.25	to 1.02	pooled	ree 2003; Moon 2009
Albumin	25 to 30 mg/L	3 (1215)	20% to 60%	0.11 [0.05, 0.23]	0.95 [0.89, 0.98]	1.91 to 2.83	0.89 to 0.97	Univariate random effects model	Chayakulkeeree 2003; Klastersky 2000; Moon 2009
ANC	0.1 X 10^9/L	2 (948)	15% to 20%	Range 0.63 to 0.79	Range 0.33 to 0.41	1.07 to 1.18	0.63 to 0.90	Not pooled	Klastersky 2000; Moon 2009
AMC	0.1 X 10^9/L	1 (192)	20%	0.68	0.57	1.60	0.55	Not pooled	Moon 2009
Platelets	50,000 /mm3	2 (948)	15% to 20%	Range 0.11 to 0.53	Range 0.83 to 0.92	1.45 to 3.12	0.57 to 0.96	Not pooled	Klastersky 2000; Moon 2009
Bilirubin	20 mg/L	2 (1023)	24% to 60%	Range 0.04 to 0.18	Range 0.96 to 0.96	1.05 to 4.92	0.85 to 1.00	Not pooled	Chayakulkeeree 2003; Klastersky 2000;
Haemoglobin	80 g/L	2 (1023)	15% to 60%	Range 0.18 to 0.50	Range 0.61 to 0.86	1.28	0.82 to 0.95	Not pooled	Chayakulkeeree 2003; Klastersky 2000;
WBC	0.5 X 10^9/L	1 (192)	20%	0.61	0.61	1.55	0.65	Not pooled	Moon 2009
Documented infection									
CRP	5 to 20 mg/L	6 (692)	29% to 75%	0.84 [0.5, 0.96]	0.35 [0.08, 0.78]	0.85 to 3.45	0.25 to 1.39	Bivariate model	Ammann 2003; Avabratha 2009; Diepold 2008; Hitoglu-Hatzi 2005; Katz 1992; Riikonen 1993
CRP	>30 to 40 mg/L	4 (373)	26% to 66%	0.95 [0, 1]	0.26 [0, 1]	0.89 to 4.05	0 to 3.00	Bivariate model	Yonemori 2001; Massaro 2007; Santolaya 1994; Manian 1995
CRP	50 mg/L	6 (683)	29% to 64%	0.58 [0.13, 0.93]	0.69 [0.57, 0.79]	0.53 to 3.83	0.13 to 1.20	Bivariate model	Ammann 2003; Hatzistilianou 2007; Hitoglu-Hatzi 2005; Katz 1992; Riikonen 1993; Secmeer 2007
CRP	90 to 100 mg/L	6 (850)	33% to 69%	0.67 [0.27, 0.92]	0.81 [0.44, 0.96]	1.49 to 4.98	0.31 to 0.82	Bivariate model	El-Maghraby 2007; Hitoglu-Hatzi 2005; Santolaya 2001; Martinez-Albarran 2009; Katz 1992; Manian 1995
ANC	0.05 to 0.1 X	6 (2898)	16% to 56%	0.58 [0.35, 0.78]	0.52 [0.26, 0.78]	0.91 to	0.51 to	Univariate	Ha 2010; Hakim 2010;

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
	10^9/L					2.03	1.75	random effects model	Klaassen 2000; Rondinelli 2006; Santolaya 2001; Tezcan 2006
AMC	0.1 X 10^9/L	5 (1709)	19% to 56%	0.73 [0.29, 0.95]	0.45 [0.10, 0.86]	1.02 to 1.73	0.40 to 0/83	Bivariate model	Ammann 2003; Rondinelli 2006; Santolaya 2001; Tezcan 2006; Klaassen 2000
Haemoglobin	70g/L	2 (750)	33% to 40%	Range 0.24 to 0.30	Range 0.79 to 0.82	1.16 to 1.68	0.85 to 0.96	Not pooled	Rondinelli 2006; Santolaya 2001
Platelets	20,000 to 75,000 /mm3	4 (1053)	14% to 40%	0.59 [0.25, 0.999]	0.63 [0.00, 0.90]	1.20 to 1.75	0.49 to 0.83	Bivariate model	Hakim 2010; Rondinelli 2006; Santolaya 2001; Klaassen 2000
Creatinine	75 mg/L	1 (237)	38%	Range 0.02 to 0.11	Range 0.91 to 0.99	1.19	0.98	Not pooled	Ammann 2003;

Abbreviations: ANC, absolute neutrophil count; AMC, absolute monocyte count; CRP, C-reactive protein; BUN, blood urea nitrogen, Sn, sensitivity; Sp, specificity.

Evidence statements

Mortality

Lactate, albumin and creatinine levels had reasonable specificity (93%, 88% and 89% respectively) but low sensitivity (53% or less) to predict short term mortality in patients with fever and neutropenia, with only data from a single study for each of these tests. Santolaya, et al., (2007) and Wilbur, et al., (2000) reported blood urea nitrogen (at thresholds of 180 and 260 mg/L respectively) had good specificity (86% to 94%) but moderate to low sensitivity (43% to 69%) to predict short term mortality.

Santolaya, et al., (2007) only reported the sensitivity and specificity of laboratory tests whose results differed significantly between patients who died and survived. In their study ANC, AMC, CRP, BUN and CRP differed significantly between those the two groups, whereas there was no significant difference between the groups in terms of platelets, creatinine, glycemia or lactate dehydrogenase (LDH).

Length of hospital stay

Pastura, et al., (2004) carried out a prospective study to derive a predictive model for length of hospital stay in children with haematological malignancy, neutropenia and presumed infection. Granulocyte count < 0.1 X 10^9/L was considered as a predictive factor in this study, but was excluded from the final multivariate model due to lack of statistical significance. Pastura, et al., final

predictive model included ill appearance, age ≥6 years, presence of CVC and disease status as relapse.

Critical care and severe sepsis

Ammann, et al., (2010) reported a prospective study of predictive factors for serious medical complications in children with fever and chemotherapy induced neutropenia. Serious medical complications were defined as death, complication requiring intensive care treatment or complication judged as potentially life threatening by the treating doctor. Ammann, et al., (2010) constructed a multivariate risk score for serious complications, by selecting factors (from a list of 31 candidates) significantly associated with serious complications on univariate analysis. Their final model included four predictive factors: chemotherapy more intensive than ALL maintenance, haemoglobin level ≥90 g/L at presentation, leukocyte count <0.3 g/L at presentation and platelet count <50 g/L at presentation.

Five studies (Ahn, et al., 2011; Erten, et al., 2004; Hamalainen, et al., 2008, 2010 and Santolaya, 2008) compared the mean levels of serum CRP at admission in patients who did and did not develop severe sepsis. Although mean serum CRP level was higher in patients who went on to develop severe sepsis (mean difference 45 mg/L higher, 95% C.I. 32 to 58 mg/L higher) there was considerable overlap between the two groups. Hamalainen, et al., (2008, 2010) recorded CRP levels in the days following admission for fever and neutropenia. They observed a widening difference between the serum CRP levels of patients with severe sepsis and others over the first days of fever – from 53 mg/L on admission to 135 mg/L after four days.

Documented infection

Meta-analysis according to cut-off threshold was done for CRP (Table 5.1). In theory sensitivity should decrease and specificity should increase as the CRP threshold is raised, but this was not the case perhaps due to heterogeneity. AMC and ANC were poor predictors of documented infection.

Some studies (Arber, et al., 2000, El-Maghraby, et al., 2007, Engel, et al., Hitoglou-Hatzi 2005, Katz, et al., 1993, Massaro, et al., 2007, Martinez-Albarran, et al., 2009, Santolaya, et al., 1994, Tezcan, et al., 2006 and Yonemori, et al., 2001) compared the mean levels of serum CRP at admission for fever and neutropenia in those patients who went on to have a documented infection and patients with fever of unknown or viral origin. Mean CRP level was invariably higher in the patients who went on to have a documented infection: mean difference 35 mg/L higher (95%C.I. 26 to 44 mg/L higher). The greatest differences were seen in studies involving children, however there was significant heterogeneity in the results from paediatric studies.

There was a large range of serum CRP levels recorded in those with documented infections and in those with fever of unknown origin with considerable overlap in the distribution of CRP levels in the two groups. Thus it is unlikely that a single CRP threshold could achieve acceptable sensitivity and specificity for the prediction of documented infection.

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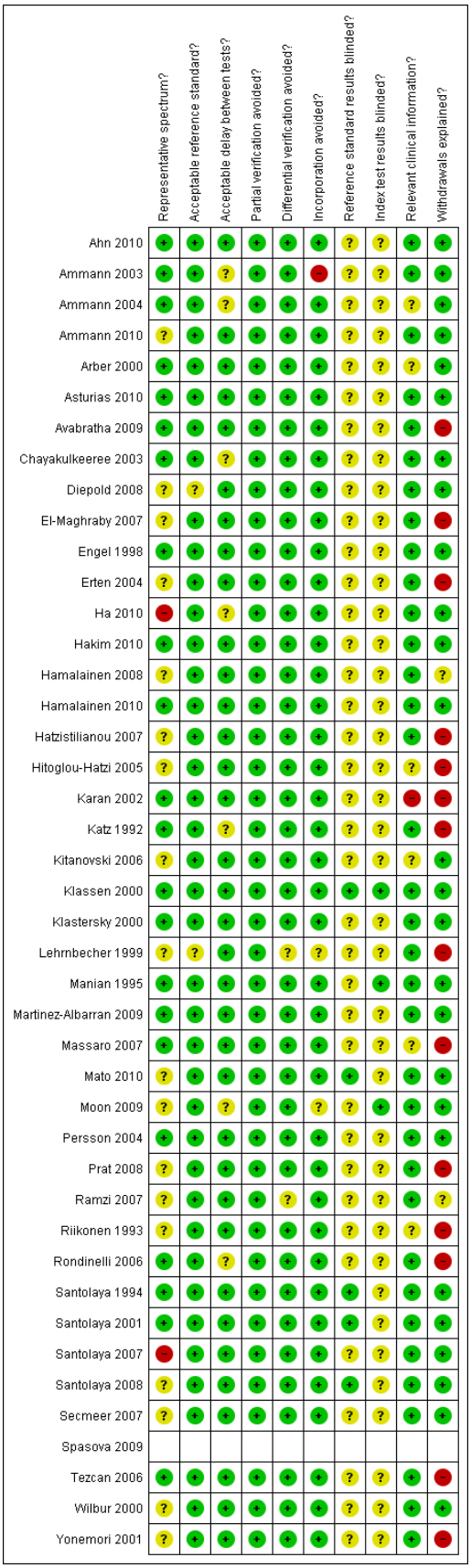
Figure 5.2. Summary of study quality using QUADAS criteria



1 ***Figure 5.3 Sensitivity and specificity of tests to predict mortality***

Serum lactate for mortality

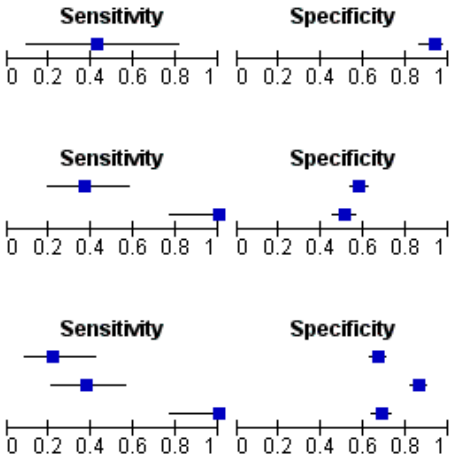
Study	TP	FP	FN	TN	Sensitivity	Specificity
Ramzi 2007	3	7	4	96	0.43 [0.10, 0.82]	0.93 [0.86, 0.97]

Monocyte count for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tezcan 2006	10	249	17	345	0.37 [0.19, 0.58]	0.58 [0.54, 0.62]
Santolaya 2007	14	176	0	183	1.00 [0.77, 1.00]	0.51 [0.46, 0.56]

Neutrophil count for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tezcan 2006	6	199	21	395	0.22 [0.09, 0.42]	0.66 [0.63, 0.70]
Wilbur 2000	12	51	20	311	0.38 [0.21, 0.56]	0.86 [0.82, 0.89]
Santolaya 2007	14	113	0	246	1.00 [0.77, 1.00]	0.69 [0.63, 0.73]



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CRP for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Santolaya 2007	11	136	3	223	0.79 [0.49, 0.95]	0.62 [0.57, 0.67]

Creatinine for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wilbur 2000	17	39	15	322	0.53 [0.35, 0.71]	0.89 [0.86, 0.92]

BUN for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Santolaya 2007	6	21	8	338	0.43 [0.18, 0.71]	0.94 [0.91, 0.96]
Wilbur 2000	22	49	10	310	0.69 [0.50, 0.84]	0.86 [0.82, 0.90]

Albumin for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wilbur 2000	8	29	20	211	0.29 [0.13, 0.49]	0.88 [0.83, 0.92]

Platelet count for mortality

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wilbur 2000	14	87	18	275	0.44 [0.26, 0.62]	0.76 [0.71, 0.80]

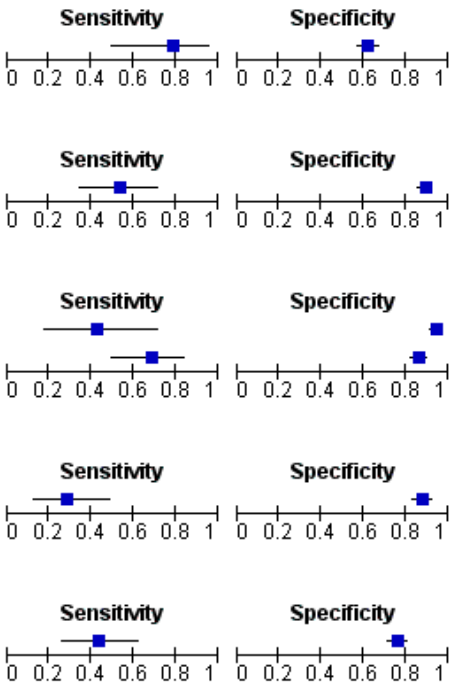

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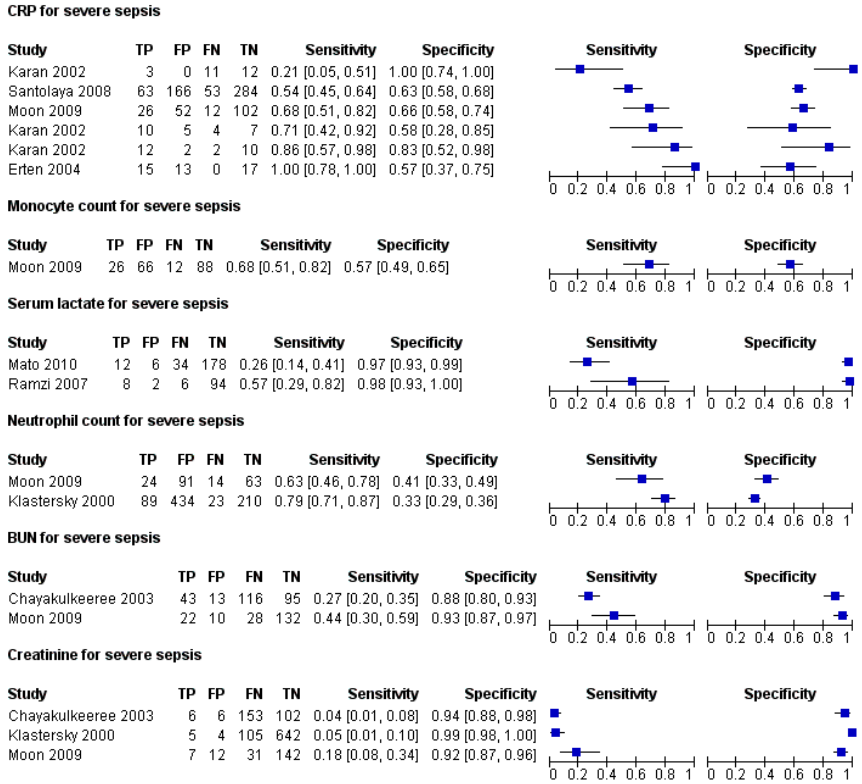
Figure 5.4 Sensitivity and specificity of tests to predict severe sepsis



Alanine transaminase for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chayakulkeeree 2003	28	5	131	103	0.18 [0.12, 0.24]	0.95 [0.90, 0.98]

Platelet count for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Klastersky 2000	12	49	97	598	0.11 [0.06, 0.18]	0.92 [0.90, 0.94]
Moon 2009	20	26	18	128	0.53 [0.36, 0.69]	0.83 [0.76, 0.89]

Aspartate transaminase for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chayakulkeeree 2003	30	129	10	98	0.75 [0.59, 0.87]	0.43 [0.37, 0.50]

Alkaline phosphatase for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chayakulkeeree 2003	56	20	103	88	0.35 [0.28, 0.43]	0.81 [0.73, 0.88]

Albumin for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Klastersky 2000	8	10	177	561	0.04 [0.02, 0.08]	0.98 [0.97, 0.99]
Chayakulkeeree 2003	25	6	134	102	0.16 [0.10, 0.22]	0.94 [0.88, 0.98]
Moon 2009	8	17	30	137	0.21 [0.10, 0.37]	0.89 [0.83, 0.93]

Bilirubin for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Klassen 2000	8	24	174	550	0.04 [0.02, 0.08]	0.96 [0.94, 0.97]
Chayakulkeeree 2003	29	4	130	104	0.18 [0.13, 0.25]	0.96 [0.91, 0.99]

Haemoglobin for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Klastersky 2000	20	92	90	554	0.18 [0.11, 0.27]	0.86 [0.83, 0.88]
Chayakulkeeree 2003	79	42	80	66	0.50 [0.42, 0.58]	0.61 [0.51, 0.70]

WBC for severe sepsis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Moon 2009	23	60	15	94	0.61 [0.43, 0.76]	0.61 [0.53, 0.69]

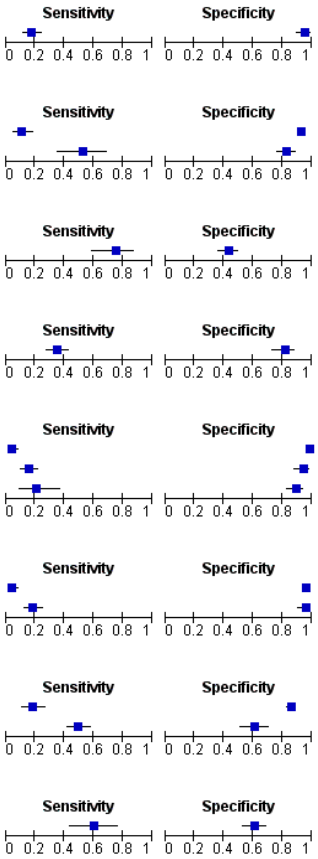


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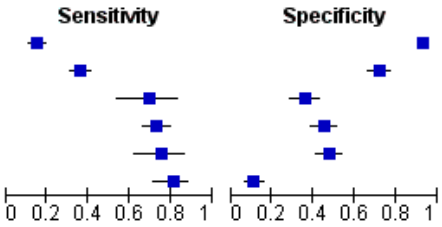
Figure 5.5 Sensitivity and specificity of tests to predict documented infection

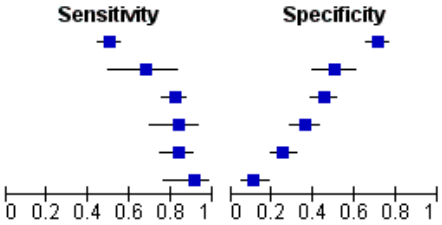
Neutrophil count for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ha 2010	55	47	307	581	0.15 [0.12, 0.19]	0.93 [0.90, 0.94]
Tezcan 2006	125	77	220	199	0.36 [0.31, 0.42]	0.72 [0.66, 0.77]
Klassen 2000	30	118	13	66	0.70 [0.54, 0.83]	0.36 [0.29, 0.43]
Santolaya 2001	130	148	48	121	0.73 [0.66, 0.79]	0.45 [0.39, 0.51]
Hakim 2010	40	145	13	132	0.75 [0.62, 0.86]	0.48 [0.42, 0.54]
Rondinelli 2006	75	169	18	21	0.81 [0.71, 0.88]	0.11 [0.07, 0.16]



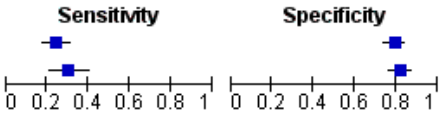
Monocyte count for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tezcan 2006	173	80	172	196	0.50 [0.45, 0.56]	0.71 [0.65, 0.76]
Ammann 2003	23	47	11	47	0.68 [0.49, 0.83]	0.50 [0.40, 0.60]
Santolaya 2001	146	148	32	121	0.82 [0.76, 0.87]	0.45 [0.39, 0.51]
Klassen 2000	36	118	7	66	0.84 [0.69, 0.93]	0.36 [0.29, 0.43]
Rondinelli 2006	78	142	15	48	0.84 [0.75, 0.91]	0.25 [0.19, 0.32]
Ammann 2003	31	84	3	10	0.91 [0.76, 0.98]	0.11 [0.05, 0.19]



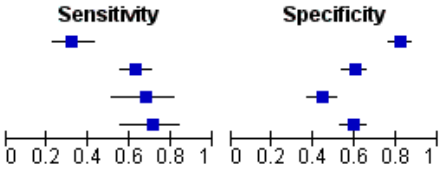
Haemoglobin for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Santolaya 2001	43	56	135	213	0.24 [0.18, 0.31]	0.79 [0.74, 0.84]
Rondinelli 2006	28	34	65	156	0.30 [0.21, 0.40]	0.82 [0.76, 0.87]



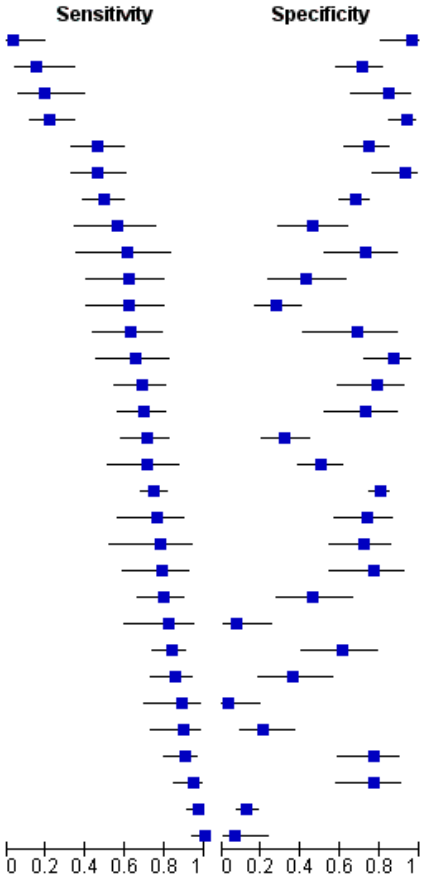
Platelet count for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rondinelli 2006	30	34	63	156	0.32 [0.23, 0.43]	0.82 [0.76, 0.87]
Santolaya 2001	112	108	66	161	0.63 [0.55, 0.70]	0.60 [0.54, 0.66]
Klassen 2000	29	103	14	81	0.67 [0.51, 0.81]	0.44 [0.37, 0.52]
Hakim 2010	32	113	13	165	0.71 [0.56, 0.84]	0.59 [0.53, 0.65]



CRP for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Massaro 2007	1	1	25	25	0.04 [0.00, 0.20]	0.96 [0.80, 1.00]
Riikonen 1993	4	19	22	46	0.15 [0.04, 0.35]	0.71 [0.58, 0.81]
Massaro 2007	5	4	21	22	0.19 [0.07, 0.39]	0.85 [0.65, 0.96]
Katz 1992	13	4	46	59	0.22 [0.12, 0.35]	0.94 [0.85, 0.98]
Katz 1992	27	16	32	47	0.46 [0.33, 0.59]	0.75 [0.62, 0.85]
Manian 1995	25	2	29	26	0.46 [0.33, 0.60]	0.93 [0.76, 0.99]
Ammann 2003	47	52	48	109	0.49 [0.39, 0.60]	0.68 [0.60, 0.75]
Secmeer 2007	14	19	11	16	0.56 [0.35, 0.76]	0.46 [0.29, 0.63]
Massaro 2007	11	7	7	19	0.61 [0.36, 0.83]	0.73 [0.52, 0.88]
Massaro 2007	16	15	10	11	0.62 [0.41, 0.80]	0.42 [0.23, 0.63]
Riikonen 1993	16	47	10	18	0.62 [0.41, 0.80]	0.28 [0.17, 0.40]
Kitanovski 2006	20	5	12	11	0.63 [0.44, 0.79]	0.69 [0.41, 0.89]
Hitoglou-Hatzi 2005	19	5	10	33	0.66 [0.46, 0.82]	0.87 [0.72, 0.96]
Manian 1995	37	6	17	22	0.69 [0.54, 0.80]	0.79 [0.59, 0.92]
El-Maghraby 2007	41	7	18	19	0.69 [0.56, 0.81]	0.73 [0.52, 0.88]
Katz 1992	42	43	17	20	0.71 [0.58, 0.82]	0.32 [0.21, 0.45]
Yonemori 2001	20	39	8	39	0.71 [0.51, 0.87]	0.50 [0.38, 0.62]
Santolaya 2001	133	54	45	215	0.75 [0.68, 0.81]	0.80 [0.75, 0.85]
Hitoglou-Hatzi 2005	22	10	7	28	0.76 [0.56, 0.90]	0.74 [0.57, 0.87]
Martinez-Albarran 2009	14	10	4	26	0.78 [0.52, 0.94]	0.72 [0.55, 0.86]
Avabratha 2009	22	5	6	17	0.79 [0.59, 0.92]	0.77 [0.55, 0.92]
Manian 1995	43	15	11	13	0.80 [0.66, 0.89]	0.46 [0.28, 0.66]
Massaro 2007	18	24	4	2	0.82 [0.60, 0.95]	0.08 [0.01, 0.25]
Diepold 2008	71	11	14	17	0.84 [0.74, 0.91]	0.61 [0.41, 0.78]
Manian 1995	46	18	8	10	0.85 [0.73, 0.93]	0.36 [0.19, 0.56]
Massaro 2007	23	25	3	1	0.88 [0.70, 0.98]	0.04 [0.00, 0.20]
Hitoglou-Hatzi 2005	26	30	3	8	0.90 [0.73, 0.98]	0.21 [0.10, 0.37]
Hatzistilianou 2007	54	8	6	26	0.90 [0.79, 0.96]	0.76 [0.59, 0.89]
Santolaya 1994	52	7	3	23	0.95 [0.85, 0.99]	0.77 [0.58, 0.90]
Ammann 2003	92	141	3	20	0.97 [0.91, 0.99]	0.12 [0.08, 0.19]
Manian 1995	54	26	0	2	1.00 [0.93, 1.00]	0.07 [0.01, 0.24]



Creatinine for documented infection

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ammann 2003	10	14	79	134	0.11 [0.06, 0.20]	0.91 [0.85, 0.95]

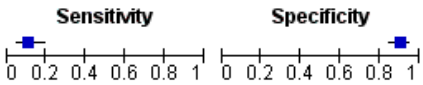


Figure 5.6 Summary ROC curves for CRP, AMC and ANC for the prediction of documented infection

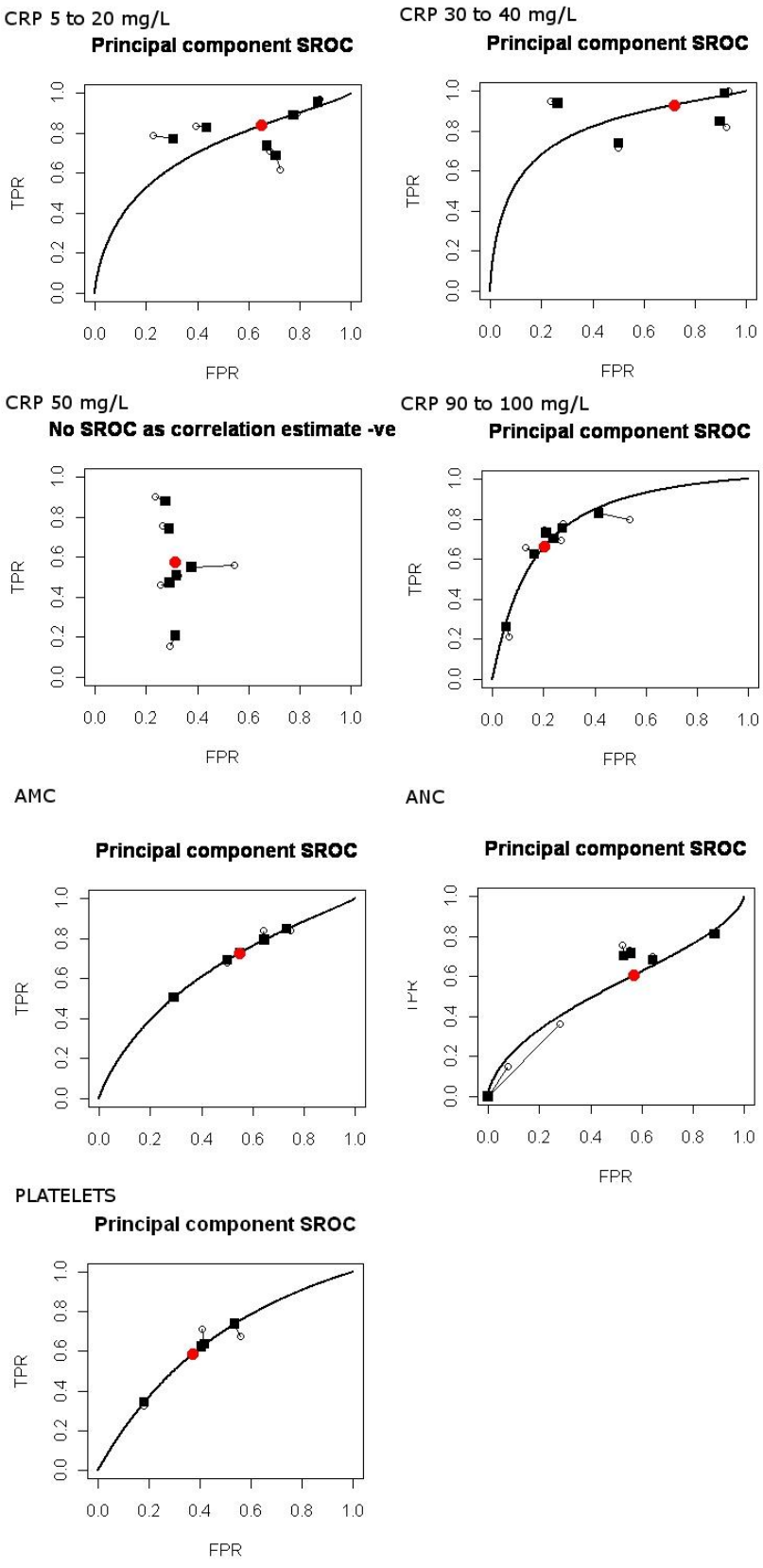


Figure 5.7 Mean difference in serum CRP between patients with severe infection and others: on the day of admission and on the following four days

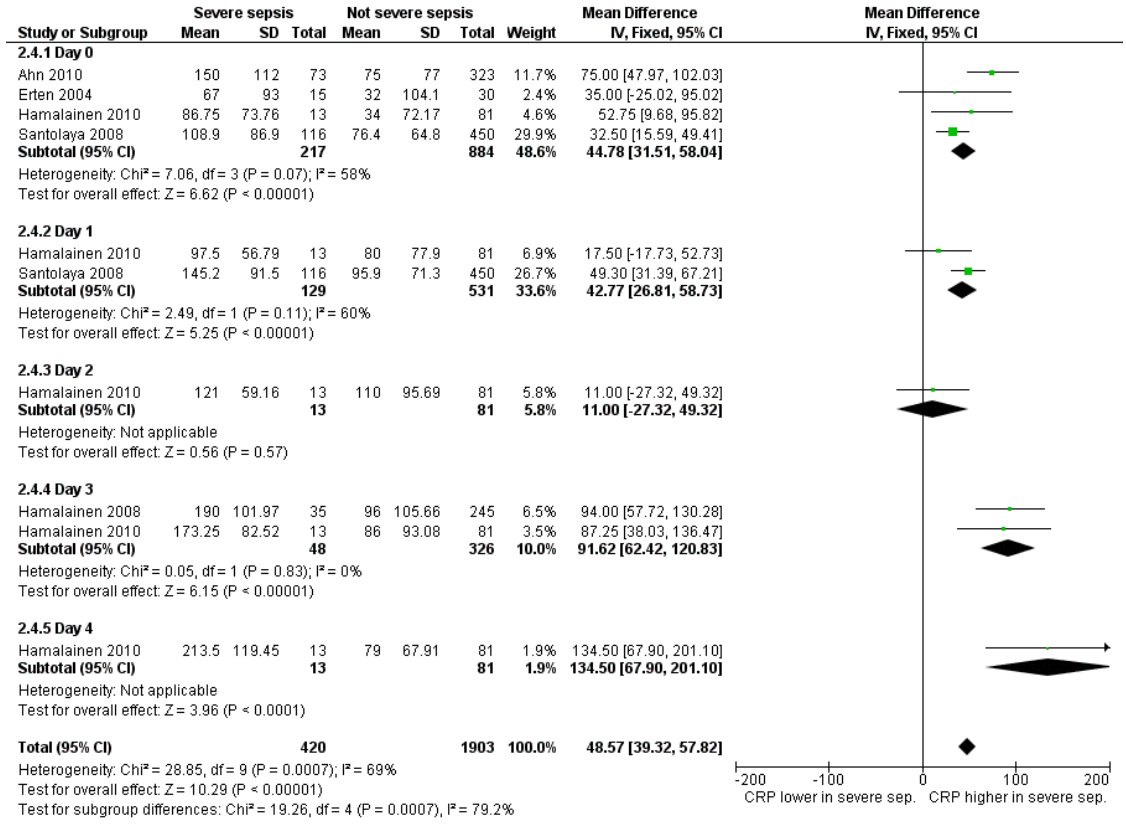
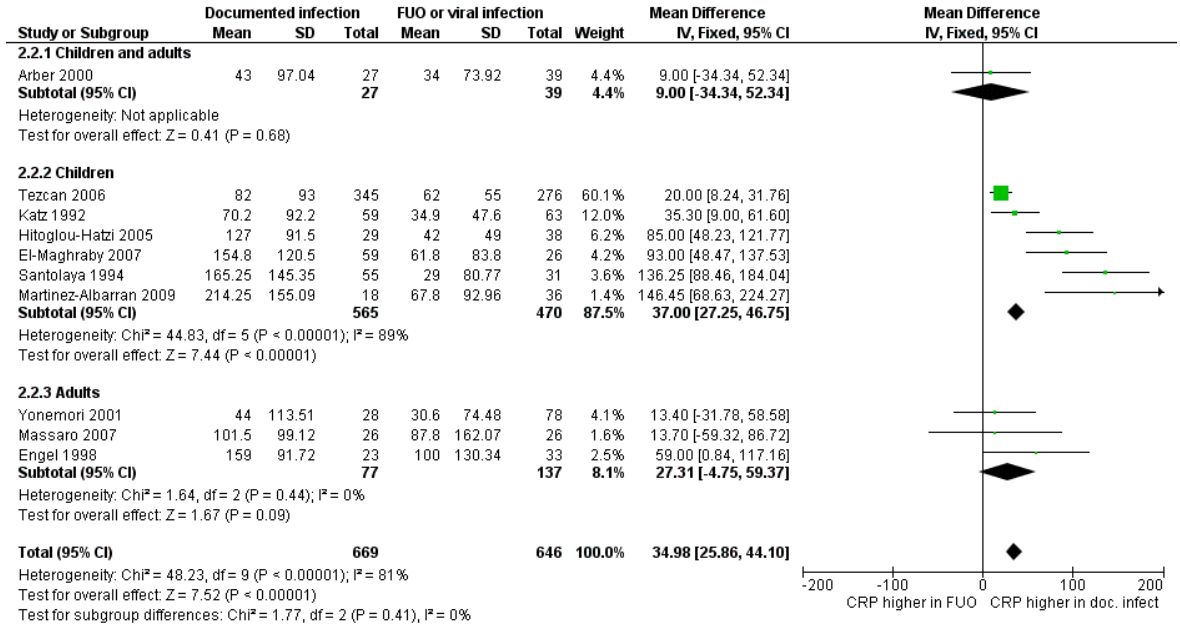


Figure 5.8. Mean difference in serum CRP level at admission between patients with documented infection and others



EVIDENCE TABLES

Ahn 2011

Clinical features and settings	Adult cancer patients (>14 years) with fever (≥38.3°C or ≥38.0°C for ≥1 hour) and neutropenia (ANC <0.5X10^9/L or predicted to fall to this), visiting the emergency department of a single institution between 2007 and 2008.
Participants	396 FN episodes in 346 patients. 73/396 episodes had serious medical complications. Median age was 55 years. 28.5% of episodes were in patients with haematological malignancy
Study design	Retrospective, consecutive case series. South Korea
Target condition and reference standard(s)	Favourable or unfavourable outcome of FN episode. Unfavourable outcome was defined as: any serious medical complication. This could include refractory hypotension, death, respiratory failure requiring endotracheal intubation and ventilator care, admission to ICU, disseminated intravascular coagulation, confused mental state, ECG changes requiring antiarrhythmic treatment, renal failure requiring renal replacement therapy.
Index and comparator tests	Tests were done on admission to the emergency department with fever and neutropenia Mean values reported for favourable versus unfavourable outcome episodes CRP, AST, ALT, BUN, creatinine, serum haemoglobin, ANC, SpO2
Follow-up	
Notes	

Ammann 2003

Clinical features and settings	Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after non-myeloablative chemotherapy.
Participants	285 FN episodes in 111 children. Median age at the first FN episode was 6.3 years. Proportion with haematological cancers was not reported. The rate of severe bacterial infection was 106/285 (37%).
Study design	Retrospective observational study. Consecutive sample. Switzerland
Target condition and reference standard(s)	Severe (significant) bacterial infection: defined as bacteraemia, positive urine culture, pneumonia, clinically unequivocal diagnosis of infection, serum CRP >150 mg/L or unexpected death from infection.
Index and comparator tests	Study does not report when tests were done, although the aim was to find predictive factors for use within the first 2 hours of fulfilment of the febrile neutropenia criteria. Haemoglobin level: thresholds > 71 g/L and >100 g/L ANC: thresholds >0.11 X 10^9/L and >0.5 X 10^9/L AMC: thresholds >0.11 X 10^9/L and >0.5 X 10^9/L Phagocyte count: thresholds >0.11 X 10^9/L and >0.5 X 10^9/L Thrombocyte count: thresholds >11 X 10^9/L and >150 X 10^9/L

	Serum CRP: thresholds >5 mg/l and > 50 mg/l (5mg/l defined as normal) Serum creatinine: thresholds >75 mg/L
Follow-up	Not reported.
Notes	Serum CRP incorporated into reference standard.

1 **Ammann 2004**

Clinical features and settings	Children (< 17 years) with cancer, fever (axillary temperature > 39.0°C or ≥ 38.5°C for 2 hours) and neutropenia (ANC < 0.5 X 10^9/l , or expected to fall to this value). Children were admitted to a single hospital during the period 1993 to 2001. FN episodes as a result of myeloablative therapy or initial bone marrow involvement of newly diagnosed leukaemia were not included in this study.
Participants	364 episodes of fever and neutropenia in 132 patients. Median age not reported. Proportion with haematological cancers not reported. Bacteraemia was detected in 87/364 episodes.
Study design	Retrospective observational study. Consecutive sample. Switzerland
Target condition and reference standard(s)	Bacteraemia: at least one positive culture using a qualitative automated culture system (BacT/ALERT; bioMerieux).
Index and comparator tests	44 variables were measured. It is unclear when tests were done, although the study aims to examine variables of relevance in the first 2 hours following the onset of fever and neutropenia to produce a decision tree. Results are only reported for those variables significantly associated with bacteraemia on univariate analysis, of these only leukocyte count was relevant for this review Leukocyte count, threshold ≤ 0.5 X 10^9/l
Follow-up	Not reported
Notes	Non significant prognostic factors were not reported.

2 **Ammann 2010**

Clinical features and settings	Paediatric cancer patients (1 to 18 years) with neutropenia (ANC <0.5 X10^9/l) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after non-myeloablative chemotherapy. Study 2004 to 2007.
Participants	423 episodes of FN in 206 patients. median age was 6.9 years. 63% had haematological malignancy. Adverse events occurred in 122/423 FN episodes (29%).
Study design	Prospective observational study. Unclear whether consecutive or random sample. Switzerland and Germany.
Target condition and reference standard(s)	Adverse events: defined as serious medical complications (including death, or complication requiring critical care) as a result of infection, microbiologically documented infection or radiologically confirmed pneumonia.
Index and comparator tests	Numerous predictor variables were included. Tests were done at presentation with FN.

	Haemoglobin level, threshold 90 g/L Leukocyte count, threshold <0.3 G/L ANC, <0.1 G/L AMC, <0.1 G/L Platelet count < 50 g/L CRP >150 mg/L Final model includes four predictive factors: chemotherapy more intensive than ALL maintenance, haemoglobin level ≥ 90 g/L at presentation, leukocyte count < 0.3 G/L at presentation and platelet count < 50 G/L at presentation
Follow-up	Patients were assessed at presentation, then again after 8 to 24 hours of inpatient therapy. Length of follow up for adverse events was not reported.
Notes	Cannot extract 2X2 tables. Model not validated in an independent sample, although statistical techniques were used to avoid over fitting of the model.

1 **Arber 2000**

Clinical features and settings	Patients (adult or child) with cancer admitted to a single haematology ward with fever (> 38.3°C or > 38.0 °C on consecutive readings) and neutropenia (ANC <0.5X10^9/L). Study period was 1997.
Participants	143 FN episodes in 71 patients. Mean age 40 years. 87% had haematological malignancy.
Study design	Retrospective case series. Consecutive sample. Switzerland.
Target condition and reference standard(s)	Cause of fever - classified as Invasive bacterial infection (positive blood culture unlikely to be due to contamination) Fungal infection: positive by culture, histology or chest CT findings Viral infection: CMV-antgenemia positive Probable infection: fever, positive bacterial cultures from body fluids plus clinical signs or symptoms of infection Acute GvHD: graded using the Glucksberg criteria. Drug related: fever associated with a certain drug and resolving after discontinuation Transfusion related: fever accompanied by shivering/bronchospasm appearing within 2 hours of transfusion Unexplained fever.
Index and comparator tests	CRP, measured on day 1 of fever and daily during follow-up. Median and range of CRP values were reported according to cause of fever.
Follow-up	
Notes	

2 **Asturias 2010**

Clinical features and settings	Children (<18 years) with fever (≥38.5°C or ≥38.0°C for a least 1hour) and neutropenia (ANC ≤ 1.0 X 10^9/L), hospitalised at a single institution during 2008. Those hospitalised for less than 48 hours, those who had received antibiotics before admission and those receiving bone marrow transplants were excluded.
Participants	96 episodes of FN in 88 patients. 74/96 (77%) episodes were in patients with haematological malignancies. Mean age was 6.5 years. Bacteraemia was found in 11/96 episodes
Study design	Prospective observational study. Consecutive sample. Guatemala
Target condition and reference standard(s)	Bacteraemia: 2 blood cultures positive for any pathogen except coagulase-negative staphylococci.
Index and comparator tests	Tests were done at admission. Serum CRP: threshold ≥96 mg/L Platelet count: ≤ 50 x 10^9/L
Follow-up	Not reported
Notes	

1 **Avabratha 2009**

Clinical features and settings	Children (<16 years) with malignancy and chemotherapy related fever (≥38.3°C or ≥38.0°C for at least 1 hour) and neutropenia (ANC < 0.5 X10^9/l or predicted to fall to this) admitted to a single hospital. Study period not reported.
Participants	50 FN episodes in 33 children. Median age 6.9 years. At least 68% of FN episodes occurred in children with haematological malignancies. There was microbiologically documented infection in 19/50 FN episodes, clinically documented infection in 9/50 episodes and fever of unknown origin in 22/50 episodes.
Study design	Prospective observational study, consecutive sample. India
Target condition and reference standard(s)	Microbiologcially documented infection: clinical and/or radiological evidence of infection and culture positivity. Clinically documented infection: identifiable site of infection without a positive culture.
Index and comparator tests	CRP: threshold 6 mg/l
Follow-up	Tests were done on day 1 and day 7 of entry into the study
Notes	

2 **Chayakulkeeree 2003**

Clinical features and settings	Adult or adolescent patients (>12 years) with febrile (>38°C) neutropenic (<0.5X10^9/L) episodes admitted to a single hospital between 1999 and 2000.
Participants	267 episodes (220 patients). 158/220 (72%) had haematological malignancy. Mean age was 44.7 years. Episodes were clinically documented infection 38/267,

	microbiologically documented infection 90/267 and fever of unknown origin 139/267
Study design	Retrospective case series. Consecutive sample. Thailand.
Target condition and reference standard(s)	Favourable outcome: fever resolved in 5 days of starting treatment and without complications Unfavourable outcome: Death, serious complications, modification of initial therapy, relapse of resolved fever or fever longer than 5 days. Reference standard was clinical follow up reported in medical records.
Index and comparator tests	Lab tests (unclear exactly when they were done) Haemoglobin < 8g/dl Creatinine ≥ 2 mg/dl Sodium ≥ 150 mmol/L Potassium < 3.5 mmol/L Bicarbonate < 24 mmol/L Alanine transaminase ≥ 74 U/L Aspartate transaminase ≥ 80 U/L Alkaline phosphatase ≥ 117 U/L Bilirubin ≥ 2mg/sl Albumin <2.5 mg/dl Globulin ≥ 3.5 mg/dl Chest X-ray Median values of full blood count in the two groups (favourable versus unfavourable) were also reported.
Follow-up	The outcome definition mentions 5 days , unclear whether deaths or serious complications outside this period were included.
Notes	

1 **Diepold 2008**

Clinical features and settings	Children and young adults (<20 years) with cancer or haematological disorders with fever (>38.5°C or >38.0°C from more than 1 hour) and neutropenia (ANC <0.5X10^9/L) admitted to a single hospital.
Participants	141 FN episodes in 69 patients (123 episodes had usable data).64/69 patients had cancer. 55% of patients had haematological cancer. Median age was 7.67 years.
Study design	Prospective observational study. Unclear whether consecutive or random sample. Germany.
Target condition and reference standard(s)	Documented infection: bacteraemia (positive blood culture) or febrile episode of five days or more (these patients were presumed to have either a serious infection or signs of clinical sepsis - without microbiologically documented infection).
Index and comparator tests	CRP (on the first day of fever): threshold 10 mg/l.

Follow-up	Blood samples were taken within 24 hours of the start of fever and then daily.
Notes	

1 **El-Maghraby 2007**

Clinical features and settings	Children with haematological cancer fever (>38.5°C or >38.0°C on 2 occasions during 6 hours) and neutropenia (ANC < $0.5X10^9$/L), who received chemotherapy at a single institution between 2004 to 2005
Participants	85 FN episodes in 76 children. Mean age was 7.8 years for those with fever of unknown origin and 6.8 years for those with documented infection. All had haematological malignancy. There was a documented infection in 59/85 FN episodes.
Study design	Prospective observational study. Unclear whether consecutive or random sample. Egypt
Target condition and reference standard(s)	Documented infection: positive blood cultures and/or documented clinical sepsis and/or local infection.
Index and comparator tests	CRP, threshold 90 mg/l (normal value defined as <6mg/l)
Follow-up	Tests were done within the first 24 hours of admission. All patients were followed until day 8 from admission or until discharge from hospital, whichever was the longest.
Notes	

2 **Engel 1998**

Clinical features and settings	Adult patients (>14 years) with haematological malignancy admitted to hospital for chemotherapy and expected to develop neutropenia (ANC < $1.0X10^9$/L) who developed fever (>38.5°C or 38.0°C in consecutive readings).
Participants	191 neutropenic episodes (104 with fever) developed in 97 patients. Median age was 47 years. All had haematological malignancy.
Study design	Prospective observational study, consecutive sample. Germany
Target condition and reference standard(s)	Clinically documented infection: fever with a clinical focus such as radiologically proven pneumonia but without microbial evidence for a causative organism. Unexplained fever: fever without documented microbiological cause and without clinical focus. Microbiologically documented infection: fever with a proven causative organism with or without a clinical focus.
Index and comparator tests	CRP (measured around the onset of fever) - median and range reported according to infection group.
Follow-up	
Notes	Use for continuous analysis of CRP versus time

1 **Erten 2004**

Clinical features and settings	Adult patients (>16 years) with haematological cancer, fever (> 38.3°C or > 38°C for at least an hour) and neutropenia (<0.5 $X10^9$/L or predicted to fall to this value). Study period was 2001 to 2002
Participants	45 episodes in 36 patients. All had haematological cancer, median age was 48 years. 9/45 had bacteraemia. 15/45 episodes were classed as severe.
Study design	Observational study (unclear whether prospective or whether consecutive/random sample). Turkey.
Target condition and reference standard(s)	Severe sepsis: defined as fever of more than 7 days, or with shock, or complex infection.Reference standard was clinical follow up.
Index and comparator tests	Blood samples were obtained on the first day of fever (after admission?) CRP: threshold 6 mg/L Procalcitonin: threshold 0.5 ng/mL
Follow-up	
Notes	

2 **Ha 2010**

Clinical features and settings	Adult patients (>18 years) after anticancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to be <500/mm^3 within 48 hours), fever (≥38.3°C or ≥38.0°C for ≥1 hour) at low risk of complications (MASCC ≥ 21). Patients presented to the emergency department of a single institution during the study period 1995 to 2007.
Participants	993 FN episodes in 802 patients. Mean age was 50 years. 27% of episodes were in patients with haematological cancers. Bacteraemia was detected in 101/993 episodes (10%).
Study design	Retrospective observational study. Consecutive sample. Korea
Target condition and reference standard(s)	Bacteraemia: defined as the isolation of bacterial pathogens from blood cultures alongside signs and symptoms of infection (excluding single positive cultures for coagulase-negative staphylococci).
Index and comparator tests	Not reported when tests were done (presumably on admission to the ED). ANC: threshold <50/mm^3 CRP: threshold ≥ 10 mg/dL
Follow-up	Not reported
Notes	

3 **Hakim 2010**

Clinical features and settings	Paediatric cancer patients (up to 17 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours), admitted to a single institution between 2004 and 2005
Participants	332 FN episodes in 332 children.

Study design	Retrospective consecutive case series. USA
Target condition and reference standard(s)	Invasive bacterial infection (bacteraemia, positive urine culture or culture negative sepsis)
Index and comparator tests	Not reported when tests were done (presumably at admission given the aims of the study) ANC, threshold $0.1X10^9/L$ Platelets, threshold $50,000/mm^3$
Follow-up	
Notes	

1 **Hamalainen 2008**

Clinical features and settings	Adult patients (16 to 69 years) with AML treated with intensive induction and chemotherapy at a single institution between 1996 and 2005.
Participants	290 FN episodes in 84 patients. Median age was 50 years, all had haematological malignancy.
Study design	Observational study, unclear whether prospective. Consecutive sample. Finland
Target condition and reference standard(s)	Severe sepsis: defined as sepsis complicated by organ dysfunction, hypoperfusion or hypotension.
Index and comparator tests	CRP was measured three times per week during neutropenia. Baseline CRP was defined as the measurement <48 hours before the rise of fever, CRP_{2-3} was defined as the measurement 2 to 3 days after the rise of fever. The CRP level immediately after the rise of fever was not reported.
Follow-up	
Notes	

2 **Hamalainen 2010**

Clinical features and settings	Adult (18 to 70 years) cancer patients who either had AML or received high dose chemotherapy supported by autologous stem cell transplant (ASCT). All were admitted to a single haematology ward between 2006 to 2008. Only patients with neutropenia and fever were included
Participants	94 FN episodes in 70 patients, Median age was 56 years. 19 had AML and 51 were ASCT recipients. 13/94 episodes involved severe sepsis.
Study design	Prospective observational study. Consecutive sample. Finland
Target condition and reference standard(s)	Severe sepsis: defined as a clinical syndrome in which systemic inflammatory response was present with infection. If sepsis was complicated by organ dysfunction, hypoperfusion or hypotension, despite adequate volume resuscitation and in the absence of other causes of hypotension it was defined as severe sepsis.
Index and comparator	The first samples for the measurement of CRP and NT-proBNP were taken at the

tests	beginning of neutropenic fever (d0). Further samples were taken every day until day 5 of the fever. Median and range of CRP was reported for severe and non-severe sepsis
Follow-up	
Notes	

1 **Hatzistilianou 2007**

Clinical features and settings	Children with acute lymphoblastic leukaemia, with fever (>38.5°C or >38°C over 6 hours) and neutropenia (ANC <0.5X109/l)
Participants	94 FN episodes in 20 children. All had haemological malignancy. Mean age was 5.8 years.
Study design	Observational study (unclear whether prospective or consecutive/random sample). Italy.
Target condition and reference standard(s)	Documented infection: defined as microbiologically documented infection or clinically documented infection.
Index and comparator tests	CRP, threshold 5 mg/ml
Follow-up	Blood samples were collected on admission and then daily for 7 days.
Notes	The quoted threshold 5mg/ml equates to 5000mg/l (extremely high!). For the analysis I assumed the threshold was 5mg/dl or 50mg/l.

2 **Hitoglou-Hatzi 2005**

Clinical features and settings	Children (<15 years) with acute lymphoblastic leukaemia and neutropenia (ANC <0.5X10^9/l or absolute leucocyte count of <1.0X10^9/l).
Participants	120 children: 29 with fever (>38.5°C or >38.0°C for at least 6 hours) and microbial infection, 38 with fever but without microbial infection and 53 without fever or microbial infection (not included in this analysis).
Study design	Prospective observational sample. Unclear whether consecutive or random sample. Greece
Target condition and reference standard(s)	Documented infection: microbiologically documented infection was defined as positive cultures of blood, urine, faeces and throat swabs. Clinically documented infection was defined as fever in connection with unambiguous signs of localised infection.
Index and comparator tests	CRP: thresholds 20,50 and 90 mg/L
Follow-up	Blood samples were collected at admission, and before the start of antimicrobial treatment.
Notes	Extracted figures from graph (fig 2) and used figures from Phillips et al review

3 **Karan 2002**

Clinical features and settings	Adult patients (>16 years) with haematological cancer and chemotherapy related fever (>38.5°C or >38.0°C on two occasions within 24 hours) and neutropenia (ANC <1.0X10^9/l). Study period not reported.
Participants	26 FN episodes in 26 patients. All had haematological cancer. Mean age was 40 years.
Study design	Observational study (unclear whether prospective or consecutive sample). Turkey
Target condition and reference standard(s)	Severe sepsis: defined as FN episode longer than 7 days, progress to septic shock or death.
Index and comparator tests	CRP, thresholds 100, 250 and 500 mg/l
Follow-up	Serum tests were done on the first day of fever, the first day of neutropenia+fever and when fever resolved.
Notes	2X2 tables extracted from figure 2. Very high threshold values used - possible confusion between mg/dl and mg/l

1

2 **Katz 1992**

Clinical features and settings	Children (< 18 years) with cancer, fever (≥38.5°C or >38°C for at least 6 hours) and neutropenia (ANC ≤ 0.5 X 10^9/L) admitted to a single institution. Study period was 1989 to 1990.
Participants	122 FN episodes in 74 children. 82/122 episodes were in patients with haematological malignancies and 40/122 in patients with solid tumours. Mean age was 6.3 years (range 2 months to 17 years).
Study design	Consecutive prospective observational study. USA
Target condition and reference standard(s)	Bacteraemia:defined as positive blood culture and toxic appearance at presentation - with or without cardiovascular instability. Documented infection: clinically or microbiologically documented infection
Index and comparator tests	CRP was measure at the initial evaluation of the patient following admission (between 8 and 24 hours following the onset of fever). CRP, thresholds 20 mg/l, 50 mg/l and 100 mg/l
Follow-up	Followup for reference standard was not reported. A random sample of 19 patients had a second CRP measurement between 11 and 96 days (median 38 days) after hospitalisation for the FN episode.
Notes	Sensitivity of CRP for bacteraemia at a threshold of 50 mg/l is not consistent with other thresholds (I have not included it in the analysis).

3

4 **Kitanovski 2006**

Clinical features and settings	Children (<19 years) with malignancy, fever (not defined), neutropenia (ANC < 0.5 10X^9/l, or expected to fall to this value within 24 hours)

Participants	68 FN episodes in 32 children. Median age 7.6 years. 50/68 had haematologic malignancy. 32/68 episodes were clinically documented infection, 36/68 were fever of unknown origin.
Study design	Prospective observational study. Unclear whether consecutive sample. Slovenia
Target condition and reference standard(s)	Clinically documented infection: bacteraemia, clinical sepsis (septic episode with negative blood cultures) or local infection (fever with clinically or microbiologically documented local infection).
Index and comparator tests	CRP: threshold > 60 mg/l (measured on the first day of the FN episode) CRP: threshold > 124 mg/l (measured on the second day of the FN episode) CRP: threshold > 111 mg/l (measured on the third day of the FN episode)
Follow-up	Complete blood counts and CRP were measured daily.
Notes	

1

2 **Klassen 2000**

Clinical features and settings	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall) and fever (≥38.5°C or multiple readings ≥38.0°C in a 12 hour period) admitted to a single institution between 1996 and 1997.
Participants	227 FN episodes in 140 children. Median ages was 6.8 years. 57% had haematological cancer. 12% had bacteraemia, 19% had significant infection.
Study design	Observational study. Consecutive sample. Canada.
Target condition and reference standard(s)	Significant infection: defined as any blood or urine culture positive for bacteria, interstitial or lobar consolidation on chest X-ray or unexpected death from infection (patient was not receiving palliative treatment) before ANC recovery.
Index and comparator tests	CBC (ANC, lymphocyte count, monocyte count and platelet count)
Follow-up	Tests were done shortly after admission. Length of follow-up for outcomes is not reported.
Notes	

3

4 **Klastersky 2000**

Clinical features and settings	Adult patients (> 16 years) with malignancy treated with chemotherapy and neutropenia (ANC >500/mm^3) and fever (>38.0°C). Study period was 1994 to 1997.
Participants	756 FN episodes in 756 patients (derivation set). Median age was 52 years. 331/756 (44%) patients had haematological cancer.
Study design	Prospective study. Consecutive or random sample (depending on participating institution). Multinational.

Target condition and reference standard(s)	Adverse events: defined as fever resolution for five consecutive days with occurrence of a serious medical complication including death.
Index and comparator tests	Tests were done at fever onset haemoglobin level: threshold < 8 g/dL Absolute neutrophil count: threshold < 0.1 X 10^9 / L Platelet count: threshold 5000 / µL Creatinine: threshold ≥ 2 mg/dL Bilirubin: threshold ≥ 2 mg/dL Albumin level: threshold < 2.5 g/dL
Follow-up	Not reported
Notes	

1

2 **Lehrnbecher 1999**

Clinical features and settings	Children and young adults (<20 years) with malignancy and chemotherapy related fever (>35.5°C or >38.0°C on 2 occasions within 4 hours) and neutropenia (ANC < 0.5 X10^9/L), admitted to a single hospital. Study period not reported.
Participants	121 FN episodes in 56 children. Mean age was 8 years. 20/121 episodes had bacteraemia with a Gram-positive organism, 5/121 had bacteraemia with a Gram-negative organism
Study design	Retrospective observational study. Unclear whether consecutive or random sample. Germany
Target condition and reference standard(s)	Bacteraemia (Gram negative or positive): not defined further.
Index and comparator tests	CRP: thresholds 2, 5 and 10 mg/dL (CHECK UNITS)
Follow-up	Tests were done before IV antibiotic therapy was started. CRP values used in analysis were the highest of two consecutive measurements in the 24 hours following admission. Diagnostic and clinical evidence of documented infection was gathered in the first 48 hours following admission.
Notes	

3

4 **Manian 1995**

Clinical features and settings	Adult patients (>18 years) neutropenia (ANC <1.0X10^9/L or expected to fall to this) suspected infection seen at a single oncology unit between 1990 and 1993.
Participants	82 FN episodes in 40 patients. 35/40 (88%) had haematological malignancy. Median age was 52 years.

Study design	Prospective observational study. Consecutive sample. USA
Target condition and reference standard(s)	Significant documented infection: documented bacterial or fungal infections with positive cultures (N=23 episodes), documented or presumed bacterial or fungal infections with negative blood cultures (N=31).
Index and comparator tests	CRP: thresholds 40, 80, 100, 150 and 200 mg/L
Follow-up	CRP was measured 1 day after diagnosis of febrile neutropenia, and then on every day until discharge.
Notes	

1

2 **Martinez-Albarran 2009**

Clinical features and settings	Children (<18 years) with cancer, fever (>38.5°C for at least an hour) and neutropenia (ANC < 0.5 $X10^9$/L) treated between 2006 and 2007.
Participants	54 FN episodes in 54 children. 18/54 had documented infection. Mean age was 6.1 years in those without documented infection and 7.6 years in those with documented infection. 32/53 (59%) had haematological cancer.
Study design	Prospective observational study. Consecutive sample. Mexico
Target condition and reference standard(s)	Severe infection: positive blood or urine culture, clinical signs of sepsis or onset of fever <7 days from the end of last chemotherapy.
Index and comparator tests	Tests were done as soon as the diagnosis of febrile neutropenia was made (before initiation of antibiotics), CRP, threshold 9.06 mg/dL (data driven threshold).
Follow-up	Patients were followed until discharge from hospital
Notes	

3

4 **Massaro 2007**

Clinical features and settings	Adult haematological cancer inpatients with fever (>38.3°C or >38°C for at least an hour) and neutropenia (ANC <0.5 X 10^9/L or expected to fall to this value), treated at a single hospital between 2004 and 2006.
Participants	52 FN episodes in 52 patients. All had haematological cancer. 26/52 (50%) had severe infection. Mean age was 40.8 years for those with severe infection and 40.0 years for those without.
Study design	Observational study, consecutive sample (unclear whether prospective). Brazil
Target condition and reference standard(s)	Severe infection: defined as fever plus documented infection (using CDC criteria) or clinical signs of sepsis.

Index and comparator tests	Tests were done before the initiation of empirical antibiotic therapy CRP, thresholds used: 21.3, 40.0, 72.0, 140.0, 173.0 and 214.50 mg/L.
Follow-up	Patients were followed up until clinical resolution (death or discharge from hospital)
Notes	

1

2 **Mato 2010**

Clinical features and settings	Adult patients (>18 years) with haematological malignancy who developed fever (>38°C) and neutropenia (ANC < 1.0 X 10^9 / L) while admitted to hospital for chemotherapy or an acute medical condition.
Participants	230 patients were included in the analysis: 46 with septic shock and 184 controls matched on length of hospital stay. Mean age was 54 years for cases and 51 years for controls.
Study design	Prospective case control study. Unclear whether consecutive or random sample. USA
Target condition and reference standard(s)	Septic shock: defined as the presence of refractory hypotension with a documented or suspected infection.
Index and comparator tests	Tests were done at the onset of febrile neutropenia. Serum lactate: threshold ≥ 2 mmol/L
Follow-up	
Notes	

3

4 **Moon 2009**

Clinical features and settings	Adult patients (>18 years) with malignancy presenting to the emergency department with neutropenia (ANC <500/mm^3) and fever (≥38.3°C or ≥38.0°C for ≥1 hours). Blood pressure > 90 mm Hg at presentation. Study period was 2004 to 2007.
Participants	192 FN events in 168 patients. Median age was 53 years. 59/168 (31%) had haematological cancers.
Study design	Retrospective observational study. Korea
Target condition and reference standard(s)	Serious medical complications: including hypotension, respiratory failure, disseminated intravascular coagulation, renal failure, severe bleeding requiring transfusion, altered mental state and arrhythmia requiring treatment. Complicated neutropenic fever: defined as fever not resolved within 5 days of starting treatment, death or serious medical complications.
Index and comparator tests	Not reported when tests were done (presumably at presentation to the emergency department)

	WBC: threshold < 0.5 X 10^9/L platelets: threshold < 50000/mm^3 AMC: threshold < 0.1 X 10^9/L ANC: threshold < 0.1 X 10^9/L Albumin: threshold < 3.0 g/dl Creatinine: threshold >1.2 mg/dl CRP: threshold > 100 mg/l
Follow-up	Not reported
Notes	Patients presenting with altered mental state were excluded.

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2 **Persson 2004**

Clinical features and settings	Adults (≥17 years) with haematological cancer, fever (>38.5°C or >38°C in 2 readings over 4 hours) and neutropenia (ANC<0.5X10^9/l) admitted to a single haematology ward. Study period not reported
Participants	94 FN episodes in 60 patients. All had haematological cancer. Median age ranged from 53 years to 56 years depending on the study group (CNS-bacteraemia, non-CNS bacteraemia, documented infection and fever of unknown origin).
Study design	Prospective observational study. Consecutive sample. Sweden.
Target condition and reference standard(s)	Non-CNS bacteraemia CNS bacteraemia
Index and comparator tests	Tests were done on entry to the study (when febrile neutropenia criteria were met). Tests were also repeated 3 times over the first 2 days of fever. CRP, threshold
Follow-up	Patients were followed for the first 2 days after admission into the study.
Notes	

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4 **Prat 2008**

Clinical features and settings	Adult patients (>15 years) with haematological malignancy with chemotherapy related fever (≥38°C) and neutropenia (ANC <0.5X10^9/l).
Participants	57 FN episodes in 56 patients. Median age was 47 years. All had haematological malignancy.
Study design	Observational study (probably prospective, unclear whether consecutive sample). Spain
Target condition and reference standard(s)	Bacteraemia: using CDC definitions and classified as either primary bacteraemia or catheter related bacteraemia. A separate analysis of Gram negative bacteraemias was also included

Index and comparator tests	PCT,(not relevant for this review) CRP: thresholds 30, 135,200 and 300 mg/l.
Follow-up	Serum samples were taken before chemotherapy, the first day of neutropenia and at 24 hour intervals after presentation with fever until 6 days
Notes	

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2 **Ramzi 2007**

Clinical features and settings	Adult patients (>21 years) with acute myeloid leukaemia, hospitalised with fever (criterion not reported) and neutropenia (ANC < 0.5 x 10^9/l or expected to decrease to that level). Study period was 2003.
Participants	110 FN episodes in 20 patients. Median age was 41 years. Clinically documented infections in 16/110, microbiologically documented in 18/110 and fever of unknown origin in 76/110.
Study design	Observational study (unclear whether prospective). Consecutive sample. Tunisia.
Target condition and reference standard(s)	Mortality from any cause Septic shock: defined as the presence of 2 or more SIRS criteria in the setting of a documented or presumed infection, with signs or symptoms of haemodynamic instability related to the onset of bacteraemia.
Index and comparator tests	Tests were done at study entry, ANC and temperature were recorded daily serum lactate: threshold 3 mmol/l serum bicarbonate: threshold 17 nmol/l
Follow-up	Mortality was reported at day 28.
Notes	

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4 **Riikonen 1993**

Clinical features and settings	Children (1 to 16 years) with fever (>39°C or >38°C on two occasions within 4 hours) and neutropenia (ANC < 0.2 X 10^9/L))caused by anti-cancer treatment. Study period 1989 to 1990.
Participants	96 FN episodes in 46 children. 57% had haematological cancers. Bacteraemia was found in 17/91 FN episodes.
Study design	Observational study, prospective. Unclear whether it was a consecutive or random sample. Finland.
Target condition and reference standard(s)	Documented infection: clinical and laboratory methods described in sufficient detail Bacteraemia: at least one positive peripheral blood culture or two positive cultures if Staphylococcus epidermidis was isolated.
Index and comparator	Tests were done on admission (and on days 1,2 and 3 of antimicrobial therapy).

tests	CRP: thresholds 20 and 50 mg/l (normal value 18 mg/l)
Follow-up	Test done daily, length of follow up not reported although results are available up to the 7th day of antimicrobial therapy.
Notes	Used figures from Phillips et al (2011) review for documented infection.

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2 **Rondinelli 2006**

Clinical features and settings	Children (< 18 years) with cancer, fever (>38°C or >37.8°C on 3 occasions within 24 hours) and neutropenia (<0.5 X 10^9/l or < 1 X 10^9/l and falling) admitted to a single hospital between 200 and 2003.
Participants	283 FN episodes in 283 patients. Mean age was 5.2 years. 48.5% had haematological cancers. 93/283 had severe (documented) infection.
Study design	Retrospective observational study. Consecutive sample. Brazil.
Target condition and reference standard(s)	Severe infection complications: defined as the presence of sepsis and/or shock and/or bacteraemia / fungaemia and/or death from infection.
Index and comparator tests	Not reported when tests were done. Granulocyte count: threshold 0.5 X 10^9/l Monocyte count: threshold 0.5 X 10^9/l Leucocytes: threshold 0.5 X 10^9/l Platelets: threshold 20000 units Haemoglobin level: threshold 7 g/dL
Follow-up	Not reported
Notes	

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4 **Santolaya 1994**

Clinical features and settings	Children admitted for treatment of malignancy at a single hospital between 1991 and 1992 were eligible. Children with fever (>38°C on 2 occasions within 24 hours) and neutropenia (ANC < 0.5 X10^9/l) were included in the study.
Participants	200 children were admitted for treatment: there were 85 FN episodes in 75 children. 85% of the children had haematological malignancy. Bacterial infection was documented in 24/85 episodes , clinically documented infection in 31/85 and in 30/85 there was either viral infection or no infection.
Study design	Observational study, consecutive sample. Chile
Target condition and reference standard(s)	Documented bacterial infection:one blood culture positive for a well recognized pathogen, or two blood cultures positive for an opportunistic pathogen, or positive cultures from a clinically relevant focus (urine or skin). Clinically documented infection: a severe clinical course or findings indicative of bacterial infection, in the absence of positive cultures.

Index and comparator tests	CRP, threshold 40 mg/l (10 mg/l was considered normal).
Follow-up	Tests were first done before the first dose of antibiotic was administered (day 1). Patients were monitored on a daily basis - blood was also drawn for tests on days 2,3, 5 and 7.
Notes	Standard deviations of CRP measured from the graph (figure 1 in the paper). The error bars on the figures are standard error of the mean - not standard deviation as reported in the text.

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2 **Santolaya 2001**

Clinical features and settings	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC ≤500/mm^3) and fever (≥38.5°C or ≥38.0°C for ≥2 hours)
Participants	447 FN episodes in 257 children. 68% had haematological malignancy. Median age was 7 years. 178/447 (40%) episodes had invasive bacterial infection.
Study design	Prospective observational study. Consecutive sample. Chile
Target condition and reference standard(s)	Invasive bacterial infection: defined as bacteraemia, a positive bacterial culture from an otherwise sterile site, clinical laboratory findings strongly suggestive of a sepsis syndrome or focal organ involvement in a child with haemodynamic instability and intense malaise.
Index and comparator tests	ANC, threshold 0.1X10^9/L AMC, threshold 0.1X10^9/L CRP, threshold 90 mg/L Platelent count 50,000/mm^3
Follow-up	
Notes	

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4 **Santolaya 2007**

Clinical features and settings	Children (≤ 18 years) with chemotherapy related fever (≥38.5°C or ≥38.0°C in two measurements within 1 hour) and neutropenia (ANC < 0.5 X10^9/l) and high risk of invasive bacterial infection, enroled in a multicentre study between 2004 and 2005.
Participants	393 FN episodes in 219 children. 76% had haematological cancer. Mean age was 7.6 years for those who survived and 9.4 years for those who died.
Study design	Propsective observational study, consecutive sample. Chile
Target condition and reference standard(s)	Death from any cause.
Index and comparator	Tests were done on enrolment to the study

tests	ANC, threshold 0.1 X10^9/l AMC, threshold 0.1 X10^9/l CRP, threshold 90 mg/l
Follow-up	Children were monitored daily until afebrile and blood counts were normal.
Notes	

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2 **Santolaya 2008**

Clinical features and settings	Children (≤ 18 years) with cancer, fever (not defined) and neutropenia (ANC ≤ 0.5 X 10^9/l), admitted to any of 6 hospitals between 2004 and 2006. Children classified as low risk (and managed as outpatients after 24 hours in hospital) were not included in this study.
Participants	646 high risk FN episodes, 566 included in the analysis (278 children). 116/566 developed severe sepsis. Median age was 9.9 years for those who developed severe sepsis and 7.2 years for the others. 74% of children in both groups had haematological cancers.
Study design	Prospective observational study. Chile
Target condition and reference standard(s)	Severe sepsis: defined as systemic inflammatory response syndrome in the presence of suspected or proven infection, plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome or 2 or more other organ dysfunctions.
Index and comparator tests	Tests were done at admission and 24 hours after admission. CRP, threshold >100 mg/l
Follow-up	Tests repeated daily until discharge from hospital.
Notes	

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4 **Secmeer 2007**

Clinical features and settings	Children (<19 years) with chemotherapy related fever (≥38.3°C or > 38°C for at least one hour) and neutropenia (not defined) admitted to a single hospital between 2004 and 2005. A random sample of afebrile patients was also included for comparison (but not included in this review).
Participants	60 FN episodes in 49 patients. 47% had haematological malignancy. 31/49 patients had documented infection. Median age was 7.7 years in those without documented infection and 7.2 in those with documented infection.
Study design	Prospective observational study. Unclear whether consecutive. Turkey.
Target condition and reference standard(s)	Documented infection: microbiologically or clinically documented infection. Bacteraemia: at least one positive culture for bacteraemia (or 2 in the case of coagulase-negative staphylococcus).

Index and comparator tests	Blood samples were collected at the 0th, 8th, 24th and 48th hours CRP, threshold 50 mg/L.
Follow-up	2 days.
Notes	

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2 **Spasova 2009**

Clinical features and settings	
Participants	
Study design	
Target condition and reference standard(s)	
Index and comparator tests	
Follow-up	
Notes	Waiting for inter-library loan of paper

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4 **Tezcan 2006**

Clinical features and settings	Paediatric cancer patients (<17 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and predicted to fall to <500) and fever (≥38.3°C or ≥38.0°C for ≥4 hours). Exclusion criteria: fever occurring after transfusion or G-CSF administration.
Participants	621 FN episodes in 240 patients. Median age was 6 years. 436/621 (70%) episodes were in children with haematological cancer. 345/621 had a documented infection.
Study design	Observational study (not reported whether it was prospective). Consecutive sample. Turkey
Target condition and reference standard(s)	Mortality, Microbiologically documented infection: bacteraemia or positive culture from a usually sterile site. Documented infection: microbiologically documented infection or clinical / lab findings suggestive of sepsis or focal organ involvement in defined cases
Index and comparator tests	Tests were done at admission to hospital. ANC, threshold 100 / µL AMC, threshold 100 / µL Mean CRP was reported for those with and without documented infection and

	with/without microbiologically documented infection.
Follow-up	Not reported
Notes	

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2 **Wilbur 2000**

Clinical features and settings	Adult patients with cancer, fever (>38.3°C or >38.0°C on 2 occasions) and neutropenia (ANC <1.0X10^9/L), who were enrolled on one of 2 randomised trials between 1982 and 1987.
Participants	394 FN episodes in 292 patients. Median age was 59 years 65% had haematological malignancy. 32/292 patients died within the first five days of antibiotic treatment.
Study design	Data were collected as part of 2 randomised trials, then analysed retrospectively. USA
Target condition and reference standard(s)	Death within the first five days of antibiotic treatment.
Index and comparator tests	ANC: threshold 0.01X10^9/L Albumin, threshold 2.5 g/dL Creatinine, threshold 1.7 mg/dL Platelets, threshold 25,000/mm^3
Follow-up	
Notes	

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4 **Yonemori 2001**

Clinical features and settings	Hospitalised adult (> 16 years) haematological cancer patients with neutropenia (< 1.0X10^9/l) who went on to develop fever (>38.0°C). Study period 1997 to 1999.
Participants	106 FN episodes in 47 patients. Median age was 56 years. All had haematological cancer. 28/106 episodes had clinically documented infection.
Study design	Retrospective observational study. Unclear whether consecutive or random sample. Japan
Target condition and reference standard(s)	Documented infection: documented bacterial or fungal infection, with positive blood cultures; or documented or presumed bacterial or fungal infections based on clinical or radiological findings with negative blood cultures
Index and comparator tests	CRP: threshold 30.8 mg/L (derived from the data)
Follow-up	Serum CRP was determined at least 3 times per week in hospitalised patients. CRP value just after the onset of fever was analysed, as was the peak CRP value during the febrile period.

Notes	CRP sensitivity and specificity are reported in the paper, but the values do not agree with those for PPV and NPV - given the patent numbers involved.

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6. Emergency assessment in secondary/tertiary care of a person with suspected neutropenic sepsis. (Topic C)

Guideline subgroup members for this topic

Paul Wallman (lead), Anne Davidson, Janie Thomas and Barbara Crosse

Review question

Should additional peripheral blood culture in patients with a central line, CRP (C-reactive protein), urinalysis, chest x-ray, lactate, blood gases be used in the emergency empirical assessment of a person with suspected neutropenic sepsis?

Rationale

Patients with acute cancer often present to hospital, by self presentation or referral by a GP or a community nurse or health worker. This may be to a specialist hospital or a local / district general hospital Emergency Department, with symptoms complicating their underlying disease or treatment thereof. Some of these symptoms may suggest the complication of neutropenic sepsis.

In such patients in the Emergency Department / Room, do any 'standard' tests that we currently perform add weight, or conversely, assist in refuting a diagnosis of neutropaenic sepsis or its source? Such a standard test would include the full blood count (FBC) to take a look at the number of white cells in the sample; neutropenic would be denoted by a low number of neutrophils in this sample. However, doing tests are not necessarily instantaneous and so there may be a delay in getting such blood results back to the 'bedside'. As clinicians, should we be waiting for the results of tests prior to the initiation of treatment of a patient with suspected neutropenic sepsis?

What are the risks and the benefits of initiating treatments prior to the results of the accepted standard tests, and conversely what are the risks or benefits of delaying the treatment of neutropenic sepsis until receipt of the test results? What does the evidence suggest and do these standard tests actually guide treatment decisions or in fact delay treatments that reduce mortality and morbidity?

Question in PICO format

Patients/population	Tests	Reference standard test	Target Condition	Outcomes
Patients in secondary or tertiary care with suspected neutropenic sepsis	• peripheral blood culture (in patients with a central line) • CRP • urinalysis • chest x-ray • lactate • blood gases	Use whatever reference standards are reported in the individual studies.	Sepsis	• Diagnostic accuracy • Clinical value of each test (does it influence treatment decisions?), • Time to diagnosis or initiation of treatment

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Psychinfo and BMI. There were no publication date limits set. The date of the search was 27th of June 2011, and it was updated on 7th November 2011.

Papers ordered for other topics (A, D1 and D2) were also checked for eligibility for this topic.

Selection of studies

The information specialist (SB) did the first screen of the literature search results. Two reviewers (NB and CL) then independently selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained and checked against the inclusion criteria.

Data synthesis

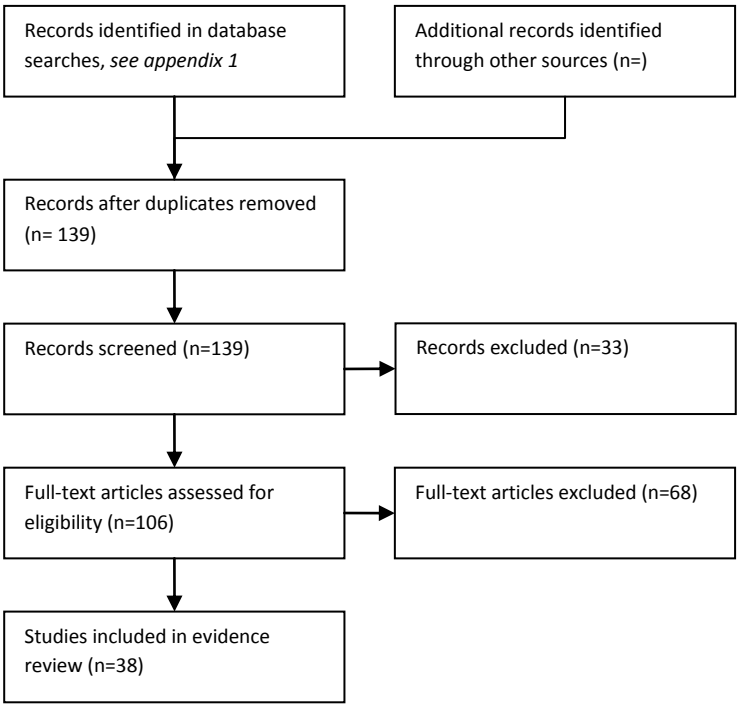
One reviewer extracted information about diagnostic accuracy into 2 X 2 tables of true/false positives and true/false negatives for each test/outcome combination in each study. A proportion of studies were appraised by a second reviewer (CL). One reviewer (NB) extracted data and assessed study quality was assessed using eight items from the QUADAS checklist for diagnostic studies.

The evidence for CRP as an initial test in patients with neutropenic fever had already been reviewed for topic D2, so this analysis was updated with any extra studies identified in the search. We also aimed to record the rate at which management decisions were influenced by each test and any influence of tests on the timing of treatment or diagnosis.

RESULTS

Results of literature searches

Figure 6.1 Study flow diagram.

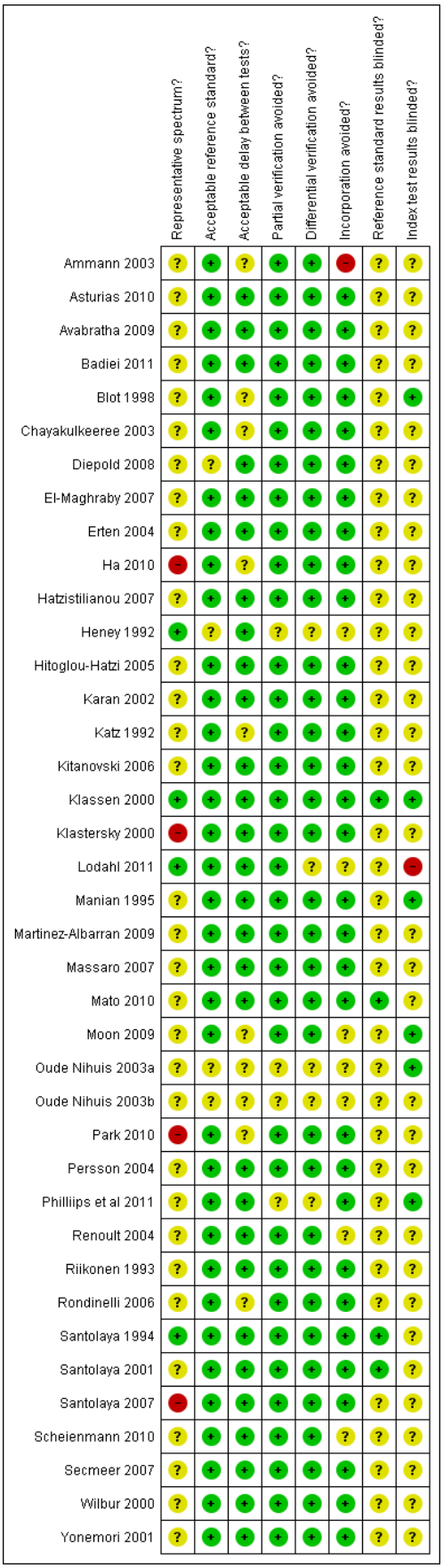


Study quality and results

The overall quality of the studies was low (Figure 6.2), because most did not include a representative spectrum of patients. 32/38 of the studies included only patients with confirmed neutropenia and fever, a subset of the relevant population of patients presenting with fever where neutropenia is suspected but not yet confirmed. The accuracy of tests in the emergency department setting could be different from that reported in the included studies.

Only 2/38 studies were carried out in emergency departments: Ha, et al., 2010 (but including only low risk patients – MASCC ≥21) and Moon, et al., (2009). The evidence is summarised in table 6.1 below.

Figure 6 .2. Study quality.



Evidence statements

Chest x-ray

Diagnosis of sepsis

Chest X-ray had a high sensitivity for bacterial pneumonia in two studies (Oude Nihuis, et al., 2003 and Renoult, et al., 2004), all cases of bacterial pneumonia were evident on the chest X-ray. A systematic review of the clinical features of radiographic pneumonia in children with fever and neutropenia (Phillips, et al,, 2011), identified 4 studies with 278 patients. The prevalence of pneumonia was 5% and Philips, et al., (2011) estimated that symptoms of respiratory distress had a negative predictive value of 98% (95% C.I. 96% to 99%). The probability of pneumonia in a child without respiratory symptoms was 1.9%.

In five studies, chest X-ray had widely varying sensitivity and specificity for severe sepsis or its complications (Badiei, et al., 2011, Chayakulkeeree, et al., 2003, Klastersky, et al., 2000, Moon, et al., 2009, and Wilbur, et al., 2000). Moon, et al., (2009) considered the use of chest X-ray in the emergency department to predict complicated fever in patients presenting with fever and neutropenia. In this study chest X-ray had a high positive likelihood ratio of 20.26 for complicated fever – a positive chest X-ray increased the odds of complicated fever by a factor of 20.

Clinical value of Test.

Two studies considered the influence of chest X-ray on clinical management (Oude Nihuis, et al., 2003 and Renoult, et al., 2004). Both concluded that the results of chest X-ray did not influence the choice of antibiotic treatment.

Time to diagnosis or initiation of treatment

None of the included studies reported this outcome.

Peripheral blood culture (in patients with a central line)

Diagnosis of sepsis

Scheienmann, et al., (2010) found that peripheral blood cultures were positive in some cases where central cultures were not. In their series of 228 episodes of bacteraemia the peripheral blood culture was the only positive culture in 28 cases. Thus doing both peripheral blood cultures and central cultures could improve sensitivity for the detection of bacteraemia.

Blot, et al., (1998) reported that in patients where both central venous and peripheral blood cultures were positive the differential time to positivity (DPT) could help indicate catheter related sepsis. Earlier positivity of the central venous culture of two or more hours, when compared to the peripheral culture, increased the odds of catheter-related sepsis by three times.

Clinical value of Test.

There was no direct evidence about the influence of peripheral blood cultures on clinical management decisions. However, Scheienmann, et al., (2010) surveyed Canadian healthcare professionals about their attitudes to obtaining peripheral blood cultures. The main reason given by the healthcare professionals for not obtaining peripheral blood cultures was that they do not provide any additional information and that phlebotomy is associated with a risk of complications

Time to diagnosis or initiation of treatment

None of the included studies reported this outcome.

CRP, Lactate and Blood gases

Evidence for these tests is reviewed in chapter 5: Investigations appropriate for risk stratification and management.

Urinalysis

Diagnostic accuracy

Moon, et al., (2009) reported a positive test for urine nitrates had sensitivity of 5% and specificity of 90% for complications of neutropenic sepsis. Thus a positive test was unlikely both in those with and without complications. Other studies mentioned using urinalysis in their initial assessment of patients with suspected neutropenic sepsis (for example Katz, et al., 1992) but did not report its results.

Clinical value of Test, Time to diagnosis or initiation of treatment

The influence of urinalysis on treatment decisions, time to diagnosis or initiation of treatment was not reported.

Table 6.1 - Chest X-ray and additional peripheral blood cultures in the emergency assessment of patients with suspected neutropenic sepsis

Test	N studies (episodes)	Prevalence (range)	Sensitivity (range)	Specificity (range)	LR + (range)	LR – (range)	References
Bacterial pneumonia							
Chest X-ray	2 (349)	2% to 5%	100%	68% to 92%	3.15 to 12.42	Not calculable	Oude Nihuis 2003, Renoult 2004
Severe sepsis or its complications							
Chest X-ray	5 (1684)	15% to 60%	23% to 72%	17% to 98%	0.87 to 20.26	0.62 to 1.66	Badiei 2011, Chayakulkeeree 2003, Klastersky 2000, Moon 2009, Wilbur 2000
DPT between central & peripheral blood cultures	1 (58)	44%	95%	69%	3.12	0.07	Blot 1998

Abbreviations:;DPT, differential time to positivity ; LR+, likelihood ratio for a positive test result; LR-, likelihood ratio for a negative test result.

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EVIDENCE TABLES

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Ammann 2003. Switzerland	Retrospecitve observational study. Consecutive sample. 1993-2001.	285 FN episodes in 111 children.	Severe bacterial infection: 106/285 (37%).	Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after non-myeloablative chemotherapy. Median age at the first FN episode was 6.3 years. Proportion with haematological cancers was not reported.	Haemoglobin level: thresholds > 71 g/L and >100 g/L ANC: thresholds >0.11 X 10^9/L and >0.5 X 10^9/L AMC:thresholds >0.11 X 10^9/L and >0.5 X 10^9/L Phagocyte count: thresholds >0.11 X 10^9/L and >0.5 X 10^9/L Thrombocyte count: thresholds >11 X 10^9/L	Study does not report when tests were done, although the aim was to find predictive factors for use within the first 2 hours of fulfilment of the febrile neutropenia criteria.	Severe (significant) bacterial infection: defined as bacteraemia, positive urine culture, pneumonia, clinically unequivocal diagnosis of infection, serum CRP >150 mg/L or unexpected death from infection.	*Diagnostic accuracy for severe bacterial infection:* See D2 evidence tables *Influence on management* Not reported *Time to diagnosis* Not reported	Not reported	Serum CRP incorporated into reference standard.

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
					and >150 X 10^9/L Serum CRP: thresholds >5 mg/l and > 50 mg/l (5mg/l defined as normal) Serum creatinine: thresholds >75 mg/L, and other tests					
Asturias 2010. Guatemala	Prospective observational study. Consecutive sample. 2008	96 episodes of FN in 88 patients.	Bacteraemia: 11/96 episodes	Children (<18 years) with fever (≥38.5°C or ≥38.0°C for a least 1hour) and neutropenia (ANC ≤ 1.0 X 109/L), hospitalised at a single institution during 2008.	Serum CRP: threshold ≥96 mg/L Platelet count: ≤ 50 x 109/L	At admission	Bacteraemia: 2 blood cultures positive for any pathogen except coagulase-negative staphylococci.	*Diagnostic accuracy , see topic D2 evidence tables* *Influence on management* Not reported	Unidad Nacional de Oncologica Pediatrica, Guatemala	

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
				74/96 (77%) episodes were in patients with haematological malignancies. Mean age was 6.5 years. Those hospitalised for less than 48 hours, those who had received antibiotics before admission and those receiving bone marrow transplants were excluded				*Time to diagnosis* Not reported		
Avabratha 2009. India	Prospective observational study, consecutive sample. Study period not reported.	50 FN episode in 33 children	Microbiologcially documented infection: 9/50 Clinically documented infection:	Children (<16 years) with malignancy and chemotherapy related fever (≥38.3°C or ≥38.0°C for at least 1 hour) and neutropenia (ANC < 0.5 X109/l or predicted to fall to this) admitted to a	Clinical examination, tests for haemoglobin, CBC, peripheral smear, blood culture and CRP	At admission – before antibiotics started.	Microbiologcially documented infection: clinical and/or radiological evidence of infection and culture positivity.	*Diagnostic accuracy , see topic D2 evidence tables* *Influence on management* Not reported	None	

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>19/50</td><td>single hospital.

Mean age 6.9 years. At least 73% of patients had haematological malignancy.</td><td>estimation.</td><td></td><td>Clinically documented infection: identifiable site of infection without a positive culture.</td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Badiei (2011).

Iran</td><td>Case series, unclear whether prospective

2008 to 2009.</td><td>120 FN episodes in 68 patients</td><td>Life threatening infection: 35/120.</td><td>Children younger than 18 years referred for fever (≥38.5°C or ≥38.0°C for at least 1 hour) and neutropenia (ANC < 0.5 X109/l) admitted to a single hospital.</td><td>Temperature,

mucositis, WBC, ANC, haemoglobin level, platelet count, chest X-ray</td><td>At the time of admission with neutropenia and fever.</td><td>Life threatening infection: positive culture from blood, CSF, urine or catheter), sepsis, septic shock or death from infection.</td><td><table><tr><th></th><th colspan="2">Life threatening infection</th></tr><tr><th></th><th>+</th><th>-</th></tr><tr><td>Chest X-ray +*</td><td>8</td><td>2</td></tr><tr><td>Chest X-ray -</td><td>27</td><td>83</td></tr></table>*lobar or interstitial infiltration</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Sn 23%, Sp 98%</td><td></td><td></td></tr>
<tr><td>Blot (1998).

France</td><td>Retrospective case series.

1994-1996.</td><td>64 patients</td><td>Catheter related sepsis:

28/64</td><td>Patients with suspected catheter related infection in whom both central and peripheral cultures were positive for the same microorganism.</td><td>DPT-differential time to positivity between simultaneous central and peripheral blood cultures.</td><td>Not reported</td><td>Catheter related sepsis

(CRS) was defined as no detectable focus of infection except the catheter plus one of the following:

1) Local signs of infection at the CVC insertion site.

2)Disappearance of CVC</td><td><table><tr><td></td><td colspan="2">Catheter related sepsis*</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>DPT > 2hrs</td><td>27</td><td>11</td></tr><tr><td>DPT ≤ 2hrs</td><td>1</td><td>25</td></tr></table>Sn 96%, Sp 69%</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>infection signs and normal temperature within 24hours of catheter removal and antibiotics

3) Positive catheter culture, with isolation of the same microorganism in the blood stream</td><td>*22 cases where diagnosis was not established were added to the CRS-column.

Influence on management

Not reported

Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Chayakulkeeree. 2003

Thailand.</td><td>Retrospective case series.
Consecutive sample.

1999 -2000.</td><td>267 episodes (220 patients).</td><td>38/267, clinically documented infection,

90/267

microbiologically documented infection</td><td>Adult or adolescent patients (>12 years) with febrile (>38°C) neutropenic (<0.5X109/L) episodes admitted to a single hospital.

158/220 (72%) had haematological malignancy. Mean</td><td>Duration of neutropenia, temperature, blood pressure, pulse rate, respiratory rate. Lab tests including white blood cell counts, BUN,</td><td>Not reported</td><td>Favourable outcome: fever resolved in 5 days of starting treatment and without complications

Unfavourable outcome:</td><td><table><tr><td></td><td colspan="2">Unfavourable outcome</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CXR +</td><td>115</td><td>90</td></tr><tr><td>CSR-</td><td>44</td><td>18</td></tr></table></td><td>Thailand Research fund.</td><td>Very high rate of abnormal chest X-rays (endemic tuberculosis?).</td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>159/267 high risk or unfavourable outcome

205/267 had abnormal chest X-ray</td><td>age was 44.7 years.</td><td>creatinine, electrolytes. Chest X-ray (CXR). Blood cultures.</td><td></td><td>Death, serious complications, modification of initial therapy, relapse of resolved fever or fever longer than 5 days.

Reference standard was clinical follow up reported in medical records.</td><td>Sn 72%, Sp 17%

<table><tr><td></td><td>Unfavourable outcome</td><td></td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>Bicarbonate < 24 mmol/L</td><td>82</td><td>51</td></tr><tr><td>Bicarbonate ≥ 24 mmol/L</td><td>77</td><td>57</td></tr></table>Sn 52%, Sp 53%

Influence on management

Not reported

Time to diagnosis</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Diepold 2008.

Germany</td><td>Prospective observational study. Unclear whether consecutive or random sample.</td><td>123 FN episodes in 69 patients.</td><td>Documented infection:

85/113

(10 were excluded from analysis)</td><td>Children and young adults (<20 years) with cancer or haematological disorders with fever (>38.5°C or >38.0°C from more than 1 hour) and neutropenia (ANC <0.5X109/L) admitted to a single hospital.

64/69 patients had cancer. 55% of patients had haematological cancer. Median age</td><td>CRP, IL-6, and IL-8. Blood and urine cultures, cultures from suspected lesions.</td><td>Within 24 hours of the start of fever</td><td>Documented infection: bacteraemia (positive blood culture) or febrile episode of five days or more (these patients were presumed to have either a serious infection or signs of clinical sepsis - without microbiologically documented infection).</td><td><table><tr><td></td><td>Doc. infection</td><td></td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 10 mgl/l</td><td>71</td><td>11</td></tr><tr><td>CRP ≤ 90 mg/l</td><td>14</td><td>17</td></tr></table>Sn 83%, Sp 59%

Influence on management

Not reported</td><td>None</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>was 7.67 years.</td><td></td><td></td><td></td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>El-Magraby 2007.

Egypt</td><td>Prospective observational study. Unclear whether consecutive or random sample.

2004 to 2005</td><td>85 FN episodes in 76 children.</td><td>Documented infection in 59/85 FN episodes.

Bacteraemia: 20/85 episodes</td><td>Children with haematological cancer fever (>38.5°C or >38.0°C on 2 occasions during 6 hours) and neutropenia (ANC < 0.5X109/L), who received chemotherapy at a single institution .

Mean age was 7.8 years for those with fever of unknown origin and 6.8 years for those with documented</td><td>CRP, threshold 90 mg/l (normal value defined as <6mg/l)</td><td>Tests were done within the first 24 hours of admission.</td><td>Documented infection: positive blood cultures and/or documented clinical sepsis and/or local infection.</td><td><table><tr><td></td><td>Doc. infection</td><td></td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 90 mgl/l</td><td>41</td><td>7</td></tr><tr><td>CRP ≤ 90 mg/l</td><td>18</td><td>19</td></tr></table>Sn 70%, Sp 73%

<table><tr><td></td><td>Bacteraemia</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
				infection. All had haematological malignancy.				<table><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > ? mgl/l</td><td>20</td><td>56</td></tr><tr><td>CRP ≤? mg/l</td><td>0</td><td>9</td></tr></table> Sn 100%, Sp 14% (unclear what the cutoff value was) *Influence on management* Not reported *Time to diagnosis* Not reported		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Erten 2004. Turkey	Observational study (unclear whether prospective or whether consecutive/random sample). 2001-2002	45 episodes in 36 patients.	9/45 had bacteraemia. 15/45 episodes were classed as severe	Adult patients (>16 years) with haematological cancer, fever (> 38.3°C or > 38°C for at least an hour) and neutropenia (<0.5 $X10^9$/L or predicted to fall to this value). All had haematological cancer, median age was 48 years..	CRP: threshold 6 mg/L Procalcitonin: threshold 0.5 ng/mL	Blood samples were obtained on the first day of fever (after admission?)	Severe sepsis: defined as fever of more than 7 days, or with shock, or complex infection. Reference standard was clinical follow up.	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Istanbul University Research Foundation	

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Ha 2010. Korea	Retrospective observational study. Consecutive sample. 1995 - 2007.	993 FN episodes in 802 patients.	Bacteraemia: 101/993 episodes (10%).	Adult patients (>18 years) after anticancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to be <500/mm^3 within 48 hours), fever (≥38.3°C or ≥38.0°C for ≥1 hour) at low risk of complications (MASCC ≥ 21). Patients presented to the emergency department of a single institution. Mean age was 50 years. 27% of episodes were in patients with haematological cancers.	ANC: threshold <50/mm^3 CRP: threshold ≥ 10 mg/Dl, plus others.	Not reported when tests were done (presumably on admission to the ED).	Bacteraemia: defined as the isolation of bacterial pathogens from blood cultures alongside signs and symptoms of infection (excluding single positive cultures for coagulase-negative staphylococci).	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td>Hatizistilianou. 2005.

Italy.</td><td>Observational study (unclear whether prospective or consecutive/random sample).</td><td>94 FN episodes in 20 children.</td><td>Microbial infection: 62/96</td><td>Children with acute lymphoblastic leukaemia, with fever (>38.5°C or >38°C over 6 hours) and neutropenia (ANC <0.5X109/l)

All had haemological malignancy. Mean age was 5.8 years</td><td>CRP, threshold 5 mg/ml</td><td>On admission with FN.</td><td>Documented infection: defined as microbiologically documented infection or clinically documented infection.</td><td>Diagnostic accuracy

See outcomes for topic D2

Influence on management

Not reported

Time to diagnosis

Not reported</td><td>Altana Pharma Canada</td><td></td></tr>
<tr><td>Heney 1992

UK</td><td>Case series (consecutive sample , unclear whether prospective)</td><td>47 febrile episode in 33 patients</td><td>Bacteraemia: 16/47</td><td>Children being treated for solid or haematological malignancies with fever (>38.5°C or >38.0°C on 2 occasions during 24 hours).

Mean age 7 years (range 0.5 to 15 years)</td><td>CRP

IL-6, blood cultures, additional cultures if indicated.</td><td>Done on admission for fever and neutropenia.</td><td>Bacteraemia: blood culture – but criteria for bacteraemia were not reported in detail.</td><td><table><tr><td></td><td colspan="2">Bacteraemia</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 40 mgl/l</td><td>9</td><td>15</td></tr><tr><td>CRP ≤ 40 mg/l</td><td>7</td><td>16</td></tr></table>Sn 56%, Sp 58%</td><td>Candle-lighters trust.</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
				66% haematological cancer.				*Influence on management* Not reported *Time to diagnosis* Not reported		
Hitoglou-Hatzi 2005. Greece	Prospective observational sample. Unclear whether consecutive or random sample.	120 children	29 with fever (>38.5°C or >38.0°C for at least 6 hours) and microbial infection, 38 with fever but without microbial infection and 53 without fever or microbial infection (not included in this analysis).	Children (<15 years) with acute lymphoblastic leukaemia and neutropenia (ANC <0.5X10^9/l or absolute leucocyte count of <1.0X10^9/l).			Documented infection: microbiologically documented infection was defined as positive cultures of blood, urine, faeces and throat swabs. Clinically documented infection was defined as fever in connection with	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							unambiguous signs of localised infection.			
Karan 2002. Turkey	Observational study (unclear whether prospective or consecutive sample).	26 FN episodes in 26 patients.	Severe sepsis: 14/26	Adult patients (>16 years) with haematological cancer and chemotherapy related fever (>38.5°C or >38.0°C on two occasions within 24 hours) and neutropenia (ANC <1.0X10^{9}/l). All had haematological cancer. Mean age was 40 years.	CRP, thresholds reported as 100, 250 and 500 mg/l	Serum tests were done on the first day of fever, the first day of neutropenia+ fever and when fever resolved.	Severe sepsis: defined as FN episode longer than 7 days, progress to septic shock or death.	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Istanbul University Research Foundation	

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Katz 1992

USA</td><td>Prospective case series

Nov 1989 – June 1990</td><td>122 episodes

74 patients</td><td>Documented infection:

52/122

Bacteraemia:

7/122</td><td>Children with malignant disease admitted to hospital because of fever in the presence of neutropenia

82/122 episodes were in patients with haematological malignancies and 40/122 in patients with solid tumours. Mean age was 6.3 years (range 2 months to 17 years).</td><td>Complete blood count

Peripheral blood culture

Central venous catheter culture

Urinanalysis

Urine culture

Chest radiograph

CRP</td><td>8-24 hours after onset of fever</td><td>Physical examination, complete blood count, peripheral blood culture, CVC blood culture, urinalysis, urine culture, chest radiograph

Bacteraemia: defined as positive blood culture and toxic</td><td><table><tr><td></td><td colspan="2">Doc. inf.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 20 mg/l</td><td>37</td><td>43</td></tr><tr><td>CRP ≤ 20 mg/L</td><td>15</td><td>20</td></tr></table>Sn 71%, Sp 32%

<table><tr><td></td><td colspan="2">Doc. inf.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 50</td><td>24</td><td>16</td></tr></table></td><td>National Institute of Health

The Children’s Cancer Fund of Dallas

Weekend to Wipe Out Cancer</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							appearance at presentation - with or without cardiovascular instability. Documented infection: clinically or microbiologically documented infection	mg/l CRP ≤ 50 mg/L: 28, 47 Sn 46%, Sp 75% *Doc. inf.* (+ / -) CRP > 100 mg/l: 11, 4 CRP ≤ 100 mg/L: 41, 59 Sn 22%, Sp 94% *Bacteraemia* (+ / -) CRP > 20 mg/l: 7, 78 CRP ≤ 20: 0, 37		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								mg/L | | Sn 100%, Sp 32% | | *Bacteraemia* | | + | - CRP > 50 mg/l | 5 | 38 CRP ≤ 50 mg/L | 2 | 77 Sn 71%, Sp 67% | | *Bacteraemia* | | + | - CRP > 100 mg/l | 5 | 33 CRP ≤ 100 mg/L | 2 | 82 Sn 71%, Sp 94%		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								Influence on management Not reported *Time to diagnosis* Not reported		
Kitanovski 2006. Slovenia	Prospective observational study. Unclear whether consecutive sample.	68 FN episodes in 32 children	32/68 episodes were clinically documented infection, 36/68 were fever of unknown origin	Children (<19 years) with malignancy, fever (not defined), neutropenia (ANC < 0.5 $10X^9$/l, or expected to fall to this value within 24 hours) Median age 7.6 years. 50/68 had haematological malignancy	Complete blood counts and CRP were measured daily.		Clinically documented infection: bacteraemia, clinical sepsis (septic episode with negative blood cultures) or local infection (fever with clinically or microbiologically documented local infection).	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Ministry of Education, Solvenia	

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Klastersky. 2000.</td><td>Prospective study. Consecutive or random sample (depending on centre). Multinational.

1994-1997</td><td>756 FN episodes in 756 patients (derivation set).</td><td>111/756</td><td>Adult patients (> 16 years) with malignancy treated with chemotherapy and neutropenia (ANC >500/mm^3) and fever (>38.0°C).

Median age was 52 years.

331/756 (44%) patients had haematological cancer</td><td>haemoglobin level: threshold < 8 g/dL

Absolute neutrophil count: threshold < 0.1 X 109 / L

Platelet count: threshold 5000 / µL

Creatinine: threshold ≥ 2 mg/dL</td><td>Tests were done at fever onset</td><td>Adverse events: defined as fever resolution for five consecutive days with occurrence of a serious medical complication including death.</td><td>Any abnormality on chest X-ray:
<table><tr><td></td><td colspan="2">Adverse event</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CXR +</td><td>37</td><td>97</td></tr><tr><td>CXR -</td><td>74</td><td>548</td></tr></table>Sn 33%, Sp 85%

Abnormality on chest X-ray suggestive of infection:
<table><tr><td></td><td>Adverse event</td></tr></table></td><td></td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
					Bilirubin: threshold ≥ 2 mg/dL Albumin level: threshold < 2.5 g/dL, Chest X-ray (CXR), and others			<table><tr><td></td><td colspan="2"></td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CXR infection +</td><td>27</td><td>53</td></tr><tr><td>CXR infection -</td><td>84</td><td>592</td></tr></table>Sn 24%, Sp 92% *Influence on management* Not reported. The study proposed a risk index score (MASCC) – but the individual influence of chest X-ray results on clinical decisions is not reported. *Time to diagnosis* Not reported		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Lodahl 2011.

Denmark</td>
<td>Prospective case series. 2000-2001</td>
<td>230 episodes in

85 patients</td>
<td>Bacteraemia. 61/230</td>
<td>Children < 16 years treated with chemotherapy or haematological disease, with fever.

Fever was >38.5°C once or >38.0° twice within 4 – 6 hours.</td>
<td>Clinical evaluation.PCT and routine blood samples drawn from CVC. Blood cultures were done before start of antibiotics</td>
<td>On admission with fever.</td>
<td>Cause of fever was classified by the treating physician using results of tests (including bacterial cultures) and the total clinical course of the episode.</td>
<td>
<table>
<tr><td></td><td>Bacteraemia</td><td></td></tr>
<tr><td></td><td>+</td><td>-</td></tr>
<tr><td>CRP > 336 nmol/l</td><td>24</td><td>71</td></tr>
<tr><td>CRP ≤ 336 nmol/l</td><td>3.7</td><td>98</td></tr>
</table>
Sn 39%, Sp 58%

<table>
<tr><td></td><td>Bacteraemia</td><td></td></tr>
<tr><td></td><td>+</td><td>-</td></tr>
<tr><td>CRP > 537 nmol/l</td><td>13</td><td>41</td></tr>
<tr><td>CRP ≤537 nmol/l</td><td>48</td><td>128</td></tr>
</table>
Sn 21%, Sp 76%
</td>
<td>Danish MRC and Brahms Diagnostica who supplied PCT LUMI test.</td>
<td>CRP was part of standard care and could have been incorporated into the reference standard.</td>
</tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								<table><tr><td></td><td colspan="2">Bacteraemia</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 679 nmol/l</td><td>5</td><td>29</td></tr><tr><td>CRP ≤679 nmol/l</td><td>56</td><td>140</td></tr></table> Sn 8%, Sp 83% Conversion 336, 537 and 679 nmol/l CRP is 8.4, 13.5 and 17.0 mg/l respectively *Influence on management* Not reported *Time to diagnosis* Not reported		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Manian 1995. USA	Prospective observational study. Consecutive sample. 1990 -1993.	82 FN episodes in 40 patients.	Significant infection: 23/82. Documented or presumed bacterial or fungal infections with negative blood cultures 32/82.	Adult patients (>18 years) neutropenia (ANC <1.0X10^{9}/L or expected to fall to this) suspected infection seen at a single oncology unit. 35/40 (88%) had haematological malignancy. Median age was 52 years	CRP: thresholds 40, 80, 100, 150 and 200 mg/L	CRP was measured 1 day after diagnosis of febrile neutropenia, and then on every day until discharge.	Significant documented infection: documented bacterial or fungal infections with positive cultures	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Beckman Instruments (CRP kits).	

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Martinez-Albarran. 2009. Mexico	Prospective observational study. Consecutive sample. 2006-2007	54 FN episodes in 54 children	18/54 had documented infection	Children (<18 years) with cancer, fever (>38.5°C for at least an hour) and neutropenia (ANC < 0.5 $X10^9$/L) treated between 2006 and 2007. Mean age was 6.1 years in those without documented infection and 7.6 years in those with documented infection. 32/53 (59%) had haematological	CRP, threshold 9.06 mg/dL (data driven threshold)	Tests were done as soon as the diagnosis of febrile neutropenia was made (before initiation of antibiotics),	Severe infection: positive blood or urine culture, clinical signs of sepsis or onset of fever <7 days from the end of last chemotherapy.	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Not reported.	

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>cancer.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Massaro

2007</td><td>Prospective case series

Aug 2004 – Sept 2006</td><td>52 episodes

52 patients</td><td>Severe infection: 26/52</td><td>Adult patients hopitalised with severe neutropenia (neutrophil count of less than 500/mm3 or less than 1000/mm3 and expected to decline to 500/mm3) and fever.</td><td>PCT

CRP</td><td>At fever onset</td><td>Patients diagnosed with severe infection (fever + positive blood culture for bacteria or fungi) or clinical signs of sepsis or proven fungal infection on the basis of clinical data including physical signs, haematology and chemistry parameters,</td><td><table><tr><td></td><td colspan="2">Severe inf.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 21 mg/l</td><td>23</td><td>25</td></tr><tr><td>CRP ≤ 21 mg/L</td><td>3</td><td>1</td></tr></table>Sn 88%, Sp 4%

<table><tr><td></td><td colspan="2">Severe inf.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 40</td><td>18</td><td>24</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							results of blood, urine and tissue secretion cultures, radiographs and CT scans of the thorax, paranasal sinuses and abdomen, when necessary.	mg/l CRP ≤ 40 mg/L: 8, 2 Sn 69%, Sp 7% *Severe inf.* (+ / -) CRP > 72 mg/l: 16, 15 CRP ≤ 72 mg/L: 10, 11 Sn 62%, Sp 42% *Severe inf.* (+ / -) CRP > 140 mg/l: 11, 7 CRP ≤ 140: 15, 19		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								mg/L | | Sn 42%, Sp 73% | | *Severe inf.* | | | + | - | | CRP > 173 mg/l | 5 | 4 | | CRP ≤ 173 mg/L | 21 | 22 | Sn 19%, Sp 85% | | *Severe inf.* | | | + | - | | CRP > 215 mg/l | 1 | 1 | | CRP ≤ 215 mg/L | 25 | 25 |		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Sn 4%, Sp 96%

Influence on management

Not reported

Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Mato 2010

USA</td><td>Prospective case control study. Unclear whether consecutive or random sample.</td><td>230 patients and 184 controls matched on length of hospital stay.</td><td>Septic shock: 46/230</td><td>Adult patients (>18 years) with haematological malignancy who developed fever (>38°C) and neutropenia (ANC < 1.0 X 10^9 / L) while admitted to hospital for chemotherapy or an acute medical condition.

Mean age was 54 years for cases and</td><td>Serum lactate: threshold ≥ 2 mmol/L</td><td>Tests were done at the onset of febrile neutropenia.</td><td>Septic shock: defined as the presence of refractory hypotension with a documented or suspected infection within 48 hours of the start of febrile neutropenia.</td><td><table><tr><td></td><td colspan="2">Septic shock</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>Lactate ≥ 2 mmol/L</td><td>12</td><td>6</td></tr><tr><td>Lactate < 2 mmol/L</td><td>34</td><td>178</td></tr></table>Sn 26%, Sp 97%

Influence on management</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>51 years for controls.</td><td></td><td></td><td></td><td>Not reported

Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Moon 2009

South Korea</td><td>Retrospective case series.

2004-2007</td><td>192 episodes

168 patients</td><td>Complicated neutropenic fever: 28/192</td><td>Adult patients (>18 years) with malignancy presenting to the emergency department with neutropenia (ANC <500/mm^3) and fever (≥38.3°C or ≥38.0°C for ≥1 hours). Blood pressure > 90 mm Hg at presentation.

Median age was 53 years. 59/168 (31%) had haematological cancers.</td><td>WBC, platelets, monocytes, neutrophils, lymphocytes, total protein, albumin, BUN, creatinine, CRP, urine nitrates,

Pulmonary infiltration on chest X-ray</td><td>Unclear, likely tests were done on presentation to the emergency department</td><td>Complicated neutropenic fever classified as not resolving within 5 days of starting treatment, death or serious medical complications</td><td><table><tr><td></td><td colspan="2">Complicated fever.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 100 mg/l</td><td>26</td><td>52</td></tr><tr><td>CRP ≤ 100 mg/L</td><td>12</td><td>102</td></tr></table>Sn 68%, Sp 66%

<table><tr><td></td><td colspan="2">Complicated fever.</td></tr><tr><td></td><td>+</td><td>-</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								<table><tr><td>X-ray +</td><td>15</td><td>3</td></tr><tr><td>X-ray -</td><td>23</td><td>151</td></tr></table> Sn 39%, Sp 98% <table><tr><td></td><td colspan="2">Complicated fever.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>Urine nitrates +</td><td>2</td><td>16</td></tr><tr><td>Urine nitrates -</td><td>36</td><td>138</td></tr></table> Sn 5%, Sp 90% Platelets<50,000/mm3, CRP > 10 mg/dl and pulmonary infiltration on chest X-ray were indenpendent predictors of complicated neutropenic fever on multivariate analysis		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Influence on management

Not reported.

Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Oude Nijuis (2003).

Netherlands</td><td>Prospective case series.

1999-2002</td><td>109 episodes of FN in 89 patients.</td><td>Bacterial pneumonia: 2/109 episodes.</td><td>Median age 45 years (range 18 to 77)

26% had haematological malignancy.

Fever was >38.5°C once or >38.0°C for 6 hours.

Neutropenia was granulocytes<0.5X10^{9}/L or leucocytes<1X10^{9}/L.</td><td>Chest X-ray, sinus X-ray, physical examination, lab tests and bacterial cultures.</td><td>Done at presentation with FN.</td><td>Not reported</td><td><table><tr><td></td><td colspan="2">Bacterial pneumonia</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>Chest x-ray +</td><td>2</td><td>34</td></tr><tr><td>Chest x-ray -</td><td>0</td><td>73</td></tr></table>
Influence on management

No changes in antibiotic therapy due to chest x-ray</td><td>University Hospital, Groningen</td><td>Total number of patients with bacterial pneumonia unclear</td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>All were hospitalised and treated with broad spectrum IV antibiotics.</td><td></td><td></td><td></td><td>results.</td><td></td><td></td></tr>
<tr><td>Oude Nijhuis, 2003.

Netherlands</td><td>Prospective case series.

1998-2000</td><td>66 episodes in 57 patients</td><td>Bacteraemia:</td><td>Patients with fever, neutropenia and cancer.

Neutropenia was granulocytes<0.5X10^{9}/L or leucocytes<1X10^{9}/L

Fever was >38.5°C once or >38.0°C for 6 hours.

Median age was 22</td><td>Not reported</td><td>Done at presentation with FN – before antibiotics were started.</td><td>Bacteraemia: presumably blood cultures but not specified in detail.</td><td><table><tr><td></td><td colspan="2">Bacteraemia</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 100 mg/L</td><td>11</td><td>12</td></tr><tr><td>CRP ≤100 mg/L</td><td>7</td><td>36</td></tr></table>Sn 61%, Sp 60%

Influence on management

Not reported</td><td>University Hospital, Groningen</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>years (range 1 to 76).

82% had haematological malignancy</td><td></td><td></td><td></td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Park 2010.

Korea</td><td>Retrospective case series</td><td>259 FN episode in 137 patients.</td><td>Serious complication: 70/259</td><td>Patients with haematological cancer and chemotherapy related febrile neutropenia.</td><td>Chest radiography, CBC, BUN, creatinine, AST, ALT. Bilirubin, albumin, bicarbonate, ESR, CRP, PT and complete urinalysis.</td><td>Just prior to the initiation of chemotherapy and on the fifth day of chemotherapy.</td><td>Serious complications: defined as hypotension (systolic blood pressure <90 mmHg), respiratory failure, altered mental staus, congestive heart failure, uncontrolled arrhythmia, hepatic or renal failure requiring treatment, blood</td><td><table><tr><th></th><th colspan="2">Serious complication</th></tr><tr><th></th><th>+</th><th>-</th></tr><tr><td>Bicarbonate < 21 mmol/L</td><td>31</td><td>25</td></tr><tr><td>Bicarbonate ≥ 21 mmol/L</td><td>39</td><td>154</td></tr></table>Sn 44%, Sp 86%</td><td>Not reported</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							transfusion due to bleeding, ICU admission or death.	<table><tr><td></td><td colspan="2">Serious complication</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP ≥ 20 mg/L</td><td>52</td><td>51</td></tr><tr><td>CRP< 20 mg/L</td><td>18</td><td>128</td></tr></table> Sn 74%, Sp 72% The authors included both CRP ≥ 20 mg/L and bicarbonate < 21 mmolo/L in their final risk stratification model *Influence on management* Not reported		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Persson, 2004.

Sweden</td><td>Prospective observational study.
Consecutive sample.

Study period not reported</td><td>94 FN episodes in 60 patients.</td><td>Bacteraemia:

29/94</td><td>Adults (≥17 years) with haematological cancer, fever (>38.5°C or >38°C in 2 readings over 4 hours) and neutropenia (ANC<0.5X10^{9}/l) admitted to a single haematology ward.

All had haematological cancer.

Median age ranged from 53 years to 56 years depending on</td><td>Samples for bacteriological cultures (blood, urine and nasopharyngeal tract) CRP, PCT and IL-6, IL-8</td><td>At time of blood culture following onset of fever</td><td>The cause of febrile episodes was determined using clinical and microbiological findings.</td><td><table><tr><td></td><td colspan="2">Bacteraemia(non coag-neg staph.)</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 94 mg/l</td><td>9</td><td>18</td></tr><tr><td>CRP ≤ 94 mg/L</td><td>12</td><td>55</td></tr></table>Sn 42%, Sp 75%

Influence on management

Not reported</td><td>Swedish Cancer Society, Orebo Un0iversity Hospital Research Foundation</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the study group (CNS-bacteraemia, non-CNS bacteraemia, documented infection</td><td></td><td></td><td></td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Phillips (2011)</td><td>Systematic review and meta-analysis,</td><td>4 studies with 278 patients and 478 FN episodes</td><td>Pneumonia

Overall 22/478 (5%)</td><td>Children of young people (18 years or less) receiving treatment for cancer or leukaemia presenting with febrile neutropenia.</td><td>Respiratory distress signs and symptoms</td><td>At presentation</td><td>Radiographically diagnosed pneumonia – (pneumonia evident on chest X-ray)</td><td><table><tr><td></td><td colspan="2">Radiographically diagnosed pneumonia</td></tr><tr><td>Resp. signs/ symptoms</td><td>+</td><td>-</td></tr><tr><td>+</td><td>17</td><td>111</td></tr><tr><td>-</td><td>5</td><td>332</td></tr></table>
Univariate meta analysis of sensitivity and specificity:

Sensitivity 77% (95% C.I. 56%</td><td>MRC</td><td>Methodological quality of the 4 included studies was variable, specifically:

¾ had definite or unclear partial verification,

2/4 had definite or unclear differential verification, ¾ unclear blinding in</td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								to 90%) Specificity 69% (95% C.I. 57% to 78%). Assuming a prevalence of pneumonia of 5%, clinical examination has a negative predictive value of 98% (95 C.I. 96% to 99%). The probability of pneumonia in someone with negative clinical examination was estimated at 1.9%.		outcome assessment

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Renoult (2004).

Canada</td>
<td>Retrospective case series.

2001-2002</td>
<td>170 episodes of FN (157 with admission chest X-ray) in 88 patients.</td>
<td>Bacterial pneumonia: 8/157 episodes.</td>
<td>Mean age 6.9 years, range (1.1 to 19.7).

52% had haematologic malignancy.

All outpatients at presentation.

Fever was >38.5°C once or >38.0°C one 2 or more occasions within 12 hours.

Neutropenia was ANC<0.5X10^{9}/L

All were hospitalised and treated with broad spectrum IV antibiotics.</td>
<td>Peripheral blood culture in those with central line, bacterial cultures of urine, throat, stool, central catheter exit site, chest x-ray (at the discretion of the admitting physician).</td>
<td>Done at the onset of febrile neutropenia (on admission)</td>
<td>The diagnosis recorded by the clinician in the discharge summary.</td>
<td>Bacterial pneumonia
<table>
<tr><td>Chest x-ray</td><td>+</td><td>-</td></tr>
<tr><td>X-ray +</td><td>8</td><td>12</td></tr>
<tr><td>X-ray -</td><td>0</td><td>137</td></tr>
</table>
Sn = 100%

Sp = 92%

Influence on management

No changes in antibiotic therapy due to abnormal chest x-ray results.

Time to diagnosis

Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Rikonen 1993 Finland.	Observational study, prospective. Unclear whether it was a consecutive or random sample. 1989-1990	91 FN episodes in 46 children.	Bacteraemia in 17/91 FN episodes.	Children (1 to 16 years) with fever (>39°C or >38°C on two occasions within 4 hours) and neutropenia (ANC < 0.2 X 10^9/L) caused by anti-cancer treatment. 57% had haematological cancers.	CRP: thresholds 20 and 50 mg/l (normal value 18 mg/l), other tests were done.	Tests were done on admission (and on days 1,2 and 3 of antimicrobial therapy).	Documented infection: clinical and laboratory methods described in sufficient detail Bacteraemia: at least one positive peripheral blood culture or two positive cultures if Staphylococcus epidermidis was isolated.	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Foundation for Paediatric Research, Helskinki	

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Rondinelli. 2006. Brazil	Retrospective observational study. Consecutive sample. 2000-2003.	283 FN episodes in 283 patients.	93/283 had severe infection.	Children (< 18 years) with cancer, fever (>38°C or >37.8°C on 3 occasions within 24 hours) and neutropenia (<0.5 X 10^9/l or < 1 X 10^9/l and falling) admitted to a single hospital. Mean age was 5.2 years. 48.5% had haematological cancers.	Granulocyte count: threshold 0.5 X 10^9/L Monocyte count: threshold 0.5 X 10^9/L Leucocytes: threshold 0.5 X 10^9/L Platelets: threshold 20000 units Haemoglobin level: threshold 7 g/dL	Not reported when tests were done.	Severe infection: defined as the presence of sepsis and/or shock and/or bacteraemia / fungaemia and/or death from infection	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported	Not reported.	

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Santolaya 1994. Chile	Observational study, consecutive sample. 1991-1992	85 FN episodes in 75 children.	Documented bacterial infection: 24/85 episodes Clinically documented infection in 31/85 In 30/85 there was either viral infection or no infection.	Children admitted for treatment of malignancy at a single hospital. Children with fever (>38°C on 2 occasions within 24 hours) and neutropenia (ANC < 0.5 $X10^9$/l) were included in the study. 85% of the children had haematological malignancy.	CRP, threshold 40 mg/l (10 mg/l was considered normal).	Tests were first done before the first dose of antibiotic was administered .	Documented bacterial infection: one blood culture positive for a well recognized pathogen, or two blood cultures positive for an opportunistic pathogen, or positive cultures from a clinically relevant focus (urine or skin). Clinically documented infection: a severe clinical course or findings indicative of bacterial	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							infection, in the absence of positive cultures.			
Santolaya 2001. Chile	Prospective observational study. Consecutive sample. 1996-1997	447 FN episodes in 257 children	178/447 (40%) episodes had invasive bacterial infection	Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC ≤500/mm^3) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) 68% had haematological malignancy. Median age was 7 years.	ANC, AMC, CRP, platelets, temperature, blood pressure, haemoglobin.	Tests were done on admission with fever and neutropenia.	Invasive bacterial infection: defined as bacteraemia, a positive bacterial culture from an otherwise sterile site, clinical laboratory findings strongly suggestive of a sepsis syndrome or focal organ involvement in	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported		

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>a child with haemodynamic instability and intense malaise.</td><td></td><td></td><td></td></tr>
<tr><td>Scheienmann (2010).

Canada</td><td>Retrospective case series 2002-2007</td><td>318 FN episodes in 224 patients</td><td>Bacteraemia: 228/318

Likely contaminant: 90/318</td><td>Children with central venous catheters receiving chemotherapy or after stem-cell transplant, who had central and peripheral cultures on the same day, where at least one was positive for a microorganism.

Median age 8.5 years (range 0.03 to 19.5 years).

68% haematological</td><td>Central and peripheral blood cultures</td><td>Before antibiotics were started</td><td>Bacteraemia: positive blood cultures with common contaminants were classified as bacteraemia if multiple cultures were positive for the same organism or if sepsis was present</td><td>28 case of bacteraemia were identified only in peripheral culture, 85 were identified only in central culture. 90 cases were considered as likely due to contaminants (not bacteraemia),

<table><tr><td></td><td colspan="2">Bacteraemia</td></tr><tr><td>Periph. culture</td><td>+</td><td>-</td></tr><tr><td>+</td><td>143</td><td>N.R.</td></tr><tr><td>-</td><td>85</td><td>N.R.</td></tr></table></td><td>Canadian Institute of Health</td><td>Study excludes bacteraemia missed on both central and peripheral cultures (may have overestimated sensitivity)</td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>cancers.

Fever was ≥38.3°C once or ≥38.0°C one 2 or more occasions within 12 hours.

Neutropenia was ANC<0.5X10^9/L</td><td></td><td></td><td></td><td>Sn 63%

<table>
<tr><td></td><td colspan="2">Bacteraemia</td></tr>
<tr><td>Central culture</td><td>+</td><td>-</td></tr>
<tr><td>+</td><td>200</td><td>N.R.</td></tr>
<tr><td>-</td><td>28</td><td>N.R.</td></tr>
</table>

Sn 88%

Influence on management

Healthcare professionals were surveyed about their attitudes to obtaining peripheral blood cultures. The main reason given for not obtaining peripheral blood cultures was</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>that they do not provide any additional information and that phlebotomy is associated with a risk of complications

Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Secmeer, 2007.

Turkey.</td><td>Prospective observational study. Unclear whether consecutive

2004 - 2005</td><td>60 FN episodes in 49 patients.</td><td>Documented infection: 25/60</td><td>Children (<19 years) with chemotherapy related fever (≥38.3°C or > 38°C for at least one hour) and neutropenia (not defined) admitted to a single hospital.

47% had haematological malignancy. 31/49 patients had documented infection.</td><td>PCT, CRP, ESR, blood cultures</td><td>On admission, and at the 8th, 24th and 48th hour after admission.</td><td>Documented infection: microbiologically or clinically documented infection.

Bacteraemia: at least one positive culture for bacteraemia (or 2 in the case of coagulase-negative staphylococcus</td><td><table><tr><td></td><td colspan="2">Doc. Infect.</td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CRP > 50 mg/l</td><td>14</td><td>19</td></tr><tr><td>CRP ≤ 50 mg/L</td><td>11</td><td>16</td></tr></table>Sn 58%, Sp 48%

Influence on management

Not reported.</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used in initial assessment</th><th>Timing of test</th><th>Reference standard</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Median age was 7.7 years in those without documented infection and 7.2 in those with documented infection.</td><td></td><td></td><td>).</td><td>Time to diagnosis

Not reported</td><td></td><td></td></tr>
<tr><td>Wilbur, 2000.</td><td>Patients were enrolled on one of 2 randomised trials. 1982-1987.</td><td>394 FN episodes in 292 patients</td><td>Early death (within first 5 days of FN episode)

32/394</td><td>Adult patients with cancer, fever (>38.3°C or >38.0°C on 2 occasions) and neutropenia (ANC <1.0X10^{9}/L), Mean age was 59 years
65% had haematological malignancy.</td><td>BUN, blood pressure, mental status, ANC,

Albumin, Creatinine,

Platelets, chest X-ray, glucose, height. Weight, temperature, ambulation, total protein, LDG, potassium, pulse rate,</td><td>Most chest X-rays were done on the day antibiotics were started but some were done up to 48 hours later.</td><td>Death within the first five days of antibiotic treatment.</td><td>Chest X-ray showing probable infection:
<table><tr><td></td><td>Early death.</td><td></td></tr><tr><td></td><td>+</td><td>-</td></tr><tr><td>CXR infection +</td><td>12</td><td>53</td></tr><tr><td>CXR infection -</td><td>17</td><td>267</td></tr></table>Sn 41%, Sp 83%

<table><tr><td></td><td>Early death.</td></tr></table></td><td>Supported in part by grants from Eli Lilly and Glaxo Inc.</td><td></td></tr>
</table>

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
					cholesterol			<table><tr><td></td><td>+</td><td>-</td></tr><tr><td>Glucose > 170 mg/dL</td><td>14</td><td>51</td></tr><tr><td>Glucose < 170 mg/dL</td><td>16</td><td>294</td></tr></table> Sn 46%, Sp 85%. *Influence on management* Not reported. *Time to diagnosis* Not reported		

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Yonemori, 2009. Japan	Retrospective case series. 1997 to 1999	106 FN episodes in 47 patients.	28/106 episodes had clinically documented infection.	Adult (> 16 years) haematological cancer patients with neutropenia (< $1.0X10^9$/l) who went on to develop fever (>38.0°C) and were admitted to hospital. Median age was 56 years. All had haematological cancer.	Not reported	Around the start of the febrile episode.	Documented infection: documented bacterial or fungal infection, with positive blood cultures; or documented or presumed bacterial or fungal infections based on clinical or radiological findings with negative blood cultures	*Diagnostic accuracy* See outcomes for topic D2 *Influence on management* Not reported *Time to diagnosis* Not reported		

7. Risk stratification scores or algorithms. (Topic E1)

Review question

Which is the most valid published risk stratification score or algorithm for influencing management and predicting outcome in patients with neutropenic sepsis?

Rationale

Patients receiving cancer treatment are at risk of potentially life threatening sepsis caused by neutropenia and early empiric broad spectrum antibiotic therapy significantly reduces mortality. Standard therapy requires hospitalisation until both the fever and neutropenia have resolved with average inpatient stays of around 5 days.

However, around 40% of patients treated for febrile neutropenia are not found to have either clinical or microbiologically proven infection. These patients may be termed at "low risk" from serious infection and various risk stratification approaches have been used to help identify low risk patients suitable for either outpatient management from the outset or for early discharge after a period of inpatient observation and investigation (a "step-down" approach).

The ideal stratification system would accurately identify a group of low risk patients with no risk of mortality from sepsis, would be simple to use by medical and healthcare professionals with little or no specific oncology or haematology experience, and use either clinical parameters or laboratory parameters which are widely available and inexpensive. In addition there are a number of "early warning" scoring systems used in both general paediatric and adult practice which have not been widely tested or validated in this population which may be useful in supporting a step-down approach.

There is no single risk stratification system is in widespread use in either adult or paediatric practice and there are considerable variations in practice. A simple, reliable and safe risk stratification system has the potential to significantly reduce hospitalisation rates without increasing overall mortality.

Question in PICO format

Patients/population	Risk score or algorithm	Outcomes
Patients with suspected neutropenic sepsis.	• *MASCC risk index* • *EWS* • *ASCO* • *EORTC*	Accuracy for prediction of • Mortality • Critical care(level 1,2 & 3) • Length of stay

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Psychinfo and BMI. The search was limited to papers published from 1999 onwards. The date of the search was 13th December 2010, and it was updated on 2nd November 2011.

Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewers (KF) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained and checked against the inclusion criteria.

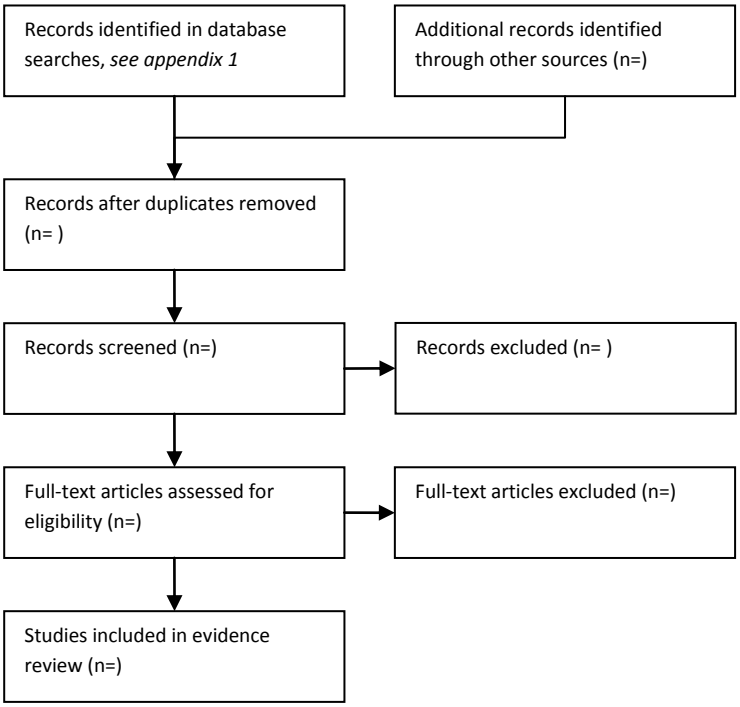
Data synthesis

One reviewer (KF) extracted information about diagnostic accuracy into 2 X 2 tables of true/false positives and true/false negatives for each test/outcome combination in each study.

RESULTS

Results of literature searches

Figure 7.1 Study flow diagram



Study quality and results

Eight prospective or retrospective observational studies were identified that validated the Multinational Association of Supportive Care in Cancer (MASCC) risk index (Baskaran, et al., 2008; De Souza Viana, et al., 2008; Innes, et al., 2008; Ahn, et al., 2010; Uys, et al., 2007; Klastersky, et al., 2006; Hui, et al., 2010 and Cherif, et al., 2006. These papers provided data on the sensitivity and specificity of this risk score in determining which adult patients presenting with neutropenia and fever, were at low risk of developing 'serious medical complications'. There was no specific evidence on 'early warning signs' in neutropenic sepsis.

Phillips, et al., (2010) presented a systematic review of the discriminatory performance of risk prediction rules in febrile neutropenic episodes in children and young people. Six of the twenty studies included studies were prospective, but the studies were at low risk of verification procedure bias and unclear risk of interpretation bias (according to the QUADAS criteria). Three other papers about paediatric clinical decision rules were identified (Dommett, et al., 2009; Ammann, et al., 2010 and Marcher, et al., 2010).

The evidence is summarised in Table 7.1.

Table 7.1 – Studies of clinical decision rules to identify patients at low risk of adverse outcome in patients with fever and neutropenia.

Studies (febrile neutropenic episodes)	Prevalence of adverse outcome (range)	Sensitivity for adverse outcome (range)	Specificity for adverse outcome (range)	LR + (range)	LR - (range)	References
MASCC score (<21) in adults for the prediction of adverse outcome						
8 (1951)	5% to 62%	40% to 88%	59% to 95%	2.11 to 11.21	0.14 to 0.66	Ahn (2010),Baskaran (2010), Carmona-Bayonas (2011), Cherif (2006), De Souza Viana (2008), Hui (2010), Innes (2008) and Klastersky (2006)
Klaassen rule						
6 (3218)	4% to 29%	37% to 100%	23% to 58%	0.88 to 1.69	0 to 1.08	Phillips, et al., (2010), Amman, et al., (2010) and Macher, et al., (2009)
Ammann rule						
3 (1038)	17% to 37%	95% to 100%	9% to 22%	1.05 to 1.29	0 to 0.52	Phillips, et al., (2010), Amman, et al., (2010) and Macher, et al .,(2009)
PINDA rule						
4 (1342)	16% to 53%	67% to 93%	20% to 76%	1.15 to 3.91	0.10 to 0.69	Phillips, et al., (2010), Amman, et al., (2010) and Macher, et al., (2009)
Alexander rule						
3 (1278)	14% to 29%	59% to 94%	9% to 65%	1.03 to 2.39	0.24 to 0.71	Phillips, et al., (2010), Amman, et al., (2010) and Dommett, et al., (2009)

Evidence Statements

Paediatric patients

Six studies evaluated the Klaassen rule which uses a single feature: an absolute monocyte count of greater than 100/mm^3 to predict paediatric patients with significant infection. Sensitivity ranged from 37% to 100% and specificity from 23% to 58%.

Evidence from three studies suggests the Amman rule (Ammann, et al., 2003) to predict paediatric patients at low risk of significant bacterial has high sensitivity (95% to 100%) but low specificity (9% to 22%). This means that most patients at low risk of adverse outcome would be labelled as high risk.

The Alexander rule to predict adverse clinical consequences was evaluated by three studies (Alexander, et al. 2002; Ammann, et al., 2010 and Dommet, et al., 2009; see Phillips et al., 2010). Results were heterogeneous with sensitivity ranging from 59% to 94% and specificity 9% to 65%.

Four studies evaluated the PINDA rule for identification of patients at low risk of significant bacterial infection. Two South American studies from the rules' authors (Santoloya, et al., 2002 and 2003; see Phillips et al., 2010) showed high sensitivity and specificity, however these findings were not replicated by two European validation studies (Ammann, et al., 2010 and Macher, et al., 2009).

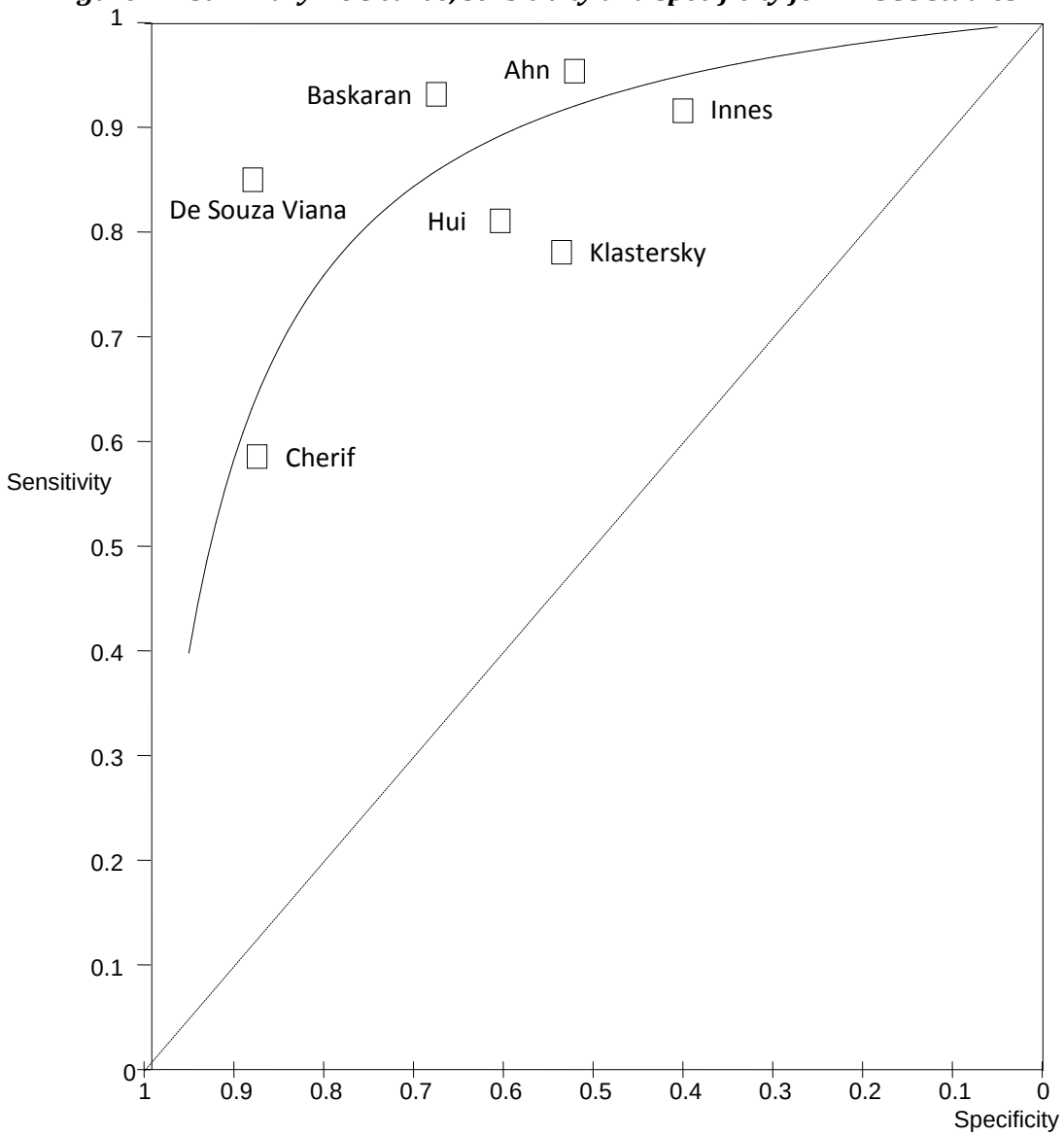
Other paediatric clinical decision rules have been proposed (Phillips, et al., 2010) but are validated by less than three studies.

Adult patients

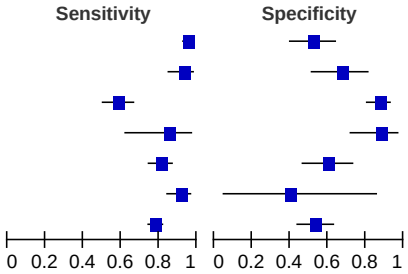
Eight studies reported the sensitivity and specificity of the MASCC risk score to identify adult patients with neutropenia and fever at low risk of serious medical complications. There was

considerable heterogeneity in study results which precluded statistical meta-analysis, but no obvious explanatory factor was identified (see Figures 7.2 and 7.3). The sensitivity of MASCC score < 21 (for the prediction of serious medical complications) ranged between 40% and 80% whilst the specificity ranged between 59% and 95%.

Figure 7.2 Summary ROC curve, sensitivity and specificity for MASCC studies

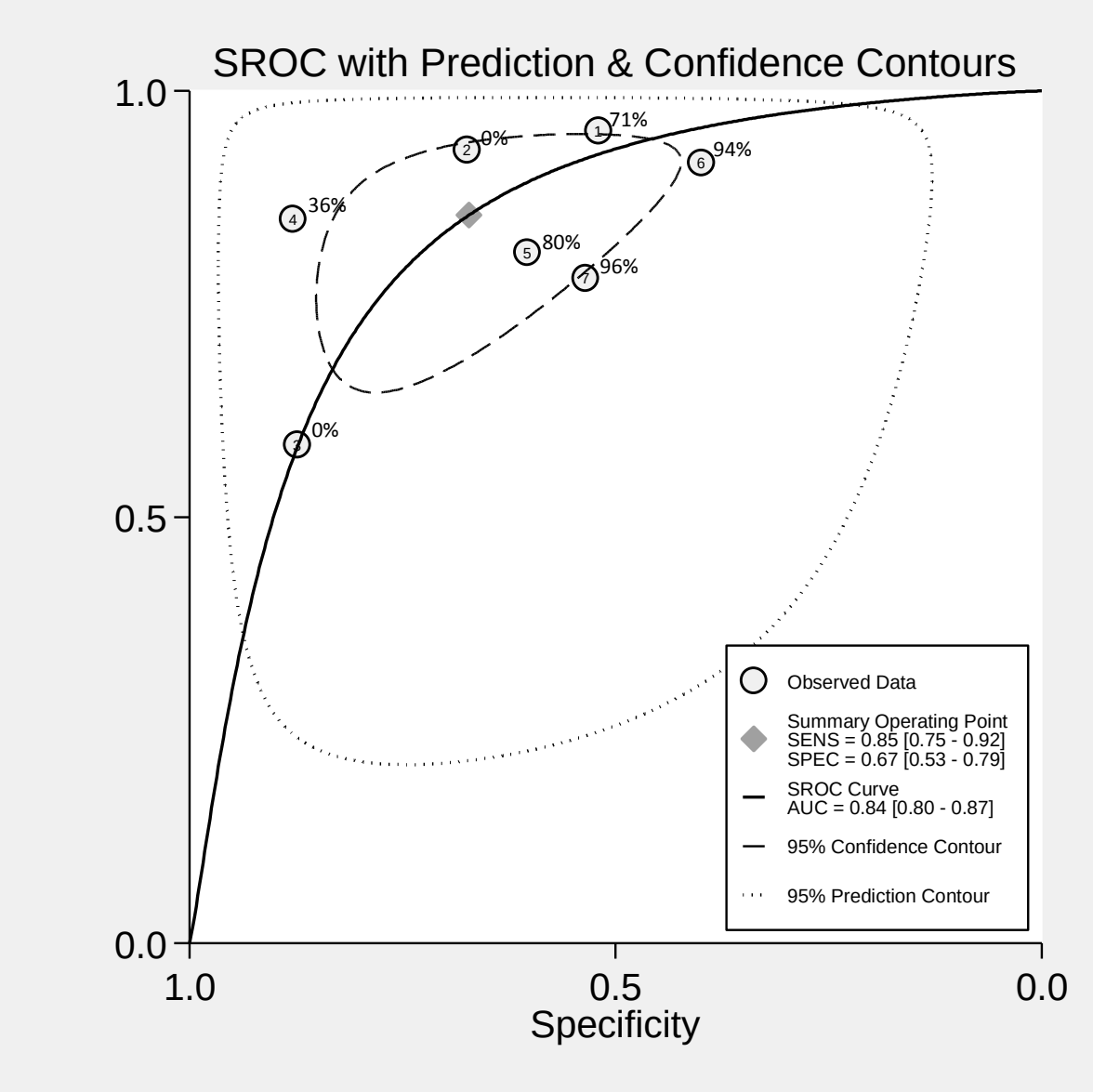


Study	TP	FP	FN	TN	Sensitivity	Specificity
Ahn, 2010	308	35	15	38	0.95 [0.92, 0.97]	0.52 [0.40, 0.64]
Baskaran, 2010	68	14	5	29	0.93 [0.85, 0.98]	0.67 [0.51, 0.81]
Cherif, 2006	89	16	63	111	0.59 [0.50, 0.66]	0.87 [0.80, 0.93]
De Souza Viana, 2008	17	4	3	29	0.85 [0.62, 0.97]	0.88 [0.72, 0.97]
Hui, 2010	137	23	32	35	0.81 [0.74, 0.87]	0.60 [0.47, 0.73]
Innes, 2008	87	3	8	2	0.92 [0.84, 0.96]	0.40 [0.05, 0.85]
Klastersky, 2006	388	53	109	61	0.78 [0.74, 0.82]	0.54 [0.44, 0.63]



*NB. The results for Uys *et al.*, 2007 were reported as sensitivity and specificity (without data) and could not therefore be included in the plot above. The sensitivity and specificity are transposed when compared to Table 7.1 as "low risk of adverse event" was the event of interest in these studies.

Figure 7.3 Summary ROC curve for MASCC studies with the added extra information of the % solid tumour patients in study. Additional bivariate diagnostic meta-analysis by clinical lead Dr. Bob Phillips, studies are numbered in alphabetical order.



1 EVIDENCE TABLES

Author(s): Baskaran *et al*., 2008

Country: Malaysia

Study participants:

68 patients with an underlying haematological malignancy admitted to a tertiary teaching hospital with febrile neutropenia between January 2004 and January 2005. The total number of febrile neutropenic admissions in these patients was 116. Median age: 40 years (range: 16-75 years).

Studies: N/A

Study Design:

Retrospective study. Data collected from in-patient and out-patient notes.

Definition of fever: single episode of oral temperature of 38.3°C or of 38°C lasting more than one hour.

Definition of neutropenia: neutrophils <500 cells per mm^3 or <1,000 cells per mm^3 with a predicted decrease to <500 cells per mm^3 within 48-72h.

Patients had to have received a course of chemotherapy prior to the episode of febrile neutropenia. Initial treatment for neutropenic fever on admission included: monotherapy with cefepime (Gram +ve and Gram –ve) then carbepenam on day 3 if there was deterioration, amphotericin B (anti-fungal) or vancomycin (Gram +ve). G-CSF was given to an unknown number of patients.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever without the development of serious medical complication or modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: hypotension (BP <90mm Hg), respiratory failure (O_2 pressure <60mm Hg), intensive care admission, disseminated vascular coagulation, confusion or altered mental status, congestive cardiac failure, bleeding requiring blood transfusion, ECG changes, arrhythmia requiring treatment, renal failure, other serious or clinically significant complications.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (5)
No COPD (4)
Solid tumour or no previous fungal infection (4)
No dehydration (3)

Burden of illness: moderate symptoms (3) Outpatient status (3) Age <60 years (2) If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality. The 'burden of illness' was defined at length.
Results: 63% of the cases of febrile neutropenia had a favourable outcome. 16/68 patients died during follow-up and the overall mortality rate of total febrile episodes was 14%. Serious medical complications occurred in 34% of cases. Sensitivity: 93.2% Specificity: 67.4% Positive predictive value: 82.9% (False +ve rate =17.1%) Negative predictive value: 85.3% Prevalence of low risk in this study: 62.9% Five patients were thought to be at high risk but had favourable outcomes; all had been classified as having had a fungal infection but this could not subsequently be confirmed with cultures. Fourteen patients were classed as low risk but developed serious medical complications including Gram –ve sepsis with hypotension (n=6), severe mucositis with dehydration (n=3), Gram +ve sepsis (n=2), congestive heart failure (n=1) and respiratory failure following haemoptysis (n=1). **Length of stay:** Not reported. **Critical care:** Not reported.

1

Author(s): Carmona-Bayonas, 2008 **Country:** Spain
Study participants: 861 chemotherapy related FN episodes in adult outpatients (≥ 18 years) with solid tumours. Fever was defined as ≥ 38°C for at least an hour, neutropenia was ANC ≤ 0.5 x 10^9/L or ANC ≤ 1.0 x 10^9/L and predicted to fall to 0.5 x 10^9/L.
Study Design: Retrospective case series
Target Condition and reference standard: Serious complications as reported in medical records.
Tests: Multinational Association for Supportive Care in Cancer (MASCC) risk score: for scores ≥21 the patient was classified as being at low risk of serious complication

Results: MASCC <21 for the prediction of adverse events

TP	FP	FN	TN	Sn [95% C.I.]	Sp [95% C.I.]	prevalence high risk	LR+	LR-
112	7	32	18	0.78 [0.70, 0.84]	0.72 [0.51, 0.88]	0.15	2.78	0.31

Length of stay: Not reported.

Critical care: Not reported.

1

Author(s): Ammann, R. A., Bodmer, N., Hirt, A., Niggli, F. K., Nadal, D., Simon, A. *et al.,* (2010). - Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. - Journal of clinical oncology :28, 2008-2014.

Country: Switzerland and Germany

Study Design: Prospective observational study. No evidence to suggest randomisation**.**

Study participants: Paediatric cancer patients (1 - 18 years) of median age 6.9 years (IQR: 3.8-11.6) with neutropenia (ANC <0.5 X109/l) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after non-myeloablative chemotherapy. Multiple episodes were allowed. 472 episodes were reported in 206 patients.

Target condition/reference standard:

Adverse events: defined as serious medical complications, including death or the need for critical care as a result of infection, microbiologically documented infection or radiologically confirmed pneumonia.

Index tests and comparators: Figures from Phillips et al updated 2010 review update

Decision rule	TP	FP	FN	TN
Klaassen	106	155	16	146
Ammann	118	264	4	37
Alexander	115	275	7	26
PINDA	114	244	8	57

Follow up: Patients were assessed at presentation, then again after 8 to 24 hours of inpatient therapy. Length of follow up for adverse events was not reported.

Comments:

Patients had presented with febrile neutropenia at four centres between January 2004 and December 2007. The aim of the study was to develop a score to predict the risk of adverse events in young patients with cancer and neutropenic fever, comparing performance either at

presentation or on a later reassessment. The investigators analysed the results using univariate logistic regression to produce odds ratios for each predictor. There were 92 adverse events in 393 episodes.

1

Author(s): Dommett, R., Geary, J., Freeman, S., Hartley, J., Sharland, M., Davidson, A. *et al.,* (2009). Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. Eur.J Cancer, 45, 2843-2849.

Country: UK

Study Design: Prospective audit.

Study participants: 762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005. Patients with haematologic and solid malignancies, Age < 18 Neutropenia (defined as ANC < $1.0x10^9$/L), Fever (single temperature of ≥ 38.5°C or sustained temperature of >38°C over 4 hours)

Target condition/reference standard: The aim was to predict patients at low risk of serious bacterial infection who could be discharged safely. Reference standard was clinical or radiological evidence of serious bacterial infection

Index tests and comparators: Figures from Phillips et al updated 2010 review update

Decision rule	TP	FP	FN	TN
Alexander	131	226	92	311

Follow up: Risk was assessed at the start of each FN episode then reassessed 48 hours later.

2

Author(s): De Souza Viana *et al*., 2008

Country: Brazil

Study participants:

53 patients with underlying haematological malignancy (n=64%) or solid tumour (36%) with neutropenia and fever were recruited into this study at hospital between March and December 2004. Between them, the patients had 60 neutropenic episodes. Most patients (53%) were less than 60 years old.

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: axillary temperature of 38°C measured by the patient or medical staff.

Definition of neutropenia: absolute neutrophil count <500 cell per µl (including polymorphonuclear leukocytes and band forms) or absolute neutrophil count <1,000 per µl with a predicted decrease to <500 per µl within 24h.

Patients had to have received a course of chemotherapy and/or radiotherapy prior to the episode of febrile neutropenia. Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including an anti-pseudomonal ß-lactam in combination with an aminoglycoside or monotherapy with a third generation cephalosporin. G-CSF was given to 34 patients (risk group unknown).

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever without the development of serious medical complication or modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: arterial hypotension (BP <90mm Hg), respiratory failure (arterial O_2 pressure <60mm Hg, respiration >24 breaths per minute), intensive care admission, disseminated vascular coagulation, confusion or altered mental status, severe gastrointestinal disorders or sepsis, dehydration, bleeding requiring blood transfusion, platelet count <20,000 per µl, abnormal serum ions, bacteraemia, antibiotic treatment change secondary to recurrent or persistent fever, renal failure, other serious or clinically significant complications.

This study, in addition to using the MASCC score, sub-grouped low risk patients into those with or without complex infections in order to develop a new model. The data comparing MASCC with this unvalidated model are not considered further.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no0 or mild symptoms (5)
No hypotension (5)
No COPD (4)
Solid tumour or no previous fungal infection (4)
No dehydration (3)
Burden of illness: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Results:

Sensitivity: 85.0%

Specificity: 87.9%

Positive predictive value: 80.9% (False +ve rate =19.1%)

Negative predictive value: 90.6%

Prevalence of low risk in this study: 37.7%

Four patients considered to be at low risk developed serious medical complications due to respiratory distress (n=3) or dehydration (n=1). NB: the figures above are derived from the data given which were reported differently in the paper as the authors designated patients at high risk and the presence of complications as positive outcomes thus reversing sensitivity/specificity and PPV/NPV.

Length of stay: Median hospital stay: 7 days (range: 2-88 days). No comparative data reported.

Critical care: Seventeen patients were admitted to the ICU. No comparative data reported.

1

Author(s): Innes *et al*., 2008

Country: United Kingdom

Study participants:

83 patients with lymphoma (6%) or a solid tumour (94%) with neutropenia and fever were recruited into this study at a cancer centre between February and September 2003. Between them, the patients had 100 febrile neutropenic episodes. The median age of low risk patients was 53 years (range: 19-77) and of high risk patients 58 years (range: 33-75).

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: temperature of ≥38°C on at least two occasions (or 38.5°C on one occasion), measured (no more than once) by the patient or by medical staff.

Definition of neutropenia: absolute neutrophil count <500 cell per µl (including polymorphonuclear leukocytes and band forms) or absolute neutrophil count <1,000 per µl with a predicted decrease to <500 per µl within 24h-48h.

Low risk patients were given: ciprofloxacin (oral) plus co-amoxiclav or doxycycline or, if for some reason patients could not take oral drugs, were given intravenous ceftazidimine with the addition of vancomycin in the case of suspected line infection. High risk patients were given combination intravenous antibiotics including either gentamicin and Tazocin or gentamicin and ciprofloxacin. However, individual treating physicians were encouraged to use their discretion in applying the drug protocols.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever within seven days without the development of serious medical complications and irrespective of modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: hypotension, respiratory/renal failure, intensive care admission, confusion or altered mental status, congestive cardiac failure, bleeding requiring blood transfusion, ECG changes, arrhythmia requiring treatment, development of fungal infection or an allergic reaction.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg)(5)
No COPD (4)
Solid tumour/lymphoma or no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)
Burden of illness: severe symptoms (0)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Results:

Sensitivity: 91.6%

Specificity: 40.0%

Positive predictive value: 96.7% (False +ve rate = 3.3%)

Negative predictive value: 20.0%

Prevalence of low risk in this study: 95.0%

One patient considered to be at low risk died after being readmitted due to progressive cancer. Two other patients at low risk developed severe medical complications: atrial fibrillation and perforation of the colon. The median hospital stay for low risk patients was 2.5 days compared with 6.5 days for high risk patients.

Length of stay: The median length of hospitalisation was 2.5 days (range: 0.5-12 days) in low risk episodes compared with 6.5 days (range: 0.3-11 days) in high risk episodes.

Critical care: Not reported.

Author(s): Ahn *et al*., 2010

Country: South Korea

Study participants:

346 patients with underlying haematological malignancy (n=28.5%) or solid tumour (71.5%) with neutropenia and fever were recruited into this study at the emergency department at a medical centre between January and December 2008. Between them, the patients had 396 neutropenic episodes. The median age of patients was 55 years.

Studies: N/A

Study Design:

Retrospective observational study.

Definition of fever: single oral temperature of ≥38.3°C or of >38.0°C for ≥1 hr.

Definition of neutropenia: absolute neutrophil count <500 cell per mm^3 or a count of <1,000 per mm^3 with a predicted decrease to <500 per mm^3 within an undefined time.

Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including an anti-pseudomonal ß-lactam in combination with an aminoglycoside or monotherapy with a third generation cephalosporin. G-CSF was given to 95.4% of patients who had a favourable outcome group and 91.8% of patients who had an unfavourable outcome.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever for five consecutive days without the development of serious medical complications and irrespective of modification of antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: refractory hypotension despite fluid therapy, respiratory failure requiring intubation, intensive care admission, disseminated intravascular coagulation, confusion or altered mental status, congestive cardiac failure, ECG changes requiring anti-arrhythmic treatment, renal failure and other complications judged serious and clinically significant by the investigator.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)

Outpatient status (3) Age <60 years (2) If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.
Result: Sensitivity: 95.4% Specificity: 52.1% Positive predictive value: 89.8% (False +ve rate = 10.2%) Negative predictive value: 71.7% Prevalence of low risk in this study: 81.6% NB: the figures above are derived from the data given which were reported differently in the paper as the authors designated patients at high risk and the presence of complications as positive outcomes thus reversing sensitivity/specificity and PPV/NPV. Of 343 events defined as low risk by the MASCC score, 35 (10.2%) were associated with serious medical complications including 5 deaths due to sepsis. **Length of stay:** Not reported. **Critical care:** Not reported.

1

Author(s): Uys *et al*., 2007 **Country:** South Africa
Study participants: 63 patients with underlying haematological malignancy (30%) or a solid tumour (70%) with neutropenia and fever were recruited into this study at a cancer centre at an unknown period before 2006. Between them, the patients had 78 neutropenic episodes. The median age of patients was 50 years.
Studies: N/A
Study Design: Prospective observational study. The main aim of the study was to compare various laboratory parameters with the MASCC score in the identification of low risk patients with febrile neutropenia. The results of this comparison are not presented here.

Definition of fever: single oral temperature of ≥39°C or of >38.0°C on two separate occasions at least four hours apart.

Definition of neutropenia: absolute neutrophil count <500 cell per µl.

Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including cefepime/ceftriaxone plus amikacin (one patient received meropenum monotherapy). Patients not responding to this empirical therapy were given vancomycin. Patients with persistent fever were also given amphotericin B. G-CSF was given during 26 episodes of febrile neutropenia (17 low risk patients).

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable, including death'. 'Serious medical complications' were defined at length but briefly included: hypotension, respiratory/renal/congestive cardiac failure, intensive care admission, confused mental status, bleeding requiring transfusion, allergic reaction, ECG changes and arrhythmia requiring treatment.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Result:

These values are as reported by the authors but could not be verified as outcome data regarding the numbers of patients in low or high risk groups who experienced serious medical complications were not reported

Sensitivity: 95%

Specificity: 95%

Positive predictive value: 98.3% (False +ve rate = 1.7%)

Negative predictive value: 86.4%

Prevalence of low risk in this study: 72.5%

Length of stay: Not reported.

Critical care: Four patients in the high risk group were admitted to ICU.

1

Author(s): Klastersky *et al*., 2006

Country: Belgium

Study participants:

All patients older than 16 years with underlying haematological malignancy (4%) or a solid tumour (96%) with neutropenia and fever were assessed by the MASCC score between January 1999 and November 2003 at a single hospital. Those patients classed as 'low risk' and eligible for oral antibiotic treatment were entered into this study and had between them 189 neutropenic episodes of which 178 first episodes. The median age of those patients was 53 years (range: 17-85 years).

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: single oral temperature of ≥38.5°C or of >38.0°C on two separate occasions during a 12 hour interval.

Definition of neutropenia: absolute neutrophil count <500 cell per µl or a count of <1,000 per µl with a predicted decrease to <500 per µl within 24 to 48 hours.

Patients with a first febrile neutropenic episode deemed to be low risk according to their MASCC score were treated by oral antibiotics, if not already on prophylactic treatment at fever onset, and were hospitalised for 24 hours under close clinical and microbiological surveillance. Where appropriate, patients could then be discharged to continue treatment and self monitoring at home, returning every two days for testing until the resolution of fever. Oral treatment included: ciprofloxacin and amoxicillin-clavulanate. A low number of patients (n=11) were instead given a quinolone with or without other antibiotics.

Target Condition:

The primary endpoint of this study was to assess the safety of the early discharge procedure with low risk patients. However, the report also included data that enabled sensitivity and specificity of the MASCC score to be determined.

'Serious medical complications' included those from a previous publication, namely: hypotension (BP <90mm HG), respiratory failure, ICU admission, intravascular coagulation, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmia or ECG changes needing treatment, renal failure requiring intervention or other complications judged serious and clinically significant.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of febrile neutropenia: no or mild symptoms (5)
No hypotension (BP >90mm HG) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of febrile neutropenia: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality. The 'burden of illness' and other items were defined at length.

Results:

79/178 low risk patients with first neutropenic episode were treated with oral antibiotics and discharged early. Of these, none experienced serious medical complications as defined above but three were re-admitted with: stomatitis and oesophagitis with change to intravenous therapy, persistent fever without therapy change and chills with change to intravenous antibiotics. The success rate of the early discharge policy was therefore 76/79 (96%). 9/178 patients had serious medical complications including: death (n=2) anaemia (n=1), hypotension with other factors (n=4), respiratory failure and confusion (n=1) and renal failure with other factors (n=1).

Of all 441 neutropenic episodes classed as low risk, the resolution rate was 88% (95%CI: 84-91%). Of the 170 neutropenic episodes classed as high risk, the resolution rate was 64% (95%CI: 56-71%). From these figures the following are computed but may not be accurate:
Sensitivity: 78.1%

Specificity: 53.5%

Positive predictive value: 88.0% (False +ve rate = 12.0%)

Negative predictive value: 35.9%

Prevalence of low risk in this study: 81.3%

Length of stay: If a patient stayed in hospital for <2 days it was classed as early discharge. 79 (44%) low risk patients were discharged early (median time to discharge: 26 hours) whereas 99 low risk patients remained hospitalised (median time to discharge: 137 hours). Data for high risk patients were not reported.

Critical care: Not reported.

1

Author(s): Hui *et al*., 2010

Country: Hong Kong

Study participants:

227 patients over the age of 16 years with underlying haematological malignancy (20.3%) or a solid tumour or lymphoma (79.7%) with neutropenia and fever were recruited into this study at a tertiary cancer centre between October 2005 and February 2008. The median age of patients was 51 years and 28.6% were aged ≥60.

Studies: N/A

Study Design:

Prospective observational study. The purpose of this study was not only to validate the MASCC scoring system but to compare it with an artificial neural network model of the authors' design. These comparative data are not presented here.

Definition of fever: single temperature of ≥38.3°C or of >38.0°C on two occasions ≥1 hr apart.

Definition of neutropenia: absolute neutrophil count <500 cell per mm^3 or a count of <1,000 per mm^3 with a predicted decrease to <500 per mm^3 within an undefined time.

Initial treatment for neutropenic fever on admission included empirical intravenous antibiotics according to the institutional guidelines. There were no further details.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'good' or 'poor'. 'Good' was defined as the resolution of fever for five consecutive days without the development of serious medical complications and irrespective of modification of antibiotic therapy. 'Poor' was defined as the resolution of fever for five consecutive days with at least one serious medical complication, including death or death before fever resolution.

'Serious medical complications' included those from the original MASCC study namely: hypotension (BP <90mm HG), respiratory failure, ICU admission, intravascular coagulation, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmia or ECG changes needing treatment, renal failure requiring intervention or other complications judged serious and clinically significant.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of febrile neutropenia: no or mild symptoms (5)
No hypotension (BP >90mm HG) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of febrile neutropenia: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of

complication or mortality. The 'burden of illness' and other items were defined at length.
Results: Sensitivity: 81.1% Specificity: 60.3% Positive predictive value: 85.6% (False +ve rate = 14.4%) Negative predictive value: 52.2% Prevalence of low risk in this study: 74.4% 160 patients were defined by the MASCC score as being 'low risk' and 67 as 'high risk'. In the low risk group, 20 patients experienced complications and 3 patients died. In the high risk group, 29 patients experienced complications and 6 patients died. There were no further details of the nature of these complications or of the causes of death. **Length of stay:** Not reported **Critical care:** Not reported

1

Author(s): Cherif *et al*., 2006 **Country:** Sweden
Study participants: 191 patients over the age of 16 years with underlying haematological malignancies with neutropenia and fever were recruited into this study at a cancer unit between November 2003 and April 2005. The median age of patients in the high risk group was 60 years (range: 21-85 years) and in the low risk group 57 years (range: 20-87 years).
Studies: N/A
Study Design: Prospective observational study. Definition of fever: temperature (oral or in the ear) of ≥38.0°C on two occasions ≥4 hr apart or ≥38.5°C on a single occasion. Definition of neutropenia: absolute neutrophil count <500 cell per mm^3. Initial treatment for neutropenic fever on admission included broad-spectrum intravenous antibiotics, in accordance with local and international recommendations, until the fever subsided. G-CSF was not routinely given but was administered to 29% of high risk patients and 36% of low risk patients. Patients deemed to be low risk according to their MASCC score and who did not

develop shock, catheter-related infection, multi-resistant infection or invasive fungal infection were considered for oral therapy 24 hours after fever had subsided. After the first dose, some of these patients were discharged and continued oral treatment at home.

Target Condition:

Patients were monitored daily for clinical complications. 'Serious medical complications' included: death, hypotension, respiratory failure, requirement for intensive care, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmias needing treatment, fungal infection, allergic reaction, renal failure or other complications judged serious and clinically significant.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of febrile neutropenia: no or mild symptoms (5)
No hypotension (5)
No COPD (4)
No previous fungal infection (4)
No dehydration (3)
Burden of febrile neutropenia: moderate symptoms (3)
Outpatient status at the time of fever onset (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Result:

Sensitivity: 58.6%

Specificity: 87.4%

Positive predictive value: 84.8%

Negative predictive value: 63.8%

Prevalence of low risk in this study: 54.5%

Serious medical complications occurred in 111/174 episodes in high risk patients and 16/85 episodes in low risk patients. The most commonly occurring complications in high risk patients were: hypotension (21%), respiratory failure (22%), invasive or superficial fungal infection (28%) and allergic reaction (14%). Death occurred in 10 high risk patients due to: septic shock (n=3), pneumonia (n=2), pulmonary aspergillosis (n=1) and other, unnamed causes (n=4). Death occurred in 2 low risk patients from: septic shock (n=1) and pneumonia (n=1).

Length of stay: Low risk patients who were able to be treated with oral antibiotics had a significantly shorter stay in hospital (6 ± 4 days) compared with high risk patients (16 ± 13 days) (P<0.0001). Those low risk patients who were discharged early spent fewer days in hospital (2.2 ±

1.8). **Critical care:** 10 patients in the high risk group had to be admitted to ICU compared with 0 patients in the low risk group (P<0.01).

1

2

Author(s): Phillips *et al*., 2010 **Country:** United Kingdom
Included studies: Prospective and retrospective cohort studies (not case controls) either published or unpublished. No language restriction.
Study participants: The intended study population was children or young people (aged 0-18 years) presenting with febrile neutropenia. The included studies reported on patients from 1 month to 23 years old.
Study Design: The aim of this paper was to review evidence on the ability of existing clinical decision rules to risk stratify children and young people presenting with febrile neutropenia. Included studies reported on either two (low and high) or three (low, medium and high) risk categories the data for which were analysed statistically by different methods and software. Where observed, between studies heterogeneity was explored and sensitivity analyses were performed.
Results: There were 8 prospective and 11 retrospective studies plus one retrospective analysis of prospectively collected data. Between them, these studies reported nearly 8,000 episodes of febrile neutropenia and described eleven outcomes which the reviewers summarised into five clusters: death, need for critical care, serious medical complications, significant bacterial infection or bacteraemia. Most studies could not be pooled as they differed too much from one another in terms of rules, outcomes, locations and populations. However, data from multiple studies validated two existing rules (Rackoff rule with an outcome of 'bacteraemia' and the Santolaya rule with an outcome 'invasive bacterial infection') and were combined in two meta-analyses. For each outcome a likelihood ratio (LR) was calculated with 95% credibility (post-test probability) or confidence intervals. • **Rackoff rule:** [Low risk: absolute monocyte count >100; mid risk: absolute monocyte count <100 with temperature <39°C; high risk: absolute monocyte count <100 with temperature ≥39°C]**:** LR [low risk] = 0.22 (95%CrI: 0.03-1.85)

LR [medium risk] = 0.79 (95%CrI: 0.12-2.06)

LR [high risk] = 3.41 (95%CrI: 0.24-18.7)

Assuming a 22% overall prevalence of bacteraemia:

Predictive value [low risk] = 6% (95%CrI: 1-34%)

Predictive value [medium risk] = 18% (95%CrI: 3-37%)

Predictive value [high risk] = 49% (95%CrI: 6-84%)

- **Santolaya rule:** [Low risk: 0 factors or isolated low platelets or >7 days from chemotherapy; High risk: >1 risk factor or isolated high CRP, hypotension or relapsed leukaemia. Risk factors: CRP ≥90, hypotension, relapsed leukaemia, platelets ≤50, chemotherapy within 7 days].

LR [low risk] = 0.17 (95%CI: 0.12-0.23)

LR [high risk] = 2.87 (95%CI: 0.24-18.7)

Assuming a 47% overall probability of invasive bacterial infection :

Predictive value [low risk] = 13% (95%CI: 9-13%)

Predictive value [high risk] = 72% (95%CI: 68-75%)

Across all studies, the clinical decision rules (CDR) fell into four broad categories: patient-related factors (such as age, disease state) treatment (such as the time since last chemotherapy cycle) clinical features specific to the episode (such as temperature, blood pressure) and laboratory values relating to the episode (such as blood components, CRP). Common features across all studies show that age, malignant disease state, circulatory and respiratory distress, high temperature and bone marrow suppression all had some predictive power.

Comments:

This high quality systematic review and meta analysis reports the findings from 21 journal articles. The search strategy was described in detail (http://www.ejcancer.info/article/S0959-8049(10)00448-X/addOns). Searches were made from ten databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Titles were independently screened and disagreements resolved by consensus. Study quality was assessed using a modified QUADAS checklist.

Included studies:

Adcock KG, Akins RL, Farrington EA. (1999). Evaluation of empiric vancomycin therapy in children with fever and neutropenia. *Pharmacotherapy* **19(11):** 1315–20.

Alexander SW, Wade KC, Hibberd PL, Parsons SK. (2002). Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. *J Pediatr Hematol/Oncol* **24(1):** 38–42.

Ammann RA, Hirt A, Luthy AR, Aebi C. (2003) Identification of children presenting with fever in

chemotherapy-induced neutropenia at low risk for severe bacterial infection. *Med Pediatr Oncol* **41(5):** 436–43.

Baorto EP, Aquino VM, Mullen CA, Buchanan GR, DeBaun MR. (2001). Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer* **92(4):** 909–13.

Gala Peralta S, Cardesa Salzman T, Garcia Garcia JJ, et al. (2005). Bacteraemia risk criteria in the paediatric febrile neutropenic cancer patient. *Clin Transl Oncol* **7(4):** 165–8.

Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A (1997). Comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* **99(3):** 580–8.

Jones GR, Konsler GK, Dunaway RP, Pusek SN. (1996) Infection risk factors in febrile, neutropenic children and adolescents. *Pediatr Hematol Oncol* **13(3):** 217–29.

Klaassen RJ, Goodman TR, Pham B, Doyle JJ. (2000) ‘‘Low-risk’’ prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clin Oncol **18(5):** 1012–9.

Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. (1996) The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* **77(4):** 791–8.

Madsen K, Rosenman M, Hui S, Breitfeld PP. (2002) Value of electronic data for model validation and refinement: bacteremia risk in children with fever and neutropenia. *J Pediatr Hematol/Oncol* **24(4):** 256–62.

Paganini HR, Aguirre C, Puppa G, et al. (2007) A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer* **109(12):** 2572–9.

Petrilli AS, Melaragno R, Bianchi A, et al. (1991) Fever and neutropenia in children with cancer: a new therapeutic proposal. *Amb; Rev Assoc Med Bras* **37(4):** 173–80.

Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PB. (1996) Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* **14(3):** 919–24.

Riikonen P, Jalanko H, Hovi L, Saarinen UM. (1993) Fever and neutropenia in children with cancer: diagnostic parameters at presentation. *Acta Paediatr Int J Paediatr* **82(3):** 271–5.

Rojo LC, Rodriguez ZN, Tordecilla CJ. (2008) Low risk febrile neutropenia in oncological pediatric patients: clinical experience [Spanish]. *Rev Chilena Pediatr* **79(2):** 157–62.

Rondinelli PIP, Ribeiro KdCB, de Camargo B. (2006) A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J Pediatr Hematol/Oncol* **28(10):** 665–70.

Santolaya ME, Alvarez AM, Avils CL, et al. (2002) Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. *Clinical Infectious Diseases* **35(6):** 678–83.

Santolaya ME, Alvarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol 2001* **19(14):** 3415–21.

Tezcan G, Kupesiz A, Ozturk F, et al. (2006) Episodes of fever and neutropenia in children with cancer in a tertiary care medical center in Turkey. *Pediatr Hematol Oncol* **23(3):** 217–29.

West DC, Marcin JP, Mawis R, et al. (2004) Children with cancer, fever, and treatment-induced neutropenia: risk factors associated with illness requiring the administration of critical care therapies. *Pediatr Emerg Care* **20(2):** 79–84.

1

2

Author(s): Macher *et al*. (2010)

Country: France

Study participants:

167 paediatric patients with haematological malignancy (59% of episodes) or solid tumours (41% of episodes) were admitted to either a cancer centre or children's hospital between January 2005 and December 2006. The total number of consecutive febrile neutropenic episodes in these children was 381 of which 377 were included for analysis. The median age of patients was 6yrs, mean age: 7.2yrs (range: 7mo – 19yrs).

Studies: N/A

Study Design:

Retrospective cohort study (two-centre).

Definition of fever: single axillary temperature of ≥38.5°C or 38°C on two occasions over a period of one hour.

Definition of neutropenia: absolute neutrophil count <500 cells per µl.

All patients were admitted and received intravenous antibiotics including a broad spectrum ß-lactam and an aminoglycoside. Some children experienced FN whilst already in hospital but children were excluded if they had had a bone marrow or stem cell transplant, were receiving palliative care or had already received antibiotics during the episode of FN prior to admission.

Target Condition:

The clinical outcomes were 'severe bacterial infection' (SBI), including invasive fungal infection, and bacteremia, including fungemia. The definitions applied to these outcomes were taken from each study.

Tests:

A comparison of six clinical decision rules in their ability to predict clinical outcomes of children admitted with febrile neutropenia. These rules were:

Rackoff *et al*. (1996): low risk of bacteremia: absolute monocyte count (AMC) ≥100 per µl at admission

Baorto *et al*. (2001): low risk of bacteremia: AMC >155 per µl at admission

Klaassen *et al.* (2000): low risk of SBI: AMC >100 per µl at admission

Santolaya *et al.* (2001): high risk of SBI: serum CRP AMC ≥90 mg per litre at admission; hypotension; relapse of leukaemia; platelets ≤50,000 per µl; chemotherapy within 7 days of hospital visit. Otherwise low risk.

Ammann *et al.* (2003): high risk of SBI: bone marrow involvement by malignancy or a leukocyte

count ≤500 per µl or no sign of viral infection or aged >6 years.

Rondinelli *et al.* (2006). For the first neutropenic episode, risk of SBI: presence of central catheter, clinical site of infection, fever ≥38.5°C, haemoglobin at admission ≤7 g per dl; upper respiratory tract infection.

Results:

Bacteraemia occurred in 36/377 episodes (10%) and serious bacterial infection in 64/377 episodes (17%). The performance for each rule was calculated using that rule's definitions for the outcomes 'bacteraemia' or 'serious bacterial infection'. These two outcome definitions were also 'homogenised' in order to make the results from the different studies comparable (see Table below).

Study (no of episodes)	Sensitivity % (± 95%CI)	Specificity % (± 95%CI)	PPV % (± 95%CI)	NPV % (± 95%CI)	LR+	LR-
Rackoff *et al.*, 1996 (n=134)	87 (62-96)	44 (35-53)	16 (10-26)	96 (87-99)	1.3	0.3
Baorto *et al.*, 2001 (n=174)	96 (79-99)	25 (19-33)	16 (11-23)	97 (87-100)	1.3	0.2
Klaassen *et al.*, 2000 (n=138)	79 (61-90)	45 (36-54)	27 (18-37)	89 (78-95)	1.4	0.5
Santolaya *et al.*, 2001 (n=249)	67 (53-80)	39 (33-46)	19 (13-26)	85 (77-91)	1.1	0.8
Ammann *et al.*, 2003 (n=371)	95 (87-98)	5 (3-8)	17 (13-21)	83 (61-94)	1.0	1.0
Rondinelli *et al.*, 2006 (n=121)	62 (36-82)	43 (35-52)	11 (6-21)	90 (79-96)	1.1	0.9

From Table ( ), the rule with the best predictive ability for 'bacteraemia was that of Baorto *et al.* (2001) and for 'SBI', Ammann *et al.* (2003) although the specificity was very low.

Using each rule's definitions, thresholds and risk factors, the current data set showed similar sensitivity to all studies but Santolaya *et al.* (2001) (non-overlapping confidence intervals) or Rondinelli *et al.* (2006) (performance data not reported). The specificity was only similar to Klassen *et al.* (2000).

Comments:

None of the studies met the required 100% sensitivity which the authors had thought necessary in order to safely apply a rule to this population. The two studies that came closest still failed to identify one or two patients deemed to be at low risk who developed bacteraemia or SBI.

The authors concluded that, given the high number of clinical variables in children with febrile neutropenia, identifying a single set of rules that could reliably classify low risk had not proved to be possible.

Papers included in this review:

Rackoff WR, Gonin R, Robinson C, *et al.* (1996). Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* **14:** 919–924.

Baorto EP, Aquino VM, Mullen CA, *et al*. (2001). Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer* **92:** 909–

913.

Klaassen RJ, Goodman TR, Pham B, *et al*. (2000). “Low-risk” prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol* **18:** 1012–1019.

Santolaya ME, Alvarez AM, Becker A, *et al*. (2001) Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol* **19:** 3415–3421.

Ammann RA, Hirt A, Lüthy AR, *et al.* (2003) Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. *Med Pediatr Oncol* **41:** 436–443.

Rondinelli PI, Ribeiro Kde C and de Camargo B. (2006) A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J Pediatr Hematol Oncol* **28:** 665–670.

1

Preventative Treatment: guideline chapter five

8. Primary prophylaxis with growth factors (for example granulocyte colony stimulating factor) and/or antibiotics (for example fluoroquinolones). (Topic F1)

Guideline subgroup members for this question

Nicola Perry (lead), Peter Jenkins, Anton Kruger, Barry Hancock and Rosemary Barnes.

Review question

Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients receiving anti-cancer treatment?

Rationale

Anticancer treatment, particularly chemotherapy, often incurs the risk of neutropaenia. The depth and duration of neutropaenia are related to the risk of infection, which may be life-threatening. One approach to reducing the risk of life-threatening neutropaenic sepsis is to prevent or moderate the degree of neutropaenia, or to prevent or reduce the likelihood of infection. These strategies may be used independently or concurrently.

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been available since the early 1990s to raise neutrophil counts, and shorten the duration of neutropaenia, by stimulating the bone marrow to produce neutrophils. However, side effects include diarrhoea, weakness, a flu-like syndrome, and rarely more serious complications such as clotting disorders and capillary leak syndrome. GCSF and GMCSF must be given by injection, and this may lead to local reactions at the site of administration, and repeated injections may not be desired by patients. Depot formulations are available but expensive.

The likelihood of infection may be reduced by the pre-emptive use of antibiotics, chosen to cover the most likely pathogens, and the time period of greatest risk for infection. The most serious bacterial infections are likely to arise from gram-negative organisms, but as the duration and degree of immunocompromise increase, significant infections can arise from other sources too. Typical antibiotics used for prophylaxis include the fluoroquinolones, and cotrimoxazole. These are given orally, but commonly incur patient-related risks of gut disturbance, allergy, etc and more general risks related to the development of antibiotic resistance in populations.

This research question seeks to establish whether the use of growth factors and/or antibiotics in patients on chemotherapy may reduce the chance of subsequent episodes of neutropaenic sepsis, and improve patient outcomes.

Question in PICO format

Patients/population	Interventions	Comparisons	Outcomes
Patients receiving anti-cancer therapy	• GCSF/GMCSF (with or without fluroquinolones or co-trimoxale) • Fluoroquinolones alone (Ciprofloxacin, Levofloxacin, Cfloxacin) • Co-trimoxazole alone	• Compared with each other, • Compared with placebo or nothing	• Incidence of neutropenic sepsis • Bacterial resistance • Secondary infection • Death (30 day mortality) • Critical care • Length of stay • Quality of life

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central.

We restricted the search to published trials and systematic reviews of such trials. A Cochrane review of prophylactic antibiotics was published in 2005 (Gafter-Gvili et al, 2005). Our literature search for antibiotic studies was therefore limited to papers published after 2004, to find trials published since Gafter-Gvili et al (2005). Our search for colony stimulating factor trials was not date restricted. The search was done on the 1st of March 2011 and updated on 7th November 2011.

Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

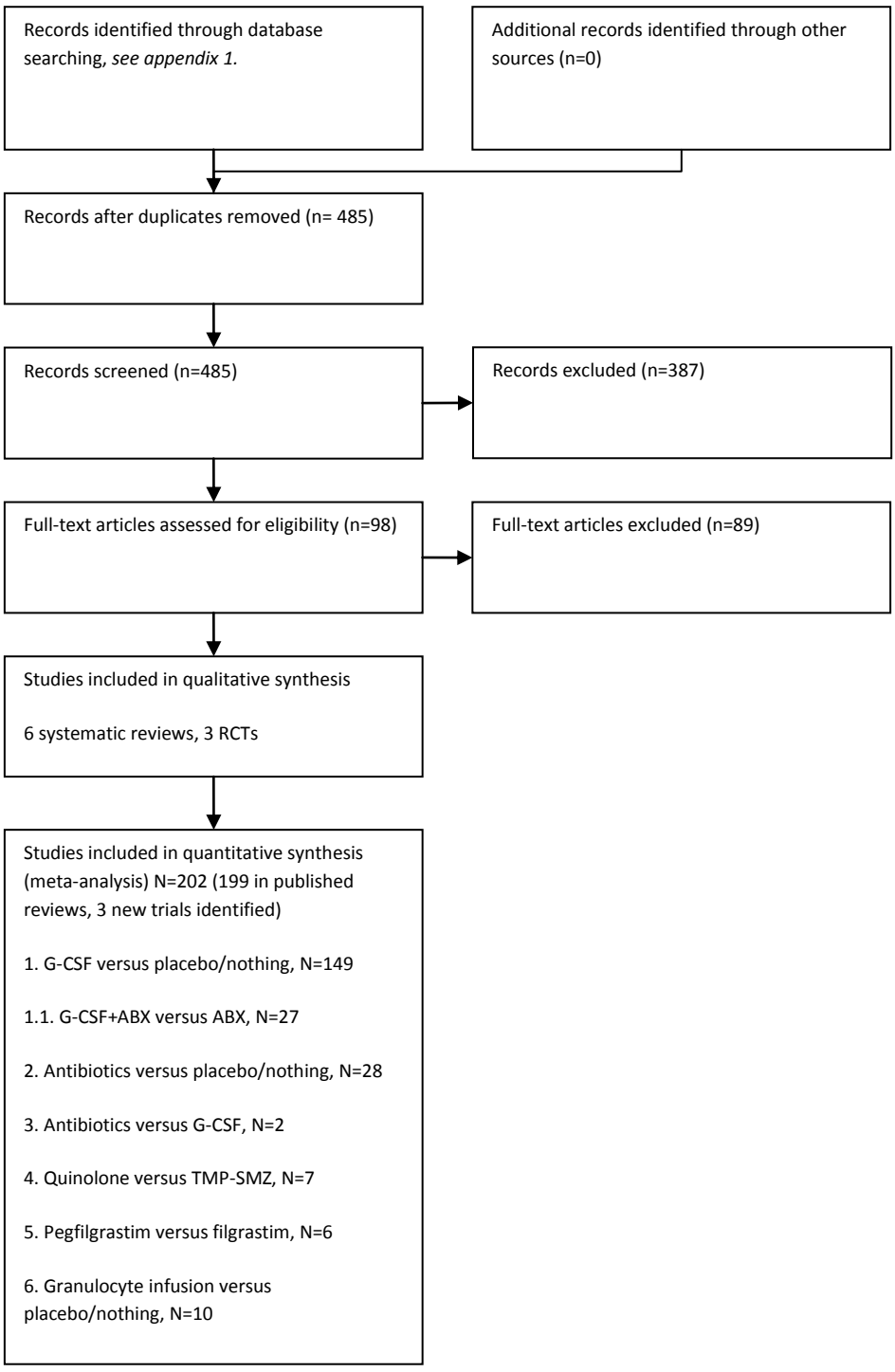
Data synthesis

The search identified several relevant meta-analyses (Gafter-Gvili et al 2005, 2007; Sung et al 2007; Herbst et al, 2009; Massey et al, 2009 and Pinto, 2007). When the searches identified new data we updated the published meta-analyses if possible. Forest plots were generated whenever additional trials were added to the published meta-analyses, or when new meta-analysis was done.

RESULTS

Results of the literature searches

Figure 8.1 study flow diagram



Comparison 1. G(M)-CSF versus placebo or nothing (with or without antibiotics)

The evidence for primary prophylaxis with colony stimulating factors comes from systematic reviews of randomised trials by Sung, et al., (2007), Bohlius, et al., (2008) and Cooper, et al., (2011). This evidence is summarised in tables 8.1 and 8.2.

Table 8.1 Characteristics of included RCTS

Total number of randomised trials	149
Age group	Paediatric (<18 years) 18, adult (18 to 65 years) 61, elderly (>65 years) 13, mixed age group 57
Treatment category	Leukaemia 40, solid tumour or lymphoma 79, any cancer 5, stem cell transplant 25
Colony stimulating factor	G-CSF 83, GM-CSF 61, PEG 2, G-CSF or GM-CSF 2
Secondary prophylaxis with G(M)-CSF permitted in control arm	Not reported in review
Prophylactic antibiotics included in the trial protocol	Yes 27, No 122 (although prophylactic antibiotics might also have been used in these studies).
Allocation concealment	Adequate 37, unclear 112
Double blinding	Yes 54, no 95

Evidence statements

Mortality

There was high quality evidence from that primary prophylaxis using G(M)-CSF did not reduce short-term all cause mortality when compared to no primary prophylaxis. No reduction in short-term mortality with G(M)-CSF was seen in sub-group analyses (Figure 8.2) according to age group (paediatric, adult or elderly), use of prophylactic antibiotics, colony stimulating factor type (G-CSF or GM-CSF), type of cancer treatment (leukaemia, lymphoma/solid tumour or stem cell transplant).

Febrile neutropenia

There was moderate quality evidence that prophylaxis using G(M)-CSF reduced the rate of febrile neutropenia when compared to no prophylaxis. The pooled estimate suggested an episode of febrile neutropenia would be prevented for every nine chemotherapy cycles that used G(M)-CSF prophylaxis.

Moderate quality evidence from subgroup analyses suggested that the effectiveness of prophylaxis with colony stimulating factors may vary according to the type of cancer treatment. In the subgroup of leukaemia studies, G(M)-CSF would need to be used for 13 cycles to prevent an additional episode of febrile neutropenia. In solid tumour/lymphoma studies the corresponding number of cycles was nine. In stem cell transplant studies there was serious uncertainty about whether G(M)-CSF helps prevent febrile neutropenia.

Antibiotic resistance

Antibiotic resistance was not reported in the included systematic reviews (Sung, et al., 2007; Bohlius, et al., 2008 and Cooper, et al., 2011).

Length of hospital stay

There was moderate quality evidence that the use of prophylactic G(M)-CSF was associated with a shorter hospital stay: the mean hospital stay was 2.41 days shorter with G(M)-CSF prophylaxis than without.

Quality of life

Quality of life was not reported in the included systematic reviews (Sung, et al., 2007; Bohlius, et al., 2008 and Cooper, et al., 2011).

Figure 8.2 Subgroup analyses of relative risks (and 95% confidence intervals) of short term all cause mortality, infectious mortality and febrile neutropenia, in trials of G(M)-CSF versus placebo or nothing (reported in Sung et al 2007)

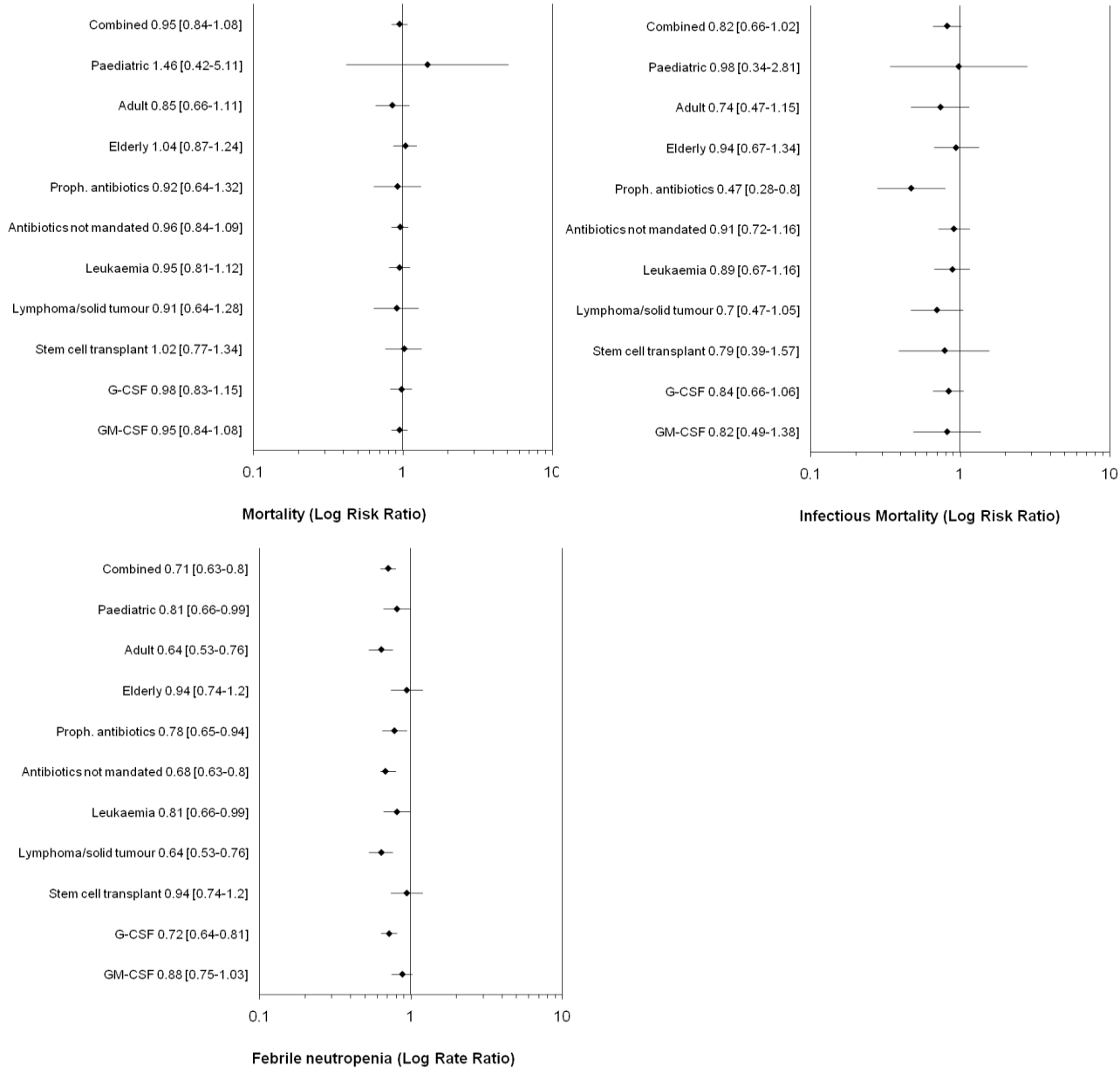


Table 8.2 - GRADE evidence profile for primary prophylaxis with G(M)-CSF versus no primary prophylaxis with G(M)-CSF (with or without antibiotics)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
Mortality											
80	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	465/6146 (7.6%)	472/5913 (8%)	RR 0.95 (0.84 to 1.08)	4 fewer per 1000 (from 13 fewer to 6 more)	HIGH
Mortality (paediatric patients)											
7	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	None	6/301 (2%)	4/303 (1.3%)	RR 1.46 (0.42 to 5.11)	6 more per 1000 (from 8 fewer to 54 more)	VERY LOW
Mortality (adult patients)											
34	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	None	105/1986 (5.3%)	117/1780 (6.6%)	RR 0.85 (0.66 to 1.11)	10 fewer per 1000 (from 22 fewer to 7 more)	LOW
Mortality (elderly patients)											
8	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	311/3778 (8.2%)	317/3586 (8.8%)	RR 1.04 (0.87 to 1.24)	4 more per 1000 (from 11 fewer to 21 more)	HIGH
Mortality (prophylactic antibiotics used)											
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	51/1045 (4.9%)	59/1056 (5.6%)	RR 0.92 (0.64 to 1.32)	4 fewer per 1000 (from 20 fewer to 18 more)	MODERATE
Mortality (prophylactic antibiotics not mandated)											
66	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	414/5101 (8.1%)	413/4857 (8.5%)	RR 0.96 (0.84 to 1.09)	3 fewer per 1000 (from 14 fewer to 8 more)	HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
Mortality (leukaemia studies)											
30	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[5]	None	263/2725 (9.7%)	277/2597 (10.7%)	RR 0.95 (0.81 to 1.12)	5 fewer per 1000 (from 20 fewer to 13 more)	HIGH
Mortality (lymphoma or solid tumour studies)											
27	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	109/2204 (4.9%)	113/2155 (5.2%)	RR 0.91 (0.64 to 1.28)	5 fewer per 1000 (from 19 fewer to 15 more)	MODERATE
Mortality (stem cell transplant studies)											
21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	93/1098 (8.5%)	79/1044 (7.6%)	RR 1.02 (0.77 to 1.34)	2 more per 1000 (from 17 fewer to 26 more)	MODERATE
Mortality (G-CSF studies)											
46	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	267/3726 (7.2%)	265/3531 (7.5%)	RR 0.98 (0.83 to 1.15)	2 fewer per 1000 (from 13 fewer to 11 more)	HIGH
Mortality (GM-CSF studies)											
34	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	193/1957 (9.9%)	193/1917 (10.1%)	RR 0.95 (0.84 to 1.08)	5 fewer per 1000 (from 16 fewer to 8 more)	HIGH
Infection related mortality											
67	randomised trials	no serious risk of bias[1,6]	no serious inconsistency	no serious indirectness	serious[5,7]	none	150/4901 (3.1%)	179/4673 (3.8%)	RR 0.82 (0.66 to 1.02)	7 fewer per 1000 (from 13 fewer to 1 more)	MODERATE
Infection related mortality (prophylactic antibiotics used)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
14	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	Serious[5]	None	18/1177 (1.5%)	42/1181 (3.6%)	RR 0.47 (0.28 to 0.8)	19 fewer per 1000 (from 7 fewer to 26 fewer)	LOW
Infection related mortality (prophylactic antibiotics not mandated)											
53	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	None	132/3724 (3.5%)	137/3492 (3.9%)	RR 0.91 (0.72 to 1.16)	4 fewer per 1000 (from 11 fewer to 6 more)	MODERATE
Febrile neutropenia											
49	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	None	1293/4529 (28.5%)	1649/4470 (36.9%)	RR 0.71 (0.63 to 0.8)	107 fewer per 1000 (from 74 fewer to 136 fewer)	MODERATE
Febrile neutropenia (leukaemia studies)											
10	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	None	389/867 (44.9%)	339/808 (42%)	RR 0.81 (0.66 to 0.99)	80 fewer per 1000 (from 4 fewer to 143 fewer)	MODERATE
Febrile neutropenia (lymphoma or solid tumour studies)											
32	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	None	730/3381 (21.6%)	1070/3412 (31.4%)	RR 0.64 (0.53 to 0.76)	113 fewer per 1000 (from 75 fewer to 147 fewer)	MODERATE
Febrile neutropenia (stem cell transplant studies)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	135/193 (69.9%)	127/172 (73.8%)	RR 0.94 (0.74 to 1.2)	44 fewer per 1000 (from 192 fewer to 148 more)	MODERATE
Documented infection											
60	randomised	serious[9]	no serious	no serious	no serious	None	1874/5921	2043/5704	Rate ratio 0.85	54 fewer per 1000 (from 29	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
	trials		inconsistency	indirectness	imprecision		(31.7%)	(35.8%)	(0.79 to 0.92)	fewer to 75 fewer)	MODERATE
Resistance to the antibiotic used for prophylaxis - not reported											
0	-	-	-	-	-	None	-	-	-	-	
Length of hospital stay (Better indicated by lower values)											
43	randomised trials	no serious risk of bias[11]	no serious inconsistency	serious indirectness[12]	no serious imprecision	None	0	-	-	Mean difference 2.41 days less with G(M)-CSF (3.13 to 1.7 lower)	MODERATE
Quality of life - not reported											
0	-	-	-	-	-	None	-	-	-	-	

[1] This review included 80 trials: 26/80 trials had adequate allocation concealment and 35/80 had double blinding. Sensitivity analyses according to allocation concealment and double blinding, did not show a significant effect of CSF treatment on mortality, infectious mortality or febrile neutropenia.
[2] None of the 7 paediatric mortality studies had adequate allocation concealment, 2/7 had double blinding
[3] Very low number of events
[4] 11/34 adult mortality studies had adequate allocation concealment, 15/34 had double blinding.
[5] Low number of events
[6] 67 trials reported infection related mortality: 19/67 had adequate allocation concealment and 29/67 had double blinding.
[7] The confidence interval for the pooled estimate spans both no effect and significant benefit.
[8] 2/14 trials had adequate allocation concealment, 4/14 double blinding.
[9] Most of the trials did not have adequate allocation concealment or double blinding
[10] Of the studies reporting febrile neutropenia 9/49 had adequate allocation concealment and 15/49 had double blinding.
[11] The quality of studies of duration of hospital stay was not reported.
[12] Hospital discharge criteria in these studies were likely to incorporate neutrophil count and thus influenced by the use of colony stimulating factors.

Comparison 1.1. G(M)-CSF plus antibiotic (quinolone or co-trimoxazole) versus antibiotic.

The trials were identified from the systematic review by Sung, et al., (2007) and from the list of excluded studies in a Cochrane review of prophylactic antibiotics versus G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy (Herbst, et al., 2009). Most (18/27) of the trials used cotrimoxazole only (specifically for Pneumocystis pneumonia prophylaxis) – these were analysed separately from the nine trials that used quinolones. Three trials that used both quinolones and cotrimoxazole were included in the quinolone group for analysis. The trials were not designed to test the interaction of G(M)-CSF with antibiotics – rather prophylactic antibiotics were part of standard care (many of the these trials also used antiviral and antifungal prophylaxis). This evidence is summarised in Tables 8.3 and 8.5 and Figures 8.3 to 8.8.

Table 8.3 Characteristics of included trials

Total number of randomised trials	27
Age group	Paediatric 8 trials, adult 19 trials
Treatment category	Leukaemia 9, solid tumour 3, non-Hodgkin lymphoma 5, stem cell transplant 10
Antibiotic used	Cotrimoxazole 18, ciprofloxacin (or quinolone not specified) 6, quinolone and cotrimoxazole 3
Adequate allocation concealment	Yes 5, no 22
Double blinding	Yes 6, no 21

Evidence statements

Mortality and Febrile neutropenia

The evidence was of low quality for febrile neutropenia and moderate quality for short term mortality from any cause. There was uncertainty as to whether primary prophylaxis with G(M)-CSF plus quinolone or quinolone alone was better in terms of these outcomes due to the wide confidence intervals of the pooled estimates.

Infectious mortality

Moderate quality evidence suggested that infectious mortality was lower when G(M)-CSF plus quinolone was used for prophylaxis than with quinolone.

Antibiotic resistance, Length of hospital stay, Quality of life

These outcomes were not reported for this subgroup of studies in Sung, et al., (2007).

1 ***Table 8.4 - GRADE evidence profile for primary prophylaxis with G(M)-CSF plus antibiotics versus primary prophylaxis with antibiotics***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G(M)-CSF+ABX**	**Antibiotics alone**	**Relative (95% CI)**	**Absolute**	
Febrile neutropenia (quinolone studies) – one trial in patients with solid tumours and one in non-Hodgkin lymphoma											
2	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	53/432 (12.3%)	71/410 (17.3%)	RR 0.703 (0.414 to 1.193)	51 fewer per 1000 (from 101 fewer to 33 more)	VERY LOW
Mortality from any cause (quinolone studies) – one trial each in patients with solid tumours , non-Hodgkin lymphoma, leukaemia and stem cell transplant											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/408 (6.1%)	33/401 (8.2%)	RR 0.817 (0.491 to 1.36)	15 fewer per 1000 (from 42 fewer to 30 more)	MODERATE
Infectious mortality (quinolone studies) – one trial each in patients with non-Hodgkin lymphoma, leukaemia and stem cell transplant; two in patients with solid tumours											
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	13/498 (2.6%)	29/486 (6%)	RR 0.478 (0.254 to 0.898)	31 fewer per 1000 (from 6 fewer to 45 fewer)	MODERATE
Febrile neutropenia (cotrimoxazole studies) – five leukaemia, two non-Hodgkin and two stem cell transplant trials											
9	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	349/504 (69.2%)	372/483 (77%)	RR 0.928 (0.86 to 1.002)	55 fewer per 1000 (from 108 fewer to 2 more)	MODERATE
Mortality from any cause (cotrimoxazole studies) – five leukaemia, two non-Hodgkin and four stem cell transplant trials											
11	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	32/706 (4.5%)	29/705 (4.1%)	RR 1.102 (0.685 to 1.773)	4 more per 1000 (from 13 fewer to 32 more)	LOW
Infectious mortality (cotrimoxazole studies) – four leukaemia, three non-Hodgkin and two stem cell transplant trials											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF+ABX	Antibiotics alone	Relative (95% CI)	Absolute	
9	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	7/731 (0.96%)	14/728 (1.9%)	RR 0.6 (0.264 to 1.367)	8 fewer per 1000 (from 14 fewer to 7 more)	LOW
Length of Hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	- -	

[1] 1/2 double blind, 0/2 adequate allocation concealment
[2] Low number of events
[3] 1/9 had adequate allocation concealment, 2/9 double blinding
[4] 1/11 had adequate allocation concealment, 2/11 double blinding
[5] 0/9 had adequate allocation concealment, 1/9 was double blind
[6] Significant heterogeneity (I^2=67%)

Figure 8.3 Relative risk of febrile neutropenia G(M)-CSF + quinolone versus quinolone

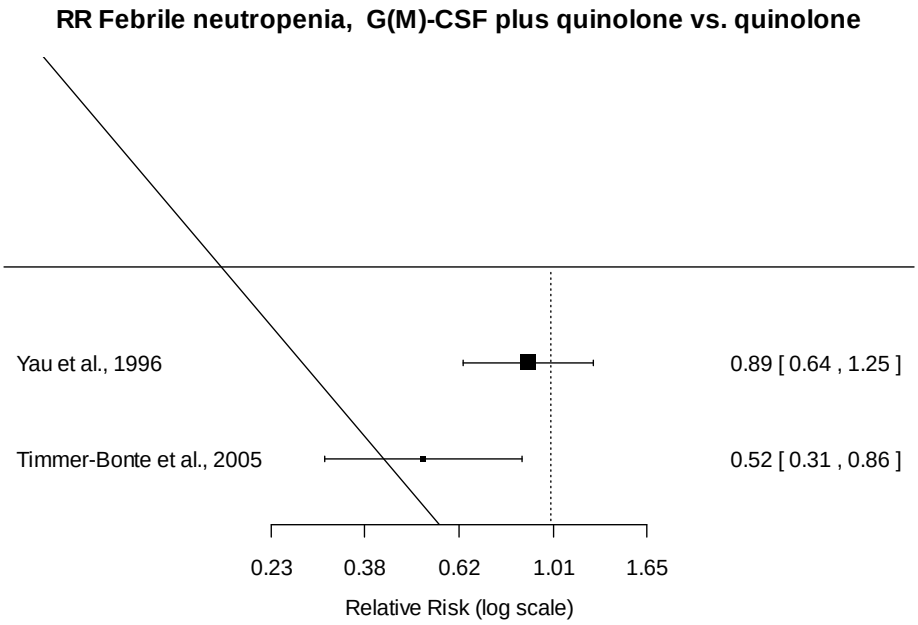


Figure 8.4 Relative risk of all cause mortality G(M)-CSF + quinolone versus quinolone

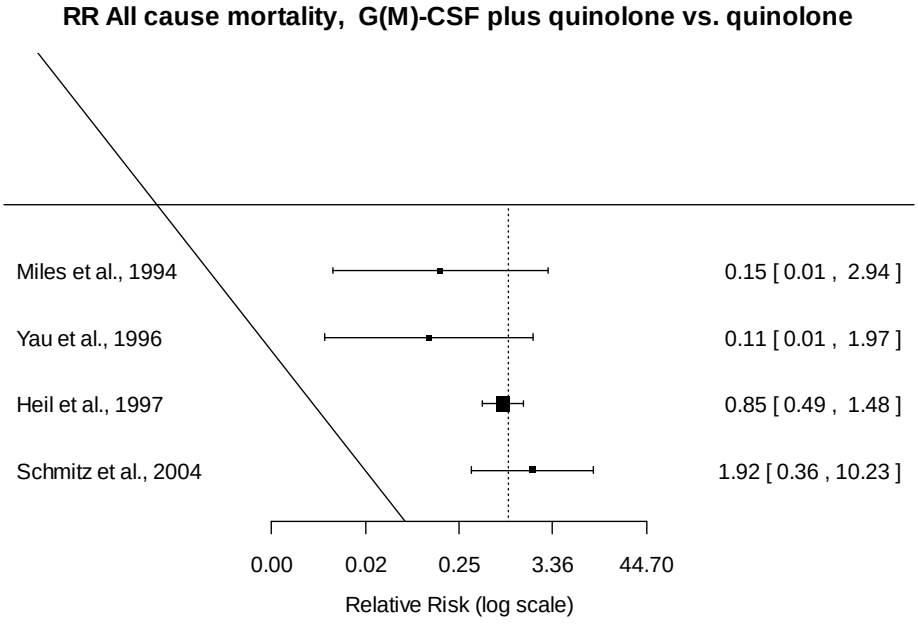


Figure 8.5 Relative risk of infectious mortality G(M)-CSF + quinolone versus quinolone

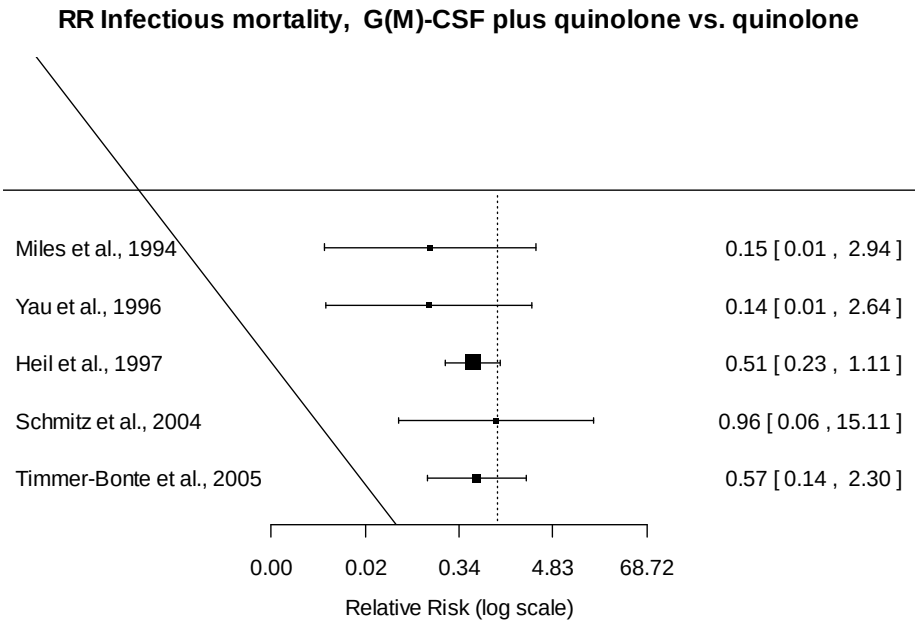


Figure 8.6 Relative risk of febrile neutropenia G(M)-CSF + cotrimoxazole versus cotrimoxazole

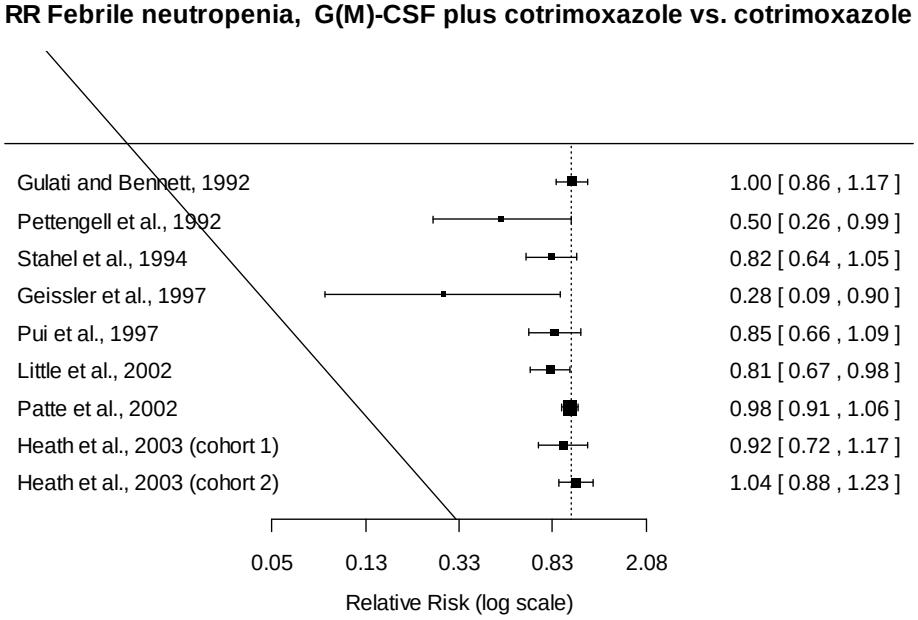


Figure 8.7 Relative risk of all cause mortality G(M)-CSF + cotrimoxazole versus cotrimoxazole

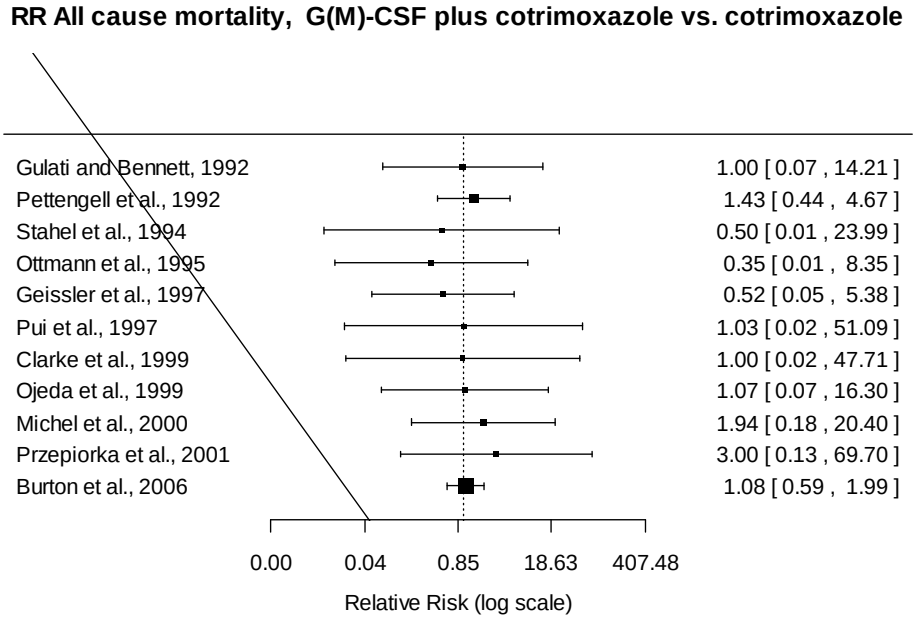
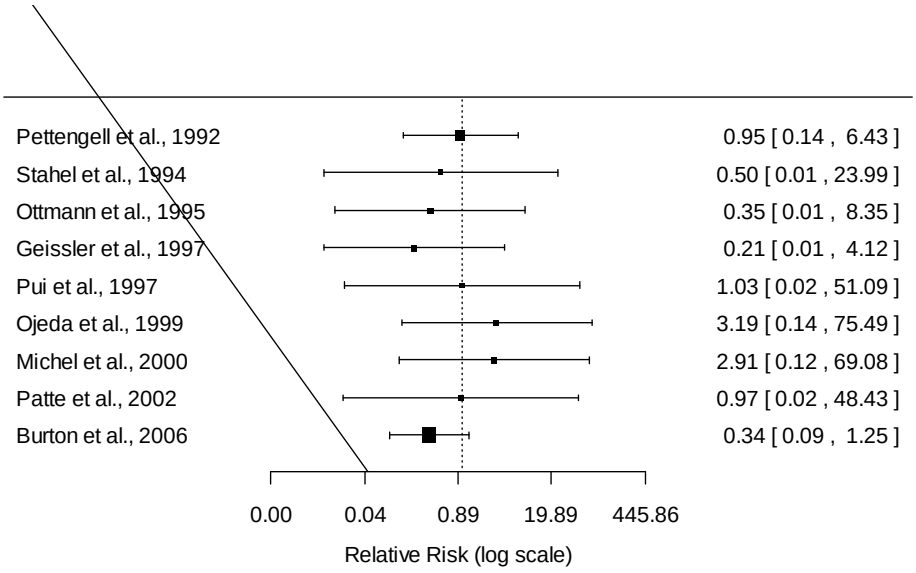


Figure 8.8 Relative risk of infectious mortality G(M)-CSF + cotrimoxazole versus cotrimoxazole



Comparison 2. Antibiotic (ciprofloxacin, levofloxacin, ofloxacin or co-trimoxazole) versus placebo or nothing

The evidence came from a Cochrane review of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following anti-cancer treatment by Gafter-Gvili, et al., (2005). Data from trials of ciprofloxacin, levofloxacin, ofloxacin or co-trimoxazole was were extracted from this review and analysed. Evidence about colonisation with resistant bacteria came from a second systematic review by the same authors (Gafter-Gvili, et al., 2007). An additional trial (Rahman and Khan, 2009) of levofloxacin prophylaxis was indentified in our literature search. The evidence is summarised in Tables 8.5 and 8.6 and in Figures 8.9 to 8.12.

Table 8.5 Characteristics of included trials

Total number of randomised trials	28
Age group	Paediatric 5 trials, adult 23 trials
Treatment category	Leukaemia 14, solid tumour or lymphoma 4, any cancer 7, stem cell transplant 2, 1 not specified
Antibiotic used	Ciprofloxacin , levofloxacin, ofloxacin, co-trimoxazole
Prophylaxis only given to neutropenic patients	7/28
Adequate allocation concealment	10/28
Double blinding	14/28

Evidence statements

Mortality

There was moderate quality evidence that prophylactic quinolones (ciprofloxacin or levofloxacin) reduced short-term all cause mortality when compared with no prophylaxis. From the pooled estimate, 59 patients would need prophylactic quinolones to prevent one additional death.

No ofloxacin studies reported the rates of all cause mortality.

Febrile neutropenia

The review analysed the rates of febrile neutropenia by patient (rather than by cycle). When patient rates were not reported, febrile episodes were used for the numerator. There was moderate quality evidence that antibiotic prophylaxis reduced the rate of febrile neutropenia, however there was inconsistency between individual study's estimates of effectiveness.

Subgroup analysis according to antibiotic suggested that levofloxacin, ofloxacin and cotrimoxazole might be more effective than ciprofloxacin in preventing febrile neutropenia.

However, even after grouping studies according to antibiotic used, there was still heterogeneity within the ofloxacin and cotrimoxazole groups.

The highest quality evidence came from the three levofloxacin trials. The pooled estimate from these trials suggested that 11 patients would need antibiotic prophylaxis to prevent one additional episode of febrile neutropenia.

Antibiotic resistance

There was moderate quality evidence that infection with bacteria resistant to the antibiotic used for prophylaxis was more likely in patients receiving antibiotic prophylaxis. The pooled estimate suggested an additional resistant infection for every 77 patients who received antibiotic prophylaxis.

There was very low quality evidence about the rates of colonisation with resistant bacteria.

Two trials reported only 8 cases of colonisation with resistant bacteria, in 143 patients. It is impossible to get an accurate estimate of the impact of antibiotic prophylaxis on resistant colonisation with such a low number of events.

None of the trials reported the rates of colonisation with resistant bacteria before antibiotic prophylaxis or how these related to rates following prophylaxis.

Length of hospital stay

Although the Gafter-Gvili, et al., (2005) review considered this outcome, data on the length of hospital stay were too sparse to allow analysis

Quality of life

Quality of life was not considered as an outcome in the systematic review.

1 ***Table 8.6 - GRADE evidence profile for primary prophylaxis with antibiotics versus no primary prophylaxis***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**No primary prophylaxis**	**Relative (95% CI)**	**Absolute**	
Mortality (quinolone studies)											
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32/1295 (2.5%)	57/1286 (4.4%)	RR 0.615 (0.4 to 0.946)	17 fewer per 1000 (from 2 fewer to 27 fewer)	MODERATE
Infection related mortality (quinolone studies)											
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	19/1295 (1.5%)	36/1286 (2.8%)	RR 0.58 (0.336 to 1.001)	12 fewer per 1000 (from 19 fewer to 0 more)	LOW
Febrile neutropenia (quinolone studies)											
10	randomised trials	serious[1,4]	serious[5]	no serious indirectness	no serious imprecision	none	419/1339 (31.3%)	594/1341 (44.3%)	RR 0.727 (0.62 to 0.852)	121 fewer per 1000 (from 66 fewer to 168 fewer)	LOW
Febrile neutropenia (ciprofloxacin studies)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,6]	none	19/56 (33.9%)	26/56 (46.4%)	RR 0.95 (0.66 to 1.35)	23 fewer per 1000 (from 158 fewer to 163 more)	LOW
Febrile neutropenia (levofloxacin studies)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	347/1160 (29.9%)	460/1160 (39.7%)	RR 0.76 (0.7 to 0.82)	95 fewer per 1000 (from 71 fewer to 119 fewer)	HIGH
Febrile neutropenia (ofloxacin studies)											
4	randomised	no serious	serious[5]	no serious	serious[2,6]	none	34/111	70/106	RR 0.35 (0.1	429 fewer per 1000 (from 594 fewer to 152	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No primary prophylaxis	Relative (95% CI)	Absolute	
	trials	risk of bias		indirectness			(30.6%)	(66%)	to 1.23)	more)	LOW
Febrile neutropenia (TMP-SMZ studies)											
16	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	none	367/713 (51.5%)	473/711 (66.5%)	RR 0.80 (0.69 to 0.92)	133 fewer per 1000 (from 53 fewer to 206 fewer)	MODERATE
Infection with bacteria resistant to the antibiotic used for prophylaxis											
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	74/1680 (4.4%)	50/1654 (3%)	RR 1.43 (1 to 2.03)	13 more per 1000 (from 0 more to 31 more)	MODERATE
Colonization with bacteria resistant to quinolones											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6,7]	none	4/75 (5.3%)	4/68 (5.9%)	RR 0.88 (0.24 to 3.22)	7 fewer per 1000 (from 45 fewer to 131 more)	LOW
Length of hospital stay - not reported											
0	-	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	-	none	-	-	-	-	

[1] Most studies did not have clear allocation concealment or double blinding.
[2] Low number of events.
[3] Confidence interval of the pooled estimate crosses both no effect and significant benefit.
[4] 9/25 had adequate allocation concealment and 13/25 double blinding
[5] Statistically significant heterogeneity
[6] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[7] Very low number of events

Figure 8.9 Antibiotic versus placebo, mortality

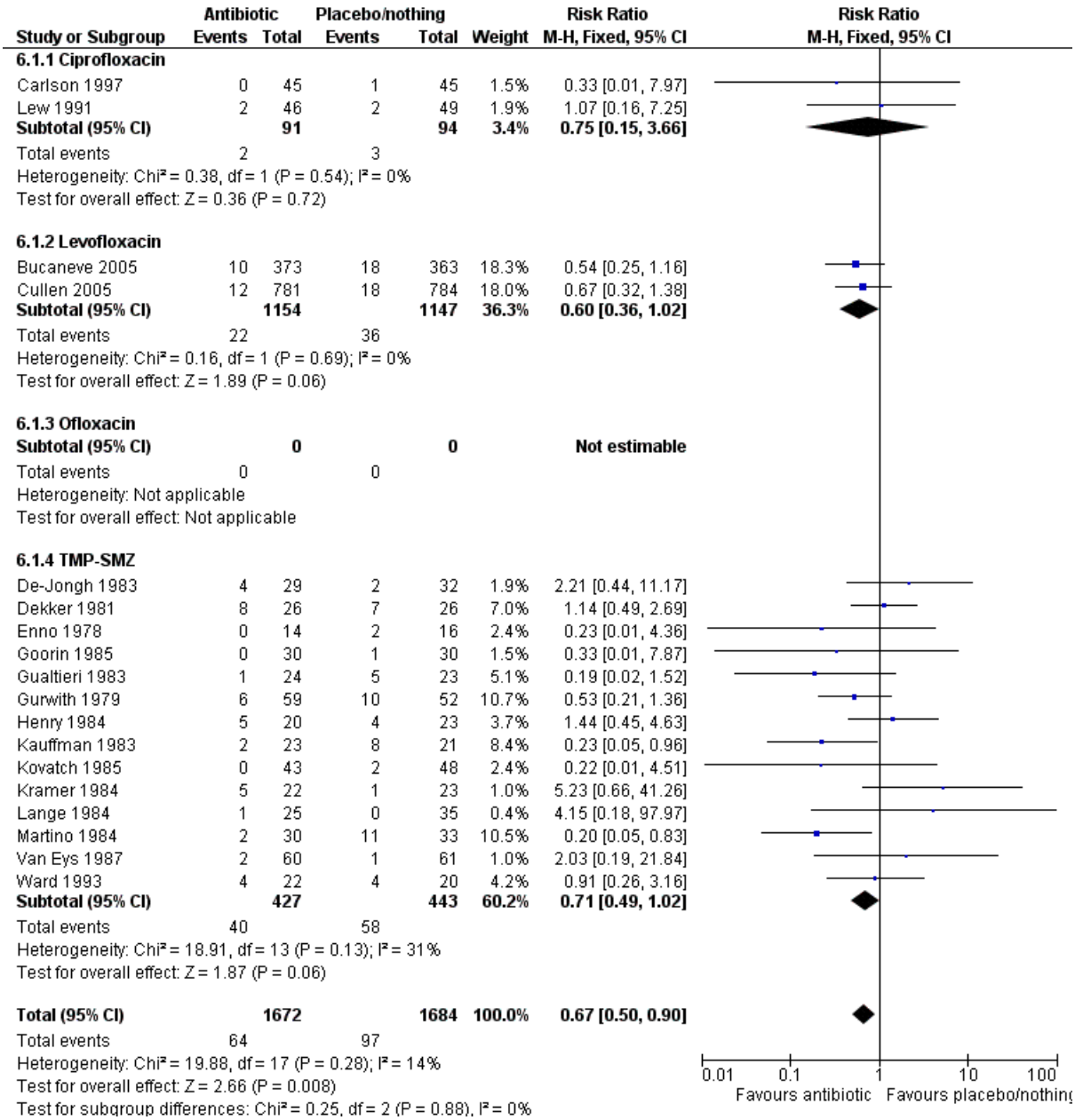


Figure 8.10 Antibiotic versus placebo, febrile neutropenia

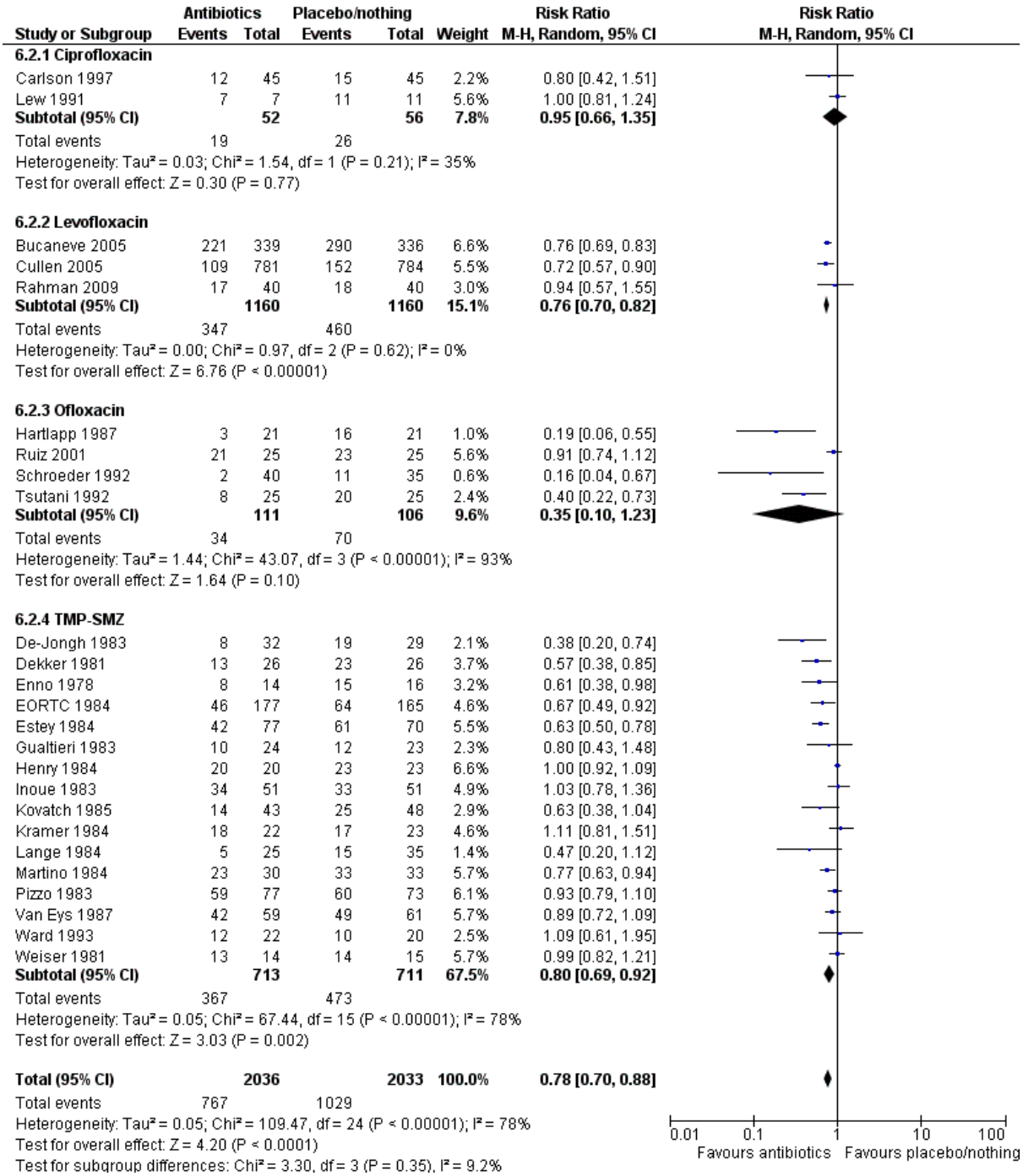


Figure 8.11 Antibiotic versus placebo, infection with bacteria resistant to the antibiotic used for prophylaxis

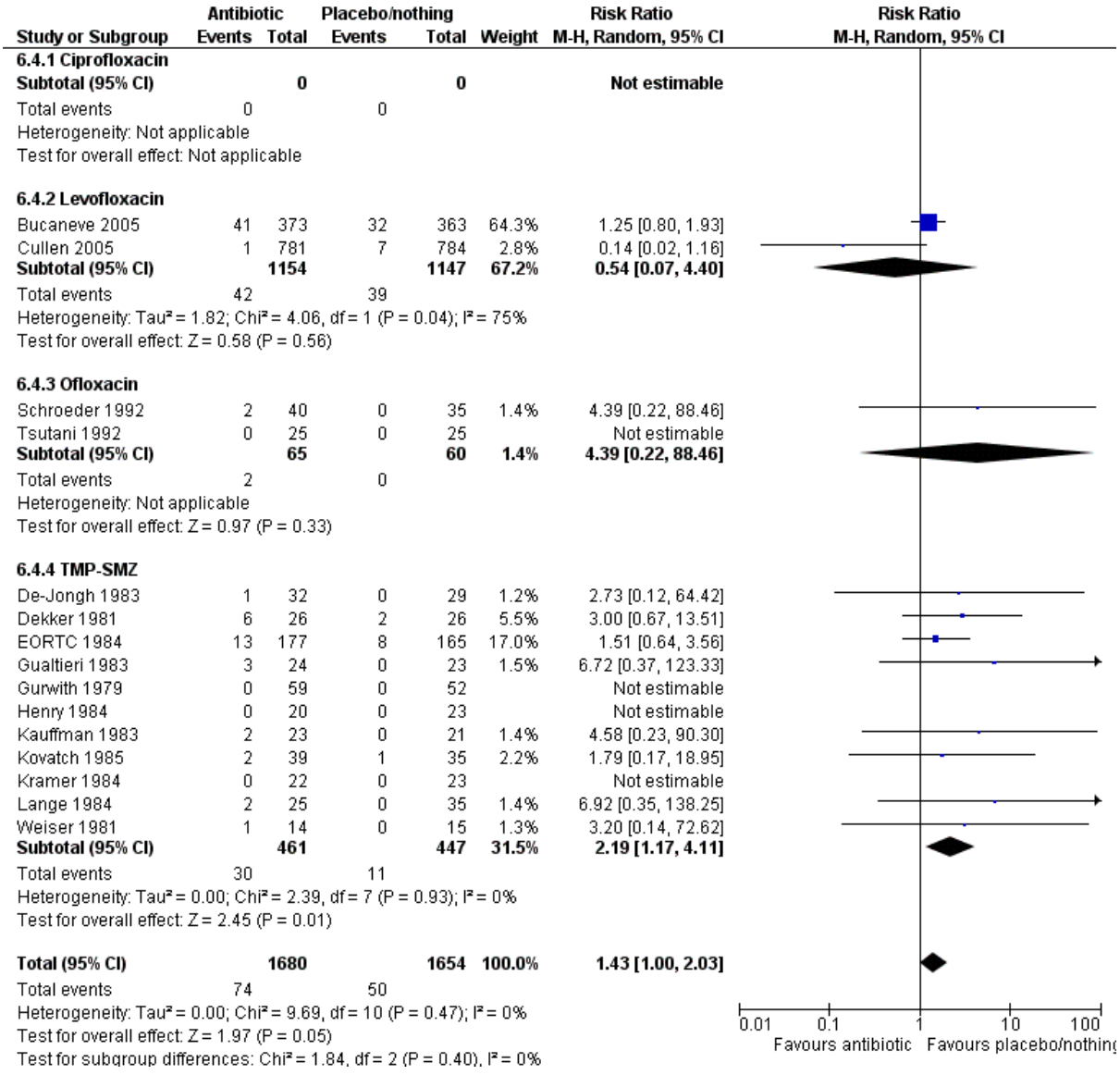
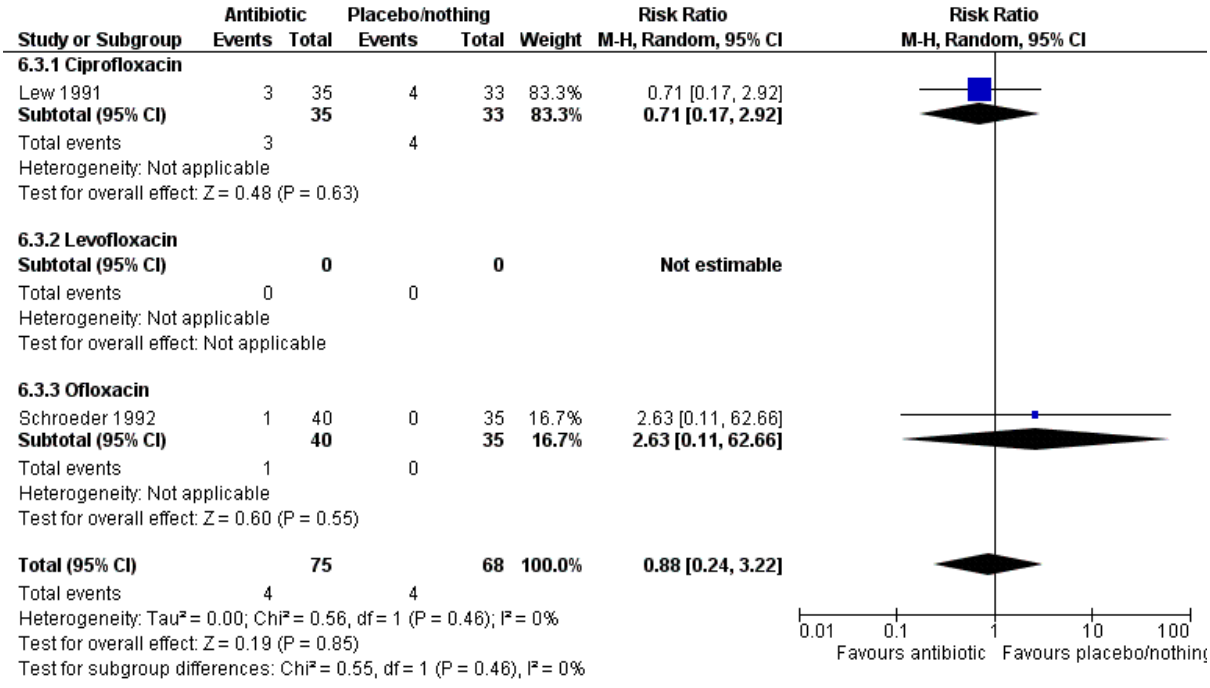


Figure 8.12 Antibiotic versus placebo, colonisation of bacteria resistant to the antibiotic used for prophylaxis



Comparison 3. Quinolone (ciprofloxacin, levofloxacin or ofloxacin) versus co-trimoxazole

Evidence came from a Cochrane review of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following anti-cancer treatment by Gafter-Gvili, et al., (2005). Evidence about colonisation with resistant bacteria came from a second systematic review by the same authors (Gafter-Gvili, et al., 2007). The evidence is summarised in Tables 8.7 and 8.8. Data from trials of comparing ciprofloxacin, levofloxacin, ofloxcain to co-trimoxazole was extracted and analysed (see Figures 8.13 to 8.16).

Table 8.7 Characteristics of included trials

Total number of randomised trials	7
Age group	Paediatric 0 trials, adult 7 trials
Treatment category	Leukaemia 6, solid tumour or lymphoma 0, stem cell transplant 1
Quinolone used	Ciprofloxacin, levofloxacin, ofloxacin
Prophylaxis only given to neutropenic patients	1/7
Adequate allocation concealment	1/7
Double blinding	1/7

Evidence statements

Mortality

There was uncertainty as to whether prophylaxis with quinolones or cotrimoxazole was better in terms of short-term mortality. The 95% confidence intervals of the pooled estimate were were wide enough to include the possibility that either antibiotic was significantly better than the other.

Febrile neutropenia

There was low quality evidence to suggest that prophylaxis of febrile neutropenia was more effective with ofloxacin than with cotrimoxazole. There was uncertainty about whether ciprofloxacin was more effective than cotrimoxazole, and there were no studies comparing levofloxacin with cotrimoxazole.

Antibiotic resistance

Low quality evidence suggested both infection and colonisation with bacteria resistant to the antibiotic used for prophylaxis was more likely with cotrimoxazole than with a quinolone.

Length of hospital stay and Quality of life

Data on length of stay were sparse and not analysed. Quality of life was not reported

1 ***Table 8.8 - GRADE evidence profile for primary prophylaxis with quinolone versus cotrimoxazole***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ciprofloxacin, levofloxacin or ofloxacin**	**Co-trimoxazole**	**Relative (95% CI)**	**Absolute**	
Mortality											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26/372 (7%)	17/317 (5.4%)	RR 1.24 (0.57 to 2.67)	13 more per 1000 (from 23 fewer to 90 more)	LOW
Febrile neutropenia (ciprofloxacin vs TMP-SMZ studies)											
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2,3]	none	161/219 (73.5%)	143/212 (67.5%)	RR 1.34 (0.88 to 2.04)	229 more per 1000 (from 81 fewer to 702 more)	LOW
Febrile neutropenia (levofloxacin vs TMP-SMZ studies) - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Febrile neutropenia (ofloxacin vs TMP-SMZ studies)											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	65/142 (45.8%)	84/131 (64.1%)	RR 0.39 (0.23 to 0.67)	391 fewer per 1000 (from 212 fewer to 494 fewer)	LOW
Colonisation with bacteria resistant to the antibiotic used for prophylaxis											
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[2]	none	39/98 (39.8%)	58/86 (67.4%)	RR 0.58 (0.44 to 76)	283 fewer per 1000 (from 378 fewer to 1000 more)	LOW
Infection with bacteria resistant to the antibiotic used for prophylaxis											
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	3/100 (3%)	6/100 (6%)	RR 0.24 (0.08 to 0.77)	46 fewer per 1000 (from 14 fewer to 55 fewer)	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin, levofloxacin or ofloxacin	Co-trimoxazole	Relative (95% CI)	Absolute	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Length of hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] 1/6 trials had adequate allocation concealment, 1/6 had double blinding
[2] Low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[4] 1/3 had adequate allocation concealment, 1/3 had double blinding
[5] No allocation concealment or blinding
[6] 1 trial had adequate allocation concealment, none had double blinding
[7] Very low number of events

Figure 8.13 Quinolone versus cotrimoxazole, mortality

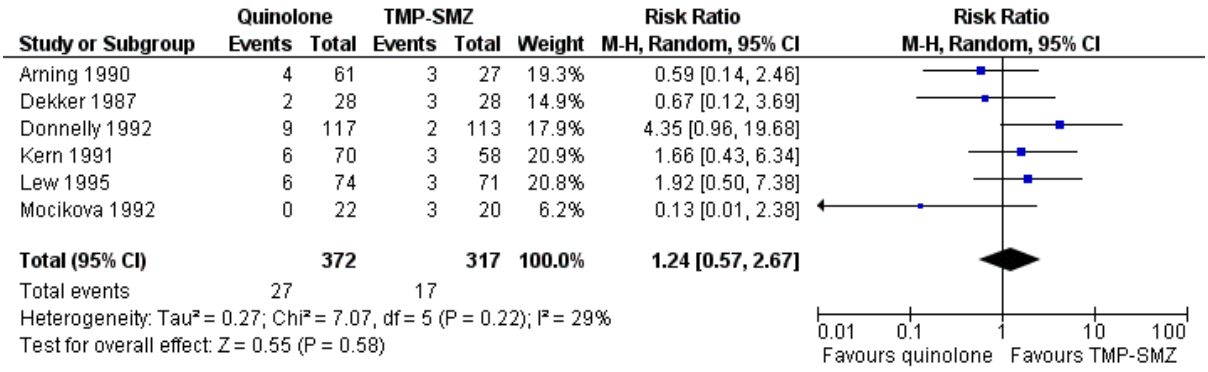


Figure 8.14 Quinolone versus cotrimoxazole, febrile neutropenia

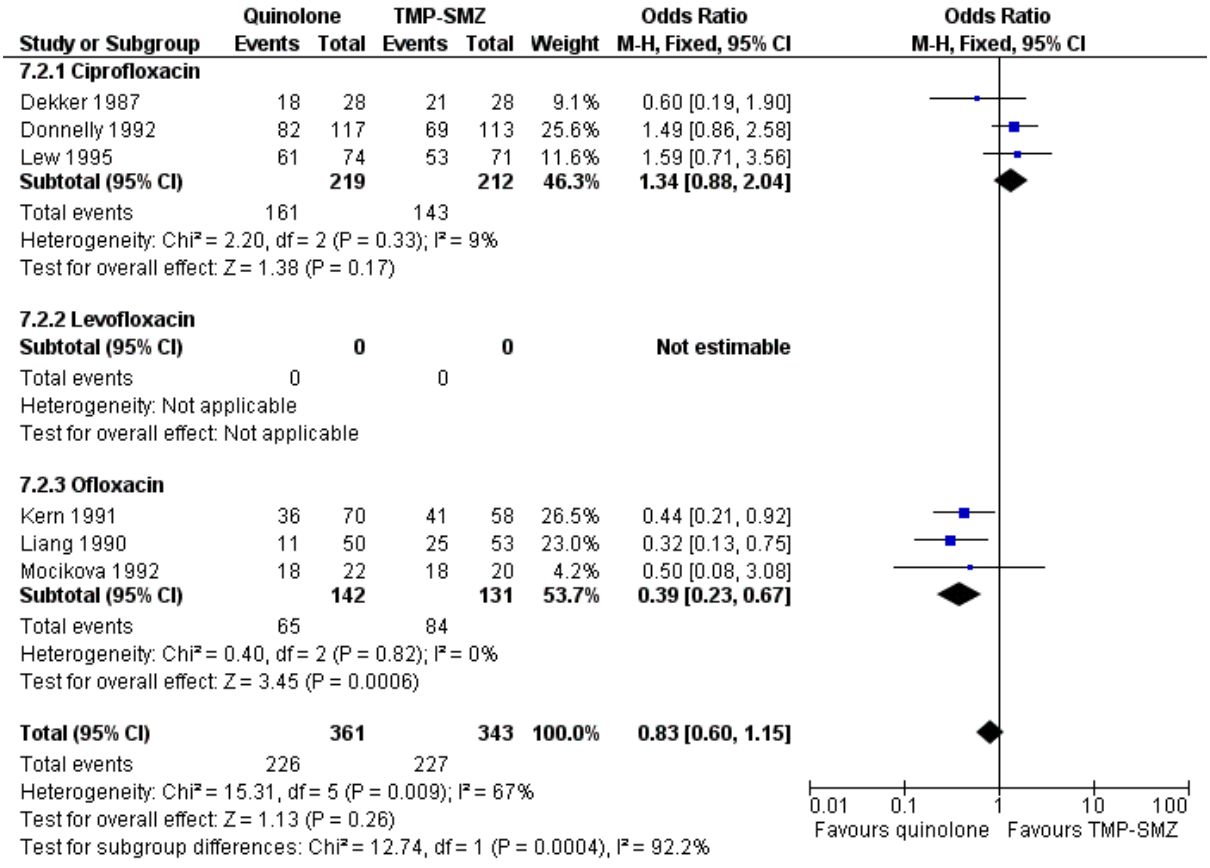


Figure 8.15 Infection with bacteria resistant to antibiotic used for prophylaxis

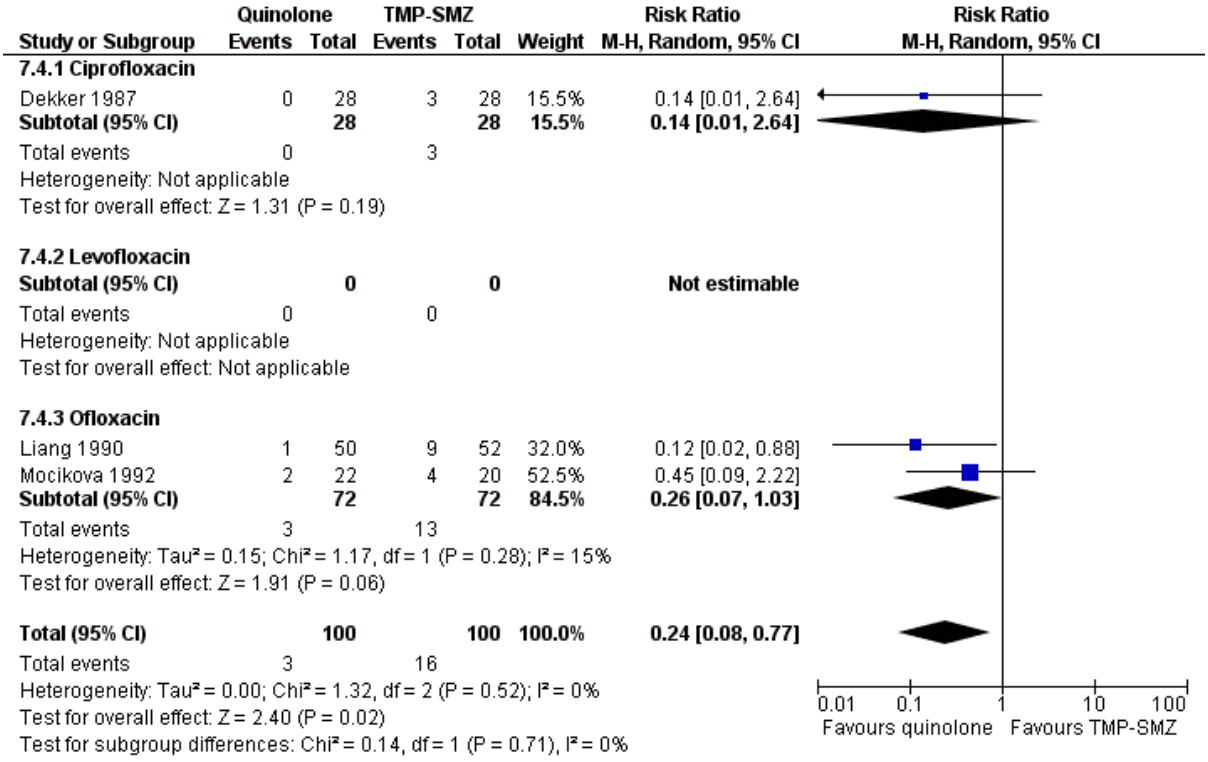
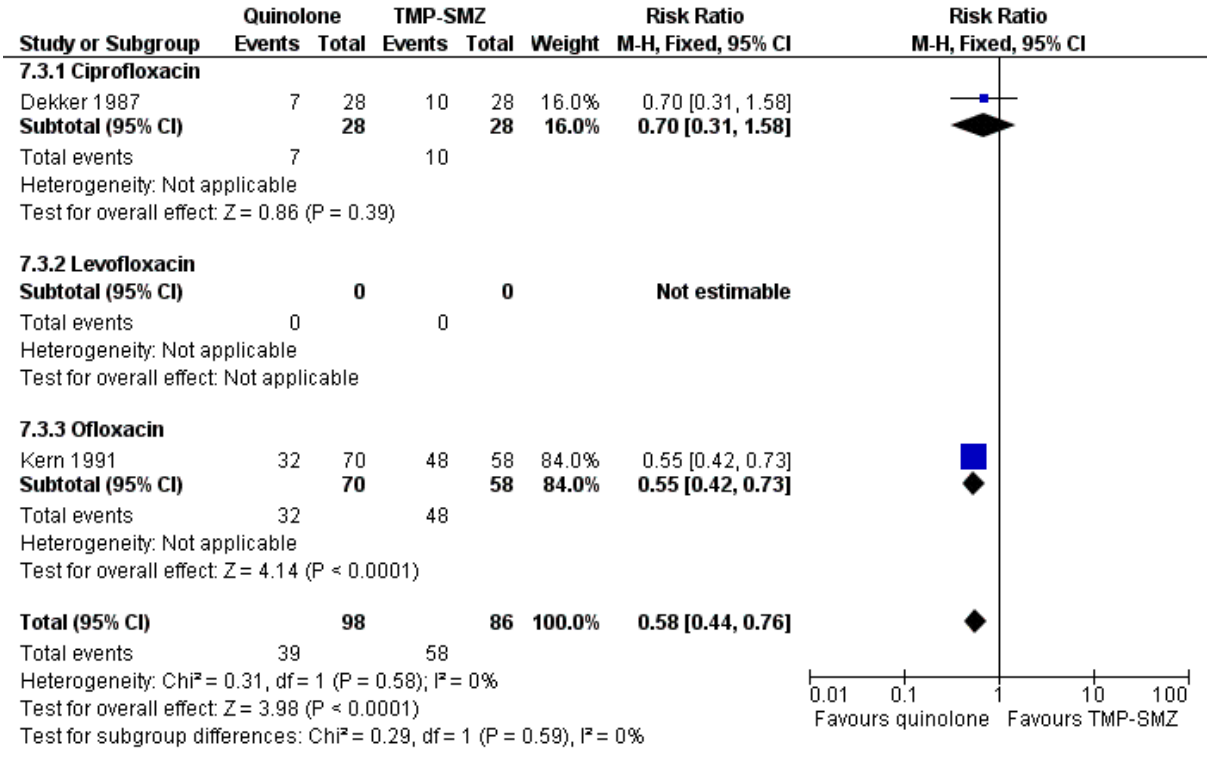


Figure 8.16 Colonisation with bacteria resistant to antibiotic used for prophylaxis



Comparison 4. G(M)-CSF versus antibiotics

Evidence came from a Cochrane review of prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy (Herbst, et al., 2009). This review included two randomised trials directly comparing G(M)-CSF with antibiotics, remarkably few given the large number of trials comparing primary prophylaxis with G(M)-CSF or antibiotics to no primary prophylaxis. Schroeder. et al., (1999) compared G-CSF to ciprofloxacin plus amphotericin B. Sculier, et al., (2001) compared GM-CSF to cotrimoxazole. The evidence is summarised in Tables 8.9 and 8.10.

Table 8.9 Characteristics of included trials

Total number of randomised trials	2
Age group	Paediatric 0, adult 2, elderly 0
Treatment category	Leukaemia 0, solid tumour or lymphoma 2, stem cell transplant 0
Prophylaxis only given to neutropenic patients	0/2
Allocation concealment	Adequate 1/2
Double blinding	0/2

Evidence statements

Mortality

One trial reported short term mortality. Due to the very low number of events there was serious uncertainty and it is not possible to conclude that the treatments are equivalent or that one is superior to the other

Febrile neutropenia

One trial reported febrile neutropenia. Due to the very low number of events there was serious uncertainty and it is not possible to conclude that the treatments are equivalent or that one is superior to the other

Antibiotic resistance

This outcome was not considered in the systematic review.

Length of hospital stay

One trial reported the median length of hospital stay was 6 days with G-CSF compared with 7 days with antibiotic prophylaxis. This difference was not statistically significant.

Quality of life

Neither of the trials reported this outcome

1 ***Table 8.10 - GRADE evidence profile for primary prophylaxis with G(M)-CSF versus antibiotic***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G-CSF**	**Antibiotics**	**Relative (95% CI)**	**Absolute**	
Mortality											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/78 (9%)	5/77 (6.5%)	RR 1.42 (0.43 to 4.68)	27 more per 1000 (from 37 fewer to 239 more)	VERY LOW
Febrile neutropenia											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/18 (38.9%)	7/22 (31.8%)	RR 1.22 (0.53 to 2.84)	70 more per 1000 (from 150 fewer to 585 more)	VERY LOW
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Antibiotic resistance - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Length of hospital stay (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Median 6 days (range 5 to 9)	Median 7 days (range 5 to 10)	-	median 1 day less with G-CSF	LOW

2 [1] No blinding or unclear allocation concealment
3 [2] Very low number of events
4 [3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm

Comparison 5. Pegfilgrastim versus filgrastim

Evidence came from systematic review and meta-analysis of prophylactic G-CSFs which included a comparison of pegfilgrastim versus filgrastim for the prevention of neutropenia in adult cancer patients with solid tumours or lymphoma undergoing chemotherapy (Cooper, et al., 2011). This review included five randomised trials. The literature search identified an additional phase II randomised trial comparing pegfilgrastim to filgrastim for prophylaxis in children with sarcoma receiving chemotherapy (Spunt, et al., 2010). The evidence is summarised in Tables 8.11 and 8.12 and in Figure 8.17.

Table 8.11 Characteristics of included trials

Total number of randomised trials	6
Age group	Paediatric and young adult 1, adult 5
Treatment category	Leukaemia 0, solid tumour or lymphoma 6, stem cell transplant 0
Trial entry criteria included neutropenia	0 (Patients were required to have ANC > 1.5 $X10^9$/l to enter the trials)
Allocation concealment	Not reported in Pinto et al (2007) review
Double blinding	2/6

Evidence statements

Short term mortality

Short term mortality was not considered in Cooper, et al., (2011). One trial included in the systematic review reported mortality, but there was only one death (in the filgrastim group). Spunt, et al., (2010) did not report mortality.

Febrile neutropenia

Low quality evidence from five randomised trials (Cooper, et al., 2011) suggested pegfilgrastim was more effective than filgrastim in the prevention of febrile neutropenia, RR = 0.66 (95% C.I. 0.44 to 0.98).

Antibiotic resistance, Length of hospital stay and Quality of life

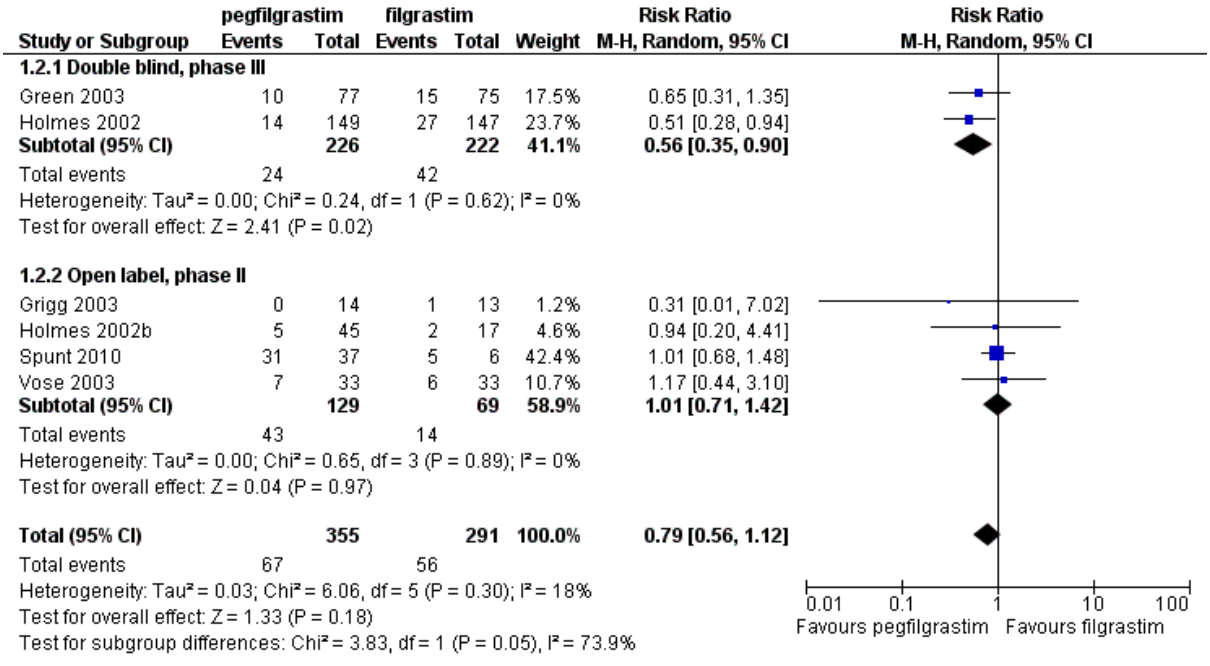
These outcomes were not considered in the systematic review.

1 ***Table 8.12- GRADE evidence profile for primary prophylaxis with pegfilgrastim versus filgrastim***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pegfilgrastim**	**Filgrastim**	**Relative (95% CI)**	**Absolute**	
Mortality - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Febrile neutropenia											
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	35/315 (11.1%)	51/291 (17.5%)	RR 0.66 (0.44 to 0.98)	60 fewer per 1000 (from 4 fewer to 98 fewer)	LOW
Antibiotic resistance - not reported											
0	-	-	-	-	-	none	-	-	-	-	
length of hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

2 [1] 2/5 trials had double blinding, 2/5 were open label. 3/5 trials were phase II studies[2] Low number of events
3 [3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.

Figure 8.17 Pegfilgrastim versus filgrastim, febrile neutropenia



Comparison 6. Granulocyte infusion versus placebo or nothing

Evidence came from a Cochrane review of granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction (Massey, et al., 2009). This review included ten trials, all but one of which were carried out before 1988. The evidence is summarised in Tables 8.13 and 8.14.

Table 8.13 Characteristics of included trials

Total number of randomised trials	10
Age group	Paediatric 0, adult 3, not reported 7
Treatment category	Leukaemia or other haematological cancer 10, solid tumour or lymphoma 0
Trial entry criteria included neutropenia	10/10
Allocation concealment	Adequate 1/10
Double blinding	0/10

Evidence statements

Mortality

Due to the relatively low number of events, there was uncertainty as to whether prophylactic granulocyte infusions reduce short-term all cause mortality in this population.

Febrile neutropenia

Due to the relatively low number of events, there was uncertainty as to whether prophylactic granulocyte infusions reduce the rate of febrile neutropenia in this population.

Antibiotic resistance

This outcome was not considered in the systematic review.

Length of hospital stay

Massey, et al., (2009) found little consistency in the reporting of duration of treatment and length of hospital stay, and chose not analyse this outcome further.

Quality of life

No trials reported this outcome

Table 8.14 - GRADE evidence profile for prophylaxis with granulocyte infusion versus no such prophylaxis

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prophylaxis with granulocyte infusion**	**No prophylaxis with granulocyte infusion**	**Relative (95% CI)**	**Absolute**	
Mortality											
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	62/347 (17.9%)	64/358 (17.9%)	RR 0.94 (0.71 to 1.25)	11 fewer per 1000 (from 52 fewer to 45 more)	LOW
Febrile neutropenia											
2	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[2]	none	46/66 (69.7%)	92/109 (84.4%)	RR 0.85 (0.69 to 1.05)	127 fewer per 1000 (from 262 fewer to 42 more)	VERY LOW
Antibiotic resistance - not reported											
0	-	-	-	-	-	-	-	-	-	-	
Length of hospital stay - not reported											
0	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	-	-	-	-	-	

[1] One trial had adequate allocation concealment, blinding was unclear in all trials
[2] Low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[4] Unclear allocation concealment and blinding
[5] Unexplained statistically significant heterogeneity

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Spunt, S. L., Irving, H., Frost, J., Sender, L., Guo, M., Yang, B. B. et al. (2010). Phase II, randomized, open-label study of pegfilgrastim-supported VDC/IE chemotherapy in pediatric sarcoma patients. Journal of Clinical Oncology, 28, 1329-1336.

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EVIDENCE TABLES

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
Cooper et al (2011)	Systematic review of RCTs	See GRADE tables for quality summary according to outcomes	23 trials. See GRADE tables for number of patients according to outcomes	Adult cancer patients with solid tumours or lymphoma	Primary G-CSF prophylaxis. Antibiotic prophylaxis permitted if identical in both trial arms.	No G-CSF prophylaxis (placebo or nothing)	All cycles of chemotherapy in the study. Number of cycles varied between studies from 4 to 11. The length of each cycle varied from 1 to 3 weeks.	Febrile neutropenia. Subgroup anaylsis according to type of G-CSF. Comparison between pegfilgrastim and filgrastim also reported (see GRADE table).	Amgen Ltd	Unclear whether FN risk was calculated using febrile patients or febrile episodes (possibly multiple per patient).
Rahman and Khan (2009) Bangladesh	RCT 2006-2007	Unclear allocation concealment, no blinding	80	Adult patients with acute leukaemia, hospitalized and at risk of neutropenia (ANC <0.5 X10^9/l)	Levofloxacin prophylaxis, 500mg, orally once daily from start of chemotherapy until resolution of neutropenia or documentation of fever	Placebo	Patients were examined daily for clinical signs of infection. The duration of follow-up was not reported	Febrile neutropenia: **Group** / **n** / **N** levofloxacin / 17 / 40 placebo / 18 / 40 Microbiologically documented infection **Group** / **n** / **N** levofloxacin / 4 / 40	Bangladesh Medical Research Council and Square Pharmaceutical Ltd.	

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
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<tr><td>Hecht et al (2010)

USA</td><td>RCT

2003-2008</td><td>Unclear allocation concealment, no blinding mentioned</td><td>252</td><td>Adult patients with colorectal cancer receiving FOLFOX, FOLFIRI or FOIL chemotherapy</td><td>Pegfilgrastim (6mg – administered per cycle on day 4)</td><td>Placebo</td><td>ANC and temperature were assessed at the start of each cycle. Between cycles patients were advised to consult their doctor in the case of fever. There was long term follow-up for overall survival up to 2 years following study period.</td><td>Neutropenic fever<table><tr><th>Group</th><th>n</th><th>N</th></tr><tr><td>pegfilgrastim</td><td>2</td><td>123</td></tr><tr><td>placebo</td><td>9</td><td>118</td></tr></table>
Mortality during the treatment period<table><tr><th>Group</th><th>n</th><th>N</th></tr><tr><td>pegfilgrastim</td><td>7</td><td>123</td></tr><tr><td>placebo</td><td>7</td><td>118</td></tr></table></td><td>Amgen Inc.</td><td></td></tr>
</table>

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
Gafter-Gvili et al (2005) Israel	Systematic review of RCTs. Search date 2005	See GRADE tables for quality summary according to outcomes	101 trials with 12599 patients. See GRADE tables for number of patients according to outcomes	Patients with cancer and neutropenia induced by chemotherapy or bone marrow transplantation.	Prophylactic antibiotics (quinolones, co-trimoxazole, and others)	Other antibiotic, placebo or no intervention	Not reported – but outcomes typically measured over one course of treatment.	See GRADE tables for results of outcomes relevant to the review question **Primary outcomes:** Mortality, measured at 30 day follow-up or at the end of the follow-up in each study. The number of patients that developed febrile episodes **Secondary outcomes:** Clinically documented infection, microbiologically documented infection, bacteraemia, superinfection rates, hospital admission rates, length of hospital stay	Not reported	
Gafter-Gvili et al (2007) Israel	Systematic review of RCTs. Search date 2006	See GRADE tables for quality summary according to outcomes	58 trials with 7878 patients. See GRADE tables for number of patients according to	Patients with cancer and neutropenia induced by chemotherapy or bone marrow transplantation.	Prophylactic antibiotics (quinolones)	Placebo, no intervention or cotrimoxazole	Not reported – but outcomes typically measured over one course of treatment.	See GRADE tables for results of outcomes relevant to the review question **Primary outcomes** Microbiologically documented infection with bacteria resistant to the antibiotic used for prophylaxis. Colonisation with bacteria resistant to the	Not reported – no conflict of interest reported.	

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
			outcomes					antibiotic used for prophylaxis. **Secondary outcomes** Colonisation by resistant bacteria in relation to the presence of resistant bacteria prior to antibiotic prophylaxis. Infections resistant to antibiotics other than quinolones following prophylaxis.		
Herbst et al (2008)	Systematic review of RCTs. Search date 200?	See GRADE tables for quality summary according to outcomes	2 trials including 195 patients. See GRADE tables for number of patients according to outcomes	Patients with cancer undergoing myeloppressive chemotherapy, bone marrow transplantation or stem cell transplantation.	G(M)-CSF prophylaxis	Antibiotic prophylaxis	Maximum follow up was 2 years (for overall survival)	See GRADE tables for results of outcomes relevant to the review question **Primary outcomes** Overall survival, microbiologically or clinically documented infection. **Secondary outcomes** Severe infections, infectious episodes, frequency of febrile neutropenia (using study definitions), all cause mortality and quality of life.	German Federal Ministry of Education and Research	

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
Sung et al (2007) USA	Systematic review of RCTs. Search date 2007	See GRADE tables for quality summary according to outcomes	148 trials with 16839 patients or cycles. See GRADE tables for number of patients according to outcomes	Patients receiving cancer chemotherapy or stem cell transplant	Prophylactic colony stimulating factors (G-CSF, GM-CSF or PEG). Prophylactic antibiotics could be used	Placebo or no prophylactic colony stimulating factor. Prophylactic antibiotics could be used	Not reported – but outcomes typically measured over one course of treatment.	See GRADE tables for results of outcomes relevant to the review question All-cause mortality, infection related mortality. Any documented infection, microbiologically documented infection, sterile site bacterial infection, documented fungal infection and clinically documented infection. Febrile neutropenia, duration of febrile neutropenia, duration of fever, time to ANC recovery. Duration of IV antibiotics, administration of systemic antifungals, duration of antifungals and duration of hospitalization.	Part funded by the Canadian Institutes of Health Research.	

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
Pinto et al 2007. USA	Systematic review of RCTs. Search date 2006.	See GRADE tables for quality summary according to outcomes. The review does not report allocation concealment was adequate in the included trials.	5 trials including 617 patients.	Adults with non-myeloid cancer including solid tumours and lymphoma.	Single sub-cutaneous injection (6 mg or 100□g/kg) of pegfilgrastim used as prophylaxis after the start of chemotherapy	Daily injection (up to 14 days) of 5□g/kg of filgrastim used as prophylaxis after the start of chemotherapy	Outcomes reported over one course of chemotherapy	See GRADE tables for results of outcomes relevant to the review question **Primary outcomes** Grade IV neutropenia, febrile neutropenia, time to ANC recovery and bone pain	Amgen Inc.	
Spunt et al 2010. USA, Australia	Multicentre phase II RCT. 2000-2007	No blinding, allocation concealment unclear.	44	Children and young adults (2 to 22 years) with sarcoma, median age 11 years.	Single sub-cutaneous injection (6 mg or 100□g/kg) of pegfilgrastim used as prophylaxis after the start of chemotherapy	Daily injection (up to 14 days) of 5□g/kg of filgrastim used as prophylaxis after the start of chemotherapy	Outcomes measured over cycle 1 and cycle 3	Febrile neutropenia (ANC <0.5 X 10^9/L and oral temperature > 38.2°C) **Group** / **n** / **N** PEG / 31 / 37 filgrastim / 5 / 6 Other outcomes: duration of grade 4 neutropenia, time to ANC recovery,	Amgen Inc., National Cancer Institute, Cancer Centre support grants	

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
								pharmacokinetics of pegfilgrastim and filgrastim.		
Massey et al (2009) UK	Systematic review of RCTs. Search date 2008	See GRADE tables for quality summary according to outcomes.	Ten RCTs including 705 patients.	Patients with neutropenia (due to treatment or disease)	Granulocyte transfusions given as prophylaxis, prior to the development of documented infection.	No granulocyte transfusion.	Time points for assessment of mortality were not clearly stated in all trials, and varied from 21 days to 100 days.	**Primary outcome** Death from any cause **Secondary outcomes** Death due to infection, number of infections, number of days of antimicrobial treatment, change in neutrophil count, duration of neutropenia		

1

9. Secondary prophylaxis with growth factors, granulocyte infusion and/or antibiotics. (Topic F2)

Guideline subgroup members for this question

Nicola Perry (lead), Peter Jenkins, Anton Kruger, Barry Hancock and Rosemary Barnes.

Review question*:*

Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients with a prior episode of neutropenic sepsis?

Rationale

Anticancer treatment, particularly chemotherapy, often incurs the risk of neutropaenia. The depth and duration of neutropaenia are related to the risk of infection, which may be life-threatening. One approach to reducing the risk of life-threatening neutropaenic sepsis is to prevent or moderate the degree of neutropaenia, or to prevent or reduce the likelihood of infection. These strategies may be used independently or concurrently.

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been available since the early 1990s to raise neutrophil counts, and shorten the duration of neutropaenia, by stimulating the bone marrow to produce neutrophils. However, side effects include diarrhoea, weakness, a flu-like syndrome, and rarely more serious complications such as clotting disorders and capillary leak syndrome. GCSF and GMCSF must be given by injection, and this may lead to local reactions at the site of administration, and repeated injections may not be desired by patients. Depot formulations are available but expensive.

The likelihood of infection may be reduced by the pre-emptive use of antibiotics, chosen to cover the most likely pathogens, and the time period of greatest risk for infection. The most serious bacterial infections are likely to arise from gram-negative organisms, but as the duration and degree of immunocompromise increase, significant infections can arise from other sources too. Typical antibiotics used for prophylaxis include the fluoroquinolones, and cotrimoxazole. These are given orally, but commonly incur patient-related risks of gut disturbance, allergy, etc and more general risks related to the development of antibiotic resistance in populations.

This research question seeks to establish whether the use of growth factors and/or antibiotics in patients on chemotherapy who have previously experienced neutropaenic sepsis, may reduce the chance of subsequent severe episodes of neutropaenic sepsis, and improve patient outcomes.

Question in PICO format

Patients	Interventions	Comparisons	Outcomes
Patients receiving anti-cancer therapy, with a prior episode of neutropenic sepsis.	• G(M)-CSF (with or without fluoroquinolones), • Fluoroquinolones alone	• Compared with each other, • Compared with placebo/nothing	• Incidence of neutropenic sepsis • Overtreatment • Death/critical care • Length of stay • Duration of fever • Quality of life

METHODS

Information sources

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The full strategy will be available in the full guideline. The search was done on 14th March 2011, and updated on 7th of November 2011.

We also screened the results of the search for topic F1 (primary prophylaxis with G-CSF or antibiotics) for any secondary prophylaxis studies. Trials comparing primary with secondary prophylaxis were excluded.

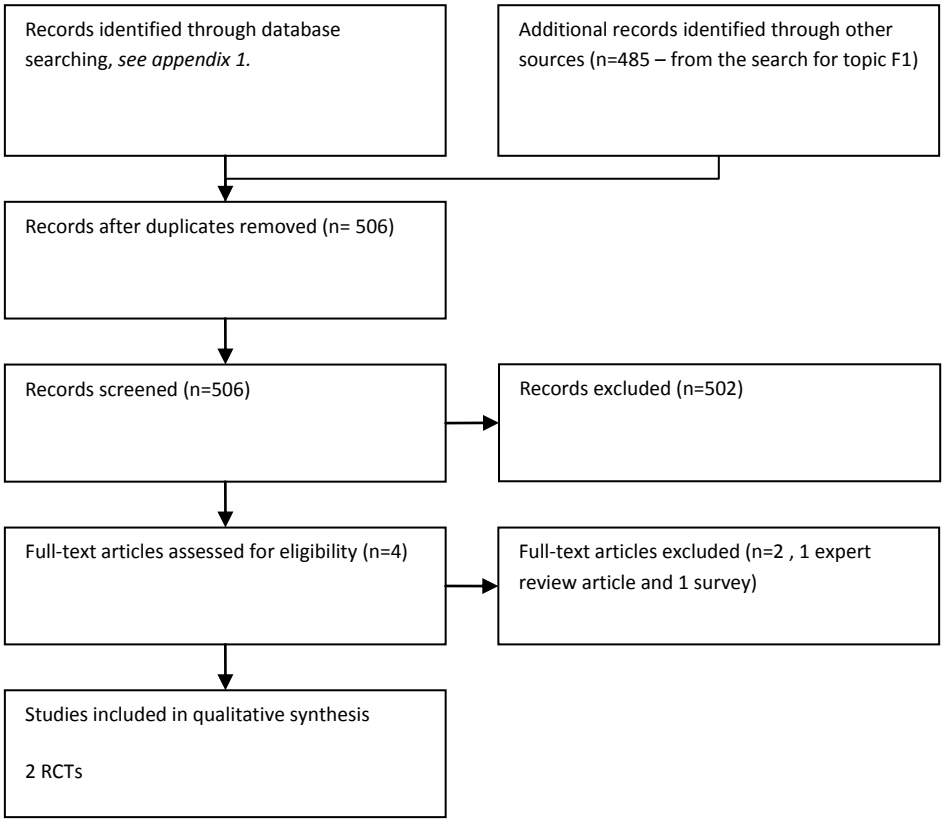
Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

RESULTS

Results of literature searches

Figure 9.1 Study flow diagram



Comparison 1. G(M)-CSF versus placebo or nothing (with or without antibiotics)

The literature search identified one randomised trial (Leonard, et al., 2009) published in abstract form only. This trial compared secondary prophylaxis using G-CSF with standard management (dose delay or reduction) in patients with early stage breast cancer receiving anthracyline or anthracycline-taxane sequential regimes. The evidence is summarised in Table 9.1.

Evidence statements

Incidence of neutropenic sepsis

The rate of neutropenic sepsis was not reported. The trial reported the rate of neutropenic events, indirectly related to neutropenic sepsis and for this reason the evidence was considered low quality. The evidence suggested approximately two patients would need secondary prophylaxis with G-CSF to prevent one additional neutropenic event.

Overtreatment, death, critical care, length of stay, duration of fever, quality of life

These outcomes were not reported

Comparison 2. Antibiotics versus placebo or nothing (with or without G(M)-CSF)

No trials of antibiotics for secondary prophylaxis were identified. One low quality randomised trial compared G-CSF plus ciprofloxacin or ofloxacin to G-CSF alone for secondary prophylaxis (Maiche and Muhonen, 1993). The evidence is summarized in Table 9.2.

In six trials comparing ciprofloxacin, ofloxacin or co-trimoxazole prophylaxis with placebo or nothing (Gafter-Gvili et al, 2005), prophylactic antibiotics were started only in neutropenic patients. However patients were randomised before they experienced neutropenia or fever, so they were not included in this review.

Evidence statements

Incidence of neutropenic sepsis

The rate of neutropenic sepsis was not reported, but Maiche and Muhonen (1993) reported the rate of documented infections. There was uncertainty as to whether prophylaxis with antibiotics plus G-CSF was more effective than G-CSF alone in preventing documented infection, due to the low number of documented infections and small size of the study.

Overtreatment, death, critical care, length of stay, duration of fever, quality of life

These outcomes were not reported

Comparison 3. G-CSF versus antibiotics

No trials were identified.

REFERENCES

Gafter-Gvili, A., Fraser, A., Paul, M., van de Wetering, M., Kremer, L., & Leibovici, L. (2005). Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. [Review] [190 refs]. Cochrane Database of Systematic Reviews.(4):CD004386, 2005., CD004386

Leonard, R. C. F., Mansi, J., Benstead, K., Stewart, G., Yellowlees, A., Adamson, D. et al. (2009). Secondary PROphylaxis with G-CSF has a major effect on delivered dose intensity: The results of the UK NCRI/anglo celtic SPROG trial for adjuvant chemotherapy of breast cancer.> . European Journal of Cancer, Supplement, Conference, 271.

Maiche, A. G. & Muhonen, T. (1993). Granulocyte colony-stimulating factor (G-CSF) with or without a quinolone in the prevention of infection in cancer patients. European Journal of Cancer, 29A, 1403-1405.

1 ***Table 9.1 - GRADE evidence profile For secondary prophylaxis with G(M)-CSF versus no secondary prophylaxis***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Secondary prophylaxis with G(M)-CSF**	**No secondary prophylaxis**	**Relative (95% CI)**	**Absolute**	
Neutropenic events											
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	36/204 (17.6%)	132/203 (65%)	RR 0.27 (0.2 to 0.37)	475 fewer per 1000 (from 410 fewer to 520 fewer)	LOW
Overtreatment, death, critical care, length of stay, duration of fever, quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

2 [1] Neutropenic events were defined as ANC <1.0 X10^9/l or neutropenic fever: thus were indirectly related to neutropenic sepsis. [2] Low number of events

3 ***Table 9.2 - GRADE evidence profile. For secondary prophylaxis with quinolone plus G-CSF versus G-CSF alone***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics plus G-CSF**	**G-CSF alone**	**Relative (95% CI)**	**Absolute**	
Documented infection											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	6/44 (13.6%)	15/48 (31.3%)	RR 0.44 (0.19 to 1.02)	175 fewer per 1000 (from 253 fewer to 6 more)	LOW
Overtreatment, death, critical care, length of stay, duration of fever, quality of life (Copy) - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Unclear allocation concealment, no blinding mentioned. [2] Low number of events, [3] 95% C.I. includes both no-effect and appreciable benefit

EVIDENCE TABLES

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcomes</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Maiche 1993 Eur J Cancer. 1993;29A(10):1403-5.</td>
<td>RCT.</td>
<td>No mention of allocation concealment or blinding</td>
<td>59 (92 courses of chemotherapy</td>
<td>Adult patients with lymphoma or solid tumours who had earlier developed an infection following antineoplastic chemotherapy</td>
<td>G-CSF plus quinolone (ofloxacin or ciprofloxacin)</td>
<td>G-CSF alone</td>
<td>Not reported – outcomes were assessed over the course of chemotherapy.</td>
<td>Documented infection rate (per course of chemotherapy)
<table>
<tr><th></th><th>n</th><th>N</th></tr>
<tr><td>G-CSF + ABX</td><td>6</td><td>44</td></tr>
<tr><td>G-GCSF</td><td>15</td><td>48</td></tr>
</table>
Microbiologically documented infection rate (per course of chemotherapy)
<table>
<tr><th></th><th>n</th><th>N</th></tr>
<tr><td>G-CSF + ABX</td><td>2</td><td>44</td></tr>
<tr><td>G-GCSF</td><td>9</td><td>48</td></tr>
</table>
Duration of leukopenia (<1.0 X 10^9/l)
<table>
<tr><th></th><th>Median (range)</th></tr>
</table></td>
<td>Not reported</td>
<td>Inconsistency between numbers in the text and tables 1. Figures from tables 1 used</td>
</tr>
</table>

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
								G-CSF + ABX 3.5 days(1-7) **G-GCSF** 4 days (1 - ∞)		
Leonard et al (2009)	RCT. 2001 to 2007	Allocation concealment adequate (according to protocol). No blinding	407	Adult patients with breast cancer and neutropenia (ANC < 1.5 X 10^9/l) or hospitalisation due to neutropenia	G-CSF (filgrastim or pegfilgrastim) as secondary prophylaxis	No G-CSF (chemotherapy dose reduction or delay)	Outcomes measured after each cycle and at the end of chemotherapy.. Long term follow up for overall survival (10 years).	**Neutropenia** proportion of patients with neutropenic events – hospitalization due to neutropenia (ANC < 1.5 X 10^9/l) or ANC low enough to require treatment delay or ≥15% dose reduction **G-CSF** n=36 N=204 **No G-GCSF** n=132 N=203 **Relative dose intensity** proportion of patients who received at least 85% of the planned RDI.	Amgen	Abstract only, trial protocol also used.

Reference and country	Study type and period	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcomes	Source of funding	Additional comments
								<table><tr><th></th><th>n</th><th>N</th></tr><tr><td>**G-CSF**</td><td>155</td><td>204</td></tr><tr><td>**No G-GCSF**</td><td>91</td><td>203</td></tr></table> **Relative dose intensity (pegfilgrastim vs filgrastim)** non-randomised comparison. <table><tr><th></th><th>n</th><th>N</th></tr><tr><td>**PEG**</td><td>64</td><td>75</td></tr><tr><td>**Filgrastim**</td><td>91</td><td>129</td></tr></table>		

1

2

Initial Treatment: guideline chapter six

10. Timing of initial antibiotic therapy. (Topic E4)

Guideline subgroup members for this question:

Anton Kruger (lead), Wendy King, Barbara Crosse, Bob Phillips and Rosemary Barnes.

Review question

Does the length of time before empiric antibiotics are given influence patient outcomes?

Rationale

Neutropenic sepsis is a serious complication of myelo-suppressive anticancer treatment or of bone marrow failure for other reasons. Very early observations established that this is a lethal condition with high mortality rates especially when the infective organism is a gram negative bacterium. Early studies of the active management of this condition showed that delaying treatment, for instance while waiting for culture results, was dangerous and carried a significant risk of death, again particularly when the infective organism was a gram negative bacterium. This led to the concept of empiric antibiotic treatment where a broad-spectrum antibiotic or combination of antibiotics is administered before the results of microbiological tests are available. A further extension of this concept implies that if time to treatment is critical, empiric treatment should be given to potentially neutropenic patients with clinical signs of sepsis even before the neutrophil count is known. This time between onset of symptoms and administration of antibiotics can be termed the "symptom-to-needle time".

There are a large number of factors that will influence the symptom-to-needle time. It may be possible to influence these factors and it would therefore be useful to establish if there is a safe or optimum interval between the onset of symptoms and treatment. Although it would appear obvious that treatment delays are a bad thing, it is possible that over-hasty treatment may also confer disadvantages. For instance, patients who are not neutropenic or who do not even have an infection may be given unnecessary antibiotics with potential adverse side effects.

This question seeks to establish whether there is an evidence base for the relationship between symptom-to-needle time and outcome in patients with potential (blood count unknown) or established (blood count known) neutropenic sepsis.

Question in PICO format

Patients/population	Factors	Outcomes
Patients with suspected neutropenic sepsis, (before neutrophil count is known)	Length of time before empiric antibiotics are given (symptom to needle time)	• Over treatment • Mortality • Severe sepsis • Length of stay • Duration of fever • Quality of life

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The search was done on 31st May 2011 and updated on 7th November 2011.

Study selection

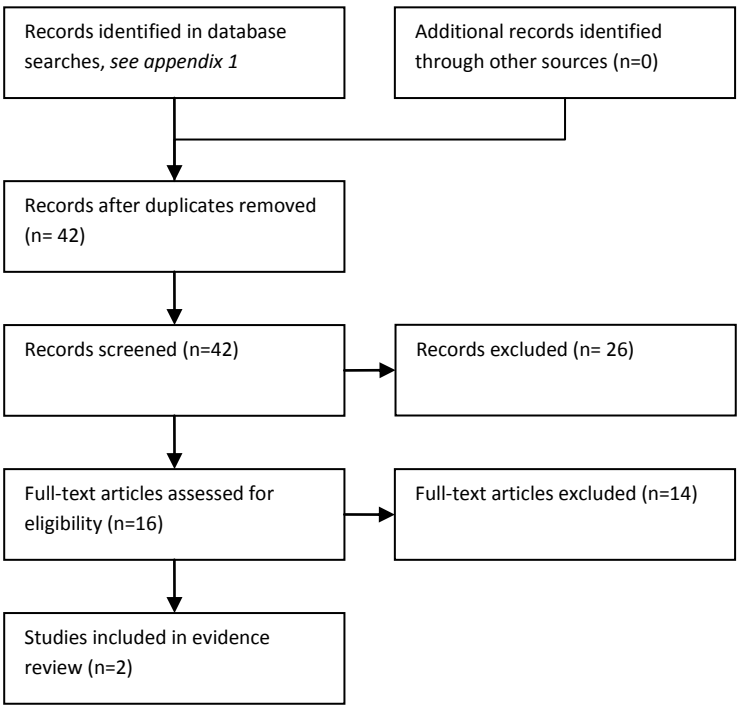
The information specialist (SB) did the first screen of the literature search results. Two reviewers (NB and CL) subsequently selected potentially eligible studies by comparing titles and abstracts to the inclusion criteria presented in the PICO question. Full text articles were obtained for all studies identified as being potentially eligible. These articles were checked against the inclusion criteria. Data were extracted by one reviewer (CL) and checked by another (NB).

RESULTS

Results of literature searches

Two observational studies of the timing of initial antibiotic therapy were identified (Larche et al 2003 and Lin et al 2008). Neither directly met the criteria set out by the PICO. One was a study of cancer patients (some neutropenic) with septic shock (Larche et al 2003); the other was a study of patients with bacteremia, some of whom were neutropenic, but it was unclear whether or not they were cancer patients (Lin et al 2008). Both were retrospective cohort studies. Both studies evaluated early versus delayed administration of antibiotics. The study by Larche et al. defined a delay as > 2 hours from ICU admission. The study by Lin et al. defined a delay as > 24 hours from index blood culture.

Figure 10.1 Study flow diagram



Evidence statements

Short term mortality (febrile neutropenia studies)

A multivariate analysis by Larche, et al., (2003) found that 30 day mortality was higher when time to antibiotic therapy was more than two hours (odds ratio (OR) = 7.05 (95% CI, 1.17 to 42.21 (P = 0.03)). (Table 10.1).

A multivariate analysis by Lin, et al., found that mortality was higher in patients with an ANC of <0.1 X 109/L when time to antibiotic therapy was > 24 hours in a non-ICU setting (OR = 18.0; 95% CI, 2.84 to 114.5; P < 0.01); and in an ICU setting (OR, 5.56; 95% CI, 0.85 to 36.3; P = 0.07). However, for patients who were non-neutropenic (ANC, >0.5 X 109/L) or had ANCs of 0.1 to 0.5 X 109/L, delay was not associated with increased mortality in ICU (OR (ANC 0.1 to 0.5 X 109/L) = 0.59; 95% CI, 0.06 to 6.22; P = 0.66; OR (ANC > 0.5 X 109/L) = 0.55; 95% CI 0.29 to 1.02) or non-ICU (OR (ANC 0.1 to 0.5 X 109/L) = 1.92; 95% CI, 0.17 to 21.3; P = 0.60; OR (ANC > 500) = 1.78; 95% CI 0.89 to 3.44).

This evidence is of very low quality and is indirect on the basis that patients had bacteraemia or septic shock

Overtreatment, Severe sepsis, Length of stay, Duration of fever and Quality of life

These outcomes were not reported by the identified studies. The outcome of severe sepsis was not relevant to the included studies, which included only participants who had bacteraemia or severe sepsis at study entry.

1 ***Table 10.1 - GRADE profile: Does the length of time before empiric antibiotics are given influence patient outcomes?***

Quality assessment							No of patients		Effect		Quality
No of study	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Non-delayed antibiotic therapy**	**Delayed antibiotic therapy**	**Relative (95% CI)**	**Absolute**	
Short term mortality: in cancer patients with septic shock [1]											
1	observational study	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	18/20 (90%)	39/68 (57.4%)	OR 6.5 (1.39 to 30.49)	324 more per 1000 (from 78 more to 403 more)	VERY LOW
Short-term mortality: in patients with bacreremia (67/1523 (4.4%) had ANC < 500)											
1	observational study	serious[2]	no serious inconsistency	serious[4]	very serious	strong association	79/983 (8%)	50/540 (9.3%)	OR 0.85 (0.59 to 1.24)-	93 fewer per 1000 (from 93 fewer to 93 fewer)	VERY LOW
Short-term mortality: in non-ICU patients with bacteremia and ANC < 100											
1	observational study	serious[2]	no serious inconsistency	serious[5]	very serious[6]	strong association	Not reported	Not reported	OR 18 (2.84 to 113.5)	Not calculable	VERY LOW
Short-term mortality: in non-ICU patients with bacteremia and ANC 100-500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,7]	very serious[6]	none	Not reported	Not reported	OR 1.92 (0.17 to 21.6)	Not calculable	VERY LOW
Short-term mortality: in non-ICU patients with bacteremia and ANC > 500											

Quality assessment							No of patients		Effect		Quality
No of study	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Non-delayed antibiotic therapy	Delayed antibiotic therapy	Relative (95% CI)	Absolute	
1	observational study	serious[2]	no serious inconsistency	very serious[5,8]	very serious[6]	none	Not reported	Not reported	OR 1.78 (0.91 to 3.45)	Not calculable	VERY LOW
Short-term mortality: in ICU patients with bacteremia and ANC < 100											
1	observational study	serious[2]	no serious inconsistency	serious[5]	very serious[6]	none	Not reported	Not reported	OR 5.56 (0.85 to 36.3)	Not calculable	VERY LOW
Short-term mortality: in ICU patients with bacteremia and ANC 100-500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,7]	very serious[6]	none	Not reported	Not reported	OR 0.59 (0.06 to 6.22)	Not calculable	VERY LOW
Short-term mortality: in ICU patients with bacteremia and ANC > 500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,8]	very serious[6]	none	Not reported	Not reported	OR 0.55 (0.29 to 1.02)	Not calculable	VERY LOW

[1] Mortality was not reported by group. These figures were calculated from the overall mortality rate and the odds ratio
[2] Observational study
[3] Cancer patients with septic shock. Very high mortality rate.
[4] Patients with bacteremia (not all neutropenic)
[5] Patients with bacteremia
[6] Very small number of events
[7] Patients with ANC 100-500

1 **EVIDENCE TABLES**

Larche, J., Azoulay, E., Fieux, F., Mesnard, L., Moreau, D., Thiery, G. et al. (2003). Improved survival of critically ill cancer patients with septic shock. Intensive Care Medicine, 29, 1688-1695.
Country: France
Design: Retrospective cohort study
Population: 88 adult patients admitted to ICU with septic shock
Inclusion criteria: Septic shock (defined on the basis of the five following criteria: a) clinical evidence of infection; b) tachycardia (>90 beats/min); c) tachypnea (>20 breaths/min) or need for mechanical ventilation; d) refractory hypotension defined by sustained decrease in systolic blood pressure <90 mmHg despite fluid replacement (500 ml), or use of vasopressor to maintain systolic blood pressure >90 mm Hg; and e) evidence of inadequate organ function / perfusion within 12 h of enrollment, as manifested by : acute alteration of mental status /arterial hypoxemia (PaO2/FiO2<280) / plasma lactate concentrations above the normal range or metabolic acidosis / oliguria / disseminated intravascular coagulation.
Exclusion criteria: Allogenic bone marrow transplantation
Interventions: None
Outcomes: 30 day mortality rate Median length of ICU stay
Results: <u>30 day mortality rate</u> 57 (65.5%) (for entire sample) <u>Odds ratio for 30 day mortality</u> Odds ratio: 7.05; 95% CI, 1.17 to 42.21 (P = 0.03)

Median length of hospital stay 5 (2–13.75) (for entire sample) (Quality of life and overtreatment were not reported. Severe sepsis was not reported on the basis that all participants were suffering septic shock at baseline. Median length of ICU stay was reported (although this was not linked to time to antibiotic treatment, reported for the entire sample), median length of hospital stay was not)
General comments: This was a retrospective study of 88 cancer patients admitted to ITU with septic shock, aiming to identify predictors of 30 day mortality. A multivariable analysis was performed using a stepwise forward selection procedure.

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Lin, M. Y., Weinstein, R. A., & Hota, B. (2008). Delay of active antimicrobial therapy and mortality among patients with bacteraemia: impact of severe neutropenia. *Antimicrobial Agents & Chemotherapy, 52,* 3188-3194.
Country: USA
Design: Retrospective cohort study
Population: Adult 1523 episodes of mono-microbial bacterial bloodstream infections
Inclusion criteria: Adults (age ≥ 18) Monomicrobial bacterial bacterial bloodstream infection
Exclusion criteria: Blood isolates of common skin commensals Anaerobes Discharge/death within one day of hospital admission Bacteremia due to a second organism within 30 days of index bacteremia
Interventions: No intervention
Follow up: 30 days
Outcomes: Mortality
Results: <u>Antimicrobial therapy delay</u> Antimicrobial agent within 24 hours of index blood culture: 983 (64.5%)

Not treated with antimicrobial agent within 24 hours of index blood culture (delayed): 540 (35.5%)

Mortality

Antimicrobial agent within 24 hours of index blood culture: 8.0%

Not treated with antimicrobial agent within 24 hours of index blood culture (delayed): 9.3%

Odds ratio for 30 day mortality

Delay versus non delay (ICU)

ANC < 100: Adjusted odds ratio, 18; 95% CI, 2.84 to 114.5 (P < 0.01)

ANC 100-500: Adjusted odds ratio, 1.92; 95% CI, 0.17 to 21.6 (P = 0.60)

ANC > 500: Adjusted odds ratio, 1.78; 95% CI, 0.91 to 3.45 (P = 0.10)

Delay versus non-delay (non-ICU)

ANC < 100: Adjusted odds ratio, 5.56; 95% CI, 0.85 to 36.3 (P < 0.01)

ANC 100-500: Adjusted odds ratio, 0.59; 95% CI, 0.06 to 6.22 (P = 0.60)

ANC > 500: Adjusted odds ratio, 0.55; 95% CI, 0.29 to 1.02 (P = 0.10)

(Over treatment, severe sepsis, length of stay, and quality of life were not reported in relation to time to antibiotic treatment)

General comments:

This was a well conducted large-scale retrospective cohort study of 1523 patients with mono-microbial bloodstream infections from 2001 to 2006. The impact of delay of active antimicrobial therapy on mortality was examined using multivariable logistic regression. Only 67/1523 (4.4%) participants had ANC < 500 cells/µl. 44/1523 (2.8%) had what was defined as severe neutropenia (ANC < 100 cells/µl). It was unclear whether participants were cancer patients.

10.1 Timing of initial antibiotic: a wider search of timing of antibiotic therapy: removing the requirement of neutropenia

Rationale

No studies meeting the criteria set out by the PICO were identified. Furthermore, only two studies containing indirect evidence were found. On this basis, a wider search was necessary to identify additional studies of time to antibiotic therapy. The requirement of participants having neutropenia was removed in the second search, in a bid to identify further indirect evidence. The search produced over 35,000 hits. It was not feasible to consider this number of studies. Consequently, 'systematic review' filter was applied.

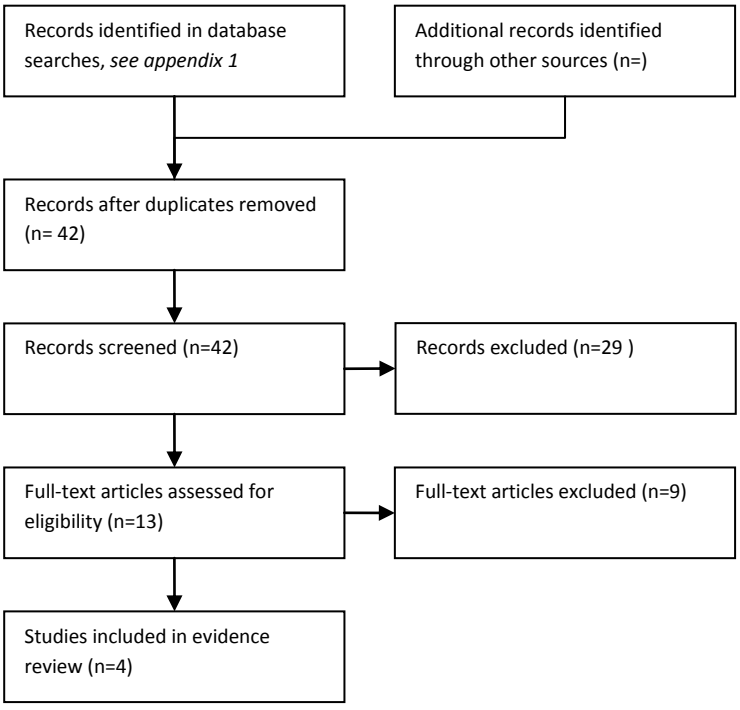
Question in PICO format

Patients/population	Factors	Outcomes
Patients with suspected bacterial infection	Length of time before empiric antibiotics are given (symptom to needle time)	• Over treatment • Mortality • Severe sepsis • Length of stay • Duration of fever • Quality of life

RESULTS

Results of literature searches

Figure 10.2 Study flow diagram



Study selection

The information specialist (SB) did the first screen of the literature search results. Two reviewers (NB and CL) subsequently selected potentially eligible studies by comparing titles and abstracts to the inclusion criteria presented in the PICO question. Full text articles were obtained for all studies identified as being potentially eligible. These articles were checked against the inclusion criteria. Data were extracted by one reviewer (CL) and checked by another (NB).

Study characteristics

Four systematic reviews considering the timing of antibiotic therapy were identified (Pines et al. 2009, Yu et al. 2008, Siddiqui et al 2010 and McGregor et al. 2007). Two were systematic reviews of studies evaluating the impact of time to antibiotic therapy in Community Acquired Pneumonia (Pines et al. 2009 and Yu et al. 2008); one was concerned with bacteremia (McGregor et al. 2007); and one was concerned with severe sepsis (Siddiqui et al. 2010). Three were systematic reviews of observational studies (Pines et al. 2009, Yu et al. 2008, and McGregor et al. 2007); one was a systematic review of Randomised Controlled Trials (RCTs). Two included only studies of adult participants (McGregor et al. 2007 and Siddiqui et al 2010); two included studies of adult and paediatric participants (Pines et al. 2009 and Yu et al. 2008). None of the identified reviews included meta-analyses. These were small systematic reviews. The number of papers identified related to the timing of antibiotic therapy ranged from 0 (Siddiqui et al 2010) to 13 (Yu et al. 2008).

Evidence statements

Overtreatment

Overtreatment was not reported by the identified systematic reviews.

Short term mortality

Two of the four systematic reviews reported data on short term mortality related to the timing of antibiotic therapy (Pines et al. 2009 and Yu et al. 2008).

Yu et al calculated individual odds ratios for each study for delayed versus non delayed administration; these ranged from 0.24 (95% CI, 0.08 to 0.71) to 1.99 (95% CI, 1.22 to 13.45) in studies with delay < 4 hours and 0.60 (95% CI, 0.37 to 1.35) to 0.96 (95% CI, 0.70 to 1.30) in studies defining a delay as < 8 hours.

Pines et al. took the approach of categorising studies in terms of whether or not they supported early administration of antibiotics: 2 supported early administration; 1 was neutral; and 5 opposed early administration. The criteria used for categorisation were unclear.

Severe sepsis

Severe sepsis was not reported by the identified systematic reviews.

Length of stay

Length of stay was not reported in relation to timing of antibiotic therapy by any of the identified systematic reviews.

Duration of fever was not reported by the identified systematic reviews.

Duration of fever and quality of life were not reported by the identified systematic reviews.

EVIDENCE TABLES

Study ID	Infection	Population	Study types	No. studies considering time to antibiotic therapy	Meta analysis	Definition of early antibiotic therapy	Results	Comments
Yu et al 2008	Community acquired pneumonia	Adult and paediatric	Observational studies	13	No	< 4 hours And < 8 hours	Odds ratios were calculated for individual studies where possible. <u>Short term mortality (<4 hours)</u> Ziss et al. 2003 (OR = 0.82; 95% CI, 0.20 to 3.40) Wilson et al. 2005 (OR = 0.24; 95% CI, 0.08 to 0.71) Houck et al. 2004 (OR = 0.85; 95% CI, 0.74 to 0.98) Marrie et al 2005 (OR = 1.02; 95% CI, 0.77 to 1.36) Bodi et al 2005 (OR = 0.82; 95% CI, 0.54 to 1.24) Waterer et al 2006 (OR = 0.36; 95% CI, 0.15 to 0.83) Silber et al 2003 (OR = 1.99; 95% CI, 1.22 to 13.45) <u>Short term mortality (<8 hours)</u> Mortensen et al 2004 (OR = 0.60; 95% CI, 0.37 to 1.35) Dedier et al 2001 (OR = 0.85; 95% CI, 0.75 to 0.96) Marrie et al 2005 (OR = 0.96; 95% CI, 0.70 to 1.30)	MEDLINE, EMBASE, and the Cochrane Library were searched. Studies considering inpatient or 30-day mortality among patients receiving early versus delayed antibiotics were included. Studies were categorized according to whether they were retrospective or prospective and whether they adjusted for severity with the Pneumonia Severity Index. Odds ratios were calculated for each study. These were not pooled.
Pines et al 2009	Community acquired pneumonia	Adult and paediatric	Observational studies	8	No	< 4 hours	Studies were categorised as 'supporting evidence', 'neutral evidence' or 'opposing evidence'.	Only one data base was searched for relevant studies (PubMed). It is doubtful that the literature search was sufficiently rigorous to

							2 studies supported door-to-needle time of < 4 hours 1 study was categorised as neutral 5 studies opposed door-to-needle time of < 4 hours. These were said to document "increased rates of mis-diagnosis"/ "interventions that might result in the inappropriate prioritization of patients for the purpose of meeting quality measures"	identify all relevant studies. Studies were categorised according to study design, but study quality was not reported. The authors did not conduct a meta-analysis. A rather subjective method of categorising studies as containing 'supporting evidence', 'neutral evidence' or 'opposing evidence' was used. The criteria for categorisation were unclear.
Siddiqi et al 2010	Severe sepsis	Adult	RCTs	0	No	< 1 hour	No RCTs considering time to antibiotic administration for severe sepsis were identified.	This was Cochrane review of early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis. No RCTs considering the impact of time to antibiotic administration for severe sepsis were found.
Mc Gregor 2007	Bacteremia	Adult	Observational studies	2	No	No definition	No results related to time to antibiotic therapy were reported	

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Lin, M. Y., Weinstein, R. A., & Hota, B. (2008). Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. *Antimicrobial Agents & Chemotherapy, 52,* 3188-3194.

McGregor, J. C., Rich, S. E., Harris, A. D., Perencevich, E. N., Osih, R., Lodise, T. P. et al. (2007). A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients. *Clinical Infectious Diseases, 45,* 329-337.

Pines, J. M., Isserman, J. A., & Hinfey, P. B. (2009). The measurement of time to first antibiotic dose for pneumonia in the emergency department: a white paper and position statement prepared for the American Academy of Emergency Medicine. [Review] [17 refs]. *Journal of Emergency Medicine, 37,* 335-340.

Siddiqui, S. & Razzak, J. (2010). Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults. [Review]. *Cochrane Database of Systematic Reviews.(10):CD007081, 2010.,* CD007081.

Yu, K. T. & Wyer, P. C. (662). Evidence-based emergency medicine/critically appraised topic. Evidence behind the 4-hour rule for initiation of antibiotic therapy in community-acquired pneumonia. [Review] [34 refs]. *Annals of Emergency Medicine, 51,* 651-662.

11. Empiric intravenous antibiotic monotherapy or empiric intravenous antibiotic dual therapy. (Topic E3)

Guideline subgroup members

Anton Kruger (lead), Wendy King, Barbara Crosse, Bob Phillips and Rosemary Barnes.

Review question

Is there a difference in the effectiveness of empiric intravenous antibiotic monotherapy and empiric dual therapy in the treatment of patients with neutropenic sepsis?

Rationale

Neutropenic sepsis is a potentially lethal condition especially when the infection is due to gram negative bacteria. Early studies focussed on empiric antibiotic treatment combinations using two, three and even five drug regimens. These early trials were small and produced inconsistent and clinically poor outcomes by today's standards. In 1973 the European Organisation for Research on Treatment of Cancer (EORTC) formed a cooperative group to research the problem. In parallel over the next three decades, a stream of new drugs based on the beta-lactam structure entered the market: some of these and the older drugs have now disappeared. Early treatments were assessed in the empiric setting, but emphasis was also placed on the effectiveness of agents in controlling infections subsequently shown to have been caused by known pathogens.

Combination therapy including a beta lactam antibiotic (penicillin or cephalosporin) combined with an aminoglycoside formed the backbone of the early studies due to theoretical and in-vitro synergism predicted for the combination and also because of known gaps in microbiological sensitivities for the earlier beta lactams. The effectiveness of these combinations was confirmed in the first EORTC study. From the early 1980's and for more than 20 years on, a number of randomised comparisons of monotherapy based on emerging new Beta-lactam antibiotics with a particularly broad spectrum of activity (and known effectiveness against dangerous organisms such as Pseudomas) versus combination therapy (beta-lactam plus aminoglycoside) have been undertaken. Many of these studies involved more than two drugs, with a "newer" Beta lactam in the trial arm being compared with an "older" cephalosporin or penicillin combined with an aminoglycoside in the control arm.

Monotherapy has potential advantages over combination therapy. These could include cost, resource and staff time and avoidance of the side effects and need for monitoring of drug levels associated with aminoglycosides. Aminoglycoside kidney toxicity is usually immediately apparent and can interfere with ongoing cancer treatment. On the other hand inner ear toxicity (deafness and balance problems) can be insidious and often presents many years after the exposure. This can result in an underestimation of this potentially crippling side effect.

A Cochrane review and meta analysis published in 2003 concluded that monotherapy (based on newer broad spectrum beta-lactams) was superior to combination regimens (with narrower spectrum beta-lactams) in terms of efficacy and associated with fewer side effects. Despite this, combination regimens are still widely employed and a further analysis of the question is warranted. There are additional reasons why aminoglycosides may still be used, including concerns about secondary infection with clostridium difficile and emerging forms of antibiotic resistance. In addition,

particular subgroups of patients may fare better with combination therapy and local knowledge of microbiological flora may also affect treatment choices. An up to date evidence base is needed to guide modern treatment decisions. This will have to take into account the historical perspective and potential microbiological consequences.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with neutropenic sepsis	Intravenous antibiotic monotherapy (Piperacillin/tazobactam Ceftazidime Meropenem Imipenem Aztreonam Ciprofloxacin)	Intravenous antibiotic dual therapy (Monotherapies plus aminoglycosides)	• Antibiotic resistance • Aminoglycoside toxicity • Death • Critical care • Length of stay • Duration of fever • Quality of life

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The full strategy will be available in the full guideline.

We restricted the search to published randomised (or quasi randomised) trials and systematic reviews of such trials. A comprehensive and good quality systematic review of this question was published in 2007 (Paul et al, 2007). Our literature search was therefore limited to papers published after 2005, to identify new evidence not included in their review. The search was done on the 23rd of October 2010 and updated on 7th November 2011.

Drug names for the literature search

- Drug names for monotherapy
  - Penicillins: Piperacillin with tazobactam [AK note: Piperacillin with Tazobactam is the only surviving Ureidopenicillin in the market. Other discontinued drugs (Azlocillin, Mezlocillon) would have been important agents in earlier randomised studies and their exclusion might inappropriately influence the review outcome if insufficient recent studies are found. Ticarcillin, a carboxypenicillin (and now combined with clavulanic acid) is still available and may appear in relevant papers. It is a less desirable drug on microbiological sensitivity criteria alone but should be included]
  - Quinolones: Ciprofloxacin
  - Cephalosporins: Ceftazidime
  - Monobactams: Aztreonam
  - Carbapenems: , Meropenem, Imipenem.
- Aminoglycosides: Gentamicin [AK note: some of the original aminoglycosides such as Netilmicin are no longer listed in the BNF and are presumably no longer marketed.

Nevertheless, relevant studies may still exist and as there relatively few differences between the drugs in this group I would include all of the currently used parenteral drugs (Amikacin, Gentamicin, Tobramycin) and Netilmicin. I am not aware of any studies that included Streptomycin but there may be some. Also be aware that some papers have used "y" instead of "i" in the "mYcin". An alternative strategy might be to search under the generic term aminoglycoside]

Selection of studies

The information specialist (SB) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Data synthesis

Where the searches identified new data we updated the meta-analyses reported by Paul et al (2007). For consistency between updated and original analyses we used the same statistical methods as the original review. Dichotomous outcomes were analysed by calculating the relative risk and its 95% confidence interval for each study. A Mantel-Haenzel fixed effect model was used for all meta-analyses in the Paul et al (2007) review, unless significant heterogeneity was observed (defined as $P < 0.1$ or $I^2 > 50\%$) in which case the random effect model was used.

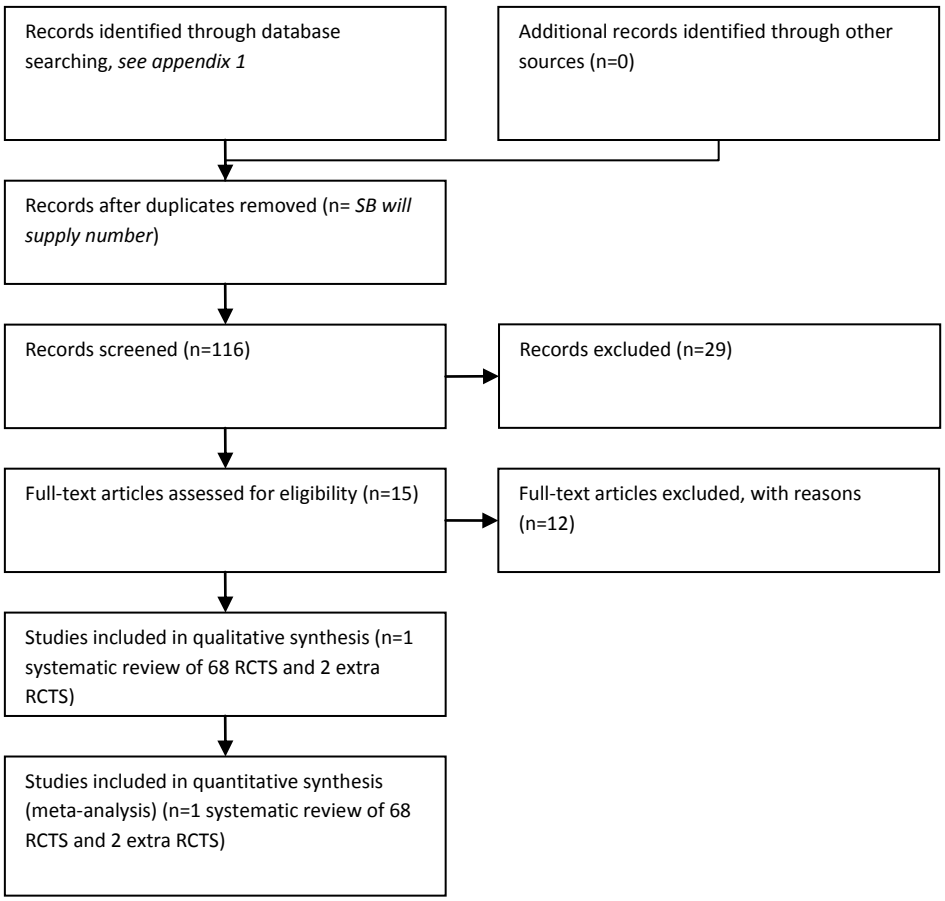
Forest plots were generated whenever additional trials were added to the meta-analyses of Paul et al (2007) (see figures 1 to 4).

Paul et al (2007) considered several patient and treatment subgroups, we can update these subgroup analyses with any new trial data if the guideline group thinks it appropriate. Patient subgroups included: patients with severe neutropenia (absolute neutrophil count < 100/m3), those with microbiologically documented infections, those with documented *Pseudomonas aeruginosa* infections, those with bacteraemia, adults versus children and those with underlying haematological malignancy or bone marrow transplantation. Treatment subgroups included: monotherapy drug, same beta-lactam used in both combined and monotherapy and aminoglycoside dosing regimen.

RESULTS

Results of the literature searches

Figure 11.1 Study flow diagram



Description of included studies

Initial screening identified 116 relevant papers, 15 of these were ordered and three included as evidence. The reasons for exclusion are noted in the list of excluded references below.

Seventy randomised or quasi randomised trials were included: 68 from the Paul et al (2007) systematic review and three later trials (Pereira et al., 2009; Yildirim et al., 2008 and Zengin et al., 2011).

Populations in the included trials:

Most of the trials were in patients with haematological cancers: 34/70 trials included only patients with haematological cancers and in a further 32/70 trials a majority of the patients had haematological cancers.

43/70 trials were in adult cancer patients, 14/70 trials included only children and 13/70 included both adults and children.

Antibiotics used in the included trials

In 15 trials the same beta-lactam was used in both arms of the trial. In these trials the beta-lactam was: ceftazidime (seven trials), piperacillin-tazobactam (three trials), cefepime (three trials), imipenem (two trials) and in one trial cefoperazone (one trial assessed more than one beta-lactam monotherapy). The other 55 trials compared a beta-lactam (typically a new drug) to a narrower spectrum beta-lactam plus an aminoglycoside. See Table 11.1 for summary of antibiotics used in the trials.

Table 11.1. Beta-lactam classes used for montherapy and combined therapy

Beta-lactam used for monotherapy	Beta-lactam used for combined therapy	Number of trials	No. of trials using same beta-lactam in both trial arms
Cephalosporin	Cephalosporin	22	11
Carbapenem	Cephalosporin	18	–
Cephalosporin	Penicillin	9	–
Carbapenem	Penicillin	9	–
Penicillin	Penicillin	6	3
Penicillin	Cephalosporin	4	–
Carbapenem	Carbapenem	2	2

The following aminoglycosides were used in combined therapy: amikacin (42 trials), tobramycin (14 trials), gentamicin (11 trials) and netilmicin (3 trials).

Overall risk of bias in the included trials

Allocation concealment was judged to be adequate in 27/70 trials. Blinding was reported in 10/70 trials (six single blinding and four double blinding). Intention to treat (ITT) analysis of treatment failure was reported in 23/70 trials; ITT analysis of mortality was reported in 25/48 trials.

The unit of randomisation was the patient in 24/70 studies and the episode of neutropenia / fever in the other trials. Studies reporting multiple episodes from the same patients did not adjust their analyses for the correlation between multiple data points from the same patient.

Fourteen trials used a pre-specified follow-up period, ranging from three days to one month following the end of treatment. Some trials described follow-up until the end of treatment, without reporting the actual duration. Two trials reported follow-up of greater than one month.

Evidence Statements

Evidence from trials directly comparing single agent with combined treatment

There was moderate quality evidence from 44 studies with over seven thousand episodes of neutropenia and fever which did not show a significant difference in the risk of all cause mortality between monotherapy and combined therapy. This evidence is summarised in table 11.2.

Moderate quality evidence from 55 studies showed that treatment failure was less likely with monotherapy than combined therapy, when combined therapy used a narrower spectrum antibiotic

than was used for monotherapy. Fifteen studies where the same beta-lactam was used for both monotherapy and combined therapy, however, found treatment failure more likely with monotherapy.

Moderate quality evidence showed that monotherapy was associated with fewer adverse events, including nephrotoxicity.

Moderate quality evidence showed that monotherapy and combined therapy had similar rates of bacterial secondary infection.

Low quality evidence showed fungal secondary infection was more likely with combined therapy.

Very low quality evidence from two studies with 152 patients suggested that colonisation of resistant Gram-negative bacteria was more likely with monotherapy, but such bacteria were only detected in six patients overall.

There was no evidence about quality of life and no useful evidence about the duration of hospital stay.

1 ***Table 11.2 - GRADE evidence profile for empiric IV antibiotic monotherapy versus empiric IV antibiotic dual therapy***

Quality assessment							Summary of findings				
							No of patients (or episodes)		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	empiric intravenous antibiotic monotherapy	empiric intravenous antibiotic dualtherapy	Relative (95% CI)	Absolute	
Death from any cause											
44	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267/3666 (7.3%)	292/3505 (8.3%)	RR 0.88 (0.75 to 1.03)	10 fewer per 1000 (from 21 fewer to 2 more)	MODERATE
Treatment failure (same beta-lactam)											
15	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	603/1355 (44.5%)	561/1406 (39.9%)	RR 1.11 (1.02 to 1.21)	44 more per 1000 (from 8 more to 84 more)	MODERATE
Treatment failure (different beta-lactam)											
55	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1573/3919 (40.1%)	1603/3749 (42.8%)	RR 0.92 (0.87 to 0.96)	34 fewer per 1000 (from 17 fewer to 56 fewer)	MODERATE
Any adverse event											
48	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	872/3675 (23.7%)	988/3665 (27%)	RR 0.86 (0.8 to 0.93)	38 fewer per 1000 (from 19 fewer to 54 fewer)	MODERATE
Any nephrotoxicity											
37	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	78/3187 (2.4%)	187/3224 (5.8%)	RR 0.47 (0.36 to 0.61)	31 fewer per 1000 (from 23 fewer to 37 fewer)	LOW

Quality assessment							Summary of findings				
							No of patients (or episodes)		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	empiric intravenous antibiotic monotherapy	empiric intravenous antibiotic dualtherapy	Relative (95% CI)	Absolute	
Severe nephrotoxicity											
18	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	1/1998 (0.1%)	19/2004 (0.9%)	RR 0.16 (0.05 to 0.49)	8 fewer per 1000 (from 5 fewer to 9 fewer)	LOW
Bacterial superinfection											
29	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/2421 (10.7%)	252/2415 (10.4%)	RR 1.00 (0.86 to 1.18)	0 fewer per 1000 (from 15 fewer to 19 more)	MODERATE
Fungal superinfection											
20	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	46/1716 (2.7%)	68/1721 (4%)	RR 0.70 (0.49 to 1)	12 fewer per 1000 (from 20 fewer to 0 more)	LOW
Colonization of resistant Gram negative bacteria											
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	Very serious[4]	none	5/152 (3.3%)	1/152 (0.7%)	not pooled	not pooled	VERY LOW
Length of stay											
4	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	0	-	not pooled	
Quality of life											
0	no evidence					none	0	0	-	not pooled	

Quality assessment							Summary of findings				
							No of patients (or episodes)		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	empiric intravenous antibiotic monotherapy	empiric intravenous antibiotic dualtherapy	Relative (95% CI)	Absolute	
	available										

[1] Less than half of studies had adequate allocation concealment or reported blinding.
[2] 4/15 trials had adequate allocation concealment, 2/15 used blinding, details about randomisation method were given in 8/15 and 4/15 reported intention to treat analysis.
[3] There was significant heterogeneity but this appears to be due to the type of beta-lactam used for monotherapy.
[4] Low or very low number of events
[5] No blinding, information on allocation concealment, one of the studies reported the method of randomisation.
[6] No blinding, allocation concealment was acceptable in 2 of the 4 trials

Death from any cause

All cause mortality (typically within one month of the start of treatment) was reported in 44 trials including 7171 episodes of neutropenia and fever. One additional trial (Pereira et al, 2009) was added to the Paul et al (2007) meta-analysis (see figure 11.2). The relative risk (RR) of mortality in the monotherapy group versus the combined therapy group was 0.88 (95% C.I. 0.75 to 1.03) suggesting a non-statistically significant 12% reduction in the risk of mortality with monotherapy.

The subgroup analyses of mortality of Paul et al (2007) were updated (Table 11.3). Data from Pereira et al (2009) were added to the different beta-lactam, haematological malignancy and children subgroup analyses. There were no significant differences in mortality in any subgroup.

Table 11.3 Subgroup analyses for all cause mortality

Subgroup	**Studies**	**Episodes**	**Risk Ratio (M-H, Fixed, 95% CI) (<1 favours monotherapy, >1 favours dual therapy)**
Overall	44	7171	0.88 [0.75, 1.03]
Same beta-lactam in both trial arms	10	1646	0.74 [0.53, 1.06]
Different beta-lactam in each trial arm	34	5525	0.91 [0.77, 1.09]
Haematological malignancies	22	3448	0.88 [0.68, 1.13]
Adults	29	4308	0.93 [0.77, 1.12]
Mixed age group or age unknown	6	2089	0.74 [0.52, 1.04]
Children	9	774	0.81 [0.40, 1.62]
Patients with severe neutropenia (ANC <100/mm^3)	6	737	0.68 [0.37, 1.24]
Patients with bacteraemia	14	676	0.74 [0.46, 1.18]

Duration of fever / Treatment failure

Duration of fever was not reported in the Paul et al (2007) review. After discussion with the lead GDG member for this topic (AK) "treatment failure" was included as an outcome because it incorporates duration of fever in its definition. Treatment failure was defined as any of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of the presenting infection; any modification of the assigned empirical antibiotic treatment. A problem with treatment failure as an outcome (as noted by Paul et al, 2007) is that treatment modification might have been biased. Most of the trials were open trials, where clinicians knew the empirical therapy the patient was receiving and this knowledge may have biased their decision to modify antibiotic treatment.

Treatment failure was reported in all 70 trials including 10429 episodes of neutropenia and fever. Two additional trials (Pereira et al, 2009; Yildirim et al, 2008) were added to the original Paul et al (2007) meta-analyses (see figure 11.3). Pooling all 70 trials gave a relative risk of 0.94 (95% C.I. 0.97 to 1.01) but there was significant there was significant heterogeneity (P=0.04, I^2 = 24%).

The subgroup analyses of treatment failure in Paul et al (2007) were updated with data from Pereira et al (2009), Yildirim et al (2008) and Zengin et al (2011). These analyses suggested that using the same beta-lactam for both monotherapy and combined therapy was related to the risk of treatment failure. In the 15 trials where the same beta-lactam was used in both trial arms, the risk of treatment failure in the monotherapy group was greater than in the combined therapy group, RR = 1.11 (95% C.I. 1.02 to 1.21). In the 55 trials where a different beta-lactam was used in each trial arm, the risk of treatment failure in the monotherapy group was less than in the combined therapy group, RR = 0.92 (95% C.I. 0.87 to 0.96).

Table 11.4 Subgroup analyses for treatment failure

Subgroup	**Studies**	**Episodes**	**Risk Ratio (M-H, Fixed, 95% CI) (<1 favours monotherapy, >1 favours dual therapy)**
Overall	70	10429	0.97 [0.92, 1.01]
Same beta-lactam in both trial arms	15	2761	1.11 [1.02, 1.21]
Different beta-lactam in each trial arm	55	7668	0.92 [0.87, 0.96]
Children, same beta-lactam in both trial arms	1	91	2.74 [1.08, 6.98]
Children, different beta-lactam in each trial arm	12	1018	0.97 [0.83, 1.13]
Mixed or unknown age group, same beta-lactam	3	985	1.01 [0.90, 1.14]
Mixed or unknown age group, different beta-lactam	10	1803	0.92 [0.83, 1.03]
Adults, same beta-lactam	11	1685	1.17 [1.04, 1.32]
Adults , different beta-lactam	29	4160	0.90 [0.85, 0.96]
Haematological malignancies, same beta-lactam	3	49	1.04 [0.90, 1.21]
Haematological malignancies, different beta-lactam	24	3603	0.93 [0.87, 1.00]
Patients with severe neutropenia (ANC <100/mm3), same beta-lactam	2	237	1.48 [1.12, 1.96]
Patients with severe neutropenia (ANC <100/mm3), different beta-lactam	9	871	0.96 [0.84, 1.10]
Patients with bacteraemia, same beta-lactam	6	395	1.05 [0.90, 1.23]
Patients with bacteraemia, different beta-lactam	20	1149	0.86 [0.78, 0.95]

Adverse events

Any adverse event was reported 48 trials including 7340 episodes of neutropenia and fever. An additional trial (Pereira et al, 2009) was added to the Paul et al (2007) meta-analysis (see Figure

11.4). Monotherapy was associated with a lower risk of adverse events than combined therapy, RR= 0.86 (95 %C.I. 0.80 to 0.93), but there was significant heterogeneity in this meta-analysis (P<0.0001, I=51%).

Subgroup analyses according to specific monotherapy drugs showed a statistically significant reduction in the risk of adverse events only with ceftazidime monotherapy (RR = 0.64; 95% C.I. 0.53 to 0.76) and moxalactam monotherapy (RR = 0.64; 95% C.I. 0.53 to 0.76), suggesting the drug used for monotherapy might account for some of the heterogeneity seen in the overall meta-analysis.

Nephrotoxicity was reported in 37 trials including 6411 episodes of neutropenia and fever. No new evidence about nephrotoxicity was identified in our literature search. The risk of any nephrotoxicity was significantly lower with monotherapy than with combined therapy, RR=0.45 (95% C.I. 0.35 to 0.57). With severe nephrotoxicity the effect in favour of monotherapy was more marked: RR=0.16 (95% C.I. 0.05 to 0.49; from 18 trials with 4002 episodes).

Paul et al (2007) did subgroup analyses of any nephrotoxicity and severe nephrotoxicity according to aminoglycoside dosing regimen (see Tables 11.5 and 11.6). No new nephrotoxicity data were identified in our literature searches. The risk of any nephrotoxicity was significantly lower with monotherapy than with combined therapy for both once daily and multiple daily aminoglycoside dosing regimens. A similar pattern was seen for severe nephrotoxicity although the difference was not statistically significant in the four studies using a once daily aminoglycoside dosing regimen.

Table 11.5 Subgroup analyses for any nephrotoxicity

Subgroup	**Studies**	**Episodes**	**Risk Ratio (M-H, Fixed, 95% CI) (<1 favours monotherapy, >1 favours dual therapy)**
Overall	37	6411	0.45 [0.35, 0.57]
Once daily aminoglycoside regimen	6	1510	0.29 [0.13, 0.63]
Multiple daily aminoglycoside regimen	31	4901	0.47 [0.36, 0.61]

Table 11.6 Subgroup analyses for severe nephrotoxicity

Subgroup	**Studies**	**Episodes**	**Risk Ratio (M-H, Fixed, 95% CI) (<1 favours monotherapy, >1 favours dual therapy)**
Overall	18	4002	0.16 [0.05, 0.49]
Once daily aminoglycoside regimen	4	1329	0.20 [0.03, 1.14]
Multiple daily aminoglycoside regimen	14	2673	0.14 [0.03, 0.60]

Secondary infection

Superinfection was defined as new, persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen or the development of a new site of infection.

Bacterial superinfection was reported 29 trials including 4961 episodes of neutropenia and fever. An additional trial (Pereira et al, 2009) was added to the Paul et al (2007) meta-analysis (Figure 11.5). There was no significant difference between treatment groups in the risk of bacterial superinfection: RR=1.02 (95% C.I. 0.87 to 1.19).

Fungal superinfection was reported 20 trials including 3437 episodes of neutropenia and fever. Our searches identified no new evidence for this outcome. The risk of fungal superinfection was lower in the monotherapy group than in the combined therapy group, RR=0.70 (95% C.I. 0.49 to 1.00). However the data for fungal superinfection were relatively sparse, with 114 events in total. Fungal superinfection occurred in around 3% of episodes and bacterial superinfection in around 11% of episodes.

Resistant colonisation

Resistant colonisation was defined as the isolation (during or following therapy) of Gram-negative bacteria resistant to the beta-lactam included in the empiric regimen, without symptoms or signs of infection. There was very little evidence about this outcome. Although seven trials supplied reported resistant colonisation only two trials reported the relative rates of resistant colonisation between the treatment groups (Cornelissen 1992; Norrby, 1987). In these trials resistant Gram-negative bacteria were detected in 5/152 patients in the monotherapy group compared with 1/152 patients in the combination therapy group.

Length of hospital stay

Four trials reported this outcome; in three of the trials the duration of hospital stay was shorter in the monotherapy group. In the other trial the duration of hospital stay was shorter in the combined therapy group. The difference was not statistically significant (at $P<0.05$) in any of these trials. Data were not pooled due to the different ways in which the trials reported hospital stay.

Quality of life

Quality of life was not an included as an outcome in Paul et al (2007). The abstracts of the trials included in the Paul et al (2007) review were checked for mention of quality of life outcomes, but none was found and neither of the new studies (Pereira et al 2009; Yildrim et al, 2008) reported quality of life as an outcome. It is debateable whether differences between the quality of life of the treatment groups would be measureable over the short period of follow-up used in these trials.

Figure 11.2 Forest plot of all cause mortality

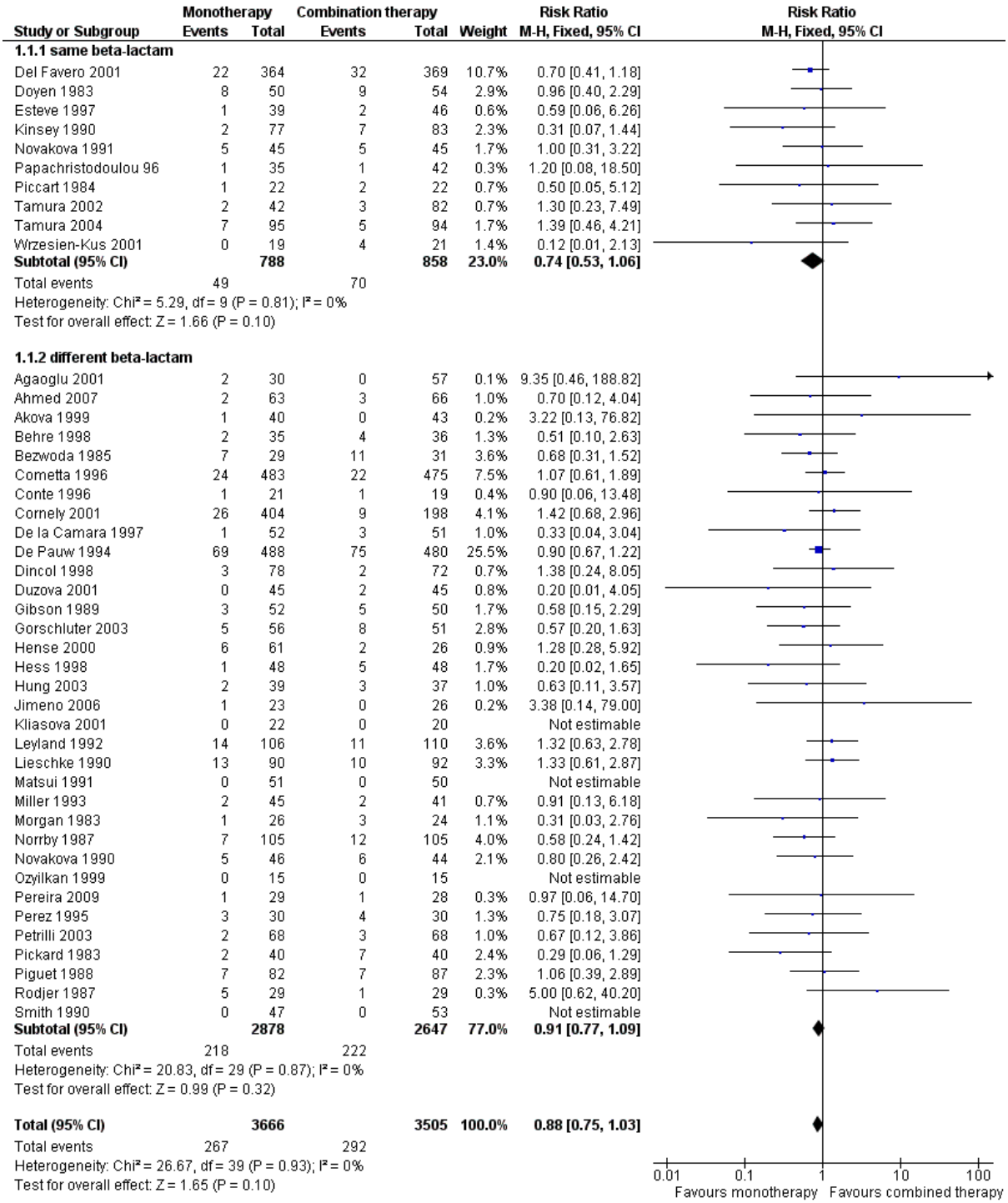


Figure 11.3 Forest plot of treatment failure

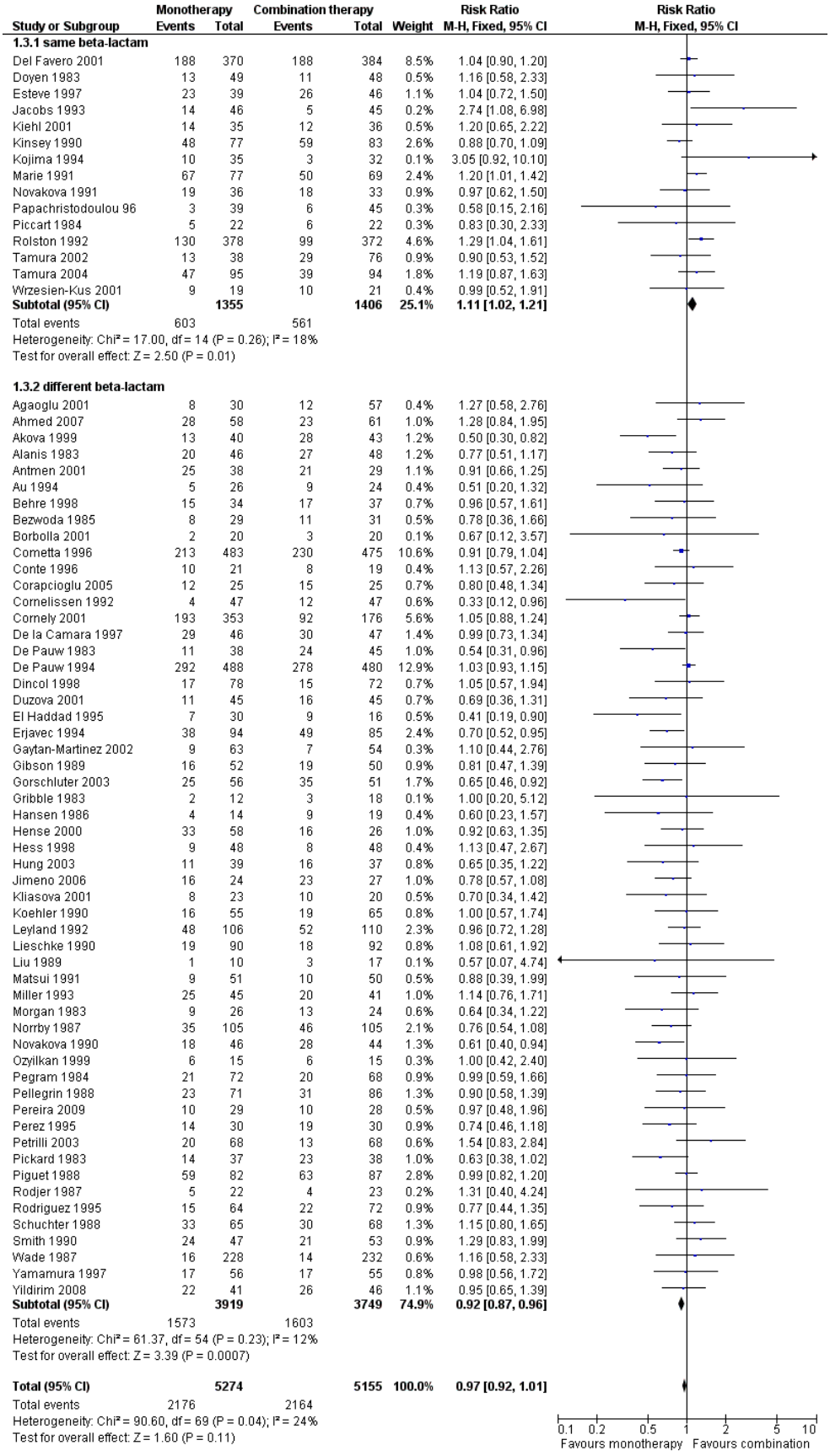


Figure 11.4 Forest plot of any adverse event

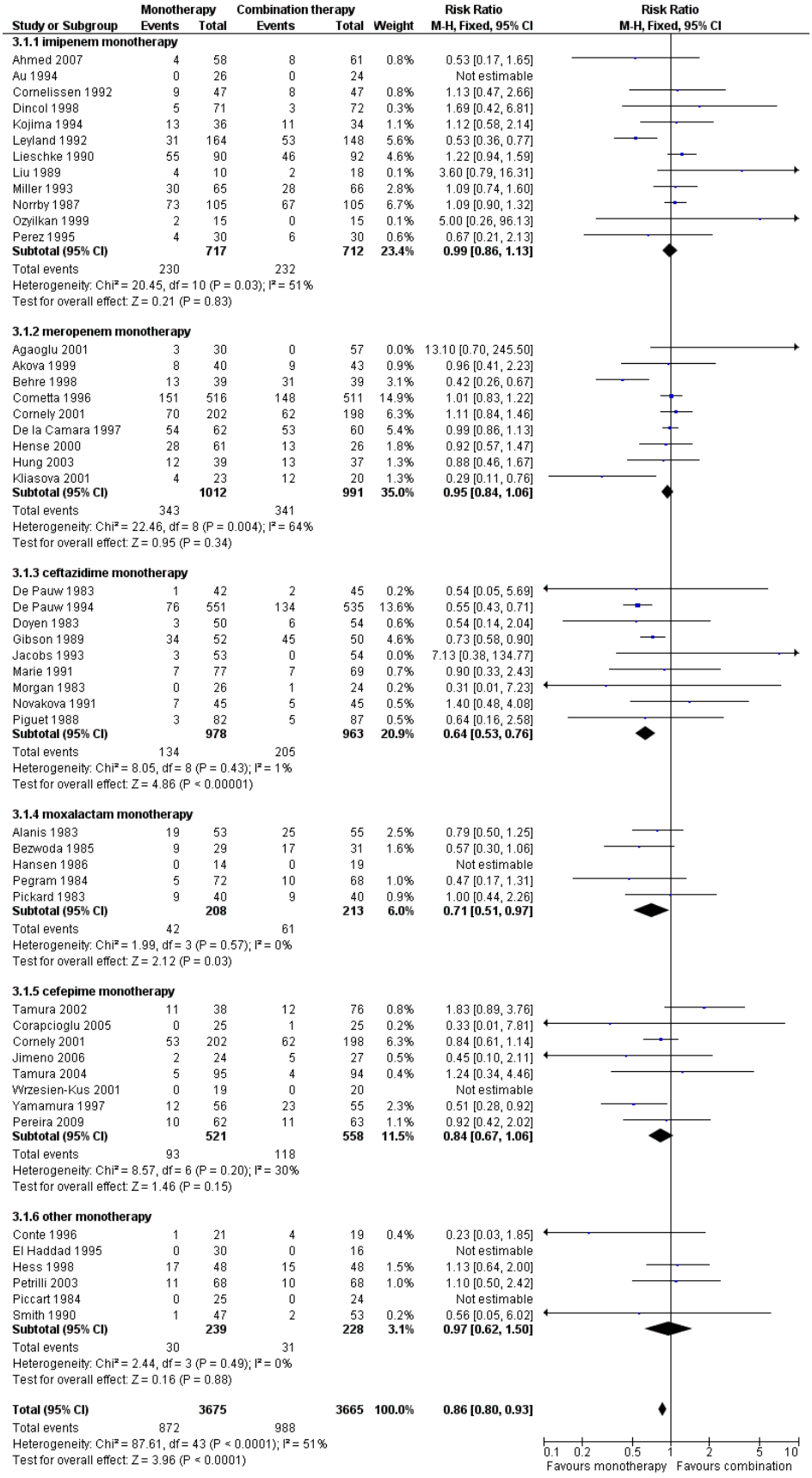
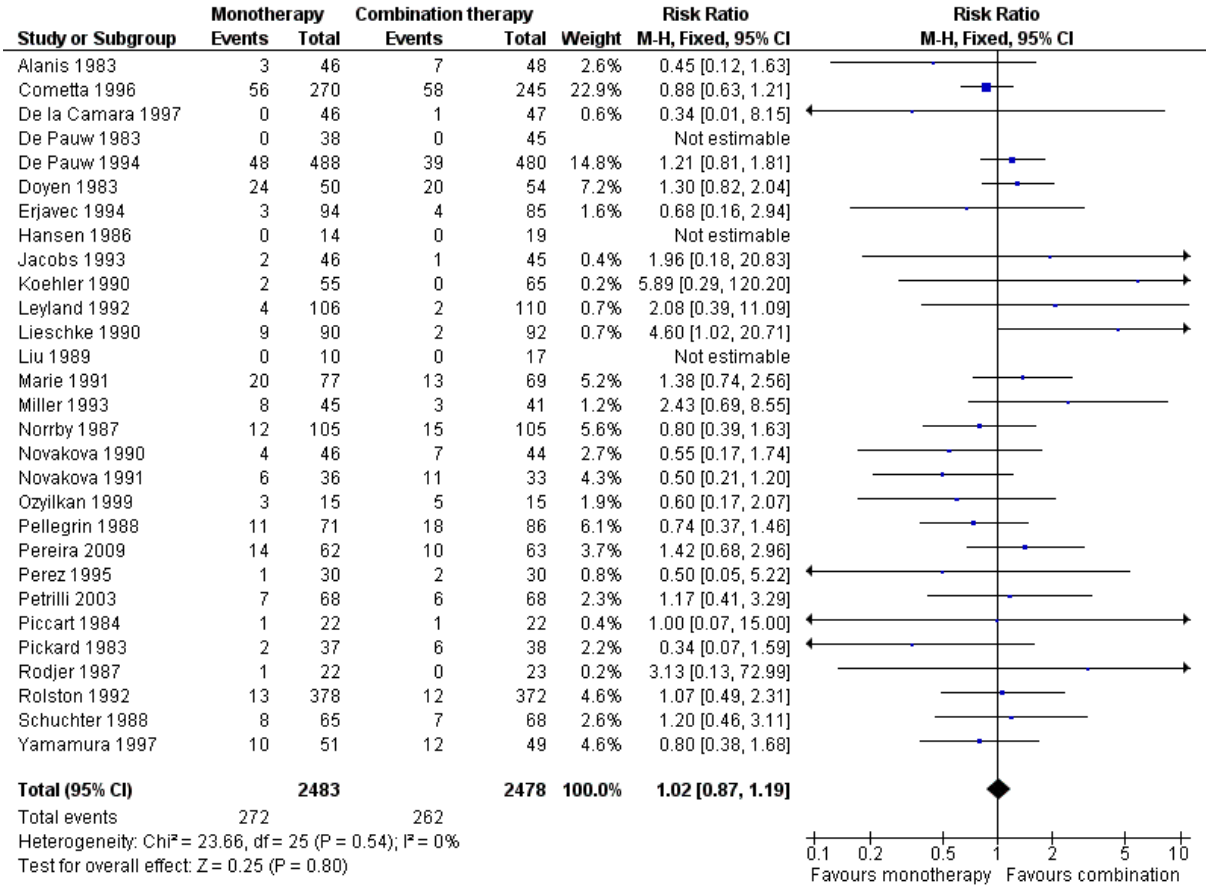


Figure 11.5 Forest plot of bacterial superinfection



Study or Subgroup	Monotherapy Events	Monotherapy Total	Combination therapy Events	Combination therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alanis 1983	3	46	7	48	2.6%	0.45 [0.12, 1.63]
Cometta 1996	56	270	58	245	22.9%	0.88 [0.63, 1.21]
De la Camara 1997	0	46	1	47	0.6%	0.34 [0.01, 8.15]
De Pauw 1983	0	38	0	45		Not estimable
De Pauw 1994	48	488	39	480	14.8%	1.21 [0.81, 1.81]
Doyen 1983	24	50	20	54	7.2%	1.30 [0.82, 2.04]
Erjavec 1994	3	94	4	85	1.6%	0.68 [0.16, 2.94]
Hansen 1986	0	14	0	19		Not estimable
Jacobs 1993	2	46	1	45	0.4%	1.96 [0.18, 20.83]
Koehler 1990	2	55	0	65	0.2%	5.89 [0.29, 120.20]
Leyland 1992	4	106	2	110	0.7%	2.08 [0.39, 11.09]
Lieschke 1990	9	90	2	92	0.7%	4.60 [1.02, 20.71]
Liu 1989	0	10	0	17		Not estimable
Marie 1991	20	77	13	69	5.2%	1.38 [0.74, 2.56]
Miller 1993	8	45	3	41	1.2%	2.43 [0.69, 8.55]
Norrby 1987	12	105	15	105	5.6%	0.80 [0.39, 1.63]
Novakova 1990	4	46	7	44	2.7%	0.55 [0.17, 1.74]
Novakova 1991	6	36	11	33	4.3%	0.50 [0.21, 1.20]
Ozyilkan 1999	3	15	5	15	1.9%	0.60 [0.17, 2.07]
Pellegrin 1988	11	71	18	86	6.1%	0.74 [0.37, 1.46]
Pereira 2009	14	62	10	63	3.7%	1.42 [0.68, 2.96]
Perez 1995	1	30	2	30	0.8%	0.50 [0.05, 5.22]
Petrilli 2003	7	68	6	68	2.3%	1.17 [0.41, 3.29]
Piccart 1984	1	22	1	22	0.4%	1.00 [0.07, 15.00]
Pickard 1983	2	37	6	38	2.2%	0.34 [0.07, 1.59]
Rodjer 1987	1	22	0	23	0.2%	3.13 [0.13, 72.99]
Rolston 1992	13	378	12	372	4.6%	1.07 [0.49, 2.31]
Schuchter 1988	8	65	7	68	2.6%	1.20 [0.46, 3.11]
Yamamura 1997	10	51	12	49	4.6%	0.80 [0.38, 1.68]
Total (95% CI)		**2483**		**2478**	**100.0%**	**1.02 [0.87, 1.19]**
Total events	272		262			

Heterogeneity: Chi² = 23.66, df = 25 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)

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EVIDENCE TABLES

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Design: Systematic review (Cochrane Review) **Country**: Israel **Aim**: To compare beta-lactam monotherapy with beta-lactam-aminoglycoside therapy combination therapy for cancer patients with fever and neutropenia.
Inclusion criteria: Randomised or quasi randomised trials comparing any beta-lactam antibiotic monotherapy to any combination of a beta-lactam and aminoglycoside antibiotic. Allocation to either regimen had to occur initially (before administration of any other types of antibiotic for that neutropenic episode) and empirically (prior to detection of pathogens or their susceptibilities).
Exclusion criteria: Trials which randomised patients with microbiologically documented infections and trials comparing short versus long course of aminoglycoside were excluded – because in both cases treatment was not fully empirical. Trials in neonates and pre-term babies were excluded.
Population Cancer patients with febrile neutropenia (as defined in the primary studies) following chemotherapy or bone marrow transplantation.
Interventions Intravenous beta-lactam antibiotic given as monotherapy. This included: • Anti-pseudomonal carboxy-penicillins or ureido-penicillins with or without beta-lacatamase inhibitor • Cephalosporins

- Carbapenems

Combination duotherapy of an intravenous beta-lactam (see above) with one of the following aminoglycosides:

- Gentamicin, tobramycin, amikacin, netilmicin or kanamycin.

Outcomes

The primary outcome was all cause mortality, defined as death within the first 30 days of follow-up for the infectious episode.

Adverse events were categorised as: any adverse event, discontinuation due to adverse event, any nephrotoxicity and severe nephrotoxicity.

Secondary outcomes:

- Treatment failure, defined as at least one of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any modification of the assigned empirical antibiotic treatment.
- Infection related mortality,
- Duration of hospital stay,
- Dropouts before the end of the study,
- Superinfection, defined as new persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen of the development of a new site of infection
- Colonisation: isolation during or following therapy of Gram-negative bacteria resistant to the beta-lactam included in the empiric regimen, with or without symptoms or signs of infection.

Results

Effectiveness

Outcome	Subgroup	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
All cause mortality	All	43	7114	Risk ratio, fixed effects model, 95% C.I.	0.87 [0.75 to 1.02]
	Same beta-lactam*	10	1646	Risk ratio, fixed effects model, 95% C.I.	0.74 [0.53 to 1.06]
	Different beta-lactam	33	5468	Risk ratio, fixed effects model, 95% C.I.	0.91 [0.77 to 1.09]
Infection related mortality	All	38	6656	Risk ratio, fixed effects model, 95% C.I.	0.80 [0.64 to 0.99]
	Same beta-lactam*	7	1331	Risk ratio, fixed effects model, 95% C.I.	0.68 [0.43 to 1.10]
	Different beta-lactam*	31	5325	Risk ratio, fixed effects model, 95% C.I.	0.83 [0.65 to 1.06]
Treatment failure	All	68	10285	Not reported	Not reported
	Same beta-	15	2761	Risk ratio, fixed	1.11 [1.02 to 1.21]

	lactam*			effects model, 95% C.I.	
	Different beta-lactam*	53	7524	Risk ratio, fixed effects model, 95% C.I.	0.92 [0.87 to 0.96]

*Trials where the same beta-lactam was given in both arms of the trial.

Subgroup analysis of mortality and treatment failure was also done for the following groups: documented infections, bacteraemia, Gram-negative infections, pseudomonas infections, haematological cancer patients, those with severe neutropenia, monotherapy regimen and adults versus children. Sensitivity analyses of mortality and treatment failure was done for various indicators of trial quality.

Adverse events

Outcome	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
Any adverse event	47	7215	Risk ratio, fixed effects model, 95% C.I.	0.86 [0.80 to 0.93]
Discontinuation due to adverse event	16	4051	Risk ratio, fixed effects model, 95% C.I.	0.61 [0.40 to 0.93]
Any nephrotoxicity	37	6411	Risk ratio, fixed effects model, 95% C.I.	0.45 [0.35 to 0.57]
Severe nephtotoxicity	18	4002	Risk ratio, fixed effects model, 95% C.I.	0.16 [0.05 to 0.49]

Subgroup analyses of any-adverse-event was also done according to the specific drug used for monotherapy. Subgroup analysis of nephrotoxicity was also done for aminoglycoside dosing regimen (once daily versus multiple daily).

Superinfections

Outcome	N studies	N participants	Statistical method for meta-analysis	Effect size (less than 1 favours monotherapy)
Bacterial superinfection	28	4836	Risk ratio, fixed effects model, 95% C.I.	1.00 [0.86 to 1.18]
Fungal superinfection	20	3437	Risk ratio, fixed effects model, 95% C.I.	0.70 [0.49 to 1.00]

Colonisation of resistant Gram-negative bacteria

Five trials reported data about any colonisation but comparison between groups of colonisation with resistant Gram-negative bacteria was only possible in two trials. Resistant Gram-negative bacteria were detected in 5/152 patients treated with monotherapy versus 1/152 in those treated with combination therapy.

Duration of hospital stay

Three trials reported this outcome, in each one the duration of hospital stay was shorter (but not statistically significantly) in the monotherapy group. Data were not pooled due to the different ways in which the trials reported hospital stay.

1

2

Reference Pereira CA, Petrilli AS, Carlesse FA, Luisi FA, da Silva KV, de Martino Lee ML. - Cefepime monotherapy is as effective as ceftriaxone plus amikacin in pediatric patients with cancer and high-risk febrile neutropenia in a randomized comparison. - Journal of Microbiology, Immunology & Infection 2009 Apr;42(2):141-7.

Study type Randomised controlled trial. **Country** Brazil

Study quality
Randomisation: "based on number lists" no further details (unclear allocation concealment). Unit of randomisation was the episode of febrile neutropenia.
Blinding: none
Intention to treat: possible
Exclusions from analysis: None reported

Number of patients 57 patients (125 febrile neutropenic episodes). Patients were randomised at the start of each neutropenic episode. Some analyses are reported according to patient and some according to neutropenic episode.

Patient characteristics Children and adolescents (0 to 21 years) with acute leukemia or stage III and IV Hodgkin and non-Hodgkin lymphomas, who were considered to be at high risk of infectious complications following admission to hospital for febrile neutropenia. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3 or <1000 cells/mm^3 before the nadir of chemotherapy. Fever was defined as an axillary temperature above 38°C or 3 measurements 37.5°C or more during a 24 hour period.
Approximately half the patients had indwelling catheters.

Intervention Cefepime monotherapy, administered at a dose of 150 mg/kg/day given three times daily. All drugs were given intravenously. Therapy was modified with the inclusion of new antibacterial or antifungal agents according to the patients' clinical status, development of clinically or microbiologically documented infection or persistence of fever.

Comparison Ceftriaxone plus amikacin. Ceftriaxone was administered at a dose of 100 mg/kg/day given twice daily. Amikacin was given at a dose of 15mg/kg/day. Therapy was modified as above.

Length of follow-up The length of follow up was not reported**.** Patients were treated for a minimum of 5 days. The average time of treatment with antibiotics was 11.1 days (range 3 to 30 days) for monotherapy and 9.7 days (range 3 to 24 days) in the dual therapy group.

Outcome measures and effect size

Outcome	Monotherapy		Dual therapy		RR [95% C.I.]*
	n	N	n	N	
Treatment failure (for first FN episode)	10	29	10	28	0.97 [0.48, 1.96]
Mortality due to any cause (during the first FN episode)	1	29	1	28	0.97 [0.06, 14.70]
Any adverse event (per episode)	10	62	11	63	0.92 [0.42, 2.02]
Secondary infection (per episode, defined as any infection occurring between 72 hours after treatment started and 1 week after discontinuation of antibiotics). It was not stated whether it was bacterial or fungal infection (assumed bacterial).	14	62	10	63	1.42 [0.68, 2.96]

*Relative risk (RR) less than 1 favours monotherapy

54 pathogens were isolated from 125 episodes of febrile netropenia but Gram-negative bacterial resistance was not reported according to empirical therapy group (one strain of Pseudomonas aeruginosa was resistant

to ceftriaxone plus amikacin).

Nephrotoxicity and quality of life were not reported.

Source of funding Not reported

General comments Need to check whether cefepime is used as monotherapy in the UK.

1

Reference Yildirim I, Aytac S, Ceyhan M, Cetin M, Tuncer M, Cengiz AB, et al. - Piperacillin/tazobactam plus amikacin versus carbapenem monotherapy as empirical treatment of febrile neutropenia in childhood hematological malignancies. - Pediatric Hematology & Oncology 2008 Jun;25(4):291-9.

Study type Randomised controlled trial **Country** Turkey

Study quality
Randomisation: Computer generated random number sequence –no further details (unclear allocation concealment). Unit of randomisation was the patient.
Blinding: none
Intention to treat: no
Exclusions from analysis: 12 patients with protocol violations were excluded from the study

Number of patients 99 patients were randomised, 87 were included in the analysis (12 were excluded for protocol violations: 4 in the dual therapy group and 8 in the monotherapy group).

Patient characteristics Patients aged 2 to 16 years with acute lymphoblastic leukaemia (N=69) or acute myeloblastic leukaemia (N=18) and neutropenic fever. Neutropenia was defined as absolute neutrophil count of ≤500 cells/mm^3 (or ≤1000 cells/mm^3 and predicted to be ≤500 cells/mm^3 within 24 hours). Fever was defined as body temperature of ≥38.5°C or at least two measurements ≥38.5°C within 24 hours. Only the first episode of febrile neutropenia was included in the analysis.
Approximately 90% of patients had a central venous catheter and G-CSF usage was 63% in both treatment groups.

Intervention Monotherapy with imipenem or meropenem (20 mg/kg three times a day). If the patient still had fever after 72 hours of empirical therapy a glycopeptide and amikacin was added to the original empirical carbapenem. The treatment was modified if results of culture or antiobiograms were positive.

Comparison Dual therapy with piperacillin/tazobactam (80 mg/kg piperacillin 10 mg/kg tazobactam four times a day) combined with amikacin (7.5 mg/kg twice a day). If the patient still had fever after 72 hours of empirical therapy a glycopeptide was added to the original empirical therapy. The treatment was modified if results of culture or antiobiograms were positive.

Length of follow-up The minimum duration of treatment was 7 days, with at least 4 days without fever. Clinical and biological documented infections were treated as long as necessary.

Outcome measures and effect size

Outcome	Monotherapy		Dual therapy		RR [95% C.I.]*
	n	N	n	N	
Treatment failure (defined as death due to infection, persistence of bacteraemia or documented breakthrough bacteraemia, or fever still persisting after 72 hours and prompting modification of initial treatment).	22	41	26	46	0.95 [0.65, 1.39]
Infection related mortality	0	41	0	46	Not estimable

*Relative risk (RR) less than 1 favours monotherapy

Duration of fever
The mean (S.D.) duration of fever was 5.9 days (4.8 days) for the carbapenem monotherapy group and 4.3 days (3.1 days) for the dual therapy group (P=0.06).

Duration of hospital stay
The mean (S.D.) hospital stay was 12.6 days (5.3 days) for the monotherapy group and 10.6 days (4.7 days) for the dual therapy group (P=0.06).

Bacterial resistance
20 cultures (in 19 patients) from 87 episodes of febrile neutropenia were positive for bacteria. These isolates were tested for resistance to the various antibiotics used in the trial but results were not reported according to empirical therapy group.

Source of funding Not reported

1

Reference Zengin E, Sarper N, and Kilic C. Piperacillin/Tazobactam Monotherapy Versus Piperacillin/Tazobactam Plus amikacin as Initial Empricial Therapy for Febrile Neutropenia in Children with Acute Leukemia. Pediatric Hematology and Oncology 2011. 28: 311 – 320.

Study type Randomised controlled trial **Country** Turkey **Study period** 2007 – 2008

Study quality
Randomisation: randomisation method and allocation concealment not reported (authors mention consecutive randomisation). It appears patients were randomised per febrile neutropenia episode (thus the same patient could be randomised more than once).
Blinding: not mentioned
Intention to treat: probably not (see below)
Exclusions from analysis: patients were excluded for protocol violation

Number of patients

Patient characteristics 42 patients aged up to 19 years with acute lymphoblastic leukaemia (N=60 episodes) or acute myeloblastic leukaemia (N=12 episodes) and neutropenic fever. Neutropenia was defined as absolute neutrophil count of ≤500 cells/mm^3 (or ≤1000 cells/mm^3 and predicted to be ≤500 cells/mm^3 within 24 hours). Fever was defined as body temperature of ≥38.5°C or ≥38°C for at least an hour. Multiple episodes of febrile neutropenia were eligible for inclusion.

Characteristic	PIP/TAZO	PIP/TAZO +amikacin
Median age (years) (range)	4.7 (0.4 to 19)	4.5 (1.56 to 19)
ALL	29	31
AML	8	4
CVC	65.3%	67.6%

Exclusion criteria: fever due to leukaemia or transfused drugs/blood products, history of hypersensitivity to trial drugs,

Intervention Piperacillin/tazobactam (PIP/TAZO) 360 mb/kg/day in 4 doses

Comparison Piperacillin/tazobactam (PIP/TAZO) 360 mb/kg/day in 4 doses plus amikacin 15/mg/kg/day in a single dose

Length of follow-up Patients were follow up for the duration of the neutropenic episode (up to 37 days).

Outcome measures and effect size

Outcome	Pip/Tazo		Pip/Tazo + amikacin		RR
	n	N	n	N	

Treatment success without modification (addition of teicoplanin, antifungal or antiviral)	17	37	15	35	
Treatment success with modification	13	37	13	35	
Protocol failure (change from empirical antibiotics in unresponsive fever)	7	37	7	35	
Glycopeptide addition	16	37	13	35	
Antifungal addition	9	37	5	35	
Infection related death	0	37	0	35	
Serious adverse events	0	37	0	35	
Median duration of fever (days) (range)	2 (1 to 13)		2 (1 to 19)		
Median duration of neutropenia (days) (range)	10 (3 to 32)		12 (1 to 37)		
Median duration of treatment (days) (range)	10 (5 to 31)		12 (4 to 30)		

Source of funding Not reported. The authors reported no conflicts of interest.

11.1 Mixed treatment comparison of empiric intravenous antibiotic monotherapy and empiric intravenous antibiotic dual therapy. (Topic E3)

Evidence Statements

A mixed treatment comparison was done using 108 trials identified in two Cochrane reviews by Paul, et al., (2007 and 2010). These trials were either comparing single agent beta-lactams with each other (Paul, et al., 2010) or comparing single agent beta-lactams with combined beta-lactam/aminoglycoside treatment (Paul, et al., 2007)

The treatment most likely to be best at reducing overall mortality was the use of a single agent ureidopenicillin. This was reflected in direct and indirect estimates (Tables 11.1.1 to 11.1.3). Carbapenems alone compared with ureidopenicillin had higher overall mortality, equivalent infectious mortality and marginally less risk of 'treatment failure'.

METHODS

Statistical analysis

We considered antibiotics in seven groups, based around antibiotic class, and agreed a priori with clinical experts in the GDG. We considered combinations of antibiotics, for example cephalosporin plus aminoglycoside, as an intervention-group, rather than the sum of effects of cephalosporin plus aminoglycoside. This decision was made considering the additional antimicrobial coverage of a second agent could vary depending on the paired therapy, and so the simple 'sum' approach may not reflect the underlying treatment. The groups were:

1 carbapenem
2 ureidopenicillins
3 3rd Generation Cephalosporin
4 4th Generation Cephalosporin
5 ureidopenicillins +aminoglycoside
6 3rd Generation Cephalosporin +aminolycoside
7 4th Generation Cephalosporin+aminoglycoside

We carried out a mixed treatment comparison using a Bayesian network model by Markov Chain Monte Carlo simulations using WinBugs software to obtain estimates of the effects of all interventions and estimates of the ranking of interventions (Caldwell, Ades & Higgins, 2005; Higgins & Whitehead, 1996; Lu & Ades, 2004 and Smith, Spiegelhalter & Thomas, 1989) . Log odds ratios of the effects of interventions were modeled using non-informative prior distributions: for normal priors, a mean of zero and variance of 10 000, for standard deviation of log-odds ratios, a uniform prior between 0 and 2. The effect size covariance was adjusted for multi-arm trials. The models are available on request. These priors were assessed in a sensitivity analysis. A burn-in sample of 10 000 iterations was followed by 100 000 iterations used to compute estimates, at which point the MCMC error was less than 1% of the standard deviation. Results are reported as median estimates of efficacy with 95% credibility intervals. We modeled the effects of specific covariates on these estimates in a series of planned sensitivity analyses. Model fit was evaluated by comparing the residual deviance with the number of data points, and selected the most parsimonious model to describe effects by comparing deviance information criterion (DIC) values.

For direct comparisons of treatments effect upon overall mortality we used the DerSimonian-Laird random effects models (DerSimonian & Laird, 1986) in STATA using the `metan` package. Results are presented as point estimates with 95% confidence intervals. Statistical heterogeneity was quantified using the I^2 statistic. A value greater than 50% was considered to be substantial heterogeneity (Higgins & Thompson, 2002 and Higgins et al., 2003).

We compared indirect and direct comparisons for consistency for all pairs where direct evidence was available (Dias et al., 2010).

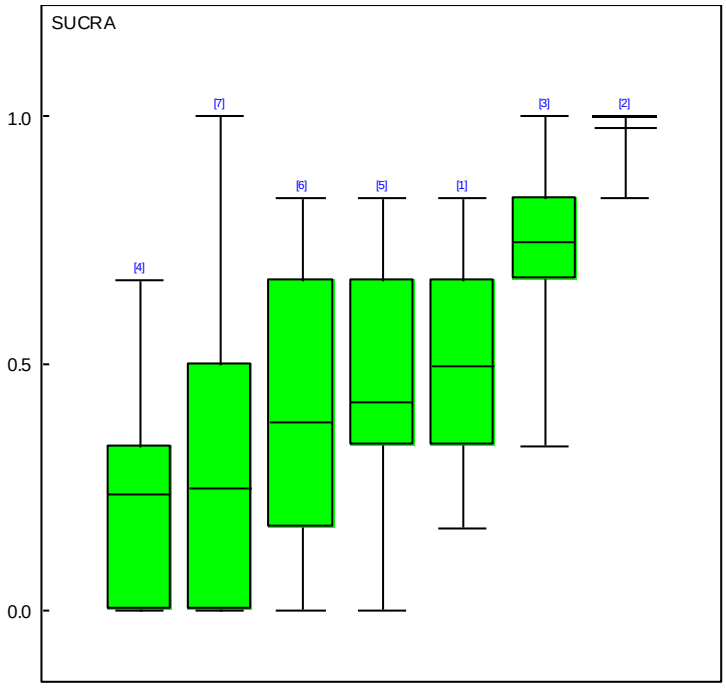
RESULTS

The summary estimates from the mixed treatment comparisons showed good model fit (residual deviance ~ 126, compared with 148 data points). The DIC was minimised when covariates indicating year of publication, age of patients, and proportion of haematological malignancy were NOT entered into the model. Additionally, none of these covariates were significant (i.e. their 95% credible intervals all crossed log-zero; no effect).

The treatment most likely to be best at reducing overall mortality was the use of a single agent ureidopenicillin (see Figure 11.1.1). This was reflective in direct and indirect estimates (see Tables 11.1.1 to 11.1.3).

Figure 11.1.1: Cumulative chance of being best at reducing overall mortality

Treatment groups are carbapenem (1), ureidopenicillins (2), 3rd Generation Cephalosporin (3), 4th Generation Cephalosporin (4), ureidopenicillins +aminoglycoside (5), 3rd Generation Cephalosporin +aminoglycoside (6) and 4th Generation Cephalosporin+aminoglycoside (7).



Antibiotic Group	Median proportion best	95% Credible intervals
Ureidopenicillins	0.83	0.83 to 1
3rd Generation Cephalosporin	0.33	0.33 to 1
Carbapenem	0.17	0.17 to 0.83
4th Generation Cephalosporin	0	0 to 0.67
Ureidopenicillins +aminoglycoside	0	0 to 0.83
3rd Generation Cephalosporin +aminolycoside	0	0 to 0.83
4th Generation Cephalosporin+aminoglycoside	0	0 to 1

1 ***Table 11.1,1: Results of Mixed Treatment Comparison Analysis***

		Mortality		Infectious Deaths		Clinical failure	
n Trials	**Comparators**	**Indirect OR**	**95% CrI**	**Indirect OR**	**95% CrI**	**Indirect OR**	**95% CrI**
3	uridipenicillin vs carbapenem	**0.57**	**0.38 to 0.88**	0.94	0.55 to 1.57	1.13	0.9 to 1.43
9	3rdGenCephalosporin vs carbapenem	0.84	0.62 to 1.19	1.03	0.68 to 1.65	1.03	0.86 to 1.22
5	4thGenCephalosporin vs carbapenem	1.18	0.81 to 1.66	1.16	0.64 to 2.22	0.97	0.78 to 1.23
4	uridipenicillin+aminoglycoside vs carbapenem	1.03	0.77 to 1.4	**1.87**	**1.04 to 3.82**	1.1	0.87 to 1.39
10	3rdGenCephalosporin+aminoglycoside vs carbapenem	1.07	0.75 to 1.54	1.31	0.8 to 2.06	1.19	0.99 to 1.44
	4thGenCephalosporin+aminoglycoside vs carbapenem	1.27	0.54 to 2.59	1.71	0.15 to 6.08	0.9	0.55 to 1.47
1	3rdGenCephalosporin vs uridipenicillin	1.5	0.91 to 2.26	1.11	0.72 to 1.73	0.91	0.72 to 1.14
3	4thGenCephalosporin vs uridipenicillin	**2.06**	**1.28 to 3.11**	1.25	0.68 to 2.15	0.86	0.68 to 1.11
2	uridipenicillin+aminoglycoside vs uridipenicillin	**1.83**	**1.2 to 2.7**	**1.98**	**1.1 to 3.84**	0.97	0.74 to 1.27
3	3rdGenCephalosporin+aminoglycoside vs uridipenicillin	**1.87**	**1.13 to 2.97**	1.4	0.74 to 2.54	1.06	0.83 to 1.37
	4thGenCephalosporin+aminoglycoside vs uridipenicillin	2.21	0.81 to 4.93	1.8	0.2 to 6.97	0.8	0.49 to 1.32
7	4thGenCephalosporin vs 3rdGenCephalosporin	1.4	0.93 to 1.96	1.12	0.64 to 2.05	0.95	0.77 to 1.19
5	uridipenicillin+aminoglycoside vs 3rdGenCephalosporin	1.22	0.9 to 1.69	**1.8**	**1.03 to 3.6**	1.06	0.86 to 1.34
7	3rdGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.25	0.89 to 1.86	1.26	0.76 to 2.11	1.16	0.96 to 1.42
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.48	0.62 to 3.16	1.62	0.17 to 6.23	0.87	0.54 to 1.44
	uridipenicillin+aminoglycoside vs 4thGenCephalosporin	0.88	0.59 to 1.34	1.61	0.72 to 3.61	1.12	0.86 to 1.49
2	3rdGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	0.89	0.61 to 1.46	1.09	0.58 to 2.29	1.23	0.95 to 1.58
2	4thGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	1.08	0.48 to 2.13	1.47	0.17 to 5.34	0.92	0.58 to 1.48
	3rdGenCephalosporin+aminoglycoside vs uridipenicillin+aminoglycoside	1.02	0.7 to 1.53	0.69	0.28 to 1.43	1.09	0.83 to 1.44
	4thGenCephalosporin+aminoglycoside vs uridipenicillin+aminoglycoside	1.2	0.49 to 2.54	0.9	0.11 to 3.55	0.82	0.49 to 1.36
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin+aminoglycoside	1.18	0.47 to 2.51	1.39	0.16 to 5.19	0.75	0.45 to 1.26

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Table 11.1.2: Comparison of pair wise and MTC analyses for mortality

n Trials	Comparators	Direct OR	95% CI	Indirect OR	95% CrI
3	uridipenicillin vs carbapenem	0.4	0.115 to 1.388	**0.57**	**0.38 to 0.88**
9	3rdGenCephalosporin vs carbapenem	0.997	0.597 to 1.664	0.84	0.62 to 1.19
5	4thGenCephalosporin vs carbapenem	1.368	0.714 to 2.624	1.18	0.81 to 1.66
4	uridipenicillin+aminoglycoside vs carbapenem	1.004	0.565 to 1.786	1.03	0.77 to 1.4
10	3rdGenCephalosporin+aminoglycoside vs carbapenem	1.065	0.691 to 1.641	1.07	0.75 to 1.54
	4thGenCephalosporin+aminoglycoside vs carbapenem	NA	NA	1.27	0.54 to 2.59
1	3rdGenCephalosporin vs uridipenicillin	1.178	0.072 to 19.167	1.5	0.91 to 2.26
3	4thGenCephalosporin vs uridipenicillin	1.56	0.73 to 3.33	**2.06**	**1.28 to 3.11**
2	uridipenicillin+aminoglycoside vs uridipenicillin	1.488	0.859 to 2.576	**1.83**	**1.2 to 2.7**
3	3rdGenCephalosporin+aminoglycoside vs uridipenicillin	2.155	0.871 to 5.333	**1.87**	**1.13 to 2.97**
	4thGenCephalosporin+aminoglycoside vs uridipenicillin	NA	NA	2.21	0.81 to 4.93
7	4thGenCephalosporin vs 3rdGenCephalosporin	1.558	0.937 to 2.589	1.4	0.93 to 1.96
5	uridipenicillin+aminoglycoside vs 3rdGenCephalosporin	1.247	0.903 to 1.722	1.22	0.9 to 1.69
7	3rdGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.204	0.685 to 2.118	1.25	0.89 to 1.86
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	NA	NA	1.48	0.62 to 3.16
	uridipenicillin+aminoglycoside vs 4thGenCephalosporin	NA	NA	0.88	0.59 to 1.34
2	3rdGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	0.593	0.07 to 4.996	0.89	0.61 to 1.46
2	4thGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	1.696	0.154 to 18.673	1.08	0.48 to 2.13
	3rdGenCephalosporin+aminoglycoside vs uridipenicillin+aminoglycoside	NA	NA	1.02	0.7 to 1.53
	4thGenCephalosporin+aminoglycoside vs uridipenicillin+aminoglycoside	NA	NA	1.2	0.49 to 2.54
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin+aminoglycoside	NA	NA	1.18	0.47 to 2.51

Table 11.1.3: Comparison of Results for Direct and Indirect Analysis of Mortality

Indirect comparisons in the upper triangle, direct comparisons in the lower triangle.

Indirect comparision **Direct comparison**	**carbapenem**	**Uridipenicillin**	**3G cef**	**4G cef**	**Uridipenicillin + aminoglycoside**	**3G cef + aminoglycoside**	**4G cef + aminoglycoside**
carbapenem	@@@@	**1.75**	1.19	0.85	0.97	0.93	0.79
	@@@@	**1.14 to 2.63**	0.84 to 1.61	0.6 to 1.23	0.71 to 1.3	0.65 to 1.33	0.39 to 1.85
uridipenicillin	0.4	@@@@	0.67	**0.49**	**0.55**	**0.53**	0.45
	0.115 to 1.388	@@@@	0.44 to 1.1	**0.32 to 0.78**	**0.37 to 0.83**	**0.34 to 0.88**	0.2 to 1.23
3G cef	0.997	1.178	@@@@@	0.71	0.82	0.8	0.68
	0.597 to 1.664	0.072 to 19.167	@@@@@	0.51 to 1.08	0.59 to 1.11	0.54 to 1.12	0.32 to 1.61
4G cef	1.368	1.56	1.558	@@@@	1.14	1.12	0.93
	0.714 to 2.624	0.73 to 3.33	0.937 to 2.589	@@@@	0.75 to 1.69	0.68 to 1.64	0.47 to 2.08
uridipenicillin+aminoglcoside	1.004	1.488	1.247		@@@@@	0.98	0.83
	0.565 to 1.786	0.859 to 2.576	0.903 to 1.722		@@@@@	0.65 to 1.43	0.39 to 2.04
3G cef + aminoglycoside	1.065	2.155	1.204	0.593		@@@@	0.85
	0.691 to 1.641	0.871 to 5.333	0.685 to 2.118	0.07 to 4.996		@@@@	0.4 to 2.13

Indirect comparision Direct comparison	carbapenem	Uridipenicillin	3G cef	4G cef	Uridipenicillin + aminoglycoside	3G cef + aminoglycoside	4G cef + aminoglycoside
4G cef + aminoglycoside				1.696			@@@@@
				0.154 to 18.673			@@@@@

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12. Role of empiric glycopeptide antibiotics (antibiotics chosen in the absence of an identified bacterium) in patients with central lines and neutropenia or neutropenic sepsis. (Topic G)

Guideline subgroup members for this question

Jeanette Hawkins (lead), Bob Phillips, Anne Higgins, Barbara Crosse and Rosemary Barnes.

Review question*:*

In patients with a central venous access device with no external signs of line infection but with suspected neutropenia or neutropenic sepsis, what are the benefits and risks of adding vancomycin, teicoplanin or linezolid to first-line antibiotics?

Rationale

It is common for cancer unit antibiotics policies to include specific guidance on the management of cancer patients with fever and neutropenia (proven or suspected) who also have a central venous access device (CVAD) inserted, to minimise the risk of potentially life threatening bacteraemia originating from or colonizing the CVAD. There is usually an assessment of the likelihood of infection in or around the catheter as a potential cause of infection, and often a "step-up" to a different line of more targeted antibiotic therapy if CVAD infection is suspected (i.e. different from broad spectrum untargeted standard treatment). Targeted antibiotic therapy is usually aimed at aerobic and anaerobic Gram-positive bacteria, including multi-resistant Staphylococci based on research showing that these are the most common pathogens for CVAD infection.

The assessment of the CVAD as a potential source of infection will usually include;

- Inspection of the catheter exit site for central lines and skin over the hub for implanted devices, for redness, swelling, or exudate.
- Inspection of the areas around the CVAD for swelling, pain or tenderness especially along the tunnel or port pocket, local joint movement restrictions, e.g. pain on movement of neck or shoulders.
- Patient history for;
    - Rigour after CVAD flush
    - Mild and / or self resolving low grade fever on several occasions after CVAD flushing
    - Pain, tenderness.
    - History of previous CVAD infection

If there are obvious signs of infection (e.g. redness, swelling, exudate) the "step-up" to targeted antibiotics covering typical colonizing organisms is accepted practice and not included in this enquiry.

If there are no external signs of infection - is there evidence for the empirical use of "step-up" targeted antibiotics, such as vancomycin, which may be higher in cost and have increased toxicity compared with standard broad spectrum antibiotics?

In the situation of "no external signs of infection" the following factors are usually taken into consideration in clinical practice in assessing the possibility of CVAD infection.

Immunocompromised patients may not produce "pus" due to lack of competent neutrophils and macrophages and therefore external signs of infection may be absent. The principle of "treating blind" is often used for treating infections in cancer patients

Rigours or low grade fevers within the first few hours after a line flush commonly indicate CVAD infection. (Myth, Experience or Research?)

History of previous CVAD infection is a common indicator of recurrent infection. (Myth, Experience or Research?)

Clinical experience that patients who have no apparent sign of CVAD infection at presentation can go on to have proven bacteraemia on blood culture from CVAD or colonisation of catheter-tip on venogram. (Myth, Experience or Research?).

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with central venous access devices and neutropenia or neutropenic sepsis, without an identified bacterium.	Empiric vancomycin, teicoplanin, linezolid in addition to first line antibiotics	First-line, broad spectrum antibiotics	• Death • critical care, • Length of stay • Line preservation / "catheter remains in situ" • Antibiotic resistance • Proven Bacteraemia • Toxicity

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The search was done on 19th July 2011 and updated on 7th November 2011. The search was restricted to published randomised (or quasi randomised) trials and systematic reviews of randomised trials.

Selection of studies

The information specialist (SB) conducted the first screen of the literature search results. Two reviewers (NB and CL) then selected potentially eligible studies by comparing their title and abstract with the inclusion criteria set out by the PICO question. Full text articles were obtained for studies identified as potentially relevant. These were read and checked against the inclusion criteria.

RESULTS

Results of searches

Eight Randomised Controlled Trials (RCTs) were identified that compared empiric vancomycin / teicoplanin / linezolid plus first-line antibiotics, to first-line broad spectrum antibiotics presented alone. Only one of these RCTs (Karp et al 1986) included *only* patients with a central venous access device. The proportion with a central line was unclear in 6 studies (de Pauw et al 1990; del Favero et al 1987; Novakova et al 1991; Marie et al 1991; Molina et al 1993; EORTC 1991). In the remaining study (Ramphal et al 1992) 61% had a central line. One systematic review that included these studies (in addition to other studies that did not meet the criteria set out by the PICO) was identified.

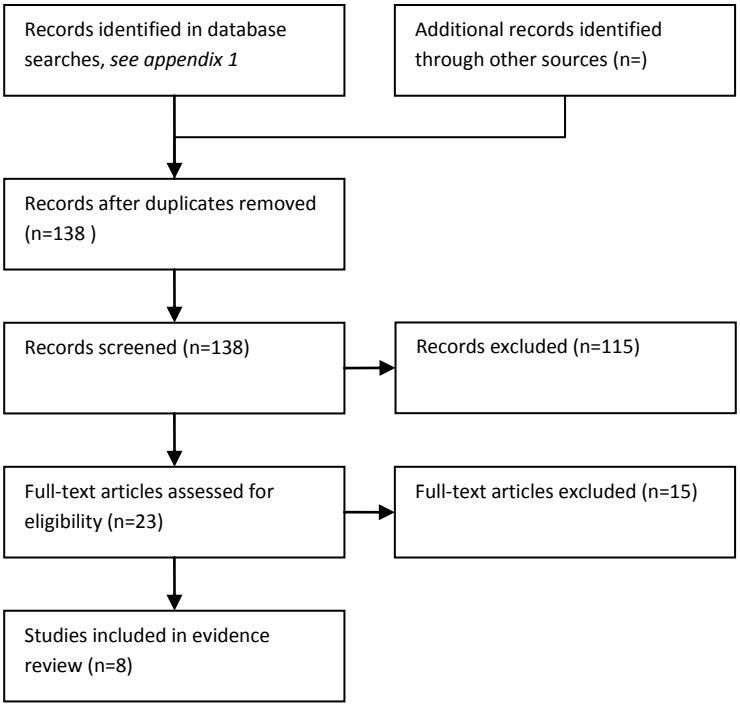
Types of participant

All participants were neutropenic cancer patients with a fever. At least a proportion of participants in each study had a central venous access device.

Types of intervention

The studies compared empiric vancomycin / teicoplanin plus first-line antibiotics, to first-line broad spectrum antibiotics administered alone.

Figure12.1 Study flow diagram



Evidence statements

The evidence for all outcomes is summarised in Table 12.1

Short term mortality

Five studies reported short term mortality (de Pauw, et al., 1990; EORTC, 1991; Ramphal, et al., 1992; Molina, et al., 1993; Novakova, et al., 1991). There was very low quality evidence of uncertainty about the difference between antibiotics administered alone, and the same empiric

antibiotics administered with the addition of glycopeptides, RR = 0.97 (95% CI 0.63 – 1.50) in four studies with1083 participants.

Critical care, length of stay and line preservation

These outcomes were not reported by any of the included studies.

Antibiotic resistance

Only one study reported antibiotic resistance (Novakova, et al., 1991). Rates of resistance were very low in both groups (2/51 (4%) in the group who received empiric antibiotics alone and 0/52 (0%) in the group who received empiric antibiotics plus glycopeptides).

Proven Bacteraemia

Two studies with 150 particpants reported proven bacteremia as an outcome (Del Favero, et al., 1987; Novakova, et al., 1991). There was very low quality evidence of uncertainty about whether antibiotics administered alone or empiric antibiotics administered with glycopeptides was more effective in terms of proven bacteraemia, RR = 0.80 (95% CI 0.42 – 1.53)

Nephrotoxicity

In five studies with 1160 participants, there was very low quality evidence of a significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides, with a greater number of individuals receiving the latter regimen experiencing nephrotoxicity, RR = 0.57 (95% CI 0.33 – 0.99).

Hepatic toxicity

Two studies with 856 participants reported hepatic toxicity as an outcome. There was very low quality evidence of a significant difference between empiric antibiotics administered alone, and antibiotics administered with the addition of glycopeptides. A greater number of individuals in the latter group experienced hepatic toxicity, RR = 0.53 (95% CI 0.33 – 0.99).

Table 12.1: GRADE profile: Role of empiric glycopeptide antibiotics (antibiotics chosen in the absence of an identified bacterium) in patients with central lines and suspected neutropenia or neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Empiric antibiotics only	Empiric antibiotics plus glycopeptides	Relative (95% CI)	Absolute	
All cause (short term) mortality											
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	Serious[3]	none	37/534 (6.9%)	39/549 (7.1%)	RR 0.97 (0.61 to 1.55)	2 fewer per 1000 (from 27 fewer to 38 more)	VERY LOW
Critical care											
0	no evidence available					none	-	-	-	-	
Line preservation/catheter remains in situ											
0	no evidence available					none	-	-	-	-	
Nephrotoxicity											
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	Serious[3]	none	19/571 (3.3%)	34/589 (5.8%)	RR 0.57 (0.33 to 0.99)	14 fewer per 1000 (from 0 fewer to 22 fewer)	VERY LOW
Hepatotoxicity											
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	51/421 (12.1%)	90/435 (20.7%)	RR 0.53 (0.36 to 0.76)	57 fewer per 1000 (from 29 fewer to 78 fewer)	VERY LOW
Length of stay											
0	no evidence available					none	-	-	-	-	
Proven bacteremia											
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29/77 (37.7%)	32/73 (43.8%)	RR 0.80 (0.42 to 1.53)	75 fewer per 1000 (from 218 fewer to 200 more)	VERY LOW
Antibiotic resistance											
0	no evidence available					none	-	-	-	-	

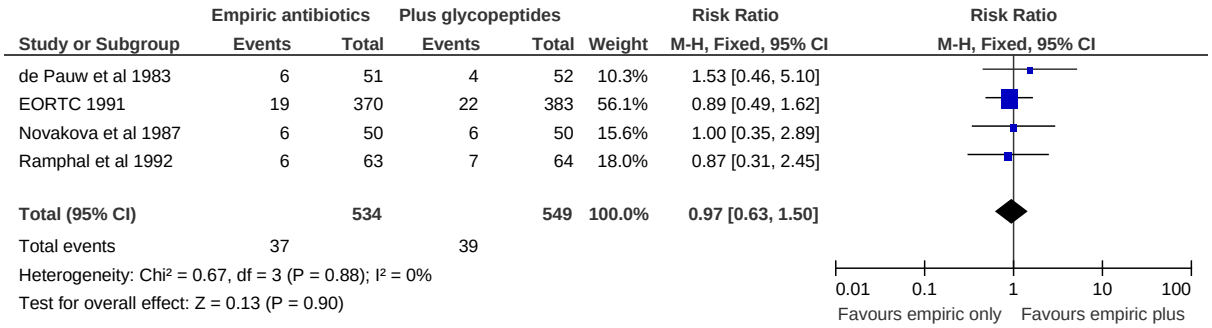
[1] Few studies were blinded. Sequence generation/allocation concealment were unclear in several studies.
[2] Only a proportion of the participants had a central venous access device. Unclear exactly how many.
[3] Low event rate.

Evidence summary and figures

Short-term mortality

There was no significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides (RR = 0.97 (0.63 – 1.50) P = 0.88; 4 studies; 1083 participants).

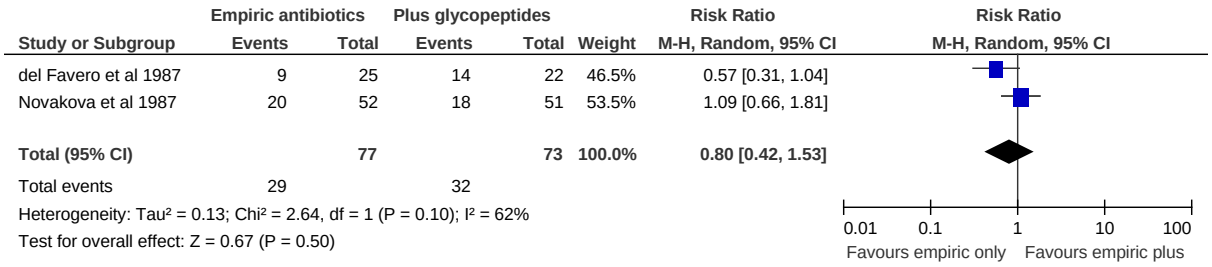
Figure 12.2 Forest plot of all cause short-term mortality



Bacteraemia

There was no significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides (RR = 0.80 (0.42 – 1.53) P = 0.10; 2 studies; 150 participants).

Figure 12.3 Forest plot of bacteraemia

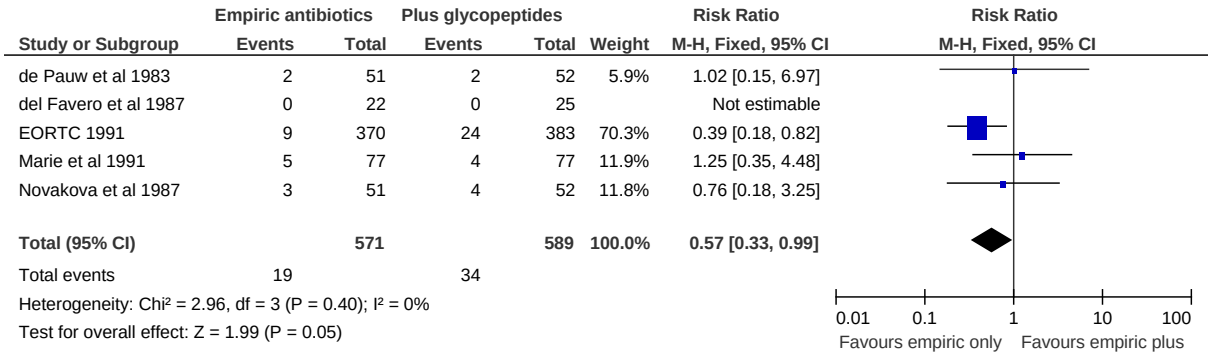


Toxicity

Nephrotoxicity

Five studies reported nephrotoxicity as an outcome. There was a significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides, with a greater number of individuals receiving the latter regimen experiencing nephrotoxicity (RR = 0.57 (0.33 – 0.99) P = 0.05; 5 studies; 1160 participants).

Figure 12.4 Forest plot of nephrotoxicity



Hepatic toxicity

Two studies reported hepatic toxicity as an outcome. There was a significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides, with a greater number of individuals receiving the latter regimen experiencing hepatic toxicity (RR = 0.53 (0.33 – 0.99) P = 0.0008; 2 studies; 856 participants).

Figure 12.4 Forest plot of hepatic toxicity

EVIDENCE TABLES

1. de Pauw, B. E., Novakova, I. R., & Donnelly, J. P. (1990). Options and limitations of teicoplanin in febrile granulocytopenic patients. *British Journal of Haematology, 76,* Suppl-5.
Country: The Netherlands
Design: Randomised Controlled Trial
Population: 120 febrile granulocytopenic patients with haematological malignancies *unclear how many patients had central lines*
Inclusion criteria: • Age > 14 years • Fever (single anxillary temperature ≥ 38.5°C or two or more readings of > 38°C taken 2-4 hours apart) • Granulocytopenic (<$1.0x10^9$/l expected to fall to <$0.5x10^9$/l)
Exclusion criteria: • No evidence of lung infiltration, skin or soft tissue infection or other obvious focus of infection at fever onset • No other parenteral antibiotics before starting therapy
Interventions: • Ceftazidime 2g 8 hourly as a short infusion Versus • Ceftazidime 2g 8 hourly as a short infusion with teicoplanin administered as an IV bolus at

800mg in two divided doses on the first day and 400mg once daily thereafter.

Outcomes:

- Death (before or after therapy modification)
- Toxicity
- Clinical response (patient survived the infection and all infectious symptoms disappeared without any change of initial therapy.
- Clinical response after therapy modification (patient survived infection but defervescence and disappearance of all infectious symptoms was achieved only after modification of the empiric regimen

Results:

Death
Ceftazidime - 6/51 (12%)
Ceftazidime + teicoplanin - 4/52 (8%)

Toxicity

Reversible rise of 50-100% in serum creatinine
Ceftazidime - 2/51 (4%)
Ceftazidime + teicoplanin - 2/52 (4%)

Greater than 3-fold rise in alkaline phosphatise and/or transaminases
Ceftazidime - 1/51 (2%)
Ceftazidime + teicoplanin - 5/52 (10%)

Clinical response
Ceftazidime - 25/51 (49%)
Ceftazidime + teicoplanin - 33/52 (63%)

Clinical response after therapy modification
Ceftazidime -20 /51 (39%)
Ceftazidime + teicoplanin -15/52 (29%)

Skin rash
Ceftazidime - 0 /51 (0%)
Ceftazidime + teicoplanin - 8/52 (15%)

Critical care
Not reported

Length of stay

Not reported

Line preservation / "catheter remains in situ"
Not reported

Antibiotic resistance
Not reported

Proven Bacteraemia
Not reported

General comments:

- Three studies by the same research group were reported in this paper. Only study 2 met the criteria set out by the PICO. This was an RCT comparing the efficacy and toxicity of ceftazidime given with and without teicoplanin.
- It was unclear how many patients had central lines.
- There was adequate sequence generation and allocation concealment. Analyses were conducted on an Intention to Treat (ITT) basis.
- The study was not blinded.

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2. Del Favero, A., Menichetti, F., Guerciolini, R., Bucaneve, G., Baldelli, F., Aversa, F. et al. (1987). Prospective randomized clinical trial of teicoplanin for empiric combined antibiotic therapy in febrile, granulocytopenic acute leukemia patients. Antimicrobial Agents & Chemotherapy, 31, 1126-1129.
Country: Italy
Design: Randomised Controlled Trial
Population: 66 febrile granulocytopenic episodes in 54 patients with haematological malignancies (age range 8-71 years) *unclear how many patients had central lines*
Inclusion criteria: • Fever (anxillary temperature ≥ 38°C in the absence of obvious non-infective causes) • Granulocytopenic (absolute granulocyte count below 1000/mm^3)
Exclusion criteria: • History of allergy to any antibiotics used in the study • Creatinine level in serum above 2mg/100ml
Interventions: • Amikacin (15mg/kg per day in 3 equal doses subsequently adjusted to maintain optimal peak (15 to 25 mg/litre) and trough (5mg/litre) levels in serum and ceftazidime 90mg/kg

per day in 3 equal doses (each dissolved in 100ml of 0.9% saline and administered intravenously over 15 to 30 min)

Versus

- Amikacin (15mg/kg per day in 3 equal doses subsequently adjusted to maintain optimal peak (15 to 25 mg/litre) and trough (5mg/litre) levels in serum and ceftazidime 90mg/kg per day in 3 equal doses (each dissolved in 100ml of 0.9% saline and administered intravenously over 15 to 30 min) plus teicoplanin 5mg/kg per day in a single dosedissolved in 10ml of sterile water and administered intravenously in 3min with an initial loading dose of 8mg/kg (maximum initial dose 600mg)

Outcomes:

- Response to therapy
- Toxicity

Results:

Death
Not reported

Toxicity
Nephrotoxicity (defined as increase in creatinine in serum of more than 0.4mg/100mlfrom baseline when other causes excluded)
Ceftazidime + amikacin - 0/22 (0%)
Ceftazidime + amikacin + teicoplanin - 0/25 (0%)

Proven Bacteraemia
Ceftazidime + amikacin - 14/22 (64%)
Ceftazidime + amikacin + teicoplanin - 9/25 (36%)

Treatment failure (treatment modification considered a failure)
Ceftazidime + amikacin - 14/25 (56%)
Ceftazidime + amikacin + teicoplanin -18/22 (82%)
(difference not statistically significant P = 0.1)

Critical care
Not reported

Length of stay
Not reported

Line preservation / “catheter remains in situ”
Not reported

Antibiotic resistance
Not reported

General comments:

- Sequence generation was adequate, but it is unclear whether concealment was sufficient
- The study was not blinded
- 29% of episodes were excluded from the analyses. ITT analyses were not conducted.
- Patients who showed greatest advantage from the teicoplanin regimen were those with profound (<100/mm^3) and persistent neutropenia (83% improvement in the group with teicoplanin vs. 30% in the group without teicoplanin)

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3. **EORTC (1991). Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group.** ***Journal of Infectious Diseases, 163,*** **951-958.**
Country: Canada
Design: Randomised Controlled Trial
Population: 747 febrile granulocytopenic patients with cancer recruited 1986 and 1989 *unclear how many had central lines*
Inclusion criteria: • Granulocytopenia (<1000 cells/mm^3) • Fever (≥ 38°C on one occasion)
Exclusion criteria: • Non-infectious cause of fever • Parenteral antibiotics for ≥ 4 days • Allergic to any of trial antibiotics • Serum creatinine > µmol/l
Interventions: • Ceftazidime plus amikacin Versus • Ceftazidime plus amikacin plus vancomycin
Outcomes: • Treatment success/failure • Death

- Superinfection
- Toxicity

Results:

Death (all cause)
Ceftazidime + amikacin – 19/370 (5%)
Ceftazidime + amikacin + vancomycin – 22/383 (6%)

Super-infection
Ceftazidime + amikacin – 28/370 (8%)
Ceftazidime + amikacin + vancomycin – 22/383 (6%)

Treatment failure (treatment modification considered a failure)
Ceftazidime + amikacin – 138/370 (37%)
Ceftazidime + amikacin + vancomycin – 89/383 (23%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Toxicity
Nephrotoxicity
Ceftazidime + amikacin – 9/370 (2%)
Ceftazidime + amikacin + vancomycin – 24/383 (6%)

Hepatic toxicity
Ceftazidime + amikacin – 50/370 (13.5%)
Ceftazidime + amikacin + vancomycin – 85/383 (22%)

Hypokalaemia
Ceftazidime + amikacin – 35/370 (9%)
Ceftazidime + amikacin + vancomycin – 55/383 (14%)

Ototoxicity
Ceftazidime + amikacin – 1%
Ceftazidime + amikacin + vancomycin – 1%

Coagulation defects
Ceftazidime + amikacin – 2%
Ceftazidime + amikacin + vancomycin – 3%

Diarrhoea

Ceftazidime + amikacin – 2% Ceftazidime + amikacin + vancomycin – 2% <u>Drug fever</u> Ceftazidime + amikacin – 1% Ceftazidime + amikacin + vancomycin – 2%
General comments: • A large sample size relative to the other included studies • Unblinded • Sequence generation was adequate, but the method of concealment was unclear • No ITT analysis

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4. Karp, J. E., Dick, J. D., Angelopulos, C., Charache, P., Green, L., Burke, P. J. et al. (1986). Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *American Journal of Medicine, 81,* 237-242.
Country: USA
Design: Randomised Controlled Trial (RCT)
Population: 60 adult patients admitted to a leukaemia service from February 1983 to June 1984 *all had central lines*
Inclusion criteria: • Diagnosis of acute leukaemia • Received intensive timed sequential therapy and augmentation therapy during early complete remission, or chemotherapy alone with fractioned total body irradiation followed by analogous bone marrow rescue transplantation • Fever • Granylocytopenia
Exclusion criteria: • Documented allergy to vancomycin or other routinely used antibiotics • Antibiotics within 7 days of admission
Interventions: • Vancomycin 500mg every 6 hours plus gentamicin 2mg/kg every 6 hours and ticarcillin 45mg/kg every 4 hours Versus • Placebo every 6 hours plus gentamicin 2mg/kg every 6 hours and ticarcillin 45mg/kg every 4 hours

All antibiotics were administered intravenously

Outcomes:

Days of fever
Superinfections

Results:

Death
Not reported (stated that there was no significant difference between groups)

Super-infections
Gentamicin + ticarcillin - 16/29 (55%)
Gentamicin + ticarcillin + vancomycin - 0/31 (0%)

Duration of fever
Gentamicin + ticarcillin - Median - 15.1 days (range 4-40)
Gentamicin + ticarcillin + vancomycin - Median - 10.3 days (range 9-35)

Toxicity
Not reported (stated that there was no added toxicity in vancomycin group

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Antibiotic resistance
Not reported

General comments:

- Sequence generation and allocation concealment were adequate
- Double blinded
- 8% of episodes were excluded from analyses
- Deaths not reported

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5. Marie, J. P., Pico, J., Lapierre, V., Maulard, C., Pappo, M., Chiche, D. et al. (1991). Comparative trial of ceftazidime alone, ceftazidime + amikacin and ceftazidime + vancomycin as empiric therapy of febrile cancer patients with induced prolonged neutropenia. *Medecine et Maladies Infectieuses, 21,* 386-388.
Country: France
Design: Randomised Controlled Trial
Population: 223 episodes of febrile neutropenia in 205 patients between October 1987 and June 1989 *unclear how many patients had central lines*
Inclusion criteria: • Underlying neoplastic disease • ≥ 18 years old • Neutropenia (neutrophil count of <500/mm^3 or ≤ 1000/mm^3 and falling) • Fever (oral temperature of ≥38°C on two occasions 6h apart or ≥38.5°C on one occasion not associated with blood product transfusions)
Exclusion criteria: • Parenteral antibiotics in the preceding 96 hours • Known allergy to any of the study drugs
Interventions: • Ceftazidime (2g intravenously every 8 hours) Versus

- Ceftazidime (2g intravenously every 8 hours) plus vancomycin (1g every 12 hours)

Vancomycin was added to the ceftazidime arm when fever persisted for more than 96 hours

Outcomes:

- Superinfection
- Tolerance

Results:

Death (all cause)
Not reported

Super-infection

Ceftazidime + vancomycin - 20/77 (26%)
Ceftazidime - 5/77 (6%)

Treatment failure (treatment modification considered a failure)

Ceftazidime + vancomycin - 53/77 (69%)
Ceftazidime - 67/77 (87%)

Tolerance
Skin rash
Ceftazidime + vancomycin - 4/77 (5%)
Ceftazidime - 4/77 (5%)

Renal problems
Ceftazidime + vancomycin - 5/77 (6%)
Ceftazidime - 4/77 (5%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Toxicity
Tolerance reported (see above)

General comments:

- This paper was published in French
- Sequence generation and concealment were unclear
- The study was not blinded

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6. Molina, F., Pedro, L., Rosell, R., Barnadas, A., Font, A., & Maurel, J. (1993). Randomized open and prospective study of two antibiotic schedules (with and without teicoplanin) for post-chemotherapy episodes of neutropenic fever. *Oncologia: IV Congresso Nacional de la SEOM, 16,* 247.
Country: Spain
Design: Randomised Controlled Trial
Population: Number randomised unknown. 36 were evaluated. *unclear how many patients had central lines*
Inclusion criteria: • Unclear (awaiting paper)
Exclusion criteria: • Unclear (awaiting paper)
Interventions: • Unclear (awaiting paper)
Outcomes: • Unclear (awaiting paper)
Results: <u>Death (all cause mortality)</u>

Awaiting paper...
General comments: • Unclear whether methods of sequence generation and allocation concealment were adequate • Study was not blinded • (awaiting paper)

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7. Novakova, I., Donnelly, J. P., & de Pauw, B. (1991). Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. Antimicrobial Agents and Chemotherapy, 35, 672-678.
Country: The Netherlands
Design: Randomised Controlled Trial
Population: 120 febrile granulocytopenic patients with haematological or solid tumours *unclear how many patients had central lines*
Inclusion criteria: • >14 years of age • Granulocytopenic (granulocyte counts expected to fall to < 0.5 x 10^9/litre) • Febrile (single anxillary temperature ≥ 38.5°C or at least 2 readings of > 38°C taken 2 to 4 hours apart) • No obvious focus of infection
Exclusion criteria: • Infective focus (such as a lung infiltrate) at the onset of fever
Interventions: • Ceftazidime in a short infusion of 2g every 8 hours Versus • Ceftazidime in a short infusion of 2g every 8 hours plus teicoplanin of 800mg in two divided doses on the first day and 400mg once a day thereafter Modification by addition or substitution was permitted in cases of marked clinical deterioration, isolation of a resistant pathogen, persistence of presenting bacteremia, diagnosis of a superinfection.

Outcomes:

- Response
- Response after modification
- Treatment failure
- Toxicity
- Bacteriological evaluation

Results:

Death (all cause mortality)
Ceftazidime - 6/50 (12%)
Ceftazidime + teicoplanin - 6/50 (12%)

Death (due to infection)
Ceftazidime - 0/50 (0%)
Ceftazidime + teicoplanin - 0/50 (0%)

Antibiotic resistance
Ceftazidime - 2/51 (4%)
Ceftazidime + teicoplanin - 0/52 (0%)

Proven Bacteraemia
Ceftazidime - 18/51 (35%) (13 caused by gram positive bacteria)
Ceftazidime + teicoplanin - 20/52 (38%) (17 caused by gram positive bacteria)

Toxicity
Nephrotoxicity (defined as 50% increase in creatinine in serum)
Ceftazidime - 3/51 (6%)
Ceftazidime + teicoplanin - 4/52 (8%)

Treatment failure (modifications classed as failure)
Ceftazidime - 26/51 (51%)
Ceftazidime + teicoplanin - 19/52 (37%)

Duration of fever
Ceftazidime
Without modification -3.5 ± 0.8
With modification - 14.6 ± 3.8
Ceftazidime + teicoplanin
Without modification - 3.8 ± 0.9
With modification - 13.6 ± 3.3

Duration of antibiotic therapy
Ceftazidime

Without modification - 7.3 ± 0.8 With modification - 22.4 ± 7.0 Ceftazidime + teicoplanin Without modification - 7.6 ± 0.8 With modification - 17.4 ± 2.3 <u>Critical care</u> Not reported <u>Length of stay</u> Not reported <u>Line preservation / "catheter remains in situ"</u> Not reported
General comments: • Unclear whether methods of sequence generation and allocation concealment were adequate • Study was not blinded • ITT analysis reported for death • The majority of patients had received oral antimicrobial prophylaxis prior to the onset of fever

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8. Ramphal, R., Bolger, M., Oblon, D. J., Sherertz, R. J., Malone, J. D., Rand, K. H. et al. (1992). Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: A randomized prospective study. Antimicrobial Agents and Chemotherapy, 36, 1062-1067
Country: USA
Design: Randomised Controlled Trial
Population: 127 adult febrile neutropenic patients *61% had central lines*
Inclusion criteria: • Underlying neoplastic disease • ≥ 18 years old • Neutropenia (neutrophil count of <500/mm^3 or ≤ 1000/mm^3 and falling • Fever (oral temperature of ≥38°C on two occasions 6h apart or ≥38.5°C on one occasion not associated with blood product transfusions)
Exclusion criteria: • Parenteral antibiotics in the preceding 96 hours • Known allergy to any of the study drugs
Interventions: • Ceftazidime (2g intravenously every 8 hours) Versus • Ceftazidime (2g intravenously every 8 hours) plus vancomycin (1g every 12 hours) Vancomycin was added to the ceftazidime arm when fever persisted for more than 96 hours

Outcomes:

- Death
- Initial response rate
- Duration of fever
- Frequency of new fever
- Microbiological cure
- Superinfection

Results:

Death (all cause)

Ceftazidime + vancomycin - 7/64 (11%)
Ceftazidime - 6/63 (10%)

Death (from infection)

Ceftazidime + vancomycin - 5/64 (8%)
Ceftazidime - 4/63 (6%)

Death (from superinfection)

Ceftazidime + vancomycin - 1/64 (2%)
Ceftazidime - 4/63 (6%)

Super-infection

Ceftazidime + vancomycin - 5/64 (8%)
Ceftazidime – 1/64 (2%)
Ceftazidime (added vancomycin) – 7/? (?%)

Treatment failure (treatment modification considered a failure)

Ceftazidime + vancomycin - 25/64 (39%)
Ceftazidime - 28/63 (44%)

Toxicity
Rashes and renal problems (not reported separately)
Ceftazidime + vancomycin - 19/64 (30%)
Ceftazidime – 6/63 (10%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ" Not reported Antibiotic resistance Not reported
General comments: • Sequence generation and concealment were adequate • The study was not blinded • There were more patients with acute leukaemia and with Hickman catheters in the monotherapy group. These individuals were thought to be higher risk of infection, but the differences did not reach a level of statistical significance.

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9. Paul, M., Brook, S., Fraser, A., Vidal, L. & Leibovici, L. (2005) Empirical antibiotics against Gram positive infections for febrile neutropenia: systematic review and meta-analysis of randomised controlled trials. Journal of Antimicrobial Chemotherapy, 55, 436-44
Country: Israel
Design: Systematic review
Population: 13 studies including 2392 participants * two studies were concerned with the treatment of persistent fever*
Inclusion criteria: • Trials comparing a standard antibiotic regimen with a regimen including the addition of an antibiotic with activity against gram-positive bacteria • Studies assessing empirical intervention both initially and for the treatment of persistent fever
Exclusion criteria: • Studies with a drop-out rate over 30%
Interventions: • Standard empirical antibiotic regimen Versus • Standard antibiotic regimen with the addition of an antibiotic with activity against gram-positive bacteria
Outcomes: • All cause mortality

- Treatment failure
- Bacterial superinfection
- Adverse events

Results:

* two studies were concerned with the treatment of persistent fever – the overall results do not therefore apply directly to topic G*

All cause mortality
RR = 0.86 (0.58 – 1.26) P = 0.83; 7 studies; 852 participants

Treatment failure
RR = 1.00 (0.79 – 1.27) P = 0.09; 6 studies; 943 participants

Treatment failure (associated with treatment modifications)
RR = 1.00 (0.61 – 0.80) P = ; 5 studies; 1178 participants

Bacterial superinfection
RR = 0.38 (0.24 – 0.59)

Adverse events
RR = 1.88 (1.10 – 3.22) ; 6 studies; 1282 participants

General comments:

- Only the studies considering initial therapy were relevant to Topic G
- Numerous online databases were searched
- Data was extracted by two reviewers independently
- The quality of studies was assessed by two reviewers using criteria suggested by the Cochrane collaboration
- No significant heterogeneity was present in any of the comparisons
- The authors concluded that the use of glycopeptides could be safely deferred until the documentation of a resistant gram-positive infection

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Del Favero, A., Menichetti, F., Guerciolini, R., Bucaneve, G., Baldelli, F., Aversa, F. et al. (1987). Prospective randomized clinical trial of teicoplanin for empiric combined antibiotic therapy in febrile, granulocytopenic acute leukemia patients. Antimicrobial Agents & Chemotherapy, 31, 1126-1129.

EORTC (1991). Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group.[Erratum appears in J Infect Dis 1991 Oct;164(4):832]. *Journal of Infectious Diseases, 163,* 951-958.

Karp, J. E., Dick, J. D., Angelopulos, C., Charache, P., Green, L., Burke, P. J. et al. (1986). Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *American Journal of Medicine, 81,* 237-242.

Marie, J. P., Pico, J., Lapierre, V., Maulard, C., Pappo, M., Chiche, D. et al. (1991). Comparative trial of ceftazidime alone, ceftazidime + amikacin and ceftazidime + vancomycin as empiric therapy of febrile cancer patients with induced prolonged neutropenia. [French]. *Medecine et Maladies Infectieuses, 21,* 386-388.

Molina, F., Pedro, L., Rosell, R., Barnadas, A., Font, A., & Maurel, J. (1993). Randomized open and prospective study of two antibiotic schedules (with and without teicoplanin) for post-chemotherapy episodes of neutropenic fever. *Oncologia: IV Congresso Nacional de la SEOM, 16,* 247.

Novakova, I., Donnelly, J. P., & de, P. B. (1991). Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. Antimicrobial Agents and Chemotherapy, 35, 672-678.

Paul, M., Brook, S., Fraser, A., Vidal, L. & Leibovici, L. (2005) Empirical antibiotics against Gram positive infections for febrile neutropenia: systematic review and meta-analysis of randomised controlled trials. Journal of Antimicrobial Chemotherapy, 55, 436-44

Ramphal, R., Bolger, M., Oblon, D. J., Sherertz, R. J., Malone, J. D., Rand, K. H. et al. (1992). Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: A randomized prospective study. Antimicrobial Agents and Chemotherapy, 36, 1062-1067

13. Indications for removing central lines in patients with neutropenia or neutropenic sepsis. (Topic H)

Guideline subgroup members for this question

Jeanette Hawkins (lead), Bob Phillips, Anne Higgins, Barbara Crosse and Rosemary Barnes

Review question:

Which patients with central venous access devices and neutropenic sepsis will benefit from removal of their central line?

Rationale

Tunnel, intra-luminal or pocket infection associated with central venous access devices (CVAD) is a potentially life threatening complication, with heightened risk in immunocompromised patients. Cancer patients with neutropenic sepsis and suspected or proven CVAD infection, require early detection of infection and prompt intervention to prevent morbidity, mortality and (where possible) to preserve long-term devices.

CVADs are frequently intended to be 'long-term' devices in cancer patients to support long-term therapy and improve quality of life for patients on treatment (and in palliative care) by reducing exposure to frequent needle sticks. CVADs reduce the risks of extravasation injury from vesicant & irritant cytotoxic infusions. CVADs also facilitate the infusion of multiple therapies more readily, e.g. concurrent chemotherapy, parenteral nutrition and antibiotics. Replacement devices are often considered when long term CVADs are removed due to infection, but device replacement is not without risk and inconvenience to the patient, and costly in terms of additional theatre and anaesthetic time for the NHS. For these reasons there has been a shift towards line preservation where possible, by attempting to treat CVAD infections. Clinicians need evidence based guidelines to weigh up the risk / benefit equation in attempting to preserve devices without increasing the risk of serious morbidity and mortality.

Assessing the need for line removal usually includes;

1. Proven Catheter related sepsis (CRS) or Catheter related blood stream infection (CRBSI) due to isolated pathogens.
2. Location of infection (proven or suspected) exit site, tunnel, intra-luminal, pocket.
3. Prolonged unresponsive fever after commencing antibiotics.
4. Severity of clinical illness
5. Recurrent infection in same CVAD
6. Failures of CVAD function with or without evidence of colonised fibrin sheath at catheter tip.

Question in PICO format

Patients/population	Prognostic factors	Outcomes
Patients with central venous access device and neutropenic sepsis	• Type of organism • Tunnel, pocket or intra-luminal infection • Signs of severe sepsis • Signs of thrombosis • Recurrent infection in CVAD • Unresponsive fever after commencing antibiotics • Catheter tip fibrin sheath	• Death/critical care, • Length of stay • Duration of fever • Line preservation • Duration of antibiotics • Infection-control complications

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Psychinfo and BMI. The full strategy will be available in the full guideline. There were no publication date limits set. The date of the search was 10th of August 2011 and was updated on 7th November 2011.

Papers ordered for topic G and topic C, were also checked for eligibility for this topic.

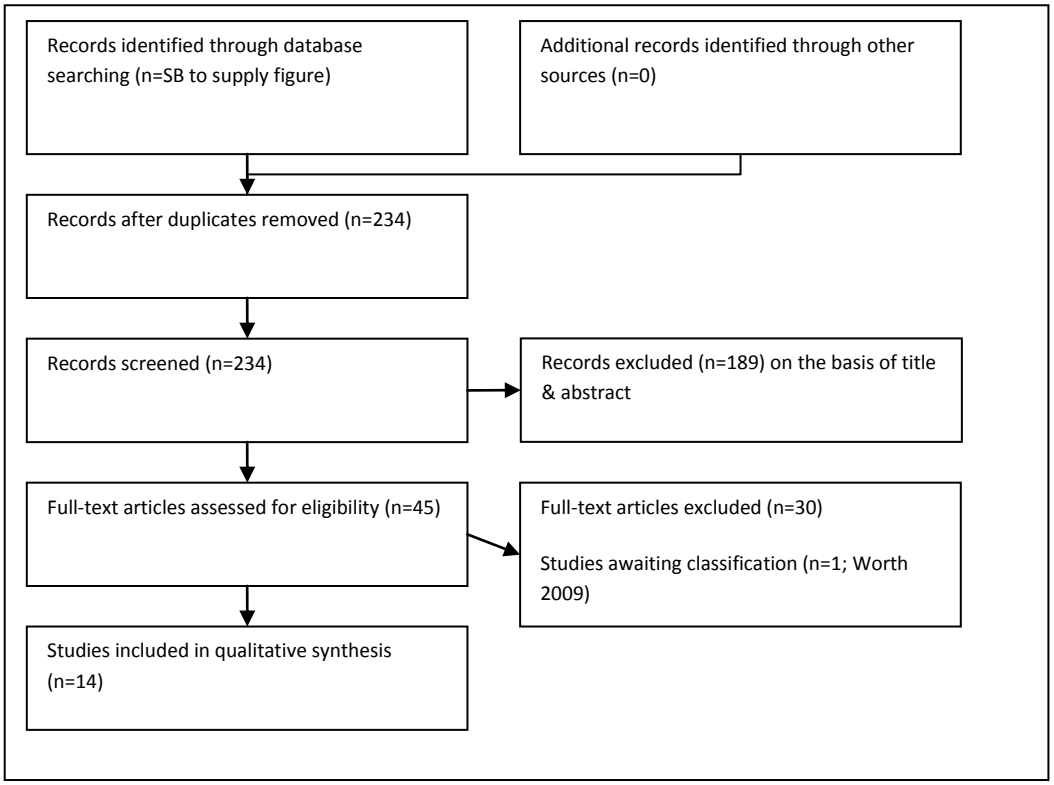
Selection of studies

The information specialist (SB) did the first screen of the literature search results. Two reviewers (NB and CL) then independently selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained and checked against the inclusion criteria.

RESULTS

Results of the literature searches

Figure 13.1 Study flow diagram



Study characteristics

- All studies were observational, five studies were prospective.
- Six studies included only children or teenagers.
- Nine studies included a majority of patients with haematological cancers.
- Five studies reported results only for patients with presumed CVC (central venous catheter)-related infections.
- Three studies reported results only for patients with specific microbiologically documented infections. De Pauw et al (1990) included only episodes with Gram positive bacterial infections, Hanna et al (2004) Gram negative infections and Park et al (2010) patients with presumed catheter-related staphylococcus aureus bacteraemia.
- Three studies came from the 1980s, four from the 1990s and seven from 2000 onwards.

Study quality

The evidence was of very low quality because there was a lack of studies comparing criteria for central line removal. Instead studies reported outcomes according to the site of the infection or infecting micro-organism. All 14 included studies were observational of which five were prospective. Six studies included only children or teenagers, nine studies included a majority of patients with haematological cancers and five studies reported results only for patients with presumed central venous catheter related infections.

Evidence Statements

Mortality

No studies considered prognostic factors for overall survival, but some reported infectious mortality.

Two studies (Al Bahar, et al., 2000; Elishoov, et al., 1998) reported infectious mortality according to the site of infection (Table 13.1). All 16 cases of infectious mortality were associated with bacteraemia or fungaemia and there were no cases of infectious mortality attributed to tunnel or exit site infections.

Elishoov, et al., (1998) reported ten occurrences of infectious mortality according to the infecting microorganisms. Microorganisms associated with infectious mortality were coagulase negative Staphylococcus aureus (1 infectious mortality in 29 infections), Streptococcus viridans (1/3), Pseudomonas aeruginosa (4/13), Candida species (2/10). There were 2 polymicrobial infectious deaths involving Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae and Proteus vulgaris in one case and Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae in another.

Park, et al., (2010) reported 2 infectious deaths in a series of 48 cases of catheter-related Staphylococcus aureus bacteraemia.

Length of hospital stay, duration of fever and duration of antibiotics

None of the included studies reported length of hospital stay.

Millar, et al., (2011) considered prognostic factors for length of the febrile episode in a prospective multicentre study of children with central venous catheters and fever. The febrile neutropeniaFN episode was longer in patients with fever, rigors and chills (FRC): HR 0.49 (95% C.I. 0.27 to - 0.88), than in those without FRC. Children infected with pathogens (organisms which would normally prompt central venous catheter removal such as Staphylococcus aureus or Pseudomonas aeruginosa) had longer febrile episodes than children without microbiologically documented infections: HR 0.48 (95% C.I. 0.19 to - 1.17). Similarly children infected with organisms typically treated with antibiotic lock or skin bacteria had longer febrile episodes than children without microbiologically documented infections: HR 0.57 (95% C.I. 0.38 to- 0.84).

The total duration of IV treatment was 3.61 times longer in patients with FRC (95% CI 0.55 to - 6.68) than without, 4.39 times longer in patients with pathogenic organisms (95% CI -0.39 to - 9.18) than those without microbiologically documented infections and 2.99 times longer in patients with other organisms or skin bacteria than in those without microbiologically documented infections (95% CI 0.91 to - 5.08).

Line preservation

Several studies (Viscoli, et al., 1988, Junqueria, et al., 2010, Holloway, et al., 1995, Al Bahar., et al., 2000, Hartman, et al., 1987, Elishoov, et al., 1998 and Hanna, et al.,, 2004) reported whether or not the central venous catheter was removed according to the site of infection (Table 13.1). Central venous catheters were often preserved in those with exit site infection or bacteraemia, but were removed in all but one case of tunnel infection.

In Millar et al., (2011) the presence of fever, rigors, chills and/or hypotension was associated with a greatly increased likelihood of central venous catheter removal, HR=16.39 (95% C.I. 4.73 to - 56.79).

Park, et al., (2010) reported the outcome of attempted Hickman catheter salvage in 33 patients with presumed catheter-related Staphylococcus aureus bacteraemia (Table 13.2). Several factors were associated with an increased chance of salvage failure: external signs of infection (tunnel or exit-site infection), positive follow up blood cultures (at 48 to 96 hours) and methicillin resistance (at a statistical significance level of $P<0.05$). Catheter salvage failed in both patients with septic shock in this study.

Joo, et al., (2011) reported the outcome of attempted catheter salvage in 38 patients with a central venous catheter related infection. There was a greater proportion of Gram-negative bacteria in the salvage failure group (8/18) than in the successful salvage group (2/20), (pP=0.027). The majority of the successful central venous catheter salvage attempts (13/20) were in patients with coagulase negative Staphylococcus infections .

Millar, et al., (2011) found in children infected with pathogens traditionally leading to central venous catheter removal, the time to central venous catheter removal was much shorter than when there was no microbiologically documented infection (HR 25.71; 95% C.I. 4.27 to - 154.7). If the child was infected with a microorganism usually treated with antibiotic lock or a skin bacteria, the time to central venous catheter removal was also shorter than if there was no microbiologically documented infection (HR 8.40; 95% C.I. 2.01 to - 35.14),).

Infection-control complications

This outcome was not reported in the included studies.

Table 13.1. Outcome according to infection site

Infection type	Infectious mortality	Line Preservation
Septic phlebitis	0/1(0%) Al Bahar (2000) 2/3(66.67%) Elishoov (1998) (with septicaemia)	0/1(0%) Al Bahar (2000)
Tunnel	0/3(0%) Al Bahar (2000) 0/3(0%) Elishoov (1998)	1/8(12.5%) Junqueria (2010) 0/3(0%) Holloway (1995) 0/3(0%) Al Bahar (2000)
CVC exit-site	0/12(0%) Al Bahar (2000) 0/25(0%) Elishoov (1998)	9/9(100%) Junqueria (2010) 2/6(33.33%) Viscoli (1988) 22/22(100%) Holloway (1995) 6/7(85.71%) Hartman (1987) 0/13(0%) Hanna (2004) 7/12(58.33%) Al Bahar (2000)
CVC related bacteraemia or fungaemia	4/51(7.84%) Elishoov (1998) 2/15(13.33%) Al Bahar (2000)	10/15(66.67%) Viscoli (1988) 25/30(83.33%) Junqueria (2010) 3/10(30%) Holloway (1995) 13/15(86.67%) Al Bahar (2000) 30/32(93.75%) Hartman (1987)
Other infection – not CVC related	2/101(1.98%) Al Bahar (2000) 6/61(9.84%) Elishoov (1998)	15/19(78.95%) Junqueria (2010) 101/101(100%) Al Bahar (2000)
Colonization only (without signs of sepsis)	0/24(0%) Elishoov (1998)	Not reported

Table 13.2. Line preservation according to infecting microorganism

Gram positive bacteria	Studies from 1980s	Studies from 2000-
Staphylococcus aureus	3/4 (75%) Hartman (1987) 21/25 (84%) De Pauw (1990) 4/6 (66.67%) Viscoli (1988)	1/3 (33.33%) Junqueira (2010) 3/3 (100%) Nosari (2008) 3/6 (50%) Joo (2011) 23/30 (76.67%) Park (2010)
Methicillin resistant staphylococcus aureus	-	5/12 (41.67%) Park (2010)
Coagulase negative staphylococcus	-	13/18 (72.22%) Joo (2011) 4/11 (36.36%) Junqueira (2010)
Staphylococcus epidermidis	68/81 (83.95%) De Pauw (1990) 7/7 (100%) Viscoli (1988) 8/8 (100%) Hartman (1987)	17/22 (77.27%) Nosari (2008)
Enterococcus species	5/7 (71.43%) De Pauw (1990) 0/1 (0%) Viscoli (1988) 2/3 (66.67%) Hartman (1987)	4/5 (80%) Nosari (2008)
Streptococcus	5/5 (100%) Hartman (1987) 9/10 (90%) De Pauw (1990) 3/4 (75%) Viscoli (1988)	6/6 (100%) Junqueira (2010) 7/7 (100%) Nosari (2008)

Gram negative bacteria	Studies from 1980s	Studies from 2000-
Pseudomonas aerguinosa	4/5 (80%) Hartman (1987) 1/2 (50%) Viscoli (1988)	0/3 (0%) Joo (2011) 4/4 (100%) Nosari (2008)
Enterobacter species	2/2 (100%) Hartman (1987) 1/1 (100%) Viscoli (1988)	3/4 (75%) Nosari (2008) 1/1 (100%) Joo (2011)
Escherichia coli	2/3 (66.67%) Hartman (1987)	0/2 (0%) Joo (2011) 8/9 (88.89%) Nosari (2008)
Klebsiella species	2/2 (100%) Hartman (1987)	1/1 (100%) Nosari (2008) 1/1 (100%) Joo (2011)

Fungi	Studies from 1980s	Studies from 2000-
Candida albicans	2/2(100%) Hartman (1987) 1/2(50%) Viscoli (1988)	-
Candida tropicalis	2/2(100%) Hartman (1987)	-
Any fungus	-	0/6(0%) Ruggiero (2010)

EVIDENCE TABLES

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Al Bahar 2000

Kuwait</td>
<td>Retrospective case series. Consecutive sample.

Study period not reported</td>
<td>133 FN episodes in 64 patients</td>
<td>Line preservation: 121/133

Clinically documented infection: 17/133

Microbiologically documented infection: 41/133

Catheter related infection: 32/133

Infectious mortality: 4/133

Overall mortality: 10/133</td>
<td>Patients with acute leukaemia, Hickman catheters, fever (38.5°C or >38°C twice within 12h) and neutropenia (<1.0 X 10^9/L)

Median age 31 years.

All had haematological cancer.</td>
<td>Infection type: catheter related versus not.

Catheter related infection, further defined as exit site infection (further definition given), tunnel infection (further definition given), catheter related blood stream infection (further definition given) or septic thrombophlebitis (further definition given</td>
<td>Catheter removal – not defined further.

Response to antimicrobial treatment

Infectious mortality</td>
<td>
<table>
<tr><th rowspan="2">Infection type</th><th colspan="2">Line preservation</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Tunnel</td><td>0</td><td>3</td></tr>
<tr><td>Exit site</td><td>7</td><td>5</td></tr>
<tr><td>CVC-related bacteraemia/fungaemia</td><td>13</td><td>2</td></tr>
<tr><td>Septic phlebitis</td><td>0</td><td>1</td></tr>
<tr><td>Not catheter related</td><td>101</td><td>0</td></tr>
</table>
<table>
<tr><th rowspan="2">Catheter related infection</th><th colspan="2">Infectious mortality</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Tunnel</td><td>0</td><td>3</td></tr>
<tr><td>Exit site</td><td>0</td><td>12</td></tr>
<tr><td>CVC-related bacteraemia/fungaemia</td><td>2</td><td>13</td></tr>
<tr><td>Septic phlebitis</td><td>0</td><td>1</td></tr>
<tr><td>None</td><td>2*</td><td>99</td></tr>
</table>
*In 2/32 cases of catheter related infection the patients died of Candida albicans septicaemia. The two patients with non CVC-related infection died of pneumonia.
<table>
<tr><th rowspan="2">Catheter related infection</th><th colspan="2">Response to antimicrobial</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Yes</td><td>30</td><td>2</td></tr>
<tr><td>No</td><td>101</td><td>0</td></tr>
</table>
</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>De Pauw</td>
<td>Retrospecti</td>
<td>123 cases of catheter</td>
<td>Catheter removal</td>
<td>Patients with microbiological</td>
<td>Type of gram-positive</td>
<td>Catheter</td>
<td>In patients with confirmed Gram-</td>
<td>Merrell Dow</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td>1990.

Netherlands</td><td>ve study.

1985-1989</td><td>infection.</td><td>20/123

Treatment success 97/123</td><td>ly documented Gram-positive Hickman catheter related infection treated with teicoplanin, unclear how patients were recruited.

Data were supplemented using Merrell Dow's UK database</td><td>bacteria</td><td>removal

Treatment success</td><td>positive CVC related infection:
<table><tr><th rowspan="2">Organism</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Staphylococcus epidermidis</td><td>68</td><td>13</td></tr><tr><td>Staphylococcus aureus</td><td>21</td><td>4</td></tr><tr><td>Streptococcus Viridans</td><td>9</td><td>1</td></tr><tr><td>Enterococci</td><td>5</td><td>2</td></tr></table></td><td>supplied teicoplanin</td><td></td></tr>
<tr><td>Elishoov 1998.

Israel</td><td>Prospective case series. Consecutive sample.

5 year study period (start not reported)</td><td>242 patients,</td><td>161 febrile episodes in 120 patients.

112 episodes of septicaemia in 90 patients.

100 catheter related infections in 81 patients.</td><td>Patients undergoing bone marrow transplant, who had Hickman or Broviac catheters.

Median age 21 (range 1 to 53 years)

All had haematological cancer</td><td>Bacteraemia: defined as a positive blood culture (further definition given).

Septicaemia: bacteraemia (or fungaemia) plus clinical signs.

Catheter related infection,</td><td>Mortality during infectious episode

.</td><td><table><tr><th rowspan="2">Infection type</th><th colspan="2">Infectious mortality</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>CVC related bacteraemia/fungaemia</td><td>4</td><td>47</td></tr><tr><td>Not CVC-related</td><td>6</td><td>55</td></tr></table>
Gram-positive organisms
<table><tr><th rowspan="2">Organism</th><th colspan="2">Infectious mortality</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Coagulase negative staphylococcus aureus</td><td>1</td><td>28</td></tr><tr><td>Streptococcus Viridans</td><td>1</td><td>2</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>(N=209) or non-malignant haematological disorder (N=33).</td><td>defined as exit site infection (further definition given), tunnel infection (further definition given), catheter related blood stream infection (further definition given) or septic thrombophlebitis (further definition given

Type of infecting microorganism</td><td></td><td>Gram-negative organisms
<table><tr><td rowspan="2">Organism</td><td colspan="2">Infectious mortality</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Pseudomonas aeruginosa</td><td>4</td><td>9</td></tr></table>
Other organisms
<table><tr><td rowspan="2">Organism</td><td colspan="2">Infectious mortality</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Candida species</td><td>2</td><td>8</td></tr><tr><td>Polymicrobial</td><td>2</td><td>7</td></tr></table>
<table><tr><td rowspan="2">Infection type</td><td colspan="2">Infectious mortality</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Septic thrombphlebitis with septicaemia</td><td>2</td><td>1</td></tr><tr><td>Tunnel infection with septicaemia</td><td>0</td><td>3</td></tr><tr><td>Exit site infection ONLY</td><td>0</td><td>25</td></tr><tr><td>CVC-related bacteraemia or fungaemia ONLY</td><td>2</td><td>42</td></tr><tr><td>Non CVC-related septiceaemia</td><td>6</td><td>56</td></tr><tr><td>Colonization only (no clinical signs)</td><td>0</td><td>24</td></tr></table></td><td></td><td></td></tr>
<tr><td>Hanna 2004.

USA</td><td>Retrospective case series.

1990-1996</td><td>72 patients</td><td>Removal of CVC, 67/72

Mortality: 34/72

Mortality due</td><td>Patients with cancer and catheter-related Gram-negative bacteraemia.</td><td>ICU, mechanical ventilation, steroids, radiotherapy, transplantation,</td><td>Removal of CVC

Relapse of infection.</td><td>In patients with CVC related Gram-negative bacteraemia:
<table><tr><td>CVC site inflammation</td><td>Line preserved</td></tr></table></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>to Gram-negative infection: 3/72</td><td>Mean age was 51 years in those with CVC removed and 49 years in the others.

26% of patients had haematological cancer.</td><td>chemotherapy, fever, CVC-stie inflammation, fever, neutropenia</td><td></td><td>
<table>
<tr><td></td><td>Yes</td><td>No</td></tr>
<tr><td>CVC site inflammation</td><td>0</td><td>13</td></tr>
<tr><td>No CVC site inflammation</td><td>5</td><td>54</td></tr>
</table>
<table>
<tr><td rowspan="2">Fever</td><td colspan="2">Line preserved</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Yes</td><td>5</td><td>62</td></tr>
<tr><td>No</td><td>0</td><td>5</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Hartman 1987</td><td>Case series

1979-1984</td><td>63 catheters in 50 patients</td><td>Complications 76 in 40 catheters .

Catheter related infections: 39/63

Mechanical complications: 24 in 20 catheters.

Death due to catheter complication:</td><td>Paediatric oncology patients selected for long term catheterization with Hickman or Broviac catheter.

Patients had demonstrated ablation of peripheral sites or were predicted to have difficult</td><td>Infectious complication type (CVC related bacteraemia or exit site/tunnel infection), infection organism, neutropenia at time of insertion.

Exit site infection: defined as</td><td>Removal of CVC</td><td>In 39 patients with CVC-related infections:
<table>
<tr><td rowspan="2">Infection type</td><td colspan="2">Line preserved</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>CVC related bacteraemia</td><td>30</td><td>2</td></tr>
<tr><td>Exit site inflammation</td><td>6</td><td>1</td></tr>
</table>
In 39 catheters with CVC-related infections there were 44</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>1/63

Tumour seeding: 1/63</td><td>induction therapy.

Median age was 3.1 years.

63% had haematological cancer.</td><td>progressive erythema of exit site or subcutaneous tunnel.

Catheter related sepsis: defined as at least one positive blood culture with fever or other signs of systemic sepsis without an identified source.</td><td></td><td>organisms isolated (some cultures yielded than one organism):

Gram positive

<table>
<tr><th rowspan="2">Organism</th><th colspan="2">Line preserved</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Staphylocccus aureus</td><td>3</td><td>1</td></tr>
<tr><td>Staphylococcus epidermis</td><td>8</td><td>0</td></tr>
<tr><td>Streptococcus</td><td>5</td><td>0</td></tr>
<tr><td>Enterococcus*</td><td>2</td><td>1</td></tr>
</table>

Gram negative

<table>
<tr><th rowspan="2">Organism</th><th colspan="2">Line preserved</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Escherichia coli*</td><td>2</td><td>1</td></tr>
<tr><td>Gram negative bacilli</td><td>3</td><td>0</td></tr>
<tr><td>Klebsiella</td><td>2</td><td>0</td></tr>
<tr><td>Acintobacter</td><td>2</td><td>0</td></tr>
<tr><td>Enterobacter</td><td>2</td><td>0</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Neisseria</td><td>1</td><td>0</td></tr>
<tr><td>Pseudomonas</td><td>4</td><td>1</td></tr>
<tr><td>Serratia</td><td>1</td><td>0</td></tr>
<tr><td>Capnocytophaga</td><td>1</td><td>0</td></tr>
</table>
* catheter removed in a single patient with both organisms.

Fungus
<table>
<tr><td rowspan="2">Organism</td><td colspan="2">Line preserved</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Candida albicans</td><td>2</td><td>0</td></tr>
<tr><td>Candida tropicalis</td><td>2</td><td>0</td></tr>
<tr><td>Unspecified fungus</td><td>1</td><td>0</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Holloway 1995.

USA</td><td>Case series- unclear whether prospective / consecutive.

1990 - 1993</td><td>105 women with 111 catheter insertions.</td><td>Removal of CVC due to complications:

13/111</td><td>Women attending a gynaecologic oncology service who were fitted with Groshong catheters.

Mean age 60 years. None</td><td>Infectious complications (tunnel infection, bacteraemia, thrombosis, cellulitis),</td><td>Catheter removal</td><td>
<table>
<tr><td rowspan="2">Infectious complications</td><td colspan="2">Line preserved</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Tunnel</td><td>0</td><td>3</td></tr>
<tr><td>CVC-related bacteraemia/fungaemi</td><td>3</td><td>7</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>had haematological cancer.</td><td></td><td></td><td><table><tr><td>a</td><td></td><td></td></tr><tr><td>Exit site</td><td>22</td><td>0</td></tr></table></td><td></td><td></td></tr>
<tr><td>Joo 2011.

Korea</td><td>Retrospective case series.

1996-2007</td><td>51 patients</td><td>Catheter removal: 13/51

Catheter salvage: 38/51

Successful salvage: 20/38</td><td>Patients with neutropenia and a catheter related infection,

Mean age was 50 years.

59% had haematological malignancy.</td><td>Gender, underlying disease, co-morbid conditions, CVC type, duration of catherization, risk group, neutropenia, initial ANC, isolated pathogens, presence of complication</td><td>Salvage attempted (CVC not removed immediately)

Successful salvage: defined as retaining the catheter at the time of discharge</td><td>In 38 patients where salvage was attempted:
<table><tr><td rowspan="2">Septic shock</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Septic shock</td><td>1</td><td>4</td></tr><tr><td>No septic shock</td><td>19</td><td>14</td></tr></table>
<table><tr><td rowspan="2">Risk group</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>High</td><td>6</td><td>8</td></tr><tr><td>Low</td><td>14</td><td>10</td></tr></table>
Gram-positive organisms
<table><tr><td rowspan="2">Organism</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Staphyloccucs aureus</td><td>3</td><td>3</td></tr><tr><td>Coagulase negative</td><td>13</td><td>5</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>staph. aureus</td><td></td><td></td></tr>
<tr><td>Micrococcus species</td><td>1</td><td>1</td></tr>
<tr><td>Corynebacteruim specis</td><td>0</td><td>1</td></tr>
<tr><td>Propionibacterium acnes</td><td>1</td><td>0</td></tr>
</table>
Gram-negative organisms
<table>
<tr><td rowspan="2">Organism</td><td colspan="2">Successful salvage</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Pseudomonas aeruginosa</td><td>0</td><td>3</td></tr>
<tr><td>Escherichia coli</td><td>0</td><td>2</td></tr>
<tr><td>Acinetobacter baumannii</td><td>0</td><td>1</td></tr>
<tr><td>Enterobacter species</td><td>1</td><td>0</td></tr>
<tr><td>Klebsiella oxytoca</td><td>1</td><td>0</td></tr>
<tr><td>Serratia marcescens</td><td>0</td><td>1</td></tr>
<tr><td>Campylobacter fetus</td><td>0</td><td>1</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Junqueira 2010.</td><td>Retrospective observation</td><td>192 catheters were inserted in 179</td><td>Catheter-related infection:</td><td>Children with acute lymphoblastic</td><td>Type of infection, infecting</td><td>Catheter removal, catheter</td><td>
<table>
<tr><td>Infection type*</td><td>Line</td></tr>
</table>
</td><td>No conflicts of interest</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Canada</td>
<td>study.
Consecutive sample.

2005-2008</td>
<td>children</td>
<td>43/192

Catheter removal due to infection:

12/192

Catheter removal due to mechanical complication:

3/192</td>
<td>leukaemia who had a port-a-catheter inserted.</td>
<td>organism</td>
<td>related infection.</td>
<td>
<table>
<tr><th></th><th colspan="2">preservation</th></tr>
<tr><th></th><th>Yes</th><th>No</th></tr>
<tr><td>Tunnel</td><td>1</td><td>7</td></tr>
<tr><td>Exit-site inflammation</td><td>9</td><td>0</td></tr>
<tr><td>CVC-related bacteraemia/fungaemia</td><td>25</td><td>5</td></tr>
<tr><td>Bacteraemia – not CVC related</td><td>15</td><td>4</td></tr>
</table>
*Some children had more than one infection type.

<table>
<tr><th rowspan="2">Organism</th><th colspan="2">Line preservation</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Coag. Neg. Staphylococcus</td><td>4</td><td>7</td></tr>
<tr><td>Staphylococcus aureus</td><td>1</td><td>2</td></tr>
<tr><td>Streptococcus species</td><td>6</td><td>0</td></tr>
<tr><td>Gram-negative organisms</td><td>N.R.</td><td>0</td></tr>
<tr><td>Polymicrobial</td><td>N.R.</td><td>0</td></tr>
</table>
</td>
<td>reported.</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Millar 2011.

UK</td><td>Prospective multicentre observational study, HTA report and systematic review.

2005-2006</td><td>181 children (179 included in analysis)</td><td>FRC (fever, rigors, chills and or hypotension associated with CVC manipulation):

13/179

At 28 days of follow-up:

CVC removal due to infection:

10/181

CVC removal for any other reason

0/181

Positive blood culture:

36/179

Pathogenic organism in blood culture (e.g S. Aureus or P. Aeruginosa):</td><td>Children, aged 0–18 years with fever having treatment for cancer or severe haematological disorder.

Participants had a tunnelled CVC or an implanted CVC port required for at least 3 months. Median age was 7yrs (IQR 3 to 11). 65% had haematological cancer

Fever was defined by an axillary or ear temperature of > 38 °C for > 4 hours, or > 38 °C on two occasions > 4 hours apart</td><td>Clinical data were collected at baseline (within 72 hours of fever presentation) and at 4 weeks later.

Age, type of cancer, number of lumens, type of CVC, duration of CVC insertion before episode, oral antibiotics within 2 weeks of episode, FRC, quantitative bacterial DNA results and blood culture result.</td><td>Duration of IV antibiotics, recurrent episode of infection requiring IV treatment, reason CVC removed, time to CVC removal and incidence of CVC removal.</td><td><table><tr><th rowspan="2">FRC</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Yes</td><td>8</td><td>5</td></tr><tr><td>No</td><td>161</td><td>5</td></tr></table>
Hazard ratios (95%) for outcomes in patients with FRC compared to those without. HR < 1.0 means the time to the outcome was *longer* in patients with FRC.

Time to end of FN episode: HR 0.49 (0.27 to 0.88), p=0.017

Time to recurrence: HR 0.37 (0.05 to 3.46), p=0.333

Time to CVC removal: HR 16.39 (4.73 to 56.79), p<0.0005

Recurrence (yes/no): RR 0.47 (0.06 to 3.46), p=0.461

Total duration of IV treatment 3.61 times longer in patients with FRC (95% CI 0.55 to 6.68), p=0.022.

<table><tr><th>Pathogens in blood culture</th><th>Line preservation</th></tr></table></td><td>HTA programme of the NIHR</td><td>Low number of CVC removal events compared the number of prognostic factors.</td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>5/179

Other organism or skin bacteria in blood culture:

31/179</td><td>within a 24-hour period, or > 38.5 °C on one occasion, or based on the oncology centre's definition of fever.</td><td></td><td></td><td>
<table>
<tr><th></th><th>Yes</th><th>No</th></tr>
<tr><td>Yes - Bacteria that normally prompt CVC removal (like S. aureus or P. aeruginosa)</td><td>3</td><td>2</td></tr>
<tr><td>Other - organisms normally treated with antimicrobial lock, or skin bacteria</td><td>26</td><td>5</td></tr>
<tr><td>None</td><td>140</td><td>3</td></tr>
</table>

Hazard ratios for outcomes in patients with pathogenic microorganisms in blood cultures versus those with negative blood cultures

Time to end of FN episode: HR 0.48 (0.19 to 1.17), p=0.105

Time to recurrence: HR 0.97 (0.13 to 7.12), p=0.976

Time to CVC removal: HR 25.71 (4.27 to 154.7), p<0.0005

Recurrence (yes/no): RR 1.17 (0.16 to 8.62), p=0.875

Total duration of IV treatment 4.39 times longer in patients with pathogenic organisms (95% CI -0.39 to 9.18), p=0.074.</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Hazard ratios for outcomes in patients with “other” organisms or skin bacteria in blood cultures versus those with negative blood cultures

Time to end of FN episode: HR 0.57 (0.38 to 0.84), p=0.005

Time to recurrence: HR 0.61 (0.21 to 1.74), p=0.355

Time to CVC removal: HR 8.40 (2.01 to 35.14), p=0.004

Recurrence (yes/no): RR 0.73 (0.26 to 2.08), p=0.560

Total duration of IV treatment 2.99 times longer in patients with “other” organisms or skin bacteria than those with negative blood cultures (95% CI 0.91 to 5.08), p=0.005</td><td></td><td></td></tr>
<tr><td>Nosari 2008.

Italy</td><td>Prospective case series

Consecutive sample

2003-2004</td><td>388 catheterizations in 279 patients</td><td>CVC malfunction 39/388

Infection:

92/388

Mortality</td><td>Adult patients with haematological cancer who were catheterized during therapy.

Mean age 49.7 years.</td><td>Infecting organism</td><td>Removal of catheter.</td><td>In patients with bacteraemia:

Gram-positive organisms

<table><tr><th rowspan="2">Organism</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Staphyloccucs epidermis</td><td>17</td><td>5</td></tr></table></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>7/388

CVC removal due to infection:

10/388</td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Staphylococcus aureus</td><td>3</td><td>0</td></tr>
<tr><td>Streptococcus species</td><td>7</td><td>0</td></tr>
<tr><td>Enterococcus specie</td><td>4</td><td>1</td></tr>
<tr><td>Other Gram-positive bacteria</td><td>6</td><td>0</td></tr>
</table>

Gram-negative organisms
<table>
<tr><td rowspan="2">Organism</td><td colspan="2">Line preservation</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Pseudomonas aeruginosa</td><td>4</td><td>0</td></tr>
<tr><td>Escherichia coli</td><td>8</td><td>1</td></tr>
<tr><td>Enterobacter species</td><td>3</td><td>1</td></tr>
<tr><td>Klebsiella species</td><td>1</td><td>0</td></tr>
<tr><td>Proteus species</td><td>2</td><td>0</td></tr>
<tr><td>Other Gram-negative bacteria</td><td>8</td><td>1</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Park 2010.

Korea</td><td>Retrospective consecutive</td><td>56 episodes of S. Aureus bacteraemia</td><td>MRSA:

20/56</td><td>Adult cancer patients with Hickman</td><td>Age, gender, chronic renal failure,</td><td>Attempted salvage: defined as</td><td>The outcome of attempted catheter salvage was known in 43/46 cases. 5 indeterminate</td><td>Not reported. No</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td>case series.

1997-2008</td><td>in 50 patients</td><td>Attempted catheter salvage:

48/56

Successful catheter salvage:

29/26

Failed catheter salvage:

14/56

SAB-related death:

2/56</td><td>catheter , neutropenia and staphylococcus aureus bacteraemia (SAB: at least one positive blood culture for S. aureus).

All had haematological cancer.

Median age was</td><td>methicillin resistance, profound neutropenia, septic shock, catheter-related infection, external signs of infection, persistent fever, positive follow-up blood culture, type of initial antibiotic therapy</td><td>catheter still in place 3 days after clinical recognition of bacteraemia.

Successful salvage: defined as catheter still in place after 12 weeks, without recurrent bacteraemia or SAB related death.</td><td>cases were excluded from analysis.

<table><tr><td rowspan="2">External signs of infection?</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>External signs of infection</td><td>1</td><td>4</td></tr><tr><td>No external signs of infection</td><td>28</td><td>10</td></tr></table>
<table><tr><td rowspan="2">Septic shock</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Septic shock</td><td>0</td><td>2</td></tr><tr><td>No septic shock</td><td>29</td><td>12</td></tr></table>
<table><tr><td rowspan="2">Persistent fever</td><td colspan="2">Successful salvage</td></tr><tr><td>Yes</td><td>No</td></tr><tr><td>Persistent fever at 72hrs</td><td>14</td><td>11</td></tr><tr><td>No persistent fever at 72hrs</td><td>15</td><td>3</td></tr></table>
<table><tr><td>Profound</td><td>Successful</td></tr></table></td><td>conflicts of interest reported.</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>neutropenia</td><td colspan="2">salvage</td></tr>
<tr><td></td><td>Yes</td><td>No</td></tr>
<tr><td>Profound neutropenia</td><td>28</td><td>13</td></tr>
<tr><td>No profound neutropenia</td><td>1</td><td>1</td></tr>
</table>
<table>
<tr><td>Methicillin resistance</td><td colspan="2">Successful salvage</td></tr>
<tr><td></td><td>Yes</td><td>No</td></tr>
<tr><td>Methicillin resistant Staphylococus aureus</td><td>5</td><td>7</td></tr>
<tr><td>Non methicillin resistant Staphylococus aureus</td><td>23</td><td>7</td></tr>
</table>
There were 2 cases of SAB related death, 5 cases of death due to underlying disease and 4 cases of recurrent SAB amongst the attempted salvage group.
</td><td></td><td></td></tr>
<tr><td>Ruggiero 2010.</td><td>Retrospective consecutive</td><td>190 Groshong catheters in</td><td>Febrile episodes:</td><td>Children with a Groshong catheter</td><td>Organism isolated in CVC-related</td><td>CVC-related infection: bacterial</td><td>Microorganisms isolated in the 36 cases of CVC-related infection (in 10 cases more than one organism</td><td>Not reported. No</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td>Italy</td><td>case series. 2000-2005</td><td>166 children.</td><td>104/190

CVC related sepsis: 36/190

Catheter removal: 128/190

Removal due to infection: 10/190

Removal due to end of treatment: 112/190

Removal due to mechanical complication 6/190

CVC-related infectious mortality: 2/166</td><td>inserted at a single centre.

Median age was 6.6 years (range 0.6 to 22)

27% had haematological cancer.</td><td>infection</td><td>abscess or cellulitis at the exit site or CVC tunnel; or septic signs/symptoms with bacteraemia in which the same organism was isolated from CVC and peripheral cultures, or from at least 2 CVC cultures or isolation of any fungus from at least one CVC culture.

Central line removal, and reason for removal.</td><td>was isolated):

<table><tr><th rowspan="2">Organism</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Gram positive</td><td>7</td><td>1*</td></tr><tr><td>Gram negative</td><td>17</td><td>3</td></tr><tr><td>Fungal</td><td>0</td><td>6</td></tr></table>*Polymicrobial Gram-positive infection

Two patients died as a result of CVC-related sepsis complicated by haematological toxicity phase.</td><td>conflicts of interest declared.</td><td></td></tr>
<tr><td>Sariosmanoglu 2008.

Turkey</td><td>Prosepective, consecutive case series.</td><td>93 catheters fitted in 83 patients.</td><td>Catheter removal due to infection: 27/93.</td><td>Patients with haematological cancer, fitted with tunnelled long-term</td><td>Previous line infection, neutropenia at the time of insertion, type</td><td>Catheter removal, unclear who decided the reason for</td><td>For the 27 catheters removed due to infection:

<table><tr><th>Previous line</th><th>Line</th></tr></table></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td>2005-2007</td><td></td><td>Catheter removal for other reasons:19/93.</td><td>catheter.

Patients were either neutropenic (ANC < 1.0 X 10^9/L) at the time of catheter insertion or became neutropenic during treatment.

Mean age 45 years (range 9 months to 80 years)</td><td>of cancer

CVC related bacteraemia: defined as more than 10 fold increase in colony forming units of an organism in a culture from the catheter compared with one from peripheral blood, or 1000 cfu of organisms in the absence of peripheral blood culture, or positive catheter tip culture in a suspected CVC infection.

Catheter tunnel infection: defined as induration, tenderness and erythema beginning more than 1</td><td>removal</td><td>
<table>
<tr><th rowspan="2">infection</th><th colspan="2">preservation</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Previous line infection</td><td>9</td><td>7</td></tr>
<tr><td>No previous line infection</td><td>57</td><td>20</td></tr>
</table>

For the 43 catheters removed :
<table>
<tr><th rowspan="2">Removal reason</th><th colspan="2">Line preservation</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Tunnel infection</td><td>-</td><td>22</td></tr>
<tr><td>CVC related bacteraemia/fungaemia</td><td>-</td><td>5</td></tr>
<tr><td>End of treatment</td><td>-</td><td>17</td></tr>
<tr><td>Mechanical problem</td><td>-</td><td>2</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>cm from the exit site and tracking up the tract.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Viscoli 1988.

Italy</td><td>Retrospective consecutive case series.

1983-1986</td><td>157 catheters in 145 patients</td><td>Febrile episodes: 102/157

Catheter related infection: 21/157

Catheter unrelated infections: 32/157

Infections of unknown source: 26/157</td><td>Paediatric patients (usually with cancer), fitted with Broviac catheters.

30% had haematological cancer.

Median age was 4 years (range 2 months to 20 years).</td><td>Type of infection, infecting organism, neutropenia at catheter insertion</td><td>Catheter removal,

Catheter-infection related mortality</td><td>In 21 cases of catheter related infections:

<table><tr><th rowspan="2">Type of infection</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Tunnel or exit site infection with or without bacteraemia</td><td>2</td><td>4</td></tr><tr><td>CVC-related bacteraemia/fungaemia only</td><td>10</td><td>5</td></tr></table>
23 organisms were isolated in 21 cases of catheter related infections:

Gram positive

<table><tr><th rowspan="2">Organism</th><th colspan="2">Line preservation</th></tr><tr><th>Yes</th><th>No</th></tr><tr><td>Staphylococcus areus</td><td>4</td><td>2</td></tr><tr><td>Staphylococcus epidermidis</td><td>7</td><td>0</td></tr></table></td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Reference and country</th><th>Study type and period</th><th>Number of patients</th><th>Prevalence</th><th>Patient characteristics</th><th>Tests used/ prognostic factors</th><th>Outcomes and reference standard</th><th>Results</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Enterococcus faecalis</td><td>0</td><td>1</td></tr>
<tr><td>Streptococcus viridians</td><td>3</td><td>1</td></tr>
</table>
Gram negative
<table>
<tr><td rowspan="2">Organism</td><td colspan="2">Line preservation</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Pseudomonas aeruginosa</td><td>1</td><td>1</td></tr>
<tr><td>Enterobacter clocae</td><td>1</td><td>0</td></tr>
</table>
Fungus
<table>
<tr><td rowspan="2">Organism</td><td colspan="2">Line preservation</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>Candida albicans</td><td>1</td><td>1</td></tr>
</table>
No patient died as a result of catheter related infection
</td><td></td><td></td></tr>
</table>

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14. Inpatient versus ambulatory (non-hospitalised) management strategies. (Topic E2)

Guideline subgroup members for this question

Anton Kruger (lead), Wendy King, Barbara Crosse, Bob Phillips and Rosemary Barnes.

Review question

Is there any difference between the outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients?

Rationale

Neutropenic sepsis is a potentially lethal condition with potentially high mortality rates especially when the infection is due to gram negative bacteria. Early studies focussed on empiric antibiotic treatment combinations specifically targeting this group of organisms and because of the historically poor outcomes and the fact that these regimens had to be given intravenously in multiple daily doses, hospital based care became the norm. In addition, many of the early studies were based on patient populations comprising a high proportion of patients with acute leukaemia. These patients represent the worst risk cases for depth and duration of neutropenia. A further driver to their inpatient management was the recognition that the physical environment may present an additional risk for such high risk patients to acquire mould infections, hence the introduction of hepa filtered rooms.

However, it is apparent that not all patients with neutropenia are at the same risk for an adverse outcome of a septic episode and that treatment and location of treatment may be tailored according to risk factors. These include patient specific factors, on the anti infective treatment received and the environment. Patient specific factors would include the underlying illness, chemotherapy regimen, presence of indwelling intravenous catheters or other devices and co- morbidities. The sensitivities and prevalence of local microbiological flora add an environmental background.

Having defined a group of “low risk” patients it has been possible to design ambulatory care treatment strategies as an alternative to inpatient intravenous care. Ambulatory care strategies include intravenous antibiotic regimens as well as oral. The advantages for ambulatory care are obvious. Most patients prefer to be treated at home, the risks of nosocomial infections is reduced and there are potential cost and resource savings. On the other hand, some ambulatory care programs might remain resource intensive, especially if based on intravenous drug regimens. There are also risks of failure of this strategy and risks particular to oral antibiotics, such as diarrhoea and infection with clostridium difficile. Some patients may also prefer the reassurance of inpatient care.

This review should establish if there is any difference between the outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients and in which groups ambulatory care may be safe?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients receiving treatment for neutropenic sepsis	In patient care	Ambulatory care (all different forms Community Outpatient Home)	• Death within 30 days • Critical care • Length of stay • Subsequent admission (outpatients) • Quality of life

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The search was restricted to published randomised (or quasi randomised) trials and systematic reviews of randomised trials.

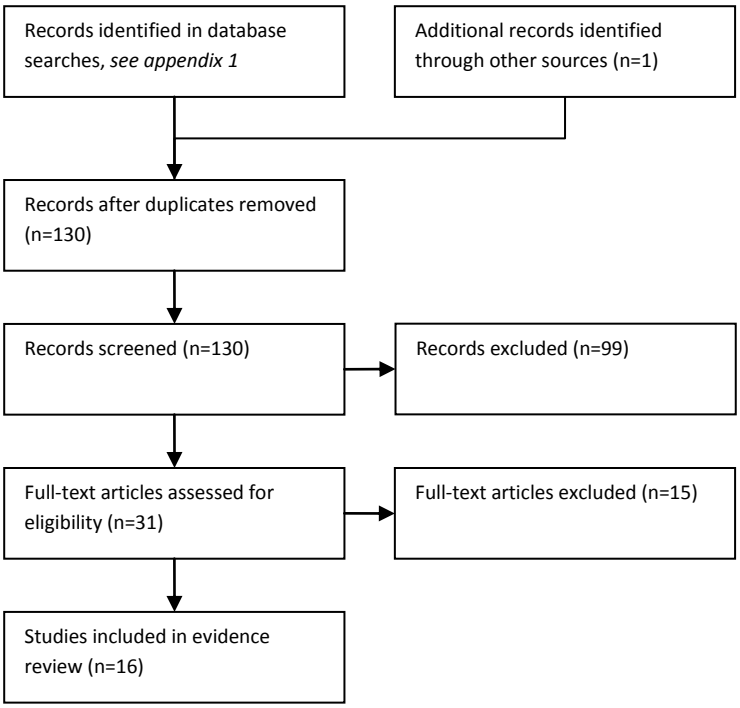
Selection of studies

The information specialist (SB) conducted the first screen of the literature search results. Two reviewers (NB and CL) then selected potentially eligible studies by comparing their title and abstract to the inclusion criteria set out by the PICO question. Full text articles were obtained for studies identified as potentially relevant. These were read and checked against the inclusion criteria. The final literature search was done on 7th November 2011. The titles and abstracts of 9 papers were compared to the PICO. One was eligible for inclusion.

RESULTS

Results of the literature searches

Figure 14.1 Study flow diagram



Description of included studies

One recent, comprehensive systematic review of the literature was identified (Teuffel et al, 2011). This review included 6 RCTs comparing inpatient antibiotic treatment to outpatient antibiotic treatment (Rapoport et al. 1999, Innes et al. 2003, Hidalgo et al. 1999, Malik et al. 1995, Ahmed et al. 2007, Santolaya et al. 2004), and 8 RCTs comparing outpatient oral antibiotic treatment to outpatient intravenous antibiotic treatment (Sebban et al. 2008, Monotti et al. 1999, Rubenstein et al 1993, Gupta et al. 2009, Petrilli et al. 2000, Paganini et al. 2003, Paganini et al 2000, Mullen et al. 1999). One additional RCT comparing inpatient antibiotic treatment to outpatient antibiotic treatment was identified by the update search (Talcott et al. 2011).

All of the RCTs included in the Teuffel et al. review had been identified by our literature search. The remaining 15 studies were excluded (6 studies treated all participants as inpatients, 8 were not RCTs, and 1 randomised participants to different antibiotics as opposed to randomising to inpatient/outpatient treatment). Excluded studies are listed at the end of the document.

Types of study

RCTs comparing any inpatient antibiotic treatment to outpatient antibiotic treatment for the management of FN in cancer patients were included. RCTs comparing any oral outpatient antibiotic treatment to any intravenous outpatient antibiotic treatment were also included and analysed separately. Characteristics of the included studies are presented in the table 14.2.

Evidence statements

Short term mortality

Low quality evidence from seven randomised trials (reviewed in Teuffel, et al., 2011), showed no statistically significant difference in the 30 day mortality of inpatients and outpatients, RR 1.11 (95% C.I. 0.41 to 3.05). Low quality evidence from eight randomised trials found no statistically significant difference in 30 day mortality according to route of drug administration in the outpatient setting (intravenous versus oral), but no patients died in these studies

Critical care

Critical care was not considered as an outcome by the Teuffel, et al., (2011), systematic review. However critical care events were probably included in the composite outcome of treatment failure. Which was defined as one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms; any addition to, or modification of the assigned intervention, including readmission.

Low quality evidence from six randomised trials showed no significant difference between the rate of treatment failure of inpatients and outpatients RR = 0.81; (95% CI 0.55 - 1.19).

Low quality evidence from eight randomised trials showed no association between route of drug administration in the outpatient setting (intravenous versus oral) and treatment failure, RR 0.93 (95% CI 0.65 –1.32)).

Three of the six studies comparing inpatient to outpatient treatment reported critical care admission. No patients were admitted to ICU in these studies (350 episodes). Four of the eight studies of outpatient IV versus outpatient oral antibiotics reported critical care admission. No patients were admitted to ICU in these studies (520 episodes).

Length of stay

Only three studies comparing inpatient to outpatient management reported length of stay in the inpatient group. Means were reported as 4.41 days, range 2 – 8 (Innes, et al., 2003), 10.4 days, range 7-19 (Ahmed et al 2007) and 5.3 days, range 3-9 (Santolaya, et al., 2004). Length of stay was not a relevant outcome in studies considering only outpatients.

Hospital readmission (outpatients)

Low quality evidence suggested that hospital readmission was less likely in patients treated with outpatient intravenous therapy than in those who received outpatient oral therapy, RR 0.46 (95% CI 0.22 - 0.97).

Quality of life

Quality of life was not considered as an outcome by the Teuffel, et al., (2011), a systematic review, and none of the included studies reported quality of life. A later study (Talcott, et al., 2011) reported results from subscales of the EORTC QLQ C-30. Moderate quality evidence suggested that role function increased more for hospitalised patients than home care patients (mean change 0.78 versus 0.58 respectively, P = 0.05). Moderate quality evidence showed emotional function scores declined for hospitalised patients but increased for home care patients (mean change -6.94 versus 3.27; P =

1 0.04). No other QLQ-C30 subscale differences were evident but the data for these subscales were
2 not reported.

Table 14.1: GRADE profile: Is inpatient management more effective than outpatient management for patients with neutropenic sepsis

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inpatient treatment**	**Outpatient treatment**	**Relative (95% CI)**	**Absolute**	
30 day mortality											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/365 (1.9%)	6/377 (1.6%)	RR 1.11 (0.41 to 3.05)	2 more per 1000 (from 9 fewer to 33 more)	LOW
Treatment failure (death; persistence, recurrence or worsening of clinical signs or symptoms; any addition to, or modification of the assigned intervention, including readmission)											
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/363 (10.7%)	50/375 (13.3%)	RR 0.81 (0.55 to 1.19)	25 fewer per 1000 (from 60 fewer to 25 more)	LOW
Critical care											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/174 (0%)	0/176 (0%)	Not estimable	-	LOW
Hospital readmission - not reported											
0[3]	-	-	-	-	-	none	-	-	-	-	
Length of stay - not reported											
0[3]	-	-	-	-	-	none	-	-	-	-	
Quality of life (measured with: EORTC QLQ C-30 Role Function subscale; Better indicated by higher values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	50	-	MD 0.20 higher (C.I. not reported)	MODERATE
Quality of life (measured with: EORTC QLQ C-30, Emotional Function subscale; Better indicated by higher values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	50	-	MD 10.21 lower (C.I. not reported)	MODERATE

[1] Few studies used adequate sequence generation and concealment; none of the studies were blinded; few reported ITT analysis
[2] Low event rate
[3] Not a relevant comparison in studies of inpatient vs. outpatient management
[4] Trial stopped early due to poor accrual

Table 14.1 Continued - GRADE evidence profile – Outpatient oral antibiotics versus Outpatient intravenous treatment

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient IV antibiotic treatment	Outpatient oral antibiotic treatment	Relative (95% CI)	Absolute	
30 day mortality											
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/426 (0%)	0/431 (0%)	Not estimable	-	LOW
Treatment failure											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/426 (16.7%)	80/431 (18.6%)	RR 0.93 (0.65 to 1.32)	13 fewer per 1000 (from 65 fewer to 59 more)	LOW
Critical care											
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/256 (0%)	0/264 (0%)	Not estimable	-	LOW
Hospital readmission											
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/299 (3.3%)	22/308 (7.1%)	RR 0.46 (0.22 to 0.97)	39 fewer per 1000 (from 2 fewer to 56 fewer)	LOW
Length of stay											
0	no evidence available					none	-	-	-	-	
Quality of life											
0	no evidence available					none	-	-	-	-	

[1] Few studies used adequate sequence generation and concealment; none of the studies were blinded; few reported ITT analysis

[2] Low event rate

Table 14.2: Characteristics of included studies (from Teuffel et al 2011; updated with data from Talcott et al. 2011)

Table 14.2: Characteristics of included studies (from Teuffel et al 2011; updated with data from Talcott et al. 2011) **INPATIENT VERSUS OUTPATIENT**									
Study ID	Febrile neutropenia episodes	Discharge	Inpatient Drug	Treatment duration (days, mean)	Outpatient Drug	Treatment duration (days, mean)	FUO (%)	Leukaemia and lymphoma patients (%)	ANC <100 (%)
Adults									
IV vs. IV									
Rapoport	44/40	After 48–72 h	Ceftriaxone and aminoglycosides	6.3	Ceftriaxone and aminoglycosides	6.0	50	36	36
Talcott	121/117	After 24 h	All patients were required to continue antibiotic regimen in use at time of enrolment	NR	All patients were required to continue antibiotic regimen in use at time of enrolment	NR	NR	32	NR
IV vs oral									
Innes	67/68	After 24 h	Piperacillin/tazo. and gentamicin	NR	Ciprofloxacin and amoxicillin/clavulanate	NR	37	5	NR
Hidalgo	50/50	Immediate	Ceftriaxone and amikacin	NR	Ofloxacin	NR	68	11	41
Oral vs oral									
Malik	91/91	Immediate	Ofloxacin	NR	Ofloxacin	NR	71	31	49
Children									
IV vs. IV									
Ahmed	63 / 66	After 72 h	Imipenem	10.4	Ceftriaxone and amikacin	9.4	28	82	57
Santolaya	71/78	After 24–36 h	Ceftriaxone and teicoplanin	6.4	Ceftriaxone and teicoplanin	6.1	38	45	NR
OUTPATIENT ORAL VERSUS OUTPATIENT INTRAVENOUS									
Study ID	Febrile neutropenia episodes	Discharge	Intravenous Drug	Treatment duration (days, mean)	Oral Drug	Treatment duration (days, mean)	FUO (%)	L & L (%)	ANC <100 (%)
Adults									
Sebban	47/49	After 24–48 h	Ceftriaxone	5[*]	Moxifloxacin		71	30[‡]	NR
Minotti	20/21	Immediate	Ceftriaxone	NR	Ciprofloxacin	NR	NR	NR	NR[§]
Rubenstein	47/49	Immediate	Aztreonam and clindamycin	8[*]	Ciprofloxacin and clindamycin	7	61	26	59
Children									
Gupta	61/62	Immediate	Ceftriaxone and amikacin	6[*]	Ofloxacine and amoxicillin/clavulanate	6	26	36	27
Petrilli	70/68	Immediate	Ceftriaxone	NR	Ciprofloxacin	NR	36	4[‡]	NR
Sequential iv - oral									
Paganini	89/88	Immediate	Ceftriaxone	4.8	Ciprofloxacin	4.5	28	64	49
Paganini	80/74	After 72 h	Ceftriaxone and amikacin	7	Cefixime	7	65	57	NR
Mullen	33/40	Immediate	Ceftriaxone	4.9	Ciprofloxacin	4.6	89	30[‡]	60

1 ***Table 14.3 Summary of outcomes***

Outcome	Trials (episodes)	Risk ratio (95% CI; *P* value)
Inpatient versus Outpatient		
Failure (PPA)	6 (738)	0.81 (0.55–1.19; 0.28)
Adults	4 (470)	0.79 (0.52–1.20; 0.27)
Children	2 (268)	0.93 (0.32–2.71; 0.89)
Mortality	7 (855)	RR 0.87 (0.30 – 2.57)
Toxicity	Data only reported by one study	
Readmission	Not applicable to this primary objective	
Critical care	No admissions to critical care in any of the included studies	
Quality of life	Data only reported by one study	
Length of stay	Not a relevant comparison. Only one group considered outpatients	
Outpatient IV versus Outpatient oral		
Failure (PPA)	8 (857)	0.93 (0.65–1.32; 0.67)
Adults	3 (218)	0.95 (0.29–3.13; 0.94)
Children	5 (639)	0.90 (0.64–1.26; 0.53)
Mortality	No deaths in any of the included studies	
Toxicity	4 (404)	0.59 (0.06–5.85; 0.65)
Adults	2 (177)	0.72 (0.02–33.74; 0.87)
Children	2 (227)	0.40 (0.02–9.55; 0.57)
Readmission	7 (816)	0.62 (0.28–1.39; 0.25)
Adults	2 (177)	0.47 (0.01–14.61; 0.66)
Children	5 (639)	0.52 (0.24–1.09; 0.08)
Critical care	No admissions to critical care in any of the included studies	
Quality of life	Data not reported by any of the included studies	
Length of stay	Not a relevant comparison in studies considering only outpatients	

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Figure 14.2: Inpatient versus Outpatient treatment – Treatment Failure

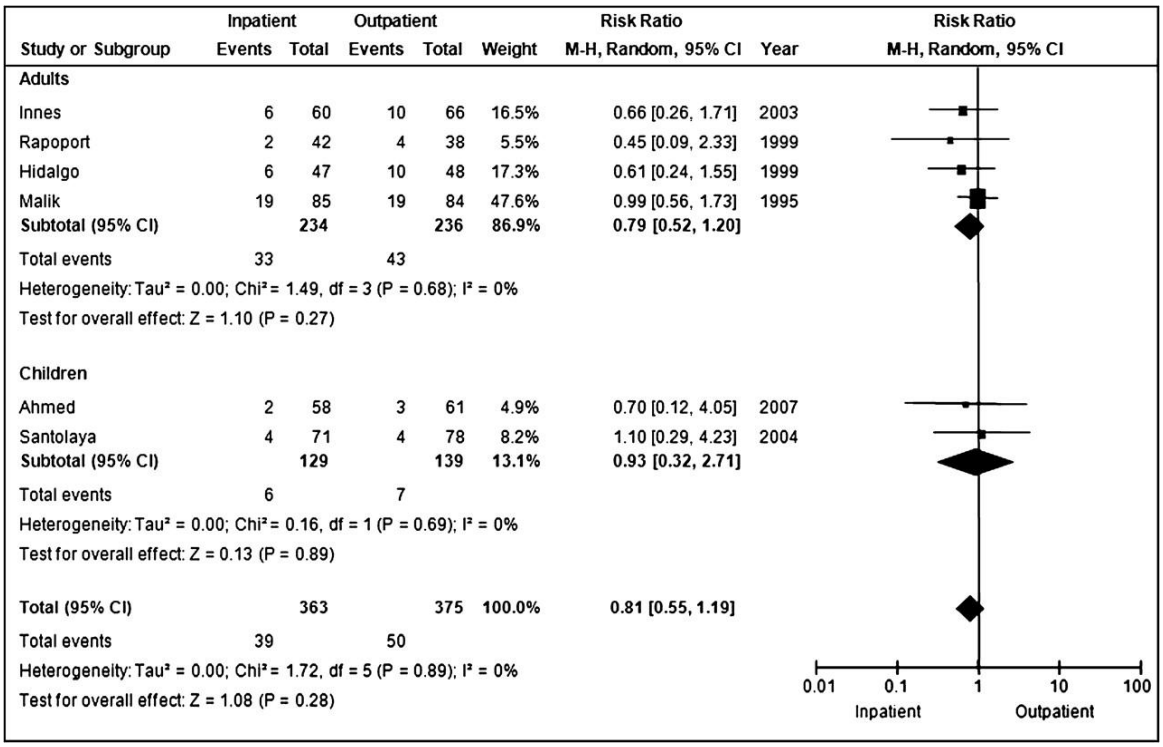
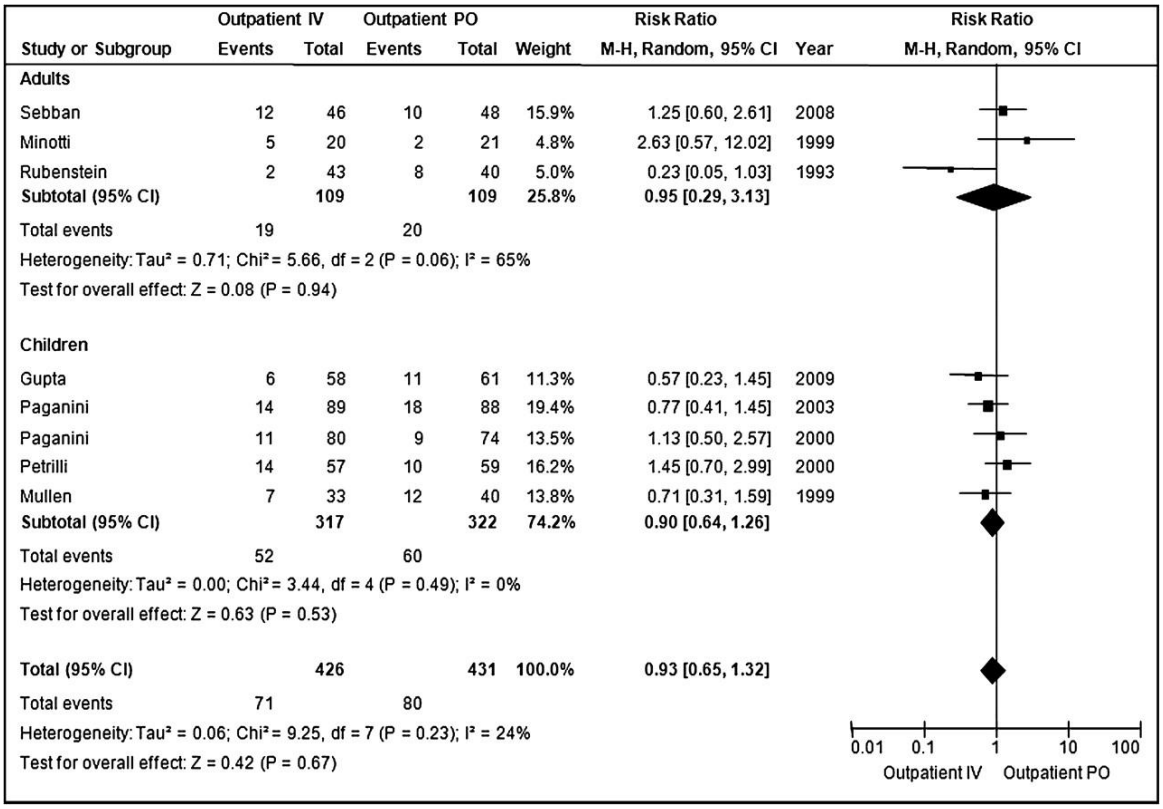


Figure 14.3: Outpatient Oral Antibiotics versus Outpatient Intravenous Antibiotics – Treatment Failure



Additional data extracted from original papers

Critical care - Inpatient versus Outpatient treatment

Study ID	Inpatient	Outpatient
Rapoport 1999	Not reported	Not reported
Innes 2003	0/60 (0%)	0/66 (0%)
Hidalgo 1999	0/48 (0%)	0/47 (0%)
Malik 1995	Not reported	Not reported
Ahmed 2007	0/66 (0%)	0/63 (0%)
Santolaya 2004	Not reported	Not reported

0/174 (0%) episodes treated on an inpatient basis were admitted to ICU.

0/176 (0%) episodes treated on an outpatient basis were admitted to ICU.

Critical care - Outpatient Oral Antibiotics versus Outpatient Intravenous Antibiotics

Study ID	Intravenous	Oral
Sebban 2008	Not reported	Not reported
Minotti 1999	Not reported	Not reported
Rubenstein 1993	Not reported	Not reported
Gupta 2009	0/54 (0%)	0/61 (0%)
Petrilli 2007	Not reported by group	Not reported by group
Mullen 1999	0/33 (0%)	0/40 (0%)
Paganini 2003	0/80 (0%)	0/74 (0%)
Paganini 2000	0/89 (0%)	0/89 (0%)
Talcott et al. 2011	Not reported	Not reported

0/256 (0%) episodes treated on an inpatient basis were admitted to ICU.

0/264 (0%) episodes treated on an outpatient basis were admitted to ICU.

Hospital readmission - Inpatient versus Outpatient treatment

Study ID	Inpatient	Outpatient
Rapoport 1999	Not reported	Not reported
Innes 2003	Not applicable	5/66 (8%)
Hidalgo 1999	Not applicable	8/47 (16%)
Malik 1995	Not applicable	18/48 (21%)
Ahmed 2007	Not applicable	2/63 (6%)
Santolaya 2004	Not applicable	Not reported
Talcott et al. 2011	Not applicable	4/47 (9%)

33/224 (15%) episodes treated on an outpatient basis required hospital readmission.

Hospital readmission - Outpatient Oral Antibiotics versus Outpatient Intravenous Antibiotics

	Intravenous	Oral
Sebban 2008	Not reported	Not reported
Minotti 1999	Not reported	Not reported
Rubenstein 1993	0/43 (0%)	6/40 (15%)
Gupta 2009	0/54 (0%)	3/61 (5%)
Petrilli 2007	Not reported by group	Not reported by group
Mullen 1999	2/33 (6%)	8/44 (18%)
Paganini 2003	6/80 (7%)	4/74 (5%)
Paganini 2000	2/89 (3%)	1/89 (1%)

10/299 (3%) episodes treated with intravenous antibiotics resulted in admission to hospital.

22/308 (7%) episodes treated with oral antibiotics resulted in admission to hospital.

1

2

1 **EVIDENCE TABLES**

2

Teuffel, O., Ethier, M. C., Alibhai, S., Beyene, J., & Sung, L. (2011). Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis. *Annals of Oncology, Advance Access*.
Country: Canada
Design: Systematic review
Population: Cancer patients (adult and pediatric) with low-risk febrile neutropenia
Inclusion criteria: Randomized controlled trials (RCTs) comparing any outpatient antibiotic treatment to any inpatient antibiotic treatment, or any outpatient oral antibiotic treatment to any outpatient intravenous antibiotic treatment, for the management of febrile neutropenia in cancer patients.
Interventions: • Outpatient antibiotic treatment versus inpatient antibiotic treatment Or • Outpatient oral antibiotic treatment versus outpatient intravenous antibiotics treatment
Outcomes: • Treatment failure (defined as one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms; any addition to, or modification of the assigned intervention, including readmission) • Mortality (30 day) • Toxicity • Readmission

Results:

Outcome	Trials (episodes)	Risk ratio (95% CI; *P* value)	Risk reduction (95% CI; *P* value)
Inpatient versus Outpatient			
Failure (PPA)	6 (738)	0.81 (0.55–1.19; 0.28)	−0.02 (−0.06 to 0.02; 0.29)
Adults	4 (470)	0.79 (0.52–1.20; 0.27)	−0.05 (−0.11 to 0.02; 0.15)
Children	2 (268)	0.93 (0.32–2.71; 0.89)	0.00 (−0.06 to 0.05; 0.85)
Mortality	6 (742)	1.11 (0.41–3.05; 0.83)	0.01 (−0.01 to 0.03; 0.54)
Adults	4 (474)	0.96 (0.27–3.43; 0.95)	0.00 (−0.02 to 0.03; 0.81)
Children	2 (268)	1.43 (0.27–7.42; 0.67)	0.01 (−0.02 to 0.04; 0.51)
Toxicity	Data only reported in one study		
Outpatient IV versus Outpatient oral			
Failure (PPA)	8 (857)	0.93 (0.65–1.32; 0.67)	−0.02 (−0.08 to 0.04; 0.52)
Adults	3 (218)	0.95 (0.29–3.13; 0.94)	0.00 (−0.18 to 0.19; 0.97)
Children	5 (639)	0.90 (0.64–1.26; 0.53)	−0.02 (−0.08 to 0.04; 0.50)
Mortality	No deaths in any of the included studies		
Toxicity	4 (404)	0.59 (0.06–5.85; 0.65)	−0.03 (−0.07 to 0.02; 0.27)
Adults	2 (177)	0.72 (0.02–33.74; 0.87)	−0.03 (−0.28 to 0.21; 0.79)
Children	2 (227)	0.40 (0.02–9.55; 0.57)	−0.02 (−0.06 to 0.02; 0.40)
Readmission	7 (816)	0.62 (0.28–1.39; 0.25)	−0.03 (−0.08 to 0.01; 0.14)
Adults	2 (177)	0.47 (0.01–14.61; 0.66)	−0.03 (−0.28 to 0.21; 0.79)
Children	5 (639)	0.52 (0.24–1.09; 0.08)	−0.03 (−0.07 to 0.01; 0.19)

General comments:

This was a well conducted, comprehensive and recent systematic review, carried out according to the recommendations of the PRISMA statement. Electronic searches of OVID Medline (from 1950 to February 2010), EMBASE (from 1980 to February 2010), and The Cochrane Central Register of Controlled Trials (CENTRAL; until the first quarter of 2010) were carried out. Relevant references and conference proceedings from 2007 to 2010 were also searched using the Web of Science and Scopus databases. Two review authors independently extracted data from included trials. The primary outcome measures were (1) all-cause mortality at 30 days, (2) adverse events requiring discontinuation/modification of therapy, and (3) readmission to the hospital. Subgroup analyses for all outcomes by age (children versus adults) were conducted. To assess methodological quality and risk of bias, included articles were examined for sequence generation, allocation concealment, blinding, incomplete outcome data, and intention-to-treat (ITT) analysis. The authors concluded that based on the current literature, outpatient treatment of FN is a safe and efficacious alternative to inpatient management, though variation between studies in terms of time to discharge, choice of antibiotic class, and age of study population may limit interpretation of the data.

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Country: USA
Design: Randomised Controlled Trial
Population: 121 episodes of febrile neutropenia in adult patients (median age 47) with post-chemotherapy fever and neutropenia recruited between September 1994 and January 1999
Inclusion criteria: • Fever (≥100.5°F at presentation or by patient measurement at home) that persisted after at least 24-hour of inpatient observation • Neutropenia (ANC less than 500/µL) that persisted after at least 24-hour of inpatient observation • Evaluated as low risk by the Talcott et al. criteria • Residence within 2 hours by surface transportation of hospital experienced in emergency care of patients with cancer • Informed consent • Permission of treating physician
Exclusion criteria • AIDS associated malignancy • Neutropenia arising more than 21 days after chemotherapy • Intensive chemotherapy requiring bone marrow or peripheral stem cell support •
Interventions: • Continued hospital care (n = 71 randomised; n = 66 analysed) Versus • Discharged to home care (n = 50 randomised; n = 47 analysed)
Outcomes:

- Duration of fever
- Duration of neutropenia
- Duration of fever and neutropenia
- Antibiotics changed after random assignment
- Hospital readmission
- Major medical complications (hypotension; other; any major complication)

Results:

	Hospital care	**Early discharge**	**All patients**
Duration of fever			
Median	3	3	3
Mean	3.2	3.4	3.3
Range	0-13	1-14	0-14
Duration of neutropenia			
Median	4	4	4
Mean	4.1	4.2	4.1
Range	1-10	1-15	1-15
Duration of fever and neutropenia			
Median	4	4	4
Mean	4.6	4.5	4.6
Range	2-13	1-15	1-15
Antibiotics changed after random assignment			
No. (%)	16 (24%)	4 (9%)	20 (18%)
Hospital readmission			
No. (%)	-	4 (9%)	-
Major medical complications (hypotension; other; any major complication)			
Hypotension	5 (8%)	3 (6%)	8 (8%)
Other (anal pain)	1 (1%)	1 (2%)	2 (2%)
Any major complication	5 (8%)	4 (9%)	9 (8%)

General comments:

- Method of randomisation and allocation concealment were adequate
- Patients randomly assigned to home treatment were discharged when home antibiotics became available. All patients were required to continue the antibiotic regimen in use at time of enrolment
- Analyses were completer only
- Clinical characteristics of both groups were similar
- The study did not report a measure of treatment failure, and this could not be determined from the presented data. It was not therefore possible to add this study to Teuffel et al's meta analysis.

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1

Subsequent Treatment: guideline chapter seven

15. Changing primary empiric treatment in patients with unresponsive fever. (Topic E6)

Guideline subgroup members for this question

Wendy King (lead), Anton Kruger, Jeanette Hawkins, Bob Phillips and Rosemary Barnes.

Review question

What is the optimal time to change the primary empiric treatment in unresponsive fever?

Rationale

Some patients admitted to hospital with neutropenic sepsis may continue to have unresponsive fever beyond 48 hours, despite been treated with primary empiric antibiotics. It is also possible that these patients will not have a focus for their infection.

What is the evidence that antibiotic therapy should be changed and is there any evidence to advise when this change should be made e.g. 24, 48, or 96 hours or later post admission? What are the risks to the patient if antibiotics are not changed at a given time? A review of the literature may help to resolve these clinical questions as at present there are different practices occurring. It is possible that continuing empiric antibiotics could result in increased length of stay, critical care admission or death.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
• Patients with unresponsive fever and clinically stable on primary empiric treatment • Patients with unresponsive fever and clinically unstable or deteriorating on primary empiric treatment	Modification to empiric therapy (report subgroups by time). Antibacterial Antifungal Antiviral	Continuing with primary empiric treatment	• Overtreatment • Death/critical care • Length of stay • Duration of fever • Quality of life

METHODS

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The search was restricted to published randomised trials and systematic reviews of randomised trials. The final search was done on 7th of November 2011.

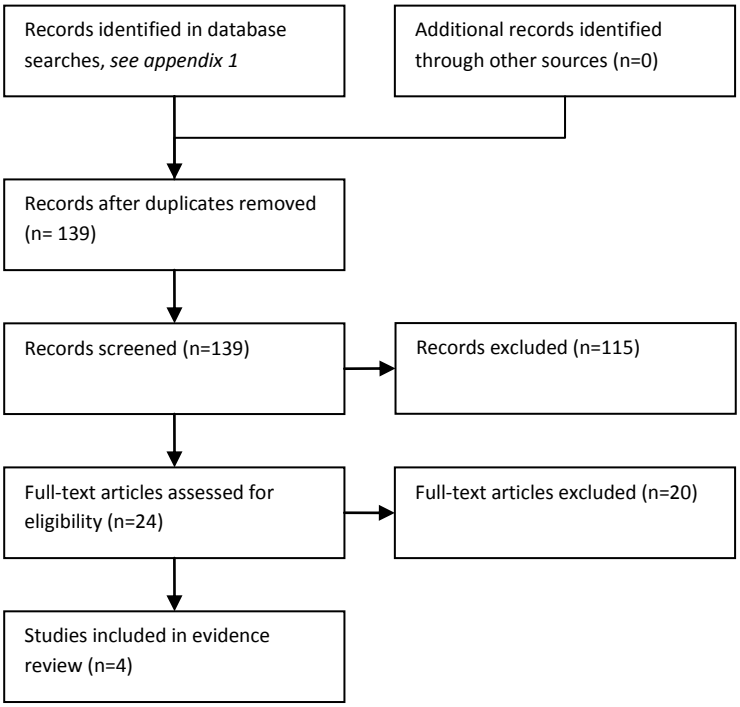
Selection of studies

The information specialist (SB) conducted the first screen of the literature search results. One reviewer (KF) then selected potentially eligible studies by comparing their title and abstract to the inclusion criteria set out by the PICO question. Full text articles were obtained for studies identified as potentially relevant. These were read and checked against the inclusion criteria.

RESULTS

Results of the literature searches

Figure 15.1 Study flow diagram



The literature searches identified 139 potentially relevant studies of which four were included as evidence. The structure of this question is such that it can only be properly answered by randomised studies comparing neutropenic patients with persistent fever, despite having been treated with an empiric antibiotic, to either stay on the empiric therapy or have some sort of treatment modification i.e. a different drug to replace or add to the empiric antibiotic. However, the overwhelming majority of papers identified in the literature search described studies in which patients had stopped empiric antibiotics before being randomised to one or two second line drugs. These studies would not answer this question.

The evidence base is very poor, consisting of four randomised studies, two of which are more than twenty years out of date. Patients (N=461 patients in total) with low granulocyte counts and persistent fever were randomised to either remain on the empiric antibiotic (alone or with an added placebo) or to primary treatment with the addition of another agent. The point at which these studies were initiated i.e. the number of days of persistent fever, varied between two and seven days. The length of stay and the incidence of over-treatment were not specifically addressed and nor was the patients' quality of life. None of the studies dealt adequately with the methods of randomisation, allocation or blinding and, although some authors stated that appropriate statistics

had been used for data analysis, the details were sometimes scant or absent and very few outcomes had more than a P (probability) value reported. For these reasons, all four studies have been classified by GRADE as being of 'low' or 'very low' quality. The variability of data and study design precluded pooling.

Evidence summary

Generally, none of the studies demonstrated a significant difference between patients kept on empiric antibiotics and those given an additional drug or drugs (Table 15.1). The general consensus seemed to be that patients seemed to respond to the initial antibiotic treatment eventually and that glycopeptides in particular could potentially be of more harm than benefit if the infectious agent did not warrant such treatment. Bearing in mind the age of these studies, these points may no longer be of relevance.

Pizzo *et al* (1981) reported on fifty patients who, having received empiric antibiotics for fever and granulocytopenia of unknown infectious aetiology, had failed to respond to treatment after seven days. These patients were randomised to stop empiric antibiotics (group 1), continue with empiric antibiotics (group 2) or continue empiric antibiotics with the addition of amphotericin B (group 3). Six patients in group 1 experienced shock compared with no patients in the other two groups ($P<0.001$). The incidence of infectious complications was significantly higher (N=9) in group 1 compared with group 3 (N=2) ($P=0.013$) but not between group 1 and group 2 (N=6) i.e. for patients stopping versus continuing antibiotics. Although no statistical analyses were presented, the low patients numbers, low event rates and wide ranges of data suggest that there was no significant difference between time to the resolution of granulocytopenia or to defervescence between the three groups. The number of non-infectious complications did not differ significantly. The numbers of fatalities appeared to be similar between groups: N=5 in groups 1 and 2 versus N=3 in group 3. There were more patients with fungal infections in group 2 (N=5) compared with the other two groups but this might be a random effect but no evidence was offered to suggest causality.

A study by the EORTC antimicrobial therapy co-operative group (1989) compiled results from two consecutive trials on the use of empiric antibodies in patients with fever and granulocytopenia. One hundred and thirty-two patients who were unresponsive to treatment after four days, were randomised to continue antibiotics with (group 1) or without (group 2) amphotericin B. Clinical response was assessed five days after randomisation and considered a failure if the patient remained febrile. Under this criterion, 47/68 (69%) of patients in group 1 versus 34/64 (53%) of patients in group 2 experienced treatment success ($P=0.09$). More patients with a clinically documented infection at day 4, had a positive clinical response with combined treatment than with antibiotics alone ($P=0.03$). Similarly, patients that had not received prior anti-fungal prophylaxis had a better response to the combined treatment regime than antibiotics only ($P=0.04$) but other sub-group comparisons were not statistically significant. Fewer patients in group 1 had died by day 30 (11 versus 14 ($P=0.039$) but most deaths were described as being due to 'other causes' rather than being specifically treatment related. More patients in group 2 developed fungal disease than in group 1 but the difference was not significant. All sub-group analyses were of very low patient number.

Cometta *et al*. (2003) reported the results of a prospective double blinded trial in which one hundred and sixty-five patients who had persistent fever after 48-60 hours, were randomised to receive an

empiric broad spectrum antibiotic plus vancomycin (group 1) or with saccharose solution (group 2). The main outcome of interest was the rate of fever resolution at three days post randomisation, which was not significantly different between study arms: 82/86 (95%) in group 1 versus 73/79 (92%) in group 2. More than half of the patients in both groups had their therapy modified, either by adding a glycopeptide to vancomycin or by stopping the placebo and giving amphotericin B. There was no significant difference in the time to fever resolution between groups, regardless of whether the treatment regime had been modified or not. Fewer (N=4) patients died in group 1 compared with group 2 (N=8) but the differences are unlikely to have been statistically significant. More patients in group 1 (N=9) experienced treatment related side effects compared with group 2 (N=3). The study had very low patient numbers and event rates and was underpowered to have detected a clinically meaningful difference between comparators for the main outcome. The study was closed for this reason.

Erjavec *et al.* (2000) conducted a randomised double blinded placebo-controlled study of one hundred and fourteen patients with febrile neutropenia who had persistent fever after three to four days of treatment with an empiric antibiotic. Group 1 continued with imipenum and added teicoplanin whilst group 2 had imipenum with a placebo. The primary outcome was the rate of treatment response after 72 hours. There was no significant difference between study arms: 25/56 (45%) in group 1 versus 27/58 (47%). The number of deaths throughout the study was 6 in group 1 and 4 in group 2. Many of the patients had received anti-bacterial prophylaxis and some had also been given G-CSF. The numbers of patients and event rates were low.

Evidence Statements

Mortality

There was very low quality evidence from 4 studies about when to change empiric antibiotics in patients with unresponsive fever (Table 7.1). No study compared changing empiric therapy at two different time points. Patients (N=461) with persistent fever were randomised to either remain on the empiric antibiotic or to primary treatment with the addition of another agent. No study detected a significant difference between the short term mortality of those who changed treatment and those who remained on the initial empiric treatment.

Critical care, quality of life and length of stay

The included studies did not report these outcomes.

Duration of fever

There was very low quality evidence about this outcome and none of the studies reported the influence of time of treatment change. Pizzo, et al., (1982) and Cometta, et al., (2003) reported shorter median time to defervesence in patients whose empiric therapy was changed (8 versus 6 days and 4.3 versus 3.5 days respectively), but there was no statistically significant difference. Erjavec, et al., (2000) reported similar rates of defervesence within 72 hours in patients who did or did not change empiric treatment.

Table 15.1 GRADE evidence profile for optimal time to change the primary empiric treatment in unresponsive fever

Quality assessment						Summary of findings					
						No of patients			Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	No empiric antibiotic	Empiric antibiotic ± placebo	Antibiotic & additional drug	Relative RR (95%CI) P value	Absolute effect	Quality
Mortality Pizzo, *et al.*, (1982)											
1	randomised trial	v. serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	5	5	2	-	-	VERY LOW
Median time to defervescence (range). Pizzo, *et al.*, (1982)											
1	randomised trial	v. serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	11 days (3-22 days)	8 days (3-23 days)	6 days (2-20 days)	-	-	VERY LOW
Mortality (within 30 days). EORTC International anti-microbial therapy co-operative group (1989)											
1	randomised trial	serious limitations[3]	N/A	no serious indirectness	serious imprecision[4]	-	14	11	P=0.04	-	VERY LOW
Median time to defervescence (95%CI). Cometta, *et al.*, (2003)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[5]	-	4.3 days (3.5-5.1 days)	3.5 days (2.4-4.4 days)	P=0.75	-	LOW
Mortality between days 14 and 31. Cometta, *et al.*, (2003)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[5]	-	8/79	4/86	RR=0.46 (0.15-1.38) P=0.29	-	LOW
Defervescence within 72 hours. Erjavec, *et al*., (2000)											
1	randomised trial	serious limitations[6]	N/A	no serious indirectness	serious imprecision[4]	-	27/58	25/56	RR=0.96 (0.64-1.43) P=0.98	-	VERY LOW
Mortality whilst aplastic. Erjavec, *et al*., (2000)											
1	randomised trial	serious limitations[6]	N/A	no serious indirectness	serious imprecision[4]	-	4/58	6/56	RR=1.55 (0.49-4.98) P=0.70	-	VERY LOW

[1] No mention of allocation concealment; randomisation method not discussed; blinding not apparent.
[2] Very low patient numbers and/or event rates.
[3] No mention of allocation concealment; randomisation method not discussed; blinding of assessment may have occurred but not of treatment.
[4] Low patient numbers and/or event rates.
[5] Low patient numbers and /or event rates. Trial terminated early.
[6] No mention of allocation concealment, scant details of randomisation of treatment.

1 EVIDENCE TABLES

Author(s): Pizzo *et al.* (1982).

Country: United States of America

Study Design: Randomised controlled trial (RCT)

Study participants: Two hundred and seventy-one young patients were treated for six hundred and fifty-two episodes of neutropenic fever. Fifty patients, who still had an undefined infectious aetiology and whose fever and granulocytopenia had not resolved after seven days of treatment with primary empiric antibiotics, were randomised into three treatment groups.

[Group 1] Median age: 15 years (range: 2-22 years). Ratio of male: female=10:6; Leukemia (N=5); Lymphoma (N=3); Solid tumour (N=8). Yeast colonisation of GI tract (N=14).

[Group 2] Median age: 16 years (range: 2-25 years). Ratio of male: female=8:8; Leukemia (N=8); Lymphoma (N=3); Solid tumour (N=5). Yeast colonisation of GI tract (N=13).

[Group 3] Median age: 18 years (range: 8-30 years). Ratio of male: female=14:4; Leukemia (N=9); Lymphoma (N=3); Solid tumour (N=6). Yeast colonisation of GI tract (N=14).

The three randomisation groups were said to be similar in all respects at baseline but no supporting statistics were offered.

Interventions and comparators:

[Group 1] (N=16) Discontinue the empiric antibiotic (Keflin® at 170mg kg^{-1} day^{-1} iv every 4h with gentamicin at 6mg kg^{-1} day^{-1} iv every 6h and carbenicillin at 500mg kg^{-1} day^{-1} iv every 4 h (KGC))*.

[Group 2] (N=16) Remain on the empiric primary antibiotic (KGC) until the resolution of fever and granulocytopenia (granulocytes >500 per µl measured twice 24h apart).

[Group 3] (N=18) Continue the empiric antibiotic (KGC) adding amphotericin B (0.5mg kg^{-1} day^{-1} iv every 24h) until the resolution of fever and granulocytopenia (granulocytes >500 per µl measured twice 24h apart).

*Patients in Group [1] resumed treatment if a clinical or microbiological source of infection was identified or if their systolic BP <80mm Hg with fever and clinical deterioration.

Outcomes: Clinical response.

Results:

Infectious complications:

[Group 1] 9/16 (56%) patients in this group experienced infectious complications a median of three days post randomisation. Six patients had a systolic BP <80mm Hg, three of whom had positive blood cultures showing micro-organisms responsive to the discontinued KGC and three patients who had negative blood cultures but responded to anti-hypotensive therapy and the reinstitution of KGC. The three other patients did not have hypotension but experienced complications associated with infection: retropharyngeal abscess, scrotal cellulitis and oesophageal candidiasis.

The first two of these patients responded to the reinstitution of antibiotics and the third to the anti-fungal therapy.

[Group 2] 6/16 (37.5%) patients who continued antibiotic therapy developed an infectious complication which occurred at a median of 8 days after randomisation. Five of these six infections were fungal and the other bacterial (*E. Coli* resistant to KGC). Two of the patients with fungal infections subsequently died whilst the other three had infections that responded to systemic amphotericin B. One additional patient died of GI haemorrhage (due to disseminated candidiasis) three days after stopping anti-fungal treatment, taken for 16 days until fever resolution.

[Group 3] 2/18 (11%) patients who received antibiotic and anti-fungal therapy experienced infectious complications. One of these patients died of disseminated cytomegalovirus after 30 days of persistent fever and neutropenia. The second patient died of severe pulmonary haemorrhage after 42 days due to invasion of the lung, via the bronchial artery, by a fungal organism resistant to amphotericin B.

The incidence of infectious complications for patients who continued KGC plus amphotericin B [Group 3] was significantly less than for patients who discontinued antibiotic therapy [Group 1] (P=0.013) but not from patients who remained on KGC [Group 2] (no P value).

The incidence of shock (6/16 patients) in Group 1, following antibiotic discontinuation, was significantly greater than patients in either Group [2] (N=0) or [3] (N=0) (P<0.02 per comparison or P<0.001 across three groups).

Time to initial defervescence after randomisation also differed betweens groups: median 6 days (range: 2-20 days) [Group 3] versus median 8 days (range: 3-23 days) [Group 2] versus median 11 days (range: 3-22 days) [Group 1]. Given the wide ranges and low patients numbers, there would be unlikely to be a significant difference between groups for this outcome but no statistics were presented.

Time to defervescence and resolution of granulocytopenia was: median 14 days (range: 4-44 days) [Group 3] versus median 10 days (range: 4-34 days) [Group 2] versus median 21 days (range: 4-42 days) [Group 1]. Given the wide ranges and low patients numbers, there would be unlikely to be a significant difference between groups for this outcome but no statistics were presented.

Non-infectious complications:

The number of non-infectious complications did not differ significantly between the three groups. The median duration of granulocytopenia was 24 days with no significant difference between the three treatment groups.

[Group 1] Electrolyte abnormalities (N=16) hepatic enzyme elevations (N=1) phlebitis (N=1).

[Group 2] Electrolyte abnormalities (N=16) hepatic enzyme elevations (N=3) rash (N=1) phlebitis (N=1).

[Group 3] Electrolyte abnormalities (N=18) hepatic enzyme elevations (N=2) azotemia (N=1) phlebitis (N=1).

Death:

[Group 1] Infectious (N=2) non-infectious (N=3)

[Group 2] Infectious (N=3) non-infectious (N=2)

[Group 3] Infectious (N=2) non-infectious (N=1)

Comments: This paper presented data from a randomised comparison of empiric anti-fungal therapy administered to patients with neutropenia who were febrile after seven days of empiric primary antibiotics. These patients were divided into two populations: those with unexplained fever and those with a documented infection. The results for the first group are further described here.

Fever was defined as three temperature elevations above 38°C during a 24-hour period or a single elevation of 38.5°C. Granulocytopenia was defined as an absolute count of <500 per µl of polymorphonuclear leucocytes and band forms.

Given their results, the authors suggested that the continuation of antibiotic therapy [Group 2] may have decreased the incidence of hypotension and early bacterial infection but increased the incidence of serious fungal infection. They pointed out that two deaths from infection in Group 1 were due to bacteria that were sensitive to the KGC regime, which had been discontinued, whilst two deaths in Group 2 were due to invasive fungal infections which might have been prevented by earlier administration of anti-fungal therapy. They considered that the combined therapy appeared to be beneficial in children and young patients who, after seven days of empiric antibiotics, remained febrile, regardless of whether or not a focus of infection was initially identified.

Although this low number study was reported as a randomised comparison, there were no methodological details provided, including randomisation or allocation, and very limited statistical analysis which rendered it of very low evidential quality.

1

Author(s): EORTC International Antimicrobial Therapy Cooperative Group (1989).

Country: Various

Study Design: Data from two **r**andomised controlled trials (RCT)

Study participants: One hundred and fifty-seven patients, from two RCTs. After four days of empiric antibiotics, patients with persistent severe granulocytopenia and fever without microbiologically documented pathogens but with clinical infection (known or likely) were randomised into two groups.

[Group 1] Mean age: 38.5 years (range: 4-78 years) Ratio of male: female = 43:25. Leukemia (N=49); Solid tumours (N=6); Other (N=13). Previous anti-fungal prophylaxis (N=31).

[Group 2] Mean age: 40.1 years (range: 1-81 years) Ratio of male: female = 37:27. Leukemia (N=50); Solid tumours (N=5); Other (N=9). Previous anti-fungal prophylaxis (N=39).

Interventions and comparators:

[Group 1] (N=68) Empiric antibiotics, including azlocillin, cefotaxime, ticarcillin, amikacin and ceftazidime (unknown schedule) plus amphotericin B (0.6mg kg^{-1} day^{-1} iv every 24h or 1.2mg kg^{-1} day^{-1} iv every 48h). Anti-fungal treatment was continued until bone marrow recovery.

[Group 2] (N=64) Empiric antibiotics only.

Protocol violations occurred in 12 Group 1 patients (for not receiving amphotericin B) and in 13 Group 2 patients (for receiving amphotericin B before day 9), leaving 132 evaluable. Amphotericin B was administered in Group 2 if a fungal infection was documented, or if a patient remained febrile 5 days after randomisation.

Outcomes: Clinical response. The response rate was calculated by assessing treatment as a failure if a patient remained febrile five days after randomisation.

Results:

More (31/45) patients in Group 1 had profound granulocytopenia at randomisation (69% univariate) than patients in Group 2 (20/43, 46% univariate) (P=0.06).

Overall response rate:

47/68 (69%) of all patients in Group 1 versus 34/64 (53%) of all patients in Group 2 were considered to have had treatment success (P=0.09).

38/57 (67%) of patients >15 years in Group 1 versus 24/51 (47%) of patients >15 years in Group 1 were considered to have had treatment success (P=0.06).

21/27 (78%) patients in Group 1 (i.e. given Amphotericin B) that had not received prior anti-fungal prophylaxis, experienced a higher treatment success rate than the 9/20 (45%) patients in Group 2 (i.e. given antibiotics only) that had also not received prior anti-fungal prophylaxis (P=0.04). Patients in both groups who had received anti-fungal prophylaxis experienced equal treatment success rates (19/31) (61%) in Group 1 versus 24/39 (61%) in Group 2.

For 22/29 (75%) patients in Group 1 with a clinically documented infection assessed at day 4, treatment was more effective than for 14/31 (41%) similar patients in Group 2 (P=0.03). There was no correlation between Amphotericin B dose and clinical response. In multivariate analysis, it was shown that age (less or more than 15 years) and previous anti-fungal prophylaxis (yes or no) were the two important prognostic factors. The treatment effect remained significant after adjustment for these two factors.

Six patients in Group 1 discontinued empiric Amphotericin B due to immediate side effects including chills, allergic reactions or infusion related high fever, or a combination of the three.

Overall survival:

There was one documented case of fungal infection in Group 1 patients, versus six cases in Group 2 (including two fatalities due to invasive candidiasis, one from a pulmonary *Aspergillus* infection and one from disseminated *Mucor*) (P=0.05 between groups). The incidence of nephrotoxicity was no higher in Group 1 (8/68 (11%)) compared with Group 2 (3/64 (4%)) but hypokalemia occurred significantly more frequently in Group 1 (33/68 (48%)) than Group 2 (16/64

(25%)) (P=0.009).

Eleven patients in Group 1 had died by day 30 versus 14 in Group 2 (P=0.039). One death was due to a pulmonary infection of undiagnosed aetiology and one from an unspecified bacterial infection. The remaining deaths were described as being due to 'other causes'. Similarly in Group 2, there were two deaths due to unspecified bacterial infections and eight from 'other causes'.

Comments: This paper presented data from patients that had been randomised into two large, multi-centre EORTC trials comparing various antibiotic regimens in patients with granulocytopenia and fever. After four days of persistent fever, patients were randomised to continue taking their primary empiric antibiotics with or without the addition of Amphotericin B.

Fever was defined as a temperature elevation above 38°C. Severe granulocytopenia was defined as an absolute count of <500 per µl of polymorphonuclear leucocytes.

The original studies may well have been conducted with rigor but there are no details of randomisation in this follow-on work, although the statistical methodology appears to be sound. There is very little detail about the incidence or identity of bacterial infections in either group.

1
2

Author(s): Cometta *et al*. (2003).

Country: Multinational

Study Design: Randomised controlled trial

Study participants: Seven hundred and sixty-three eligible patients were enrolled on this study. After 48-60 hours of empiric antibiotics, one hundred and sixty-five patients with neutropenia and persistent fever, either of unknown cause, clinically documented infection or microbiologically documented infection with a Gram +ve organism, were randomised into two groups.

[Group 1] Mean age: 42 years (range: 4-76 years) Adults: 81/86 (94%) Leukemia (N=53); Lymphoma or Hodgkin disease (N=31); Other (N=2). Gram +ve bacteremia (N=10); Clinically documented infection (N=14) Fever of unknown origin (N=62).

[Group 2] Mean age: 42 years (range: 4-78 years) Adults: 75/79 (95%) Leukemia (N=48); Lymphoma or Hodgkin disease (N=26); Other (N=5). Gram +ve bacteremia (N=8); Clinically documented infection (N=13) Fever of unknown origin (N=58).

Exclusions: Age <2 years; a known allergy to any of the protocol drugs; previously included in the study; having received an iv antibiotic within 4 days of study initiation; likelihood of death in the following two days; renal failure; poor creatinine clearance; catheter related infection; known HIV infection; pregnant or with a lung filtrate.

Interventions and comparators:

[Group 1] (N=86) Empiric antibiotic: Piperacillin-tazobactam (P-T) at 4.5g every 6 hours iv (less for smaller children) plus vancomycin at 15mg kg^{-1} every 12 hours (max daily dose of 2g).

[Group 2] (N=79) Empiric antibiotic plus placebo (saccharose solution).

Patients were treated until resolution of fever and/or infection for a minimum of four consecutive days. After that, patients with persistent fever were treated at the discretion of the clinician.

Outcomes: Time to defervescence, defined as a period of three days with a temperature of <38°C and the numbers of patients in each arm who had resolution of fever. All other clinical outcomes.

Results:

Fever resolution:

82/86 (95%) of Group 1 patients experienced fever resolution versus 73/79 (92%) of Group 2 patients (P=0.52).

Therapy was not modified in 42/86 (49%) of Group 1 patients or 36/79 (46%) of patients in Group 2. The most frequent modification was the addition of a glycopeptide to vancomycin and the stopping of the placebo for patients who then received vancomycin or teicoplanin. 31/86 (36%) of patients in Group 1 and 30/79 (38%) of patients in Group 2 received amphotericin B.

Median time to defervescence overall was 3.5 days (95%CI: 2.7-4.4) in Group 1 versus a median of 4.3 days (95%CI: 3.5-5.1) in Group 2 (P=0.75). HR: 1.03 (95%CI: 0.75-1.43).

Median time to defervescence for those patients who received the allotted regimen for the four days was 3.1 days (95%CI: 2.3-4.0) in Group 1 (N=76) versus a median of 4.0 days (95%CI: 3.3-4.7) in Group 2 (N=66) (P=0.91).

Mortality:

[Group 1] 4/86 patients (5%) died between days 14 and 31 after study entry. Deaths were due to: Gram –ve infection (N=1); extensive cancer (N=2) and haemorrhage (N=1).

[Group 2] 8/79 patients (10%) died between days 7 and 35 after study entry. Deaths were due to: Gram –ve infection (N=2); diffuse peritonitis (N=1); haemorrhage (N=3) and extensive cancer (N=3)

Adverse events:

[Group 1] 9/86 (10%) patients experienced adverse treatment-related events: rash (N=3); pruritis (N=2); nephrotoxicity (N=2); swelling of the lips (N=1) and red man syndrome (N=1).

[Group 2] 3/79 (4%) patients experienced adverse treatment-related events: colitis (N=1); diarrhoea (N=1) and rash (N=1).

Comments: This paper describes the results of randomised controlled trial for which 859 patients were enrolled between December 1997 and June 2000 at 34 centres throughout Europe, the Middle East and North America. The aim was to determine the effect of the addition of a Gram +ve antibiotic to empiric broad spectrum antibiotics given to cancer patients with unresolved neutropenia and fever.

Granulocytopenia was defined as an absolute granulocyte count ≤1,000 cell mm-3 which was expected to fall to <500 cells mm^{-3} within 24-48 hours and remain at that level for >7 days after the onset of fever. Fever was defined as an oral or axillary temperature of ≥38.5°C once or >38°C on ≥2 occasions at least one hour apart within a 12 hour period.

The study was designed to detect an improvement in the time to defervescence of 36 hours in the intervention group from 96 hours to defervescence in the placebo group. The sample size should have been 113 patients in each arm for 85% power but, clearly, the numbers fell well short (the trial was closed early for this reason) and hence the trial was underpowered.

The authors concluded that, despite the underpowering of their study, the addition of vancomycin to the empiric antibiotic regime did not appear to be justified.

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Author(s): Erjavec *et al.* (2000)

Country: The Netherlands

Study Design: Randomised controlled trial (RCT)

Study participants: One hundred and fifteen eligible adult patients were enrolled on this study. After 72-96 hours of empiric antibiotics, one hundred and fourteen patients with neutropenia and persistent fever, either of unknown cause, clinically documented infection or microbiologically documented infection with a Gram +ve organism, were randomised into two groups.

[Group 1] Mean age: 50.7 years (SD: 13.9 years) Adults: 81/86 (94%) Ratio of male: female = 28:28; Leukemia (N=32); Non-Hodgkin's lymphoma (N=9); Autologous stem cell transplant (N=12); Other (N=3). Antibacterial prophylaxis (N=51); Clinically documented infection (N=13) Fever of unknown origin (N=28).

[Group 2] Mean age: 42 years (range: 4-78 years) Adults: 75/79 (95%) Ratio of male: female = 35:23; Leukemia (N=37); Non-Hodgkin's lymphoma (N=9); Autologous stem cell transplant (N=10); Other (N=2). Antibacterial prophylaxis (N=52); Clinically documented infection (N=11) Fever of unknown origin (N=32).

Exclusions: identification of micro-organisms known to be resistant to protocol drugs; suspicion of fungal infection; signs or symptoms of a central line infection; clinical deterioration; known allergy to protocol drugs; renal failure; severe cardiac, hepatic or neurological disease.

Interventions and comparators:

[Group 1] (N=56) Empiric antibiotic: Imipenem at 500mg four times daily iv. plus teicoplanin at 400mg per 24h.

[Group 2] (N=58) Empiric antibiotic plus placebo.

Assigned treatments were given twice on the first day of randomisation and, for patients with a positive response, for five afebrile days thereafter. After 72 hours, non-responders in the placebo group were treated with teicoplanin and anti-fungal or anti-viral drugs as indicated (open label).

Outcomes: Survival, cause of death, time to fever resolution.

Results:

Fever resolution:

[Group 1] Response within 72 hours: 25/56 (45%) patients. Bone marrow regeneration was assumed in 9 patients amongst the responders.

[Group 2] Response within 72 hours: 27/58 (47%) patients. Bone marrow regeneration was assumed in 7 patients amongst the responders.

The lack of response was, in the majority of patients, for an unknown reason.

Survival:

[Group 1] Death whilst aplastic: 6/56 (11%)

[Group 2] Death whilst aplastic: 4/58 (7%)

Four patients died from a fungal infection in the teicoplanin arm, three of which were from a superinfection [Group 1] compared with a similar death in Group 2. Other causes of death in Group 1 included septicaemia and respiratory distress syndrome. In the placebo arm, one patient died from tumour progression and two from unrelated cardiac events.

Micro-organisms were isolated as follows: 13 Gram +ve, 2 Gram -ve and 5 non-bacterial organisms in Group 1 compared with 9 Gram +ve, 2 Gram -ve and 5 non-bacterial organisms in Group 2.

Comments:

Neutropenia was defined as an absolute neutrophil count ≤1,000 cell mm^{-3} which was expected to fall with chemotherapy or <500 cells mm^{-3}. Fever was defined as an axillary temperature of >38°C once or >38°C for 24 hours. Persistent fever was defined as a temperature at least 38°C on two consecutive readings 4-8 hours apart.

The trial was 85% powered to detect a 28% significant ($P<0.05$) difference in survival between study arms. Details of randomisation were unsatisfactory (defined as 'computer-assisted') and there were no details of allocation. There was no indication of blinding from the point of view of the administration of placebo and teicoplanin but investigators were apparently blinded in some analyses.

Many of the patients had received anti-bacterial prophylaxis and some had G-CSF. There were no statistical analyses presented, although the authors stated that patient outcomes had been analysed with X^2 testing. Despite any shortcomings, the authors concluded that they 'strongly advocated' the omission of empirical glycopeptides. They found no difference between study arms in the number of patients who became afebrile by three days after randomisation.

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EORTC International Antimicrobial Therapy Cooperative Group (1989). Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med*. 1989 Jun **86(6 Pt 1):** 668-72.

Erjavec Z, de Vries-Hospers HG, Laseur M, Halie RM and Daenen S (2000) A prospective, randomized, double-blinded, placebo-controlled trial of empirical teicoplanin in febrile neutropenia with persistent fever after imipenem monotherapy. *J. Antimicrob. Chemother.* **45(6):** 843-849.

Pizzo PA, Robichaud KJ, Gill FA and Witebsky FG (1982). Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am. J Med. 72: 101-111

16. Switching from intravenous to oral antibiotic therapy. (Topic E5)

Guideline subgroup members for this question

Anton Kruger (lead), Wendy King, Barbara Crosse, Bob Phillips and Rosemary Barnes.

Review question

When is the optimal time to switch (step down) from intravenous to oral antibiotic therapy?

Rationale

Empiric antibiotic therapy for patients with neutropenic sepsis is, by definition, given without a microbiological diagnosis. If an organism is identified subsequently, the treatment regimen and duration can be adjusted appropriately. However, for a substantial proportion of patients, ongoing therapy remains empiric. These individuals may have an undetected bacterial infection or could be unwell for other reasons. The standard approach to treatment is to continue with empiric antibiotics for a predetermined length of time after resolution of the fever or symptoms or neutrophil recovery.

The outcome of any episode of neutropenic sepsis will depend on a number of patient specific factors, on the anti infective treatment received, the environment and on the nature of the infective organism. Patient specific factors would include the underlying illness, chemotherapy regimen, presence of indwelling intravenous catheters or other devices and co- morbidities. The sensitivities and prevalence of local microbiological flora may also play a part. Depending on these factors, it is possible to devise strategies that allow for “step-down” from empiric intravenous to empiric oral antibiotics based on specific criteria or pre treatment risk scores or depending on response to the current treatment episode. Alternatively, a blanket policy of step-down therapy may be possible for all patients who are on empiric treatments in a particular setting.

Almost all currently recommended empiric antibiotic regimens comprise one or two intravenous drugs with a broad microbiological spectrum given in multiple daily doses. Treatment is most likely to have to be administered in hospital or, even if ambulatory care is possible, will be heavily dependent on resources such as nursing time. The advantages for a step down approach to care are therefore obvious. Hospital stays may be shortened since oral treatments allow for ambulatory care, patients can be freed of intravenous cannulae which are in themselves an infective risk and specific side effects of the intravenous agents may be avoided. On the other hand there are risks of failure of this treatment strategy and risks particular to oral antibiotics, such as diarrhoea and infection with *Clostridium difficile*.

This research question seeks to find evidence that defines suitable patient groups and the optimum time to switch from empiric intravenous antibiotic to oral therapy in neutropenic sepsis.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with neutropenic sepsis on intravenous antibiotics	Switch to oral antibiotics (intervention subgrouped by time) Ciprofloxacin Levofloxacin Augmentin (Co-amoxiclav) Amoxycillin	Remain on intravenous antibiotics	• Overtreatment • Death/critical care • Length of stay • Duration of fever • Quality of life

METHODS

Information sources and eligibility criteria

The full search strategy is available in appendix X. We restricted the search to published randomised trials and systematic reviews of such trials. The search was done on the 23rd of November 2010 and updated on 2nd November 2011.

Selection of studies and data synthesis

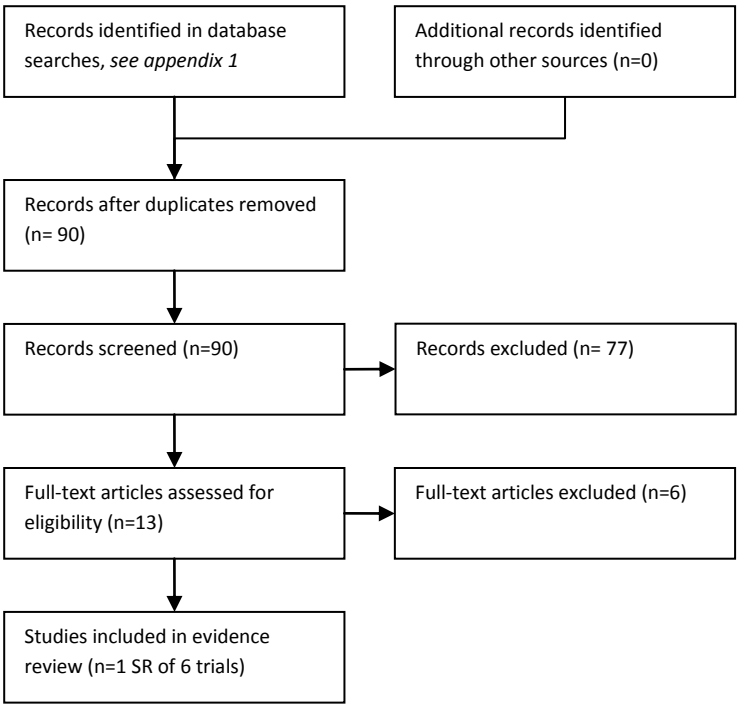
The information specialist (SA) performed an initial screening of the literature search results. One reviewer (MSH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question.

It was anticipated that evidence would come from trials comparing different times for switching to intravenous to oral antibiotics. However, in the absence of such studies, subgroup analyses was done (according to time-of-switch) in trials which compared switching from intravenous to oral antibiotics with continued intravenous antibiotics.

RESULTS

Results of the literature searces

Figure 16.1 Study flow diagram



90 studies were identified in the literature searches. Of these, 83 were excluded because they were narrative reviews (N = 6), not in PICO (N = 59), not RCT (N = 16), reporting data already included (N = 1) or a comment (N = 1).

One Cochrane review (Vidal et al., 2004) was indentified for inclusion. The review included 6 RCTs (Flaherty et al., 1989; Giamarellou et al., 2000; Mullen et al., 1999; Paganini et al., 2000, 2003; Shenep et al., 2001). These 6 trials were also checked individually for outcomes not reported in the Cochrane review.

Detailed information about the populations, interventions, outcomes and overall risk of bias in the included trials is given in the Evidence and Grade Tables below.

Evidence Statements

Death or critical care

Very low quality evidence from a Cochrane review (Vidal, et al., 2004, Table 7.2) suggested uncertainty about the relative effectiveness of the two treatment strategies for IV-to-oral versus IV-only the relative risk of short term mortality was 1.14 (95%C.I. 0.48 to 2.73). Critical care was not included as an outcome in any of the included studies, although one study (Paganini, et al.,, 2003) did report that none of their patients required admission to the intensive care unit.

Overtreatment, Length of stay and Quality of life

These outcomes were not reported in any of the included studies.

Duration of fever / Treatment failure

Duration of fever was not reported in the systematic review (Vidal, et al., 2004). Three of the included trials reported this outcome but none of these reported a statistically significant difference in the duration of fever between treatment groups.

Vidal, et al., (2004) reported treatment failure as a composite outcome comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention Low quality evidence suggested no significant difference in the rate of treatment failure in the IV-to-oral group compared to the IV only group, RR 1.07 (0.9 to 1.27).

REFERENCES

Vidal L, Ben dor I, Paul M, Pokroy E, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD003992. DOI: 10.1002/14651858.CD003992.pub2.

Table16.1 - GRADE evidence profile, Switching from intravenous to oral antibiotic therapy

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV-to-oral antibiotics at any time	IV antibiotics	Relative (95% CI)	Absolute	Quality
Death											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/442 (2.5%)	8/422 (1.9%)	RR 1.14 (0.48 to 2.73)	3 more per 1000 (from 10 fewer to 33 more)	VERY LOW
Treatment failure (composite measure[3])											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none	158/482 (32.8%)	137/464 (29.5%)	RR 1.07 (0.9 to 1.27)	21 more per 1000 (from 30 fewer to 80 more)	LOW

[1] Two of the trials observed a number of deaths whereas no deaths were observed in the remaining 4 trials.
[2] The number of events was very low, with no events observed in 4/6 trials. This clearly suggests that the trials were not powered to detect this outcome.
[3] Treatment failure defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention.
[4] Relatively low number of events.

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV-to-oral antibiotics after 72 hours of IV antibiotics and response to IV antibiotics	IV antibiotics	Relative (95% CI)	Absolute	Quality
Death											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/173 (6.4%)	8/152 (5.3%)	RR 1.14 (0.48 to 2.73)	7 more per 1000 (from 27 fewer to 91 more)	VERY LOW
Treatment failure (Composite outcome[3])											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none	98/180 (54.4%)	87/162 (53.7%)	RR 1.01 (0.83 to 1.23)	5 more per 1000 (from 91 fewer to 124 more)	LOW

[1] The designs of the included trials were both compromised either by providing no information about the method of randomisation and about whether allocation concealment or blinding was used or by not using intention to treat analysis.
[2] The number of events was very low. This clearly suggests that the trials were not powered to detect this outcome.
[3] Treatment failure defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention.
[4] The number of events was < 300

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV-to-oral antibiotics after 48-72 hours of IV antibiotics	IV antibiotics	Relative (95% CI)	Absolute	
Death											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/174 (0%)	0/180 (0%)	Not estimable	-	VERY LOW
Treatment failure (Composite outcome[3])											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	29/174 (16.7%)	29/180 (16.1%)	RR 1 (0.64 to 1.56)	0 fewer per 1000 (from 58 fewer to 90 more)	VERY LOW

[1] The design of one of the included trials was compromised by providing no or inadequate information about whether allocation concealment or blinding was used and by not using intention to treat analysis.
[2] There were no events in either trial which indicates that these trials were not powered for this outcome.
[3] Treatment failure defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention.
[5] The number of events was very low.

1 EVIDENCE TABLES

Citation: Vidal L, Ben dor I, Paul M, Pokroy E, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD003992. DOI: 10.1002/14651858.CD003992.pub2.

Design: Cochrane Systematic Review
Country: International

Aim: To compare the efficacy of intravenous (IV) antibiotic treatment to that of sequential IV-to-oral antibiotic treatment in patients with cancer and chemotherapy-induced neutropenia or patients with cancer who underwent a bonemarrow transplantation who presented with fever.

Inclusion criteria
Randomised controlled trials (RCTs) comparing any single or combination IV antibiotics to any single or combination sequential IV-to-oral antibiotics for the treatment of febrile neutropenia in cancer patients.

Exclusion criteria

Population
6 studies were included in the review:
Flaherty et al. (1989): N = 77 cancer patients with 86 episodes of fever and neutropenia; age range = 29-82 years; type of malignancy: Acute leukaemia (30%), Chronic leukemia (22%), lymphoma (6%), solid tumour (35%). USA 1988-89.
Giamarellou et al. (2000): N = 263 cancer patients with fever and neutropenia; mean age ≈ 54.4 (SD ≈ 17) years; all had with haematologic malignancies or aplastic anaemia. Greece 1992-95.
Mullen et al. (1999): N = 44 cancer patients with 76 episodes of fever and neutropenia; age range = 3-20 years; type of malignancy: Leukaemia (30%), non-leukemia (70%). USA 1995-97.
Paganini et al. (2000): N = 124 cancer patients with 154 episodes of fever and neutropenia; age range = 9 months-16.6 years; type of malignancy: Leukaemia (52%), lymphoma (5%), solid tumours (43%). Argentina 1997-98.
Paganini et al. (2003): N = 135 cancer patients with 177 episodes of fever and neutropenia; median age = 7.5 (range 1.6–15.8) years; type of malignancy: Acute leukaemia (59%), lymphoma (4%), solid tumours (37.5%). Argentina 2000-2002.
Shenep et al. (2001): N = 156 cancer patients with 200 episodes of fever and neutropenia; age range = 1.3–19) years; type of malignancy: Acute lymphoblastic leukaemia (53.5%), acute non-lymphoblastic leukemia (7%), solid tumours (38%), other leukemia or blood disorder (1.5%). USA 1991-1995.

Interventions
Flaherty et al. (1989): 3 regimens (as inpatients; episodes were randomised):
(1) Ciprofloxacin 300mg IV every 12 hours and azlocillin 4g IV every 6 hours with conversion to ciprofloxacin 750mg orally every 12 hours after 72 hours, if a favourable clinical and bacteriologic response to IV antibiotics had occurred and the patient was able to take oral medications;
(2) Ceftazidime 2g IV every 8 hours and amikacin 7.5mg/kg IV every 12 hours;
(3) Ceftazidime 2g IV every 8 hours and amikacin 7.5mg/kg IV every 12 hours with conversion to ciprofloxacin 750mg orally every 12 hours after 72 hours if clinical and bacteriologic response was appropriate.
Giamarellou et al. (2000): 2 regimens (as inpatients; patients were randomised):
(1) Ciprofluoxacin 400mg IV every 8 hours with conversion to oral ciprofluoxacin 750mg every 12 hours after 72 hours if successful response to IV antibiotics had occurred and the patients were able to tolerate oral medication.
(2) Ceftazidime 2g IV every 8 hours and amikacin 15 mg/kg of body weight/day IV over 30 min divided into two doses.

Mullen et al. (1999): 2 regimens (as outpatients; episodes were randomised):
(1) Single dose of ceftazidime 50mg/kg max 2g IV, change to oral ciprofluoxacin 12.5mg/kg every 12 hours.
(2) Ceftazidime 50mg/kg max 2g IV every 8 hours.
Paganini et al. (2000): 2 regimens (as outpatients; episodes were randomised):
(1) Ceftriaxone 100 mg/kg/day IV every 12 hours and amikacin IV 15 mg/kg/day every 24 hours) for 3 days, then conversion to oral cefixime 8 mg/kg/day every 24 hours for 4 days
(2) Ceftriaxone 100 mg/kg/day IV every 12 hours and amikacin IV 15 mg/kg/day every 24 hours) for 7 days.
Paganini et al. (2003): 2 regimens (as outpatients; episodes were randomised):
(1) Ceftriaxone 100 mg/kg per day as a single IV dose (maximum dose, 2 g) plus amikacin 15 mg/kg per day as a single IV dose the first day followed by ciprofloxacin 20 mg/kg per day orally every 12 hours,
(2) Ceftriaxone 100 mg/kg per day as a single IV dose (maximum dose, 2 g) plus amikacin 15 mg/kg per day as a single IV dose the first day followed by ceftriaxone 100mg/kg/day IV.
In both groups, antibiotic therapy was stopped when patients remained afebrile for 24 hours and the neutrophil count > 100/mm^3.
Shenep et al. (2001): 2 regimens (as inpatients; episodes were randomised):
(1) IV Tobramycin (or amikacin) + ticarcillin +vancomycin OR ceftazidime +vancomycin until randomisation after 48-72 hours and then change to oral cefixime suspension 4mg/kg every 12 hours.
(2) IV tobramycin every 6 hours 60mg/m^2 (or amikacin) + ticarcillin 2.25g/m^2 max 18g/day + vancomycin 300mg/m^2 max 4g/day or ceftazidime 1.5g/m^2 +vancomycin if renal failure or nephrotoxic chemotherapy.
All patients received prophylactic trimethoprim-sulfamethoxazole 150 mg/m^2 in 2 divided doses on 3 consecutive days each week.

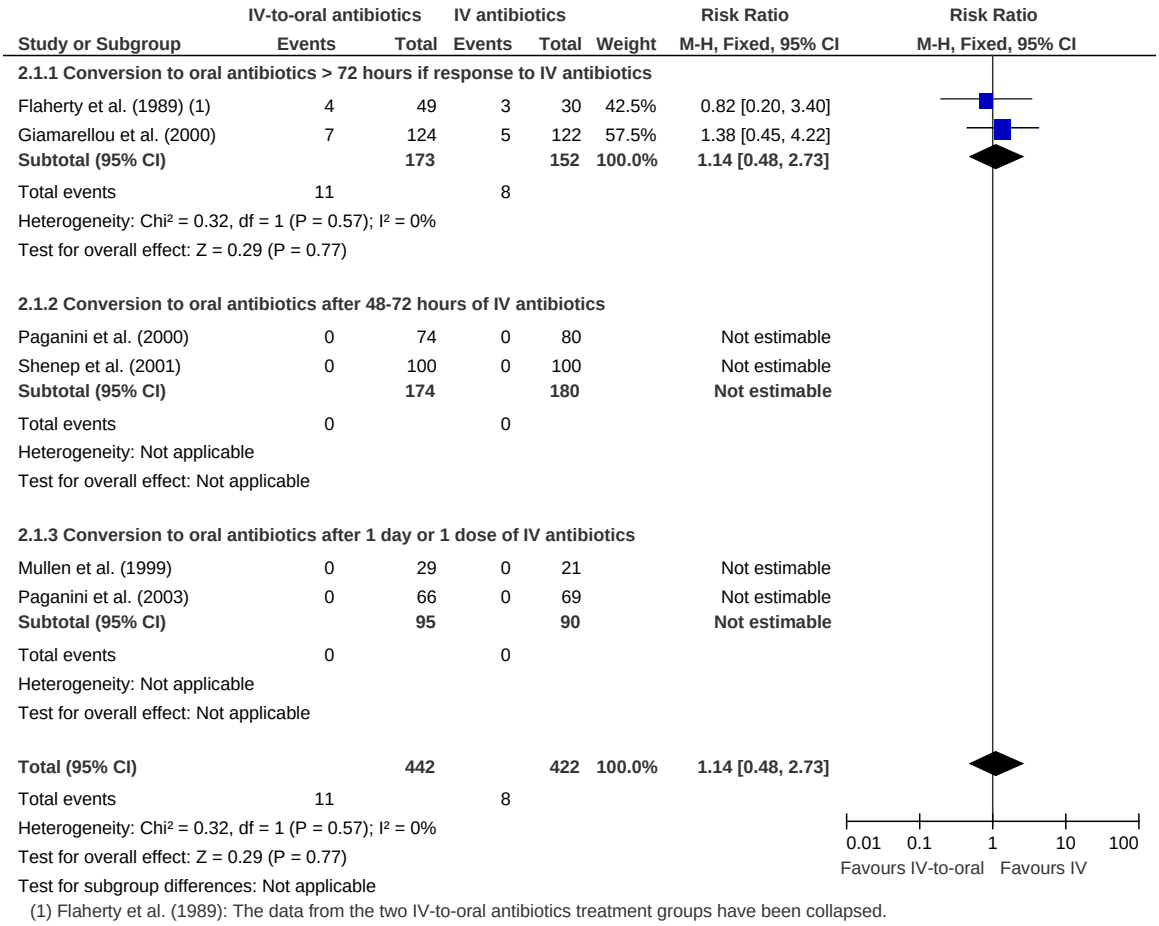
Outcomes

Vidal et al (2004; i.e., Cochrane review):
Primary outcomes: All cause mortality at 30 days follow-up, mortality caused by the infectious episode at end of follow up (restricted to 30 days), treatment failure (restricted to 30 days). Treatment failure defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention.
Secondary outcomes: Treatment failure not due to modification of the primary intervention, lost to follow up before end of study (dropouts).
Adverse effects: Life threatening or associated with permanent disability, requiring discontinuation of therapy.
Flaherty et al. (1989): All cause mortality, treatment failure, number of patients who become afebrile, length of febrile episode, duration of therapy, adverse events (requiring discontinuation). Definitions of failure: any death prior to neutrophil recovery; addition of antibiotics (success with modification).
Giamarellou et al. (2000): All cause mortality, infection-related mortality, duration of therapy, adverse events (any, requiring discontinuation). Definitions of failure: Death due to infection, fever and/or pathogen did not respond necessitating a modification in the assigned regimen, clinical or microbiological relapse within 7 days after discontinuation, superinfection.
Mullen et al. (1999): All cause mortality, treatment failure, length of febrile episode, length of hospital stay, lost to follow up, adverse events (?-are all reported?). Definitions of failure: Hospitalisation for any reason (indications for admission: positive blood culture and > 3 days fever, > 5 days fever, emesis, hypersensitivity, life threatening treatment related complications, deterioration).
Paganini et al. (2000): All cause mortality, treatment failure, treatment failure not due to modification of the primary intervention, length of febrile episode, lost to follow up, adverse events. Definitions of failure: Re-admission due to recurrence of fever.
Paganini et al. (2003): All cause mortality, treatment failure, treatment failure not due to modification of the primary intervention, adverse events.
Shenep et al. (2001): All cause mortality, treatment failure, treatment failure not due to modification of the primary intervention, lost to follow up, adverse events requiring discontinuation. Definitions of failure: Death,

addition of antibiotics, recurrence of fever, bacteraemia, documented or suspected localized bacterial infection, a new pulmonary infiltrate other than atelectasis, colonization with MRSA or P.auroginosa detected after randomisation, sepsis, severe mucositis in association with fever >=38.3 or discontinuing participation by patient or their physician.

Results

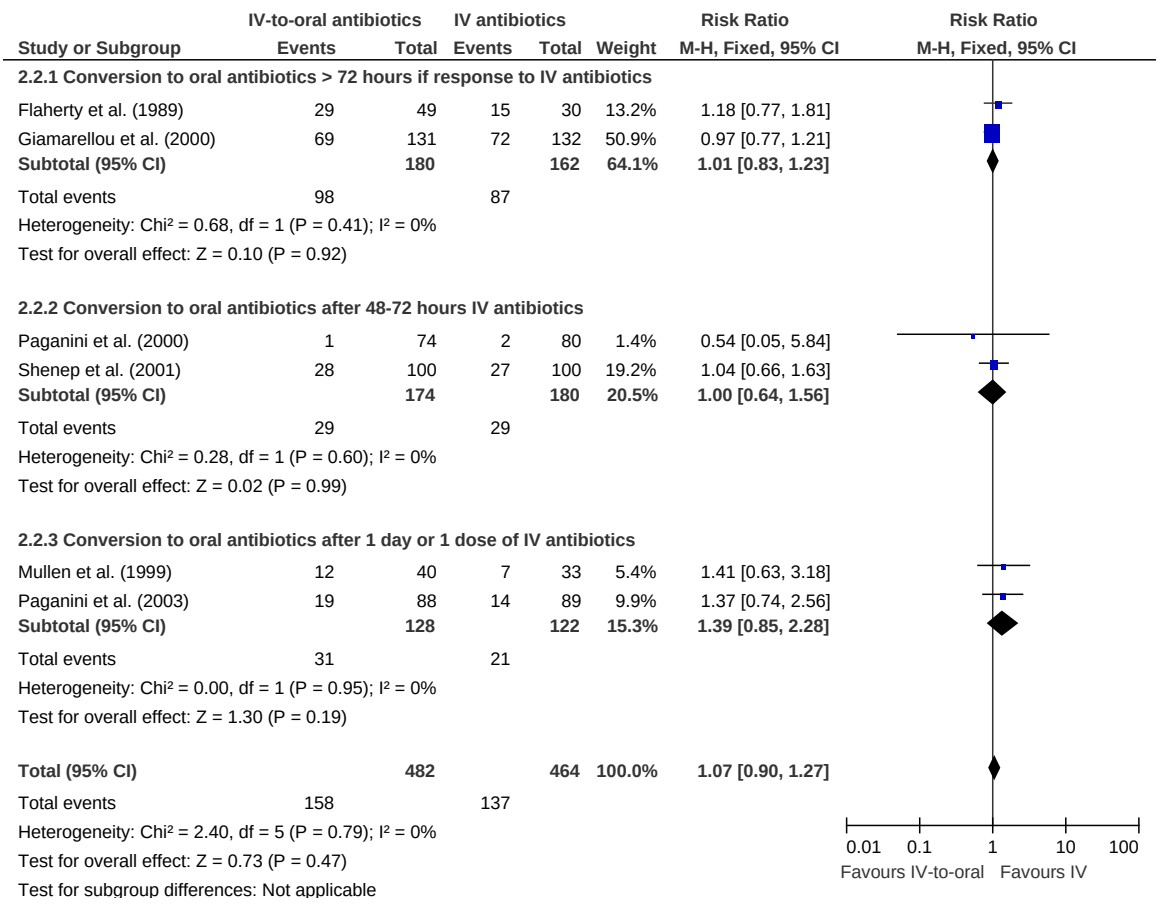
Mortality: Overall and by time of IV-to-oral switch:



(1) Flaherty et al. (1989): The data from the two IV-to-oral antibiotics treatment groups have been collapsed.

No deaths occurred in Mullen et al. (1999), Paganini et al. (2001, 2003) and Shenep et al. (2001). The risk of death did not differ between the patients who received IV antibiotics only and those patients who were switched from IV to oral antibiotics after 72 hours if they had responded to IV antibiotics (Flaherty et al., 1989; Giamarellou et al., 2000); Risk ratio = 1.14 (95% CI .48-2.73), p = .77, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure: Overall and by time of IV-to-oral switch:



The overall risk of treatment failure did not differ between the patients who received IV antibiotics only and those patients in the IV-to-oral antibiotics treatment groups (Risk ratio = 1.07 (95% CI .9-1.27), p = .47, I^2 = 0%, that is, there was no heterogeneity). The risk of treatment failure was also not found to differ between the treatment groups within the 3 'time of switch from IV to oral antibiotics' subgroups (see forest plot for individual subgroup risk ratios).

Vidal et al. (2004): Further meta-analyses:

Treatment failure (per protocol analysis): All 6 studies were included; total N = 470 in IV-to-oral group and 451 in IV group with 142 events in the IV-to-oral group and 122 events in the IV group; Risk ratio = 1.07 (95% CI .88-1.29), p = .51, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (children): Mullen et al. (1999), Paganini et al. (2000, 2003), and Shenep et al. (2001) were included; total N = 302 in IV-to-oral group and 302 in IV group with 60 events in the IV-to-oral group and 50 events in the IV group; Risk ratio = 1.17 (95% CI .84-1.62), p = .36, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (adults): Flaherty et al. (1989), and Giamarellou et al. (2000) were included; total N = 180 in IV-to-oral group and 162 in IV group with 98 events in the IV-to-oral group and 87 events in the IV group; Risk ratio = 1.01 (95% CI .83-1.23), p = .92, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (out-patients): Mullen et al. (1999), and Paganini et al. (2003) were included; total N = 128 in IV-to-oral group and 122 in IV group with 31 events in the IV-to-oral group and 21 events in the IV group; Risk ratio = 1.39 (95% CI .85-2.28), p = .19, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (in-patients): Flaherty et al. (1989), and Giamarellou et al. (2000) were included; total N = 180 in IV-to-oral group and 162 in IV group with 98 events in the IV-to-oral group and 87 events in the IV group; Risk ratio = 1.01 (95% CI .83-1.23), p = .92, I^2 = 0%, that is, there was no heterogeneity.

Treatment failure (quinolones only): Flaherty et al. (1989), Giamarellou et al. (2000), Mullen et al. (1999), and

Paganini et al. (2003) were included; total N = 308 in IV-to-oral group and 284 in IV group with 129 events in the IV-to-oral group and 108 events in the IV group; Risk ratio = 1.08 (95% CI .9-1.31), p = .41, I^2 = 0%, that is, there was no heterogeneity.
Treatment failure (cefixime): Paganini et al. (2000) and Shenep et al. (2001) were included; total N = 174 in IV-to-oral group and 180 in IV group with 29 events in the IV-to-oral group and 29 events in the IV group; Risk ratio = 1 (95% CI .64-1.56), p = .99, I^2 = 0%, that is, there was no heterogeneity.
Adverse events requiring discontinuation of antibiotics: All studies apart from Paganini et al. (2003) were included; total N = 389 in IV-to-oral group and 370 in IV group with 10 events in the IV-to-oral group and 13 events in the IV group; Risk ratio = .57 (95% CI .26-1.25), p = .16, I^2 = 0%, that is, there was no heterogeneity.
Gastrointestinal adverse events (post-protocol analysis): Included studies were Giamarellou et al. (2000), Paganini et al. (2000, 2003), Shenep et al. (2001); total N = 388 in IV-to-oral group and 396 in IV group with 14 events in the IV-to-oral group and 5 events in the IV group; Risk ratio = 2.81 (95% CI 1.03-7.66), p = .044, I^2 = 0%, that is, there was no heterogeneity. **The risk of experiencing gastrointestinal adverse events was 2.81 times higher for the patients in the IV-to-oral group compared to the patients in the IV group**.

Further results from the individual studies:
Flaherty et al. (1989):
Exclusions from analysis: 7/86 episodes of unknown treatment assignment.
Follow up period: End of fever and neutropenia.
Giamarellou et al. (2000):
Exclusions from analysis: 17/263 patients (no difference between treatment groups).
Follow up period: 7 days following end of antibiotic treatment.
Mullen et al. (1999):
Exclusions from analysis: 3/76 episodes of unknown treatment assignment.
Follow up period: End of antibiotic treatment.
The groups did not differ statistically significantly in duration of fever or treatment or in number of hospitalisations.
Paganini et al. (2000):
There were no exclusions from analysis.
Follow up period: 30 days following randomisation (which took place on day 3 of treatment).
The groups did not differ statistically significantly in duration of fever.
Paganini et al. (2003):
There were no exclusions from analysis.
Follow up period: Episode of fever and neutropenia, at least 7 days.
The groups did not differ statistically significantly in duration of fever and none of the patients required admission to the intensive care unit.
Shenep et al. (2001):
There were no exclusions from analysis.
Follow up period: End of antibiotic treatment.

General comments
The papers included in this systematic review have been comprehensively evaluated for bias and overall quality and are of varying quality (see next paragraph for further details about the quality of the included studies). Although no heterogeneity was evident in any of the analyses, the included studies used different patient populations (children and adults), different treatments and different times/criteria for switching from IV to oral antibiotics. These differences are likely to impact on the results and were therefore explored in subgroup analyses. However, only six studies were included in total and it is therefore unlikely that the subgroup analyses were sufficiently powered to detect any potential differences between the treatments and these must therefore be treated with caution.

Methodological features of the included studies:

Flaherty et al. (1989): No information about randomisation, allocation concealment, and blinding. Intention to treat analysis not used.

Giamarellou et al. (2000): No information about randomisation, adequate allocation concealment, and no blinding. Intention to treat analysis not used.

Mullen et al. (1999): No information about allocation concealment and blinding. Intention to treat analysis not used. Randomisation performed using a computer program.

Paganini et al. (2000): No information about blinding. Unclear whether allocation concealment was employed. Intention to treat analysis not used. Randomisation performed using a computer program.

Paganini et al. (2003): No blinding. Adequate allocation concealment. Intention to treat analysis was possibly used (episodes), but not explicitly reported. Randomisation performed using a computer program.

Shenep et al. (2001): Blinding of treatment providers. Adequate allocation concealment. Intention to treat analysis was used. Randomisation with stratification performed using a computer program.

References of Included Studies (For systematic reviews):

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17. Duration of inpatient care. (Topic E8).

Guideline subgroup members for this question

Wendy King (lead), Anton Kruger, Jeanette Hawkins, Bob Phillips and Rosemary Barnes.

Review question

What is the optimal duration of inpatient care for patients receiving empiric treatment for neutropenic sepsis?

Rationale

The risk and pattern of infection in patients with cancer and/or neutropenia depends on the primary diagnosis and the type, duration and intensity of the treatment.

Fever in the neutropenic patient requires prompt investigation and treatment with intravenous antibiotics, selected at first empirically in the light of known possible pathogens and the clinical circumstances. The most frequent pathogens are: Staph. Epidermidis, various Streps, Gram-negative rods and staph aureus. The most rapidly lethal are E. Coli, Klebsiella and Pseudomonas aeruginosa.

Any patient with neutropenic sepsis is unable to mount a response to infection. They are therefore at risk of an overwhelming infection and in particular a gram negative sepsis, which could ultimately result in a critical care admission or death. There is no way of telling which febrile neutropenic patients have potentially life-threatening infection.

Patients with neutropenic sepsis are usually admitted to hospital and commenced on empiric intravenous antibiotic treatment. However, there appears to be little evidence to support what the optimal duration of inpatient care should be. Currently there are different practices across the country with paediatric areas discharging low risk patients after 48 hours (if they have negative blood cultures, neutrophils above 0.1 and are clinically well) and adult units keeping patients in hospital until they are afebrile for 48 hours. A review of the evidence might help to standardise practice and provide evidence to improve outcomes.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Inpatients receiving empiric treatment for neutropenic sepsis	Early discharge	Continued inpatient care until antibiotics discontinued for at least 24 hours	• Overtreatment • Death/critical care • Quality of life • Re-admission rate • Adverse events (hospital acquired infection)

Information sources and eligibility criteria

The information specialist (SB) searched the following electronic databases: Medline, Premedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI), ISI proceedings and Biomed Central. The full strategy is available in appendix 1 to the evidence review

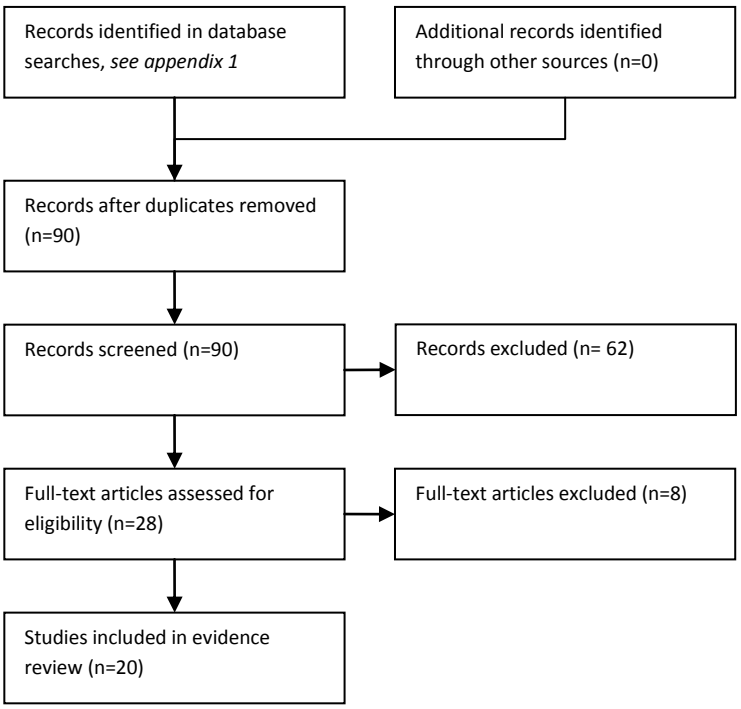
Study selection

The information specialist (SB) did the first screen of the literature search results. Two reviewers (CL and NB) subsequently selected potentially eligible studies by comparing titles and abstracts to the inclusion criteria presented in the PICO question. Full text articles were obtained for all studies identified as being potentially eligible. These articles were checked against the inclusion criteria. Data were extracted by one reviewer (CL) and checked by another (NB).

RESULTS

Results of the literature searches

Figure 17.1 Study flow diagram



Two Randomised Controlled Trials (RCTs) evaluating duration of inpatient care in the management of suspected bacterial infection (Innes et al 2003 and Santolaya et al 2004) were identified. One non-randomised comparative feasibility study was identified (Lau et al 1994). Eight prospective observational studies (Cherif et al 2006; Girmenia et al 2007; Klastersky 2006; Nijhuis et al 2005; Dommett 2009; Lehrnbecher 2002 and Bash 1994) and seven retrospective observational studies (Tordecilla et al 1994; Aquino 1997; Mullen et al 1990; Griffin et al 1992; Wacker et al 1997; Hodgson-Viden et al 2005 and Tomiak et al 1994) evaluated optimal inpatient duration. We identified one survey of the management of febrile neutropenia. One systematic review published 11 years ago was also identified (Castagnola et al 2000).

Studies in adult patients

We identified one RCT that addressed the question of inpatient duration in the management of suspected bacterial infection in adult patients (Innes et al 2003). Detailed criteria for stratifying patients according to risk of complications were presented based on those proposed by Talcott et al (1988). Patients were randomised to oral or IV antibiotic therapy. Although the duration of inpatient

care was shorter for the oral group, both groups were eligible for discharge irrespective of ANC. Three prospective consecutive case series considered duration of inpatient treatment for febrile neutropenia (FN) in adults (Cerif et al 2006, Girmenia et al 2007, Klatersky et al 2006). Two of the three studies considered only patients with FN subsequent to chemotherapy for haematologic malignancies. The other study considered FN following chemotherapy for both haematologic and solid malignancies. The MASCC criteria for stratifying FN patients according to risk of complications was used in all three studies. All used a cut off score of ≥ 21 to indicate low risk. In each study patients were discharged early with oral antibiotics. One study posed the requirement that patients were afebrile for 24 hours (Cherif et al. 2006); one required patients to be afebrile for 48 hours; and the other study (Girmenia et al 2007) indicated a requirement for patients to be hospitalised for a minimum of 24 hours. One prospective case series considered adult and paediatric patients (Nijhuis 2005). This study did not use the MASCC. A range of criteria were used, including the necessity of being afebrile for 12 hours. One retrospective case series of adult patients was identified (Tomiak 1994). This study gave negative blood cultures as the only criteria for early discharge.

Studies in paediatric patients

We identified one RCT that addressed the question of inpatient duration in the management of suspected bacterial infection in paediatric patients (Santolaya 2004). This study randomised low risk patients to ambulatory or hospital-based antibiotic treatment after 24 to 36 hours of hospitalisation. We identified one non-randomised feasibility study, which switched low risk patients from IV to oral antibiotics, subsequently treating the first 12 patients as inpatients, and the next 11 as outpatients.

Eleven case series of paediatric patients were identified (Dommett 2009; Lehrnbecher 2002; Bash 1994; Tordecilla et al 1994; Aquino 1997; Mullen et al 1990; Griffin et al 1992; Wacker et al 1997; Hodgson-Viden et al 2005 and Tomiak et al 1994). There were no set criteria for determining eligibility for early discharge in studies of paediatric patients. The requirement of being afebrile for at least 24 hours, and having negative blood cultures were common. Many studies also added the subjective criteria of the patient "appearing well".

Evidence statements

The evidence is summarized in Tables 17.1 and 17.2.

Early discharge rates

In four observational studies the percentage of adult patients meeting the criteria for early hospital discharge ranged from 38% to 90% (Cherif. et al., 2006; Girmenia, et al., 2007; Klastersky, et al., 2006 and Tomiak, et al., 1994). In order to be discharged early, low risk patients were required to meet additional criteria including ability to tolerate oral antibiotics, no history of poor compliance and ability to read a thermometer. The percentage of patients who were actually discharged early ranged from 13% to 69% (Cherif, et al., 2006; Girmenia, et al., 2007; Klastersky. et al., 2006 and Tomiak. et al., 1994).

In eleven observational studies the percentage of paediatric patients meeting the criteria for early hospital discharge ranged from 27% to 63% (Lau, et al., 1994; Dommett, et al., 2009; Lehrnbecher, et al., 2002; Bash, et al., 1994; Tordecilla, et al., 1994; Aquino, et al., 1997; Mullen, et al., 1990; Griffin, et al., 1992; Wakcker, et al., 1997; Hodgson-Veiden, et a.,l 2005 and Santos-Muchado, et al., 1999).

Most of these studies were retrospective and patients were not prospectively assigned to high/low risk groups. These studies reported the outcomes of those who were actually discharged early, which ranged from 19% to 68%.

Hospital readmission

In the Innes, et al., (2003) randomised trial, 5% of patients discharged early required hospital readmission

In four observational studies the rate of hospital re-admission for adult patients discharged early ranged from 0% - 13%. Re-admission rates ranged from 0% to 9% in eleven observational studies of paediatric patients.

Short term mortality

Patients selected for early discharge were at low risk of adverse events thus mortality data were sparse: in the Innes, et al., (2003) trial there were no deaths during follow-up. The reported short term (within 30 days of follow up) mortality rate was 0% for patients discharged early from hospital in all but one study of adult patients (Tomiak, 1994). This study reported one death (a mortality rate of 3%). This was the only study of adult patients that did not use the MASCC criteria to stratify patients according to risk.

The reported short term mortality rate was 0% for patients discharged early from hospital in all studies of paediatric patients.

Quality of life and overtreatment

These outcomes were not reported by any of the identified studies of adult or paediatric patients

1 ***Table 17.1 - GRADE evidence profile for early discharge with continued inpatient care.***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early discharge**	**Continued inpatient care**	**Relative (95% CI)**	**Absolute**	
Short term mortality in paediatric observational studies											
11	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	0/934 (0%)	-	-	-	VERY LOW
Hospital readmission in paediatric observational studies											
9	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	42/889 (4.7%)	-	-	-	VERY LOW
Short term mortality in adult case series using MASCC ≥ 21 as criteria for early discharge											
3	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	very serious[3]	none	0/215 (0%)	-	-	-	VERY LOW
Hospital readmission in adult case series using MASCC ≥ 21 as criteria for early discharge											
3	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	8/215 (3.7%)	-	-	-	VERY LOW
Short term mortality in paediatric RCT (Santolaya, et al., 2004)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	0/78 (0%)	1/71 (1.4%)	-	-	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early discharge**	**Continued inpatient care**	**Relative (95% CI)**	**Absolute**	
Short term mortality in adult RCT (Innes, et al., 2003)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	0/66	0/60	-	-	LOW
Overtreatment - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Adverse events - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Case series
[2] Case series
[3] Low number of events
[4] Method of randomisation was unclear. No blinding (but this was unlikely to affect outcome

1 ***Table 17.2 Early discharge criteria and rates***

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
Randomised Controlled trials										
1. Innes 2003	Adult	Haematologic and solid malignancies	1997-2000	102	126	Anticipated duration of neutropenia < 7 days Haemodynamically stable No signs or symptoms that required IV fluid support Adequate renal function Ability to maintain satisfactory oral intake Living with responsible adult prepared to act as a carer Patient or carer able to read a thermometer	N.A.	N.A.	5 (13%)	0 (0%)
2. Santolaya 2004	Paediatric	Haematologic and solid malignancies	2000 - 2003	390	390	Serum C-reactive protein (CRP) levels lower 90 mg/L No hypotension No relapse of leukaemia as cancer type Platelet count of more than 50,000/µL No recent (≤ 7 days) chemotherapy	N.A.	N.A.	Not reported	0 (0%)
Open un-randomised comparative study										
3. Lau 1994	Paediatric		1990-1991	21	23	Negative blood culture	N.A.	11 (only	Not reported	0 (0%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
								considered low risk patients)	by group	
Prospective case series										
4. Cherif 2006	Adult	Haematologic malignancies	2003-2005	279	191	MASCC (score ≥ 21) Afebrile for 24 hours Discharged with oral antibiotics	105 (38%)	67 (24%)	3 (4%)	0 (0%)
5. Girmenia 2007	Adult	Haematologic malignancies	2001-2002	100	87	MASCC (score ≥ 21) Afebrile for 48 hours Discharged with oral antibiotics	90 (90%)	69 (69%)	2 (3%)	0 (0%)
6. Klastersky 2006	Adult	Haematologic and solid malignancies	1999-2003	611	441	MASCC (score ≥ 21) Hospitalised for minimum of 24 hours Discharged with oral antibiotics	383 (63%)	79 (13%)	3 (4%)	0 (0%)
7. Nijhuis 2005	Adult and Paediatric	Haematologic and solid malignancies	1999-2002	196	128	No local bacterial infection / abnormal vital signs (systolic blood pressure less than 99 mmHg, or both heart rate higher than 100/min in adults or less than -2SD for age in children and respiratory rate higher than 20/min in adults or both heart and respiratory rate higher than +2 SD for age in children suggesting sepsis. Interleukin 8 level below cut off value of 60 ng/L Antibiotics completely withheld.	36 (18%)	36 (18%)	0 (0%)	0 (0%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
						Afebrile for 12 hours				
8. Dommett 2009	Paediatric	Haematologic and solid malignancies	2004-2005	762	368	Excluded from low risk protocol if: Age<1 year, shock/ compensated shock, haemorrhage, dehydration, metabolic instability, altered mental status, pneumonitis, mucositis, respiratory distress/ compromise, peri-rectal / other soft tissue abscess, rigors, irritability/meningism, organ failure, acute lymphoblastic leukaemia at diagnosis/relapse <28 d, acute lymphoblastic leukaemia not in remission >28 d acute myeloid leukaemia, infant acute lymphoblastic leukaemia, intensive B-NHL protocols, haemopoietic stem cell transplant, sequential high dose chemotherapy with PBSC rescue, intensive care admission during last FN episode, non adherence (social concerns or patient), inability to tolerate oral antibiotics, positive blood culture result at 48 h, ANC < 0.1 · 109/L at 48 h, child not clinically well at 48 h (clinician judgement). Hospitalised for minimum of 48 hours Discharged with oral antibiotics	212 (27%)	143 (19%)	8 (6%)	0 (0%)
9. Lehrnbecher 2002	Paediatric	Haematologic and solid malignancies	1994-1996	106	56	Patients were not formally categorised as high / low risk. Were eligible for discharge when following criteria met:	N/A	24 (23%)	0 (0%)	0 (0%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
						good clinical condition, negative blood culture results, no infectious focus, absence of fever for at least 24 hrs. Early discharge only allowed in cases of fever of unknown origin Hospitalised for minimum of 72 hours. Afebrile for 24 hours. Antibiotics ceased before discharge				
10. Bash 1994	Paediatric	Haematologic and solid malignancies	1989-1990	131	74	Appeared clinically well Negative blood cultures Exhibited control of local infection Hematologic evidence of bone marrow recovery Antibiotics ceased before discharge	82 (63%)	78 (58%)	7 (9%)* *these patients said to violate the early discharge protocol	0 (0%)
Retrospective case series										
11. Tordecilla 1994	Paediatric	Solid malignancies	1992-1993	84	50	*retrospective analysis, patients were not prospectively assigned to low/high risk groups Appeared well Negative blood cultures Normal chest x-ray Afebrile Discharged with/ without antibiotics	N.A.	30 (35.7%)	0 (0%)	0 (0%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
12. Aquino 1997	Paediatric	Haematologic and solid malignancies	1992 - 1995	580	253	*retrospective analysis, patients were not prospectively assigned to low/high risk groups Clinically well appearance Sterility of all blood cultures Control of local infection with antibiotic therapy (defined as reduction or resolution of local signs of inflammation such as erythema, induration and tenderness) Evidence of bone marrow recovery (defined as any sustained increase in platelet count and ANC or APC) Afebrile for 24 hours Discharged with/without oral antibiotics	N.A.	330 (57%)	21 (6%)	0 (0%)
13. Mullen 1990	Paediatric	Haematologic and solid malignancies	1988-1999	114	61	*retrospective analysis, patients were not prospectively assigned to low/high risk groups Negative blood cultures (Usually) some evidence of bone-marrow recovery Afebrile for 1-2 days	N.A.	77 (68%)	3 (3.9%)	0 (0%)
14. Griffin 1992	Paediatric	Haematologic and solid malignancies	1989	107	64	Initial blood cultures were sterile after 48 hours	N.A	70 (65%)	1/70 (1%)	0 (0%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
						Appeared well Any identified infection is under control Afebrile for 24 hours				
15. Wacker 1997	Paediatric	Haematologic and solid malignancies	1992-1995	88	30	*retrospective analysis, patients were not prospectively assigned to low/high risk groups No documented infection (no pathogenic organisms identified on cultures) throughout hospital course Normal physical exam Afebrile for 24 hours	44 (50%)	25 (28%)	2 (8%)	0 (0%)
16. Hodgson-Viden 2005	Paediatric	Haematologic and solid malignancies	1997 - 2002	276	127	*retrospective analysis, patients were not prospectively assigned to low/high risk groups No formal criteria for early discharge. Decision based solely on clinician's judgement. Patients were discharged on the day intravenous antimicrobial therapy (IVAMT) was ceased. Early discharge was defined as discontinuation of IVAMT with an ANC ≤ 500/mm^3.	N.A.	112 (41%)	0 (0%)	0 (0%)
17. Tomiak 1994	Adult	Haematologic and solid malignancies	1991-1993	134	134	*retrospective analysis, patients were not prospectively assigned to low/high risk groups Negative blood cultures	N.A.	37 (28%)	2 (5%)	1 (3%)

Study ID	Population	Cancer	Study period	Episodes febrile neutropenia	Number of patients	Criteria for discharge	No. meeting basic criteria for early discharge	No. discharged early	Hospital re-admission in early discharge group	Death in early discharge group
						Afebrile and clinically stable for 48 hours				
18. Santos-Muchado 1999	Paediatric	Haematologic and solid malignancies	1996	79	46	Negative blood cultures Afebrile for 24 hours Discharged with oral antibiotics (in most cases)	N.A.	34 (43%)	Not reported	0 (0%)

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Country: United Kingdom
Design: Randomised Controlled Trial
Population: 126 episodes of low risk neutropenia in 102 patients between February 1997 and August

2000
Inclusion criteria: Age ≥ 18 Neutropenia (defined as (ANC) ≤ 0.5 x 10^9 1^{-1}, or (ANC) ≤ 1 x 10^9 1^{-1} but anticipated to fall to (ANC) ≤ 0.5 x 10^9 1^{-1} within 24 hours of entry into the study) Fever (defined as a temperature ≥38°C on two oral measurements 4 hours apart within a 24 h period, one of which could have been measured by the patient prior to admission, or ≥38.5°C on one occasion) Anticipated duration of neutropenia < 7 days Haemodynamically stable No signs or symptoms that required intravenous fluid support Adequate renal function Ability to maintain satisfactory oral intake Living with responsible adult prepared to act as a carer if eligible for early discharge Either patient or carer required to be able to read a thermometer Written informed consent
Exclusion criteria: Autologous bone marrow or peripheral blood stem-cell transplantation Antibacterial medication within 7 days of enrolment. Use of CSFs and cytokines Any coexisting medical condition that would require in-patient treatment or monitoring Clinically documented infection in the opinion of the investigator, likely to require targeted or prolonged duration of antibiotic therapy (e.g. cellulitis, abscess, pneumonia, CVC tunnel infection) Inability to tolerate oral medication Known allergy to study drugs

History of poor compliance
Interventions: Oral regimen: Ciprofloxacin 750 mg every 12 h plus amoxicillin–clavulanate (amoxicillin 500 mgþclavulanate 175 mg) every 8 h for a total of 5 days. Participants were eligible for discharge following 24 h of hospitalisation if clinically stable, symptomatically improved, and willing. Patients supplied with daily diary to record temperature at 6-hourly intervals and any associated symptoms, and telephone contact was maintained. Those randomised to the oral arm who were not discharged after the 24 h assessment were reassessed daily including their eligibility for discharge. Intravenous regimen: Gentamicin 80 mg every 8 h and dose adjusted according to therapeutic levels plus tazocin (piperacillin 4 gþtazobactam 500 mg; Lederle, Maidenhead, UK) every 8 h until hospital discharge. *** BOTH GROUPS WERE ELIGIBLE FOR DISCHARGE IRRESPECTIVE OF ANC***
Outcomes: Success (defined by the EORTC guidelines) Lysis of fever Recurrence within 7 days Frequency of serious medical complications Frequency of deaths Duration of hospital admission Frequency of readmission Toxicity
Results: Success (according to EORTC guidelines) Oral: 90% of episodes treated successfully without antibiotic modification IV: 84.8% of episodes successfully without antibiotic modification Death Oral: 0 IV: 1

Significant clinical deterioration

Oral: 1 ((during initial 24 hours of inpatient monitoring)
IV: 0

Length of hospital stay

Oral: 2 days (range 1–16 days)
IV: 4 days (range 2–8)

Readmission to hospital
Oral: 5 (13.2%)

Toxicity
Oral: 1 episode CTC grade 3; 14 patients CTC grade 1-2 diarrhoea; 5 patients CTC grade 1-2 nausea/vomiting
IV: No episodes of toxicity CTC grade > 1

General comments:

This was a well conducted RCT. The sample size was fairly small, but a power calculation was reported. The definition of 'low-risk' was based on the definition proposed by Talcott et al (1988), but given the intention of early hospital discharge and the high incidence of complications and readmissions in Talcott's initial pilot study, the definition was extended to exclude central venous catheter infections, pneumonia and cellulitis and an expected duration of neutropenia of over 7 days. Eligible patients were randomly assigned to study groups by means of consecutively drawn sealed envelopes. Patients could be entered more than once following subsequent episodes of febrile neutropenia. The study was conducted before development of the MASCC. The authors concluded that oral antibiotics in conjunction with early hospital discharge for patients who remain stable after a 24 h period of in-patient monitoring offers a feasible and cost-effective alternative to conventional management of low-risk neutropenic fever.

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Santolaya, M. E., Alvarez, A. M., Aviles, C. L., Becker, A., Cofre, J., Cumsille, M. A. et al. (2004). Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. Journal of Clinical Oncology, 22, 3784-3789.

Country:

Chile

Design: Randomised Controlled Trial
Population: 390 episodes of febrile neutropenia at six hospitals in Santiago, Chile between June 2000 and February 2003.
Inclusion criteria: Age ≤ 18 Fever (one axillary recording of 38.5°C or greater or two recordings of 38°C or greater separated by at least 1 hour) Severe neutropenia (ANC < 500/µL)
Interventions: Children at low risk of Invasive Bacterial Infection (IBI) were admitted to the hospital. Empirical IV antimicrobial treatment was administered (ceftriaxone 100 mg/kg/d every 24 hours, and IV teicoplanin 20 mg/kg/d every 12 hours for the first day followed by 10 mg/kg/d every 24 hours). They were re-evaluated after 24 to 36 hours to determine whether they continued in the low-risk category. After completing a minimum of 3 days of IV therapy, those who met criteria for low risk switched therapy to oral cefuroxime axetil, 50 mg/kg/d every 12 hours and randomly assigned to receive ambulatory or hospital management.
Outcomes: Unfavorable outcome defined by: (1) hemodynamic instability not attributable to volume loss; (2) axillary temperature more than 38°C in two or more daily recordings after day 4; (3) increase in temperature after a 48-hour afebrile period persisting for at least 24 hours; (4) an ascending CRP curve or a nondescending curve over normal limits (a value > 40 mg/L and < 30% decrease from a previous recording) after day 3 persisting for at least 2 consecutive days; (5) isolation of a bacterial pathogen from a significant sample obtained on day 3; and (6) death occurring during the febrile episode attributable to infection.

Results:

161 (41%) of 390 febrile neutropenic episodes were classified as low risk

149 were randomly assigned to ambulatory (n = 78) or hospital-based (n = 71) treatment.

Favourable outcome

Ambulatory-treated children: 74/78 (95%)

Hospital-treated children: 67/71 (94%)

Mortality

Ambulatory-treated children: 0/78 (0%)

Hospital-treated children: 1/71 (1%)

General comments:

Work by the authors from 1996 to 1997, aimed to identify clinical and laboratory variables present at the time of first consultation that could help identify children at high or low risk of an IBI. The following five independent risk variables (ranked by order of significance) were identified: serum C-reactive protein (CRP) levels of 90 mg/L or greater, presence of hypotension, relapse of leukemia as cancer type, platelet count of 50,000/μL or less, and recent (≤ 7 days) chemotherapy. IBI occurred in 2%, 17%, 48%, 75%, and 100% of episodes presenting with none, one, two, three, or four or more risk factors, respectively. During 1999 to 2000, the model was prospectively validated. Sensitivity, specificity, and positive and negative predictive values for this model were 92%, 76%, 82%, and 90%, respectively. This study aimed to evaluate the hypothesis that children at low risk for IBI can be treated as outpatients and have a comparable outcome to children treated in hospital. It is unclear how patients were randomised. A power calculation is presented. The authors concluded that for children with febrile neutropenia at low risk for IBI, ambulatory management is safe and significantly cost saving compared with standard hospitalised therapy.

1

Lau, R. C., Doyle, J. J., Freedman, M. H., King, S. M., & Richardson, S. E. (1994). Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. Pediatric Hematology & Oncology, 11, 417-421.

Country:

Canada
Design: Open un-randomised comparative feasibility study
Population: 23 episodes of febrile neutropenia in 21 patients admitted to hospital between October 1990 and July 1991
Inclusion criteria: Fever (no definition) Neutropenia after chemotherapy (no definition)
Exclusion criteria: Fever longer than 48 hours after receiving IV antibiotics Blood culture positive Sepsis clinically suspected
Interventions: All patients were initially treated with 72 hours of intravenous antibiotic therapy (tiracillin 200 mg/kg/day every 6 hours) and gentamicin (7.5mg/kg/day every 8 hours). After 72 hours, IV antibiotics changed to oral antibiotics if all following criteria met: negative blood cultures, temperature 38ºC or lower for 24 hours, absolute neutrophil count (ANC) less than 0.5 X 10_9/L, absence clinical sepsis. Oral antibiotics were cefixime (8mg/kg/day; maximum 400mg) as a single dose and cloxacillin (100mg/kg/day in 4 divided doses; maximum, 1g per dose) First 12 patients monitored as inpatients Remaining 11 patients were discharged and followed as outpatients: Asked to record temperature daily and have a complete blood count done every 3 days.
Outcomes: Fever recurrence Clinical deterioration

Results: Fever recurred in 3 patients (13%). IV was reinstated in 2 cases, and oral antibiotics continued in the third. No patients showed clinical deterioration
General comments: This was a very small scale open feasibility study of paediatric cancer patients presenting with febrile neutropenia. They were treated with intravenous and then oral antibiotics if meeting criteria indicating low risk. The first 12 patients were treated as inpatients and the remaining 11 as outpatients. It is unclear why these patients were not randomly assigned to groups. The results were very badly reported. Fever recurred in three patients, but it is unclear whether these were in the inpatient or outpatient group. Indeed, it is unclear how the two groups differed in terms of any outcome. The authors concluded that the approach could be used safely in a carefully selected group of patients.

1

Bash, R. O., Katz, J. A., Cash, J. V., & Buchanan, G. R. (1994). Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. Cancer, 74, 189-196.
Country: USA
Design: Prospective consecutive case series
Population: 131 episodes of febrile neutropenia in 74 patients admitted to a children's medical centre between November 1989 and July 1990
Inclusion criteria: Fever (single temperature ≥ 38.5°C or serial measurements of ≥ 38°C for more than 6 hours) Neutropenia (defined as ANC ≤ 500/mm^3) Parental informed consent
Interventions:

Intravenous ceftazidime (50mg/kg/dose, maximum dose 2.0g) administered to all patients and repeated every 8 hours. Additional antibiotics were administered for specific indications at the clinicians discretion

Patients were eligible for discontinuation of antibiotics and early discharge if they met the following criteria:

1. Afebrile for at least 24 hours
2. Appeared clinically well
3. Negative blood cultures for at least 48 hours
4. Control (improvement or resolution) of local infection
5. Evidence of bone marrow recovery for at least 1 day (increase in leukocyte, APC, ANC, and/or platelet count)

If localised infection had not fully resolved: discharged with oral antibiotics.

Discharged patients maintained daily telephone contact and were monitored as outpatients every 2-3 days as outpatients as long as they remained neutropenic.

Outcomes:

% patients discharged early

Hospital readmission

Mortality

Results:

82/131 (63%) episodes were eligible for early discontinuation of IV antibiotics

78/131 (58%) were discharged early

Hospital readmission

7 (9%) patients were re-admitted (although these were retrospectively said not to meet the full criteria for early discharge)

Mortality

0 (0%) died

General comments:

This was a prospective case series with a relatively small sample size of 74 patients.

Criteria for early discharge were presented. It is unclear however what specifically is meant by the criterion "clinically well". It is reported that additional antibiotics were given alongside empiric IV antibiotics, but no details are given as to what these were, or how many patients received them. 8/78 patients discharged early were said to be protocol violations on the basis that there had been no sustained rise in leukocyte, ANC, APC, or platelet count. 6/8 (75%) were readmitted. The results reported in the abstract ignore these readmissions, reporting only that none of the 70 they retrospectively deemed to meet criteria were re-hospitalised. The authors concluded that low risk children with cancer who are hospitalized and treated for fever and neutropenia but appear clinically well may have intravenous antibiotics discontinued and be discharged safely irrespective of the ANC, as long as their granulocyte count is rising.

1

Cherif, H., Johansson, E., Bjorkholm, M., & Kalin, M. (2006). The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. Haematologica, 91, 215-222.
Country: Sweden
Design: Prospective consecutive case series
Population: 191 adult patients, who developed 279 episodes of febrile neutropenia (participants could be re-entered into the study for a second time (but not a third) providing neutrophile count had returned to normal between episodes). Represented all adult patients admitted to a medical unit between November 2003 and April 2005 for the treatment of fever and neutropenia associated with chemotherapy.
Inclusion criteria: Fever (defined by a temperature of ≥38°C on two occasions at least 4 hours apart during a 24-hour period or ≥38.5°C on a single occasion) Neutropenia (defined as ANC ≤ 0.5 x 10^9/L) Written informed consent
Interventions: All participants were hospitalised to receive IV antibiotics "in accordance with local and

international recommendations".

Low risk patients according to MASCC criteria (score ≥ 21), who had not developed clinical complications, were transferred to oral antibiotics 24 hours after fever subsided. The first dose was administered in hospital, and if no acute complications arose, they were subsequently monitored as outpatients. Oral antibiotic treatment was continued for 5 days.

Outcomes:

Sensitivity, specificity and positive predictive value of MASCC

Mortality

Hospital re-admission

Results:

Low risk according to MASCC: 105 (38%) episodes occurring in 81 patients

High risk according to MASCC: 174 (62%) episodes occurring in 132 patients

MASCC specificity: 87%

MASCC sensitivity: 58%

MASCC positive predictive value: 84%

36% of low-risk group were ineligible for oral antibiotics

Of the 67 patients who received oral antibiotics and early discharge, 64 (95%) remained afebrile, 3 required re-admission, and there was no mortality.

General comments:

This was a reasonably well conducted prospective case series including all adult patients admitted to a medical-centre between November 2003 and April 2005 for the treatment of fever and neutropenia associated with chemotherapy. The methodology allowed collection of data from the same participant up to two times, which somewhat compromises the data-set overall. It is unclear why this was allowed, whilst excluding third cases. The MASCC was developed using a single episode per patient, and its validity for second episodes is currently known. Including multiple episodes is however the case in the vast majority of studies considered here. No demographic information was included (e.g. age, gender, ethnicity), which might have been useful in providing context to the results. 36% of the low-risk group were ineligible for oral antibiotic. The authors concluded that the MASCC risk-index was a valuable tool for identifying febrile

neutropenic patients at low risk for complications and that oral antibiotic treatment following discharge from the hospital 24 hours after defervescence offered a safe and cost-effective alternative to the conventional management of carefully selected low-risk patients.

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Girmenia, C., Russo, E., Carmosino, I., Breccia, M., Dragoni, F., Latagliata, R. et al. (2007). Early hospital discharge with oral antimicrobial therapy in patients with hematologic malignancies and low-risk febrile neutropenia. Annals of Hematology, 86, 263-270.
Country: Italy
Design: Prospective consecutive case series
Population: 100 episodes of febrile neutropenia in 87 consecutive patients hospitalised between March 2001 and August 2002
Inclusion criteria: Age ≥ 16 Haematological malignancy Neutropenia (defined as ANC < 500 cells /µl of blood) Fever (defined as temperature ≥ 38.5ºC on one occasion, or ≥ 38 ºC for more than an hour)
Interventions: All patients were treated with empiric intravenous ceftriaxone (2g/24h) plus amikacin (20 mg/kg/24h) within an hour of arrival at EU. The therapeutic plan was to continue antibiotics for 6 consecutive afebrile days had passed, or until microbiological and/or clinical evidence of infection had disappeared. The Multinational Association of Supportive Care in Cancer (MASCC) criteria were used to categorise patients as high risk (score < 21) or low risk (score ≥ 21). This classification

dictated subsequent management. High risk patients: managed in hospital for entire course of antibiotic treatment regardless of neutropenia recovery and response to treatment. Low risk patients: discharged from hospital early if free from fever for 48 hours, in a good general condition and not receiving supportive treatment requiring hospitalisation.
Outcomes: Length of hospital stay Fever recurrence Mortality
Results: Of 90 low-risk episodes, 69 (76.7%) cases were discharged early after a median of 4 days, and continued home therapy with oral cefixime (78%) or other antibiotics 5 (7.2%) of those discharged early had fever recurrence 21 low-risk patients were not discharged early due to worsening conditions (three deaths), need of multiple daily dose therapy, or discharge refusal 0 (0%) early discharge patients died
General comments: Consecutive cases were prospectively evaluated. The sample size was fairly small. The authors concluded that the MASCC risk-index was a useful aid in the identification of high-risk febrile neutropenia needing their entire treatment in hospital. They also noted that hospitalisation for the first few days of fever was required on the basis that ¼ of low-risk patients required prolonged hospitalisation, and three died of non-infectious causes.

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Klastersky, J., Paesmans, M., Georgala, A., Muanza, F., Plehiers, B., Dubreucq, L. et al. (2006) Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. Journal of Clinical Oncology, 24 (25) 4129-4134
Country: Belgium
Design:

Prospective consecutive case series
Population: 383 febrile neutropenic episodes with low risk of complications who were treated with chemotherapy from January 1999 to November 2003
Inclusion criteria: Age ≥ 16 Neutropenia (defined by ANC ≤ $0.5x10^9$/L) Fever (defined by temperature ≥38.5ºC on one occasion, or ≥38 ºC twice during a 12 hour interval) Able to swallow Free of contraindications for oral drugs Informed consent Low risk was defined as MASCC score ≥ 21
Exclusion criteria: History of allergy to penicillin or quinolones
Interventions: Oral antibiotics (ciprofloxacin and amoxicillin-clavulanate); discharged if they clinically stable or improving after an initial observation period.
Outcomes: Early discharge Hospital readmission Clinical complications

Results: 178 of 383 first febrile neutropenic episodes predicted at low risk of complication (score of 21 or less on the MASCC) were treated orally. These cases constituted the analysis. Early discharge 79 (44%) were discharged early (median time to discharge of 26 hours); Clinical complications 0 (0%) clinical complications occurred Hospital readmission 3 (4%) patients had to be readmitted to hospital Success rate of 96% (95% CI, 92% to 100%).
General comments: All febrile neutropenic patients between January 1999 and November 2003 were screened and assessed on the MASCC. The majority of participants (81%) were female. A power calculation was reported. A major limitation of the study was the fact that most patients with hematologic tumours were excluded. The institution routinely provided antibacterial prophylaxis for these individuals, and this was an exclusion criterion for oral antibiotic administration. Exclusion of these patients acted as an additional filter independent of the tool under investigation. The authors concluded that oral therapy followed by early discharge was feasible in a small but significant proportion of low risk patients (although this conclusion cannot be generalised to individuals with hematologic tumours)

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Tomiak, A. T., Yau, J. C., Huan, S. D., Cripps, M. C., Goel, R., Perrault, D. J. et al. (1994). Duration of intravenous antibiotics for patients with neutropenic fever. *Annals of Oncology, 5,* 441-445.
Country: Canada
Design: Retrospective consecutive case series
Population: 134 episodes of febrile neutropenia in adult neutropenic admissions to a medical

oncology ward between September 1991 and March 1993
Inclusion criteria: Fever (defined as single temperature ≥ 38.5°C, or two or more recordings ≥ 38.0°C within hours). Neutropenia (defined as ANC less than 0.5 x 10^9/L)
Exclusion criteria: Developed febrile neutropenia while in hospital
Interventions: A policy of early discontinuation of intravenous antibiotics was adopted in April 1992. This consisted of discontinuation of intravenous antibiotics in culture negative patients who remained afebrile and clinically stable for 48 hours, regardless of their absolute neutrophil counts. (Clinically stable was defined as hemodynamically stable with no clinical signs of worsening infection and able to maintain adequate oral intake.) Patients were started on oral antibiotics and discharged at the discretion of the attending physician. Patients were generally monitored for an additional 24-48 hours prior to discharge to ensure that they remained afebrile and clinically stable; the length of observation varied between attending physicians and their level of comfort with early discharge. Oral antibiotics were generally continued for a total of 7-10 days. In order to observe the effect of this policy the study period was divided into three intervals with equal number of admissions in each interval. Group 1: patients managed prior to the initiation of policy. Antibiotics were continued in culture negative patients until resolution of both fever and neutropenia or at the discretion of attending physicians. Group 2: patients admitted after starting the policy of early discontinuation of intravenous antibiotics. Group 3: included to monitor if the policy was still implemented.
Outcomes: Hospital readmission Reinstitution of IV antibiotics

Mortality Median duration of IV antibiotic Median duration of hospital stay
Results: <u>Early discharge</u> 37/134 (28 %) <u>Hospital readmission</u> 2/37 (5%) <u>Reinstitution of IV antibiotics</u> 0 (0%) <u>Mortality</u> 1/37 (3%) <u>Median duration of IV antibiotic</u> Group 1: 7 days Group 2: 5 days Group 3: 4 days <u>Median duration of hospital stay</u> Group 1: 10 days Group 2: 7 days Group 3: 6 days
General comments: This was a retrospective review of patient records. A policy of early discharge had been implemented, and the authors aimed to compare patient data before implementation, after implementation and at a later date. Patients in Group 1 were treated up to two years before Group 3. It is unclear whether there were any other changes to treatment regimens during this time. Patients were treated at different times of the year (groups 1 and 3 over the summer, and group 2 over the winter). It appears that each episode of

FN represented an individual patient. The authors do not state that subsequent episodes were excluded, but it seems unlikely that none of these patients developed FN for a second time. 27% of patients were discharged early, but it is unclear whether these patients belonged to group 1, 2, or 3.

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Lehrnbecher,T.; Stanescu,A.; Kuhl,J. (2002) Short courses of intravenous empirical antibiotic treatment in selected febrile neutropenic children with cancer. Infection, 30 (1), 17-21
Country: Germany
Design: Retrospective consecutive case series
Population: 106 episodes of chemotherapy induced neutropenia and fever in 56 children admitted to an oncology ward between January 1994 and June 1996
Inclusion criteria: Aged < 18 Neutropenia (defined as less than 500 neutrophils/ml, or patients who had recently received chemotherapy and had evidence of rapidly dropping neutrophil counts with an ANC of less than 500/µl within 72 hours were also included). Fever (defined as temperature ≥ 38.5ºC on one occasion, or two measurements of ≥ 38 ºC within 4 hours)
Exclusion criteria: Antibiotics within 72 hours of admission (apart from trimethoprim sulfamethoxazole prophylaxis)
Interventions: Until April 1995: initial empirical antibiotic therapy – ceftazidime 150mg/kg/d in three divided doses and teicoplanin 10mg/kg/d twice the first day and then once daily From May 1995: initial empirical antibiotic therapy – imipenem monotherapy

50mg/kg/d divided in four doses. Teicoplanin 10mg/hg/d twice the first day and then once daily was added if fever persisted longer than 72h and neutrophil recovery was not evident

In both treatment regimens initial antibiotic therapy was continued in patients with FUO who were in good clinical condition and ANC was rising or there was indication of bone marrow recovery. Antibiotic therapy was discontinued and patients were discharged from hospital when they met the following criteria: good clinical condition, negative blood culture results and no infectious focus, absence of fever for at least 24 h without antipyretics and antibiotic treatment for a minimum of 72 h. An ANC greater than 500/µl or evidence of bone marrow recovery were not a precondition for the discontinuation of antibiotic therapy. Parents monitored temperature three times daily

In patients with microbiologically or clinically documented infection, antibiotic therapy was continued for at least 7 days. Empirical antifungal therapy was started in neutropenic patients with persistent or recrudescent fever that occurred after 5 days of broad-spectrum antibiotics. Standard regimens were modified if the patient had microbiological or clinical evidence of an infection that was not adequately treated.

Outcomes:

Mortality

Reoccurrence of fever

Rehospitalisation

Results:

24 out of the 41 neutropenic FUO treated with empirical monotherapy with imipenem, fever resolved within the first 72 h and patients were discharged after 24 h of defervescence regardless of ANC

Reoccurrence of fever

0 (0%) showed recurrent fever

Rehospitalisation

0 (0%) had to be rehospitalized

Mortality

0 (0%) died

General comments:

This was a retrospective analysis of patients who received a short course of IV antibiotic therapy, which allowed early hospital discharge and discontinuation of antibiotic therapy regardless of ANC or evidence of bone marrow recovery, as long as patients were afebrile for at least 24 hours and had been treated for a minimum of 72 hours. Initial empirical antibiotic therapy was changed during the period of time the study reviewed. Only 24 patients were discharged early, so results related to this sub-group is based on a very small sample size. The authors conclude that discontinuation of intravenous antibiotics regardless of ANC or evidence of bone marrow recovery seems safe and effective in pediatric cancer patients with FUO when children are afebrile for at least 24 h and are treated for a minimum of 72 h.

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Dommett, R., Geary, J., Freeman, S., Hartley, J., Sharland, M., Davidson, A. et al. (2009). Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. European Journal of Cancer, 45, 2843-2849.
Country: United Kingdom
Design: Retrospective consecutive case series
Population: 762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005
Inclusion criteria: Age < 18 Neutropenia (defined as ANC < $1.0x10^9$/L)

Fever (single temperature of ≥ 38.5°C or sustained temperature of >38°C over 4 hours)
Interventions: All children with FN were hospitalised and received empirical intravenous piperacillin/tazobactam 90 mg/kg · 4/d and once daily intravenous gentamicin (7 mg/kg) or amikacin (20 mg/kg). Patients with persistent fever after 96 h of antibiotics commenced intravenous amphotericin B (0.3 mg/kg) or liposomal amphotericin (1 mg/kg). A checklist of risk factors was administered at the start of each FN episode and 48 hours later. Episodes were designated low risk if no risk factors were identified at either time point. All other episodes were designated standard risk. Fever at 48 hours did not exclude from the low risk strategy. The checklist was as follows: Age<1 year, shock or compensated shock, haemorrhage, dehydration, metabolic instability, altered mental status, pneumonitis, mucositis (unable to tolerate oral fluids or requiring IV analgesia), respiratory distress/compromise, peri-rectal or other soft tissue abscess, rigors, irritability/meningism, organ failure, acute lymphoblastic leukaemia at diagnosis/relapse <28 d, acute lymphoblastic leukaemia not in remission >28 d acute myeloid leukaemia, infant acute lymphoblastic leukaemia, intensive B-NHL protocols, haemopoietic stem cell transplant, sequential high dose chemotherapy with PBSC rescue, intensive care admission during last FN episode, non adherence (social concerns or patient), inability to tolerate oral antibiotics, positive blood culture result at 48 h, ANC < 0.1 · 109/L at 48 h, child not clinically well at 48 h (clinician judgement). Low risk episodes: discharged at 48 h taking oral co-amoxiclav until 48 h after resolution of fever (<37.5ºC). The dose of co-amoxiclav was: 0.8 ml/kg/d of 250/62 suspension in three divided doses (maximum 32 ml/d); or 625 mg tablet · 3/d if age > 12 years; or Augmentin Duo suspension 400/57 0.3 ml/kg · 2/d aged 1–2 years, 5 ml · 3/d aged 2–6 years and 10 ml · 2/d aged 7–12 years. Patients remaining febrile at 96 hours were readmitted to hospital for intravenous antibiotics and amphotericin preparation. Children could also be readmitted at other times if concerns were raised.
Outcomes: Hospital readmission Intensive care admission Mortality
Results:

In 40% of episodes no clinical or microbiological focus could be found. At 48 hours, 212 (27%) of episodes were classified as low risk 143 (19%) were managed on the low risk protocol. <u>Hospital readmission</u> 8 /143 (5.6%) were re-admitted to hospital <u>Intensive care admission</u> There were no intensive care admissions <u>Mortality</u> There were no deaths.
General comments: This was a well conducted, reasonably large scale prospective study/audit of practice at four non-specialist paediatric oncology centres. Using a step-down strategy only 19% of patients were managed using the Low Risk protocol, despite 28% being eligible. The most common reason for failure to manage according to the low risk strategy was 'clinical decision'. The exact reasons for these decisions were not elaborated upon, but the authors suggest that there may have been a wariness to adopt the strategy, which may be remedied as data on the safety of the approach is disseminated. The authors concluded that rapid step down to oral antibiotics was a feasible and safe management strategy for LR FN in the shared care setting in England.

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Tordocilla, C. J., Campbell, B. M., Joannon, S. P., & Rodriguez, R. N. (1994) Neutropenia and fever. Revista Chilena de Pediatria, 65 (5) 260-263
Country: Chile
Design: Retrospective consecutive case series
Population:

84 episodes of FN in 50 patients admitted to a children's hospital in Santiago, Chile, between April 1992 and July 1993.
Inclusion criteria: Age < 18 Neutropenia (ANC ≤ 500 cells per cubic millimetre) Fever (temperature ≥ 39°C on a single occasion, or ≥ 38°C on separate occasions within 4 hours)
Interventions: Patients were discharged early if they became afebrile, appeared well, had negative blood cultures, and had normal chest x-ray, in spite of ANC.
Outcomes: Length of hospital stay Hospital readmission Mortality
Results: 30 episodes of fever and neutropenia (35.7%) were discharged early <u>Length of hospital stay</u> Mean 5.1 days of hospitalization <u>Hospital readmission</u> 0 (0%) patients required readmission to hospital within the next seven days <u>Mortality</u> 0 (0%) patients died
General comments: This paper was written in Spanish. Data was extracted from the English language abstract. The authors concluded that some low risk patients with cancer and febrile neutropenia could be discharged early in spite of neutropenia.

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Aquino, V. M., Buchanan, G. R., Tkaczewski, I., & Mustafa, M. M. (1997) Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. Medical and Pediatric Oncology, 28 (3), 191-195
Country: USA
Design: Retrospective case series
Population: 580 consecutive episodes of chemotherapy induced febrile neutropenia in 253 children and adolescents with cancer between June 1992 and May 1995
Inclusion criteria: Neutropenia (defined as ANC<500 cells/mm^3) Fever (temperature of >38.5°C on a single occasion, or 2 measurements of 38.0°C in a 24 hour period)
Exclusion criteria: Bone marrow transplantation
Interventions: Most patients received empiric ceftazidime as initial antimicrobial therapy. Patients were treated according to a number of oncology protocols (exact details not provided). Episodes in which patients were discharged before their ANC was >500/mm^3 were retrospectively analysed to determine if they had indeed met the criteria for early discharge.
Outcomes: Readmission related to prior febrile episode
Results: Patients were characterised as being at relatively low risk if they had sterile blood

cultures, were afebrile for > 24 hours, appeared well, and were thought to have evidence of marrow recovery. 330 episodes ended in discharge before the patient's ANC was ≥ 500/mm3. At the time of discharge median ANC was 156/mm3. Of the 330 episodes, 21 (6%) were associated with admission for recurrent fever over the subsequent 7 days. Six of the 21 (2% of the original 330) cases readmitted had evidence of bone marrow recovery. None of the 21 had positive blood cultures. All patients meeting low risk criteria fared well during their second hospitalisation.
General comments: This retrospective study reviewed 580 consecutive episodes of chemotherapy induced febrile neutropenia in 253 children and adolescents with cancer. It had become common practice to discontinue therapy with broad spectrum antibiotics and discharge the patient before recovery from neutropenia if the child exhibited certain low-risk criteria. The article summarised centre's experiences. Patients had not received identical treatment. The sample size is however large enough to create an illuminating summary of the experience of implementing an early discharge policy. The authors concluded that the early discharge strategy was safe and resulted in substantial cost savings.

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Mullen, C. A. & Buchanan, G. R. (1990). Early hospital discharge of children with cancer treated for fever and neutropenia: identification and management of the low-risk patient. Journal of Clinical Oncology, 8, 1998-2004.
Country: USA
Design: Retrospective consecutive case series
Population: 114 consecutive episodes of neutropenia in 61 patients treated between February 1988 and February 1999

Inclusion criteria:

Age < 18 Neutropenia

(defined as ANC ≤ 500 cells per cubic milimeter) Fever (defined as

temperature of greater than 38°C for longer than 6 hours)

Interventions:

Initial treatment with broad spectrum cephalosporin antibiotic. There was no standard treatment protocol. Early discharge (with/without oral antibiotics) considered after being afebrile for 1-2 days if child had negative blood cultures, and (usually) if they had some evidence of bone-marrow recovery.

Outcomes:

Reoccurrence of fever

Re-hospitalisation

Results:

77 (68%) patients were still neutropenic at the time of discharge after being afebrile for 1-2 days on parenteral antibiotics, had negative blood cultures, appeared well, and usually had some evidence of bone-marrow recovery.

Reoccurrence of fever / re-hospitalisation

3 (3.9%) of the 77 patients developed recurrent fever and required hospitalisation within 7 days of discharge. All had a brief uneventful second hospitalisation.

General comments:

Patients were treated according to a wide variety of Paediatric Oncology Group and institutional protocols. As a consequence the results do little to inform our understanding of any individual protocol/regimen. There was no written management protocol in place for early discharge, and records were reviewed to evaluate the safety of early discharge on the basis that "all attending physicians shared the philosophy of discharging children to home care as soon as they were afebrile and appeared well". The criteria for early discharge were vague. The authors conclude that the approach of routinely continuing hospitalisation until resolution of neutropenia may be unnecessary in low-risk patients.

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Wacker, P., Halperin, D. S., Wyss, M., & Humbert, J. (1997). Early hospital discharge of children with fever and neutropenia: a prospective study. Journal of Pediatric Hematology/Oncology, 19, 208-211.
Country: Switzerland
Design: Prospective consecutive case series
Population: 88 consecutive cases of FN in 30 post-chemotherapy children (12 leukaemia and 18 solid tumours) entered into the study between May 1992 and May 1995
Inclusion criteria: Neutropenia (defined as ANC<0.5x10^9/L) Fever (temperature of ≥38.5°C on a single occasion, or 2 measurements ≥ 38.0°C in a 24 hour period)
Interventions: IV antibiotics on admission:piperacillin (200mg/kg/day in four doses) and tamicin (5mg/kg/day in three doses) or imipenem (100mg/kg/day in four doses) Children with FN divided into 3 groups: Group A – *No documented infection* – discharged without antibiotics if afebrile for 24 hours with a normal physical exam. Outpatient visit scheduled within 48 hours, and CBC's were done every day until resolution of neutropenia. Parents monitored children 3 times a day and returned to hospital if fever recurred. Group B – *Clinical or viral infection but no bacteremia* – some children who were afebrile for 24 hours with a normal physical exam were discharged with or without oral antibiotics. Outpatient visit scheduled within 48 hours, and CBC's were done every day until resolution of neutropenia. Parents monitored children 3 times a day and returned to hospital if fever recurred. Remainder stayed in hospital receiving IV antibiotics. Group C – *Bacteremia* – Remained in hospital receiving IV antibiotics.

Outcomes:

Length of hospital stay

Recurrence of fever

Duration of fever before and after antibiotics

CBC values

Results:

Group A (no infection)

44 episodes (50%) occurred in 20 patients

Hospitalisation for a median of 4 days

On 25 occasions (57%), IV antibiotics were stopped before recovery of neutropenia.

2 children were re-hospitalised for recurrent FN but recovered without complications

Group B (clinically documented infection)

30 episodes (34%)

Early discharge was allowed in eight cases of minor infections (27%); six received oral antibiotics.

Group C (bacteremia)

14 episodes (16%) in 10 patients

General comments:

This was a prospective study of brief IV antibiotic therapy in selected children with cancer experiencing fever and neutropenia after chemotherapy. Episodes of FN were consecutive. Group assignment was based only on presence/absence of infection/bacteraemia, representing much simpler criteria than other studies. It is unclear what criteria were used to decide whether patients in group B were discharged "with" versus "without" oral antibiotics. Although length of hospital stay was stated as an outcome measure, this was not reported for groups B or C. The authors concluded that children hospitalised for fever without documented infections, and some children with minor infections can be discharged before evidence of bone marrow recovery if afebrile and in good general condition

Hodgson-Viden, H., Grundy, P. E., & Robinson, J. L. (2005). Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. *BMC Pediatrics, 5,* 10.
Country: Canada
Design: Retrospective consecutive case series
Population: 276 episodes of FN in 127 patients
Inclusion criteria: Age ≤ 17 years Fever (defined as temperature ≥ 38.0°C at home or in hospital) Neutropenia (defined as ANC ≤ 500/mm^3)
Exclusion criteria: Leukaemia not in remission
Interventions: Details of exact treatment regimens are not given. 75% of patients were treated with IV piperacillin/tobramycin. Patients were discharged on the day intravenous antimicrobial therapy (IVAMT) was ceased. Early discharge was defined as discontinuation of IVAMT with an ANC ≤ 500/mm^3.
Outcomes: Early discharge Fever recurrence
Results: 112/199 (41%) patients were discharged before resolution of neutropenia 0 (0%) readmitted 0 (0%) died

General comments: This was a retrospective review of medical records. The definition of a fever was less stringent than other studies, requiring only one measurement ≥ 38.0°C at home or in hospital. There was no use of standard criteria for early discharge. Decisions were said to be based solely on the clinician's judgement. On this basis, the study is not very informative. The authors concluded that clinicians were skilled at selecting

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Griffin, T. C. & Buchanan, G. R. (1992). Hematologic predictors of bone marrow recovery in neutropenic patients hospitalized for fever: implications for discontinuation of antibiotics and early discharge from the hospital. Journal of Paediatrics, 121, 28-33.
Country: USA
Design: Retrospective consecutive case series
Population: from April 1999 to November 1999
Inclusion criteria: Neutropenia (defined as ANC <500 cells/mm^3) Fever (defined single temperature of at least 38.5°C or 38.0°C if persistent for 6 hours or longer)
Exclusion criteria:

Hospitalised for other reasons
Interventions: Patients were given ceftazidime at a dosage of 150 mg/kg per day in three divided doses. At the institution in question, patients did not necessarily remain in the hospital until recovery of neutropenia. Could be discharged early if: 1. Initial blood cultures were sterile after 48 hours 2. Appeared well 3. Any identified infection is under control 4. Fever absent for at least 24 hours. Patients were given no oral antibiotic therapy Daily CBCs were not performed after the patient's discharge. Blood cultures were examined for 5 days before being classified as sterile.
Outcomes: Signs of early marrow recovery: total leukocyte count, absolute neutrophil count, absolute phagocyte count, and platelet count.
Results: 70/107 (65%) episodes were discharged with an absolute neutrophil count of fewer than 500 cells/mm^3 69/70 (99%) episodes had signs of early marrow recovery before discharge; Sustained increases were observed in these patients' leukocyte, absolute neutrophil, absolute phagocyte, and platelet counts 2 or more days before their discharge in 41%, 49%, 50%, and 39% of cases, respectively. None of the 69 patients who had evidence of marrow recovery at discharge had recurrence of fever.
General comments: This was a study conducted in the late 1980s. The aim was to evaluate the timing and pattern of changes in the complete blood cell count that preceded marrow recovery. Four measures derived from serial daily measurement of the complete blood cell count were evaluated: total leukocyte count, absolute neutrophil count, absolute phagocyte count, and platelet count. The authors concluded that that children with cancer who were hospitalised for fever

during periods of neutropenia have increases in the peripheral blood cell count that herald imminent bone marrow recovery, often several days before the absolute neutrophil count recovers to 500 cells/mm ^{3}.

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Nijhuis, C. O., Kamps, W. A., Daenen, S. M., Gietema, J. A., van der Graaf, W. T., Groen, H. J. et al. (2005). Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 23 (30)
Country: The Netherlands
Design: Prospective consecutive case series
Population: 196 episodes of fever with chemotherapy induced neutropenia in 76 paediatric and adult patients between April 1999 and October 2002
Inclusion criteria: Fever (defined as single temperature ≥ 38.5°C, or two or more recordings ≥ 38.0°C during a 6-hour period). Neutropenia (defined as ANC less than 0.5 x 10^{9}/L or leukocytes less than 1.0 x 10^{9}/L. Written informed consent
Exclusion criteria: Antibiotics during previous month Stem cell transplant during previous month
Interventions: All patients were admitted to hospital. Patients with signs of a local bacterial infection and/or abnormal vital signs suggesting sepsis were classified as high risk. Abnormal vital signs indicating sepsis were defined as: systolic blood pressure less than 90 mmHg in adults or less than -2 SD for age in

children, or both heart rate higher than 100/min and respiratory rate higher than 20/min in adults or both heart and respiratory rate higher than +2 SD for age in children.

Patients with plasma IL-8 level below the cut-off value were classified as low risk.

Patients with an IL-8 above the cut-off value were classified as medium risk.

For the first 75 episodes the cut off was 60 ng/L. It was then raised to 60 ng/L.

Low-risk patients did not receive intravenous antibiotics, except for those with severe mucositis who received oral amoxicillin-clavulanic acid. They were discharged once afebrile for 12 hours irrespective of their ANC. Following discharge, low-risk patients were contacted daily by the research physician until day 8 of the study protocol.

High-risk and medium-risk adults received intravenous cefuroxim (1,500 mg, three times daily) and tobramycin (3 mg/kg, once daily), and children ceftazidime (50 mg/kg, three times daily to a maximum of 6 g/d). Antibiotic treatment was stopped and patients were discharged when the blood culture was negative, patients were afebrile for at least 24 hours, and the ANC was greater than 0.5 x 10^9/L.

Outcomes:

Number of failures in the low-risk group (defined as either positive blood cultures at the time of admission, persistent fever, or recurrent fever in combination with prolonged neutropenia. Persistent fever was defined as a body temperature higher than 38.5°C for a minimum of 12 hours during the period of 48 to 72 hours after admission. Recurrent fever was defined as a new fever during the first 5 days of the study period, after having been afebrile for a minimum of 24 hours).

Diagnostic value of the risk assessment model (evaluated by assessing the sensitivity, specificity, and predictive values of the risk assessment model for the presence of bacteremia. Other secondary end points were duration of fever, neutropenia, intravenous antibiotic therapy, hospitalization (related to the febrile episode), and costs in the three risk groups).

Results:

Low risk

36 (18%) of patients

No intravenous antibiotics were given to patients in the low-risk group

0 failures

Median duration of hospitalisation: 3 days

Diagnostic value: Bacteremia was detected in none of the patients allocated to the low-risk group by the risk assessment model

Sensitivity of the risk assessment model was 100%

Specificity, positive predictive value, and negative predictive value were 21%, 13%, and 100%, respectively

Medium risk group

84 (43%) of patients

Intravenous antibiotic therapy was given for a median duration of 6 days in the medium-risk group

Median duration of hospitalisation: 7 days

High risk group

76 (39%) of patients

Intravenous antibiotic therapy was given for a median of 6 days in the high-risk group

Median duration of hospitalisation: 7 days

General comments:

This was a prospective case series. A power calculation was presented. Adult and paediatric patients were included and analysed as one group. It was unclear what proportion of the sample were adults/children. Low risk criteria were changed after 75 episodes on the basis of a safety analysis. The authors concluded that the risk assessment model appeared to identify febrile neutropenic patients at low risk for bacterial infection, and that antibiotics could be withheld in well-defined neutropenic patients with fever.

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Dommett, R., Geary, J., Freeman, S., Hartley, J., Sharland, M., Davidson, A. et al. (2009). Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. European Journal of Cancer, 45, 2843-2849.

Country:

United Kingdom

Design:

Retrospective consecutive case series

Population:

762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005

Inclusion criteria:

Age < 18

Neutropenia (defined as ANC < $1.0x10^9$/L)

Fever (single temperature of ≥ 38.5°C or sustained temperature of >38°C over 4 hours)

Interventions:

All children with FN were hospitalised and received empirical intravenous piperacillin/tazobactam 90 mg/kg · 4/d and once daily intravenous gentamicin (7 mg/kg) or amikacin (20 mg/kg). Patients with persistent fever after 96 h of antibiotics commenced intravenous amphotericin B (0.3 mg/kg) or liposomal amphotericin (1 mg/kg).

A checklist of risk factors was administered at the start of each FN episode and 48 hours later. Episodes were designated low risk if no risk factors were identified at either time point. All other episodes were designated standard risk. Fever at 48 hours did not exclude from the low risk strategy.

The checklist was as follows: Age<1 year, shock or compensated shock, haemorrhage, dehydration, metabolic instability, altered mental status, pneumonitis, mucositis (unable to tolerate oral fluids or requiring IV analgesia), respiratory distress/compromise, peri-rectal or other soft tissue abscess, rigors, irritability/meningism, organ failure, acute lymphoblastic leukaemia at diagnosis/relapse <28 d, acute lymphoblastic leukaemia not in remission >28 d acute myeloid leukaemia, infant acute lymphoblastic leukaemia, intensive B-NHL protocols, haemopoietic stem cell transplant, sequential high dose chemotherapy with PBSC rescue, intensive care admission during last FN episode, non adherence (social concerns or patient), inability

to tolerate oral antibiotics, positive blood culture result at 48 h, ANC < 0.1 · 109/L at 48 h, child not clinically well at 48 h (clinician judgement). Low risk episodes: discharged at 48 h taking oral co-amoxiclav until 48 h after resolution of fever (<37.5ºC). The dose of co-amoxiclav was: 0.8 ml/kg/d of 250/62 suspension in three divided doses (maximum 32 ml/d); or 625 mg tablet · 3/d if age > 12 years; or Augmentin Duo suspension 400/57 0.3 ml/kg · 2/d aged 1–2 years, 5 ml · 3/d aged 2–6 years and 10 ml · 2/d aged 7–12 years. Patients remaining febrile at 96 hours were readmitted to hospital for intravenous antibiotics and amphotericin preparation. Children could also be readmitted at other times if concerns were raised.
Outcomes: Hospital readmission Intensive care admission Mortality
Results: In 40% of episodes no clinical or microbiological focus could be found. At 48 hours, 212 (27%) of episodes were classified as low risk 143 (19%) were managed on the low risk protocol. Hospital readmission 8 /143 (5.6%) were re-admitted to hospital Intensive care admission There were no intensive care admissions Mortality There were no deaths.

General comments:

This was a well conducted, reasonably large scale prospective study/audit of practice at four non-specialist paediatric oncology centres. Using a step-down strategy only 19% of patients were managed using the Low Risk protocol, despite 28% being eligible. The most common reason for failure to manage according to the low risk strategy was 'clinical decision'. The exact reasons for these decisions were not elaborated upon, but the authors suggest that there may have been a wariness to adopt the strategy, which may be remedied as data on the safety of the approach is disseminated. The authors concluded that rapid step down to oral antibiotics was a feasible and safe management strategy for LR FN in the shared care setting in England.

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Santos-Machado, T. M., De Aquino, M. Z., Almeida, M. T. A., Bakhit, S., Cristofani, L. M., Maluf, P. T. et al. (99 A.D.). Short-term intravenous antibiotic therapy and early discharge of febrile neutropenic patients. International Journal of Pediatric Hematology/Oncology, *6 (1) 33-38*

Country:

Brazil

Design:

Retrospective consecutive case series

Population:

79 consecutive episodes of febrile neutropenia in 46 paediatric inpatients from June to December 1996

Inclusion criteria:

Age < 18

Neutropenia (defined as APC < 1000/mm^3)

Fever (temperature of > 38°C)

Interventions:

<u>Early discharge:</u> IV antibiotic therapy (no details given) for 24 hours after defervescence if the following conditions met:

1. Negative blood cultures

2. No fever

In most cases patients were discharged with oral antibiotics. Followed up on an outpatient basis.

Customary procedure: IV antibiotic therapy for more than 24 hours. Discharged when APC recovery to 500 mm^3 minimum or after being on antibiotics for a minimum period of 72 hours after defervescence.

Outcomes:

Recurrence of fever

Results:

IV antibiotic therapy

Recurrence of fever

Early discharge: 4 (11.8%)

Customary procedure: 10 (22.2%)

There was no mortality

General comments:

This was a small scale retrospective study. No power calculation was reported. The definitions of fever and neutropenia were less stringent than in other studies. There was little detail provided with regards to treatment regimens. The authors did not report on the rate of hospital re-admission. The authors concluded that short term IV antibiotics could be safely used in FN patients with negative cultures and good clinical conditions.

Innes, H., Lim, S. L., Hall, A., Chan, S. Y., Bhalla, N., & Marshall, E. (2008). Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in

routine clinical practice. Supportive Care in Cancer, 16, 485-491.
Country: United Kingdom
Design: Survey
Population: 128 clinicians representing 50 cancer departments
Inclusion criteria: Consultant oncologists with an interest in antibiotic management of FN
Outcomes: Use of tools to assess the risk of complications in FN patients Use of oral antibiotics as a first-line treatment for patients with FN Criteria used to determine suitability for discharge, and whether there are policies in place for early discharge
Results: 38% of respondents stratify patients according to risk There is substantial variation in the criteria defining 'low-risk' Only one department (the author's) used structured pre-defined criteria Only 22% of clinicians use oral antibiotics as first-line treatment in any patients with FN, but this was significantly greater among clinicians who do compared to those who do not stratify patients by risk, 51 vs 4% (P<0.0001). 84% of respondents confirmed their willingness to participate in a trial of oral antibiotics combined with early discharge in low-risk FN
General comments: This was a survey of UK clinicians, aiming to determine whether recent advances in terms of risk stratification and the evolving role of oral antibiotics with early hospital discharge had been translated into clinical practice. The response rate was low (47.4%), and it is possible that those who routinely stratified patients according to risk were

more likely to respond. Furthermore, respondent's from the author's own department were included, which may bias the results. The authors interpret the findings as suggesting a slow and/or cautious introduction of newer strategies for the management of low-risk FN in the UK.

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Castagnola, E., Paola, D., Giacchino, R., & Viscoli, C. (2000). Clinical and laboratory features predicting a favorable outcome and allowing early discharge in cancer patients with low-risk febrile neutropenia: a literature review. Journal of Hematotherapy & Stem Cell Research, 9, 645-649.
Country: Italy
Design: Systematic review
Population: 27 studies including 5208 episodes of febrile neutropenia
Inclusion criteria: Studies of febrile granulocytopenia in which a patient and disease oriented risk assessment led to identification of a low risk patients' subgroup
Results: Favourable outcome (survival from febrile neutropenia) in more than 90% of episodes 7.4% needed rehospitalisation for any cause Overall mortality of 87 (0.8%) Features of low-risk patients who developed life-threatening infectious disease were related to general clinical condition, cancer control, bone marrow function, presence of clinical signs of infection, and social features.
General comments: This review was published 11 years ago. Literature published in the previous 11 years was searched. Only one database (medline) was searched. A good range of search terms were used (neutropenia, fever, cancer, home-antibiotic therapy, short course of antibiotic therapy, and early discharge). The authors concluded that careful risk assessment could allow safe recognition of low-risk patients with febrile neutropenia who can be discharged early and can be used to follow outpatient treatment programs to improve patients' quality of life as well as the use of economic resources.

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18. Duration of empiric antibiotic therapy. (Topic E7)

Guideline group members for this question

Rosemary Barnes (lead), Wendy King, Anton Kruger, Jeanette Hawkins, and Bob Phillips.

Review question

What is the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis?

Rationale

The risk and pattern of infection in patients with cancer and/or neutropenia depends on the primary diagnosis and the type, duration and intensity of the treatment.

There is no way of telling which febrile neutropenic patients have potentially life-threatening infection. For this reason, the assessment and treatment of febrile neutropenia is always a medical emergency. Signs of infection and CXR changes may be minimal or absent in the presence of neutropenia. The type and risk of infection is influenced by the following:

- Duration and severity of neutropenia
- Associated gut toxicity, due to cytotoxic drugs and/or total body irradiation (TBI)
- Previous radiotherapy, particularly TBI or whole neuraxis irradiation
- Long term immunosuppressive treatment, as in continuing maintenance therapy for ALL
- Presence of indwelling intravenous access device

Fever in the neutropenic patient requires prompt investigation and treatment with intravenous antibiotics, selected at first empirically in the light of known possible pathogens and the clinical circumstances. The most frequent pathogens are: Staph. Epidermidis, various Streps, Gram-negative rods and staph aureus. The most rapidly lethal are E. Coli, Klebsiella and Pseudomonas aeruginosa.

Currently patients admitted with neutropenic sepsis receive empiric antibiotic therapy for a certain period of time. This can range from 48 hours to 14 days with different criteria been applied to determine when the empiric antibiotic therapy should be discontinued. A review of the evidence might help to standardise practice. It is important to know whether stopping empiric antibiotics early will have a negative impact on clinical outcomes and wheat other influences impact of the decision to stop empiric antibiotics early

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with neutropenic sepsis receiving empiric antibiotic therapy	Stop empiric antibiotics early	Continuing empiric antibiotics until afebrile with recovered neutrophil count	Overtreatment Death/critical care Length of stay Duration of fever Quality of life

METHODS

Information sources and eligibility criteria

The search strategy will be available in the full guideline.

We restricted the search to published randomised trials and systematic reviews of such trials. The search was done on the 9th of May 2011 and updated on 7th November 2011.

Selection of studies and data synthesis

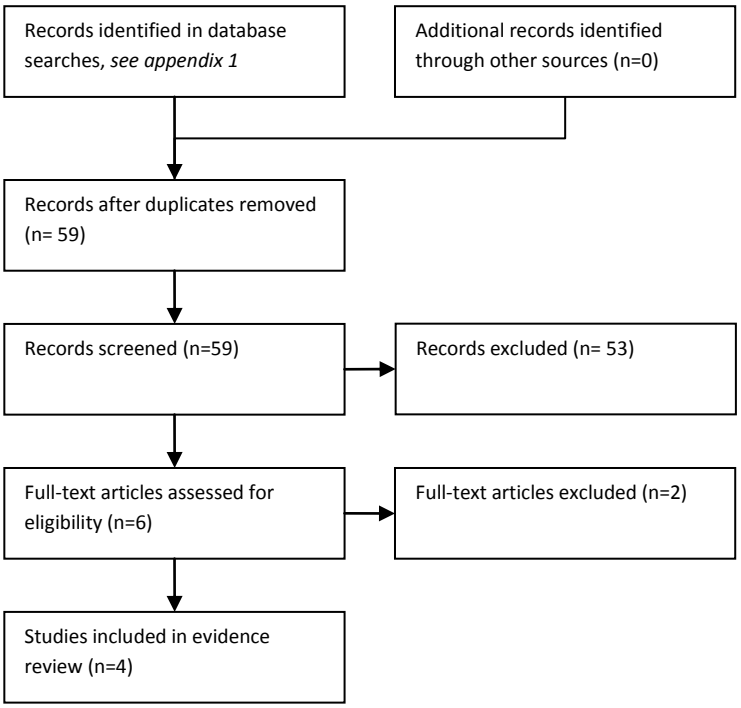
The information specialist (SB) performed an initial screening of the literature search results. One reviewer (MSH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question.

It was anticipated that results from studies which compare early stopping with continuing empiric antibiotics until afebrile with a recovered neutrophil count would be pooled with the potential of doing subgroup analyses to compare the different stopping criteria for empiric antibiotics (e.g., neutrophil count) used by the included randomised trials.

RESULTS

Results of the literature searches

Figure 18.1 Study flow diagram



Description of included studies

59 studies were identified in the literature searches. Of these, 55 were excluded because they were narrative reviews (N = 9), not in PICO (N = 36), not RCT (N = 9), or a protocol (N = 1).

Four RCTs were indentified for inclusion (Bjornsson, 1977; Klaassen, 2000; Pizzo, 1979; Santolaya, 1997). Two of these studies were conducted in children (Klaassen, 2000; Santolaya, 1997), one was

conducted in adults (Bjornsson, 1977) and one study was conducted in a mixed population of children and adults (Pizzo, 1979). These four studies examined a variety of different antibiotic regimens. Detailed information about the populations, interventions, outcomes and overall risk of bias in the included trials is given in the Evidence and GRADE profile (Table 18.1) below.

Evidence statements

Death (short term mortality)

Very low quality evidence from four randomised trials suggested an increased odds of short term mortality in patients whose empirical antibiotics were stopped early compared with those who continued treatment, OR = 5.18 (95% C. I. 0.95 to 28.16). In two studies (Klaassen, 2000; Santolaya, 1997) there were no deaths while in the other two studies seven deaths occurred within 30 days (Bjornsson, 1977 Pizzo, 1979). The two studies in which deaths occurred were both from the 1970s and used first generation empiric antibiotic treatment.

Overtreatment,critical care and quality of life

These outcomes were not reported by any of the included trials.

Length of stay

One paediatric study (Santolaya, 1997) reported this outcome. There was low quality evidence that stopping antibiotics before resolution of neutropenia and fever had uncertain benefit in terms of length of stay. The mean length of stay was 0.7 days less in those who stopped empricial antibiotics early (95% C.I. 5.54 less to 4.41 more).

Duration of fever

One paediatric study (Santolaya, 1997) reported this outcome. There was low quality evidence that stopping antibiotics before resolution of neutropenia and fever had uncertain benefit in terms of duration of fever. The mean duration of fever was 0.8 days less in those who stopped empirical antibiotics early (95% C.I. 2.08 days less to 0.48 more).

1 ***Table 18.1: GRADE evidence profile for duration of empiric antibiotic therapy***

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Shorter duration empiric antibiotics**	**Longer duration empiric antibiotics**	**Relative (95% CI)**	**Absolute**	
Death (within 30 days)											
4	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/95 (5.3%)	2/103 (1.9%)	OR 5.18 (0.95 to 28.16)	74 more per 1000 (from 1 fewer to 339 more)	VERY LOW
Length of stay (Better indicated by lower values)											
1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	36	39	-	mean 0.7 days lower (5.54 lower to 4.41 higher)	LOW
Duration of fever (Better indicated by lower values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	36	39	-	mean 0.8 days lower (2.08 lower to 0.48 higher)	LOW

2 [1] 3 of the 4 studies were not placebo-controlled and reported no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis.
3 [2] 2 of the 4 studies were from the 1970s and used first generation antibiotic agents and all the deaths occurred in these two older trials.
4 [3] Very low event rate.
5 [4] Unclear allocation concealment, insufficient details about randomisation and not placebo controlled
6 [5] Uncertainty in the estimate of effect, the confidence interval spans both appreciable benefit and harm.

1 EVIDENCE TABLES

Citation: Bjornsson S, Preisler H, Henderson ES. A study of antibiotic therapy in fever of unknown origin in neutropenic cancer patients. Medical & Pediatric Oncology 1977;3(4):379-85.

Design: RCT

Country: USA

Aim: To determine whether neutropenic cancer patients with fever of unknown origin benefits from treatment with broad-spectrum antibiotics for > 3 days.

Inclusion criteria

Patients with:

- temperature 38°C (not judged to be secondary to blood-product transfusions)
- peripheral blood granulocyte count < 500/μl
- no response to antibiotic treatment consisting of carbenicillin (500 mg/kg/day IV), cephalothin (150 mg/kg/day IV) and gentamicin (5 mg/kg/day IV; dosage adjusted to maintain serum levels of 2-8 μg/ml) within days 1-3 of treatment and no focus of infection or likely aetiological organism isolated within these first 3 days of antibiotic treatment
- no exposure to antibiotics during ≥ 2 days immediately preceding onset of fever

Exclusion criteria None reported

Population

Control: N = 6; median age = 45.5 (range = 25-55) years. N = 5 had acute myelocytic leukemia (AML) and N = 1 had lymphoma.

Chloramphenicol/clindamycin: N = 11; median age = 49 (range = 21-66) years. N = 9 had AML and N = 2 had lymphoma. N = 6 received antibiotics + chloramphenicol and N = 5 received antibiotics + clindamycin.

All patients were receiving or had recently finished a course of anti-cancer chemotherapy.

Interventions

After no response and continuous fever of unknown origin after 3 days of treatment with carbenicillin (500 mg/kg/day IV), cephalothin (150 mg/kg/day IV) and gentamicin (5 mg/kg/day IV; dosage adjusted to maintain serum levels of 2-8 μg/ml) the patients were randomised to one of the following 3 groups:

- Control: Stop antibiotic treatment
- Chloramphenicol: Continue with the antibiotic treatment outlined above + chloramphenicol (50 mg/kg/day IV) for an additional 7 days.
- Clindamycin: Continue with the antibiotic treatment outlined above + clindamycin (30 mg/kg/day IV) for an additional 7 days.

Granulocyte transfusions were not given during the first 3 days on study [that is, the 3 days preceding randomisation], but were subsequently given as clinically indicated.

Outcomes See below

Results

Mortality:

- 2 weeks after randomisation 11/11 chloramphenicol/clindamycin patients and 3/6 control patients were still alive (p = .029). Further details of the 3 deaths: Patient 1: Off 3 days, blood grew klebsiella, no remission of AML, died in 1 week, autopsy showed systemic candida and klebsiella in lung. Patient 2: Remained febrile, autopsy showed systemic candida and klebsiella in heartblood. Patient 3: Remained febrile, off 2 days, blood grew klebsiella, urine e. coli., restarted, one blood culture grew candida, no remission [from AML?], died 3 days later (no autopsy).
- 4 weeks after randomisation 9/11 chloramphenicol/clindamycin patients and 3/6 control patients were still alive (p = .21). Further details of the 2 additional deaths: Patient 4: Became afebrile after 5 days, developed

pseudomonas pneumonia, no remission of AML, died in 18 days (no autopsy). Patient 5: Remained febrile, no remission of AML, died in 27 days.
WBC transfusions:
- Control: 3 patients had no WNC transfusions and 3 patients had 3 WBC transfusions.
Chloramphenicol/clindamycin: 4 patients had no WNC transfusions, 4 patients had 1 WBC transfusion and 3 patients had 4 WBC transfusions.

General comments
This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis and has a very small sample size. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.

References of Included Studies (For systematic reviews):

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Citation: Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. J Pediatr Hematol Oncol 2000 Sep;22(5):405-11.

Design: Randomised, double-blind placebo-controlled trial

Country: Canada

Aim: To determine whether antibiotics can be safely discontinued without an increase in fever recurrence or bacterial infection before neutrophil recovery in paediatric oncology patients at low-risk for bacterial infection who had resolved fever but persistent neutropenia at the time of discharge.

Inclusion criteria

Paediatric oncology patients:
- aged 6 months to 18 years
- admitted to hospital for the management of fever (oral or equivalent temperature >38.5°C once or >38°C on two or more occasions during a 12-hour period) and neutropenia (ANC $<0.5 \times 10^9$/L).
- treated initially with broad-spectrum intravenous antibiotics (piperacillin 50 mg/kg per dose every 6 hours and gentamicin 2.5 mg/kg per dose every 8 hours, or a similar combination. Other antibiotics may have been administered in addition to these if there was a suspicion of a localized infection).
- who continued to have neutropenia between 48 and 120 hours after admission and who were afebrile > 24 hours, had negative blood culture results, and an absence of clinical sepsis (decreased level of consciousness, decreased systolic blood pressure (<5% for age), hypoxemia (oxygen saturation <95%), tachycardia (>90th percentile for age), tachypnea (>90th percentile for age), metabolic acidosis (pH <7.28), or decreased urine output (<0.5 mL/kg per hr for >1 hr) (18).

Enrolled patients were eligible to re-enter the trial if they fulfilled the inclusion and exclusion criteria during subsequent episodes of fever and neutropenia.

Exclusion criteria

- Allergy to penicillin or cephalosporin antibiotics
- bacteremia
- localized infection necessitating antibiotic therapy
- fever > 96 hours after starting intravenous antibiotics
- inability to tolerate oral medications
- underlying cancer not in bone marrow remission
- comorbid conditions necessitating continued inpatient stay.

Population *73 episodes in 54 patients were enrolled in the study.*

Intervention: N = 37 episodes, 43% males; median age = 4.9 years; median discharge ANC ($\times 10^9$/L) = 0.08; median discharge monocyte count ($\times 10^9$/L) = 0.2; median discharge platelet count ($\times 10^9$/L) = 108; bone marrow recovery at discharge = 78%; median peak temperature (°C) = 38.9; median documented neutrophil recovery (days after admission) = 9; concomitant G-CSF therapy = 8%; tumor type acute lymphocytic leukemia

(ALL) = 51%, acute myeloid leukemia (AML) = 14%, brain tumour = 11%, non-Hodgkin lymphoma (NHL) = 5%, other = 19%.
Control: N = 36 episodes, 39% males; median age = 4.3 years; median discharge ANC (×10^9/L) = 0.1; median discharge monocyte count (×10^9/L) = 0.16; median discharge platelet count (×10^9/L) = 110; bone marrow recovery at discharge = 75%; median peak temperature (°C) = 39; median documented neutrophil recovery (days after admission) = 9; concomitant G-CSF therapy = 17%; tumor type acute lymphocytic leukemia (ALL) = 58%, acute myeloid leukemia (AML) = 8%, brain tumour = 8%, non-Hodgkin lymphoma (NHL) = 8%, other = 18%.
There were no statistically significant differences between the two treatment arms on the above variables.

Interventions

Intervention: Cloxacillin syrup or capsules 75 to 100 mg/kg per day four times daily, and cefixime syrup 8 mg/kg per day one dose daily. Oral therapy continued until the ANC exceeded 0.5 × 10^9/L, or until a total of 14 days of intravenous plus oral treatment had been administered.
Control: Appropriate placebos.

Outcomes

Primary: Recurrence of fever or newly documented bacterial infection before neutrophil recovery.
Secondary: Medication side effects, and compliance.

Results

- Recurrent fever: Two episodes (6%; 95% CI 0-13%) in the control group and five episodes (14%; 95% CI 2-25%) in the intervention group were readmitted to hospital with recurrent fever while still neutropenic (p = .43).
One of the readmissions in the control group had positive central and peripheral blood cultures for viridans group streptococci, which responded to a full course of intravenous antibiotics. Cultures in the remaining six readmitted patients were negative. All of the readmissions were uneventful and no deaths occurred during the study period.
- Compliance: Compliance did not differ significantly between the intervention (mean compliance: cefixime = 91%, cloxacillin = 84%) and control groups (mean compliance: cefixime = 90%, cloxacillin = 94%) *Based on patient reported data from 74% of the episodes and a pharmacy-conducted dose count from 87% of the episodes.*
- Side effects: 31% of intervention episodes and 11% of placebo episodes (p = .095). *Based on patient reported data from 74% of the episodes.*
Overall, diarrhoea was the most common side effect (13%), followed by nausea and vomiting (11%), and rash (6%). *Based on patient reported data from 74% of the episodes.*

General comments

In this RCT patients were centrally randomised with stratification for discharge ANC, and if the patients were re-enrolled during a subsequent episode of fever and neutropenia, they were re-stratifified and re-randomised. Blinding of both patient and physician was employed and all variables were recorded blinded to outcome. However, it is unclear which method of randomisation was employed and whether there was adequate allocation concealment, - although central randomisation is likely to have gone some way in ensuring the latter. The study appears to be adequately powered and employed intention to treat analysis. Therefore this study is unlikely to be subject to a high risk of bias and can be regarded as constituting moderate to high quality evidence although for the present purposes there is limited overlap between the reported outcomes and the pre-specified outcomes of interest to the GDG.

References of Included Studies (For systematic reviews):

1

Citation: Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Levine AS, Deisseroth AB, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. The American journal of medicine 1979;67(2):194-200.

Design: RCT

Country: USA

Aim: To evaluate the effectiveness of continuing compared to discontinuing antibiotic treatment after day 7 of antibiotic treatment in patients initially presenting with fever and granulocytopenia who remain granulocytopenic but not febrile on treatment day 7.

Inclusion criteria

Patients of the pediatric oncology branch with:
- fever (either 3 oral temperature elevations above 38°C during 24 hour period or a single temperature elevation ≥ 38.5°C) on day 1
- granulocytopenia (absolute granulocyte count < 500 polymorphonuclear leukocytes and bandforms/mm^3) on day 1
- no documented infection after 7 days of treatment with an empiric antibiotic regimen consisting of Keflin (170 mg/kg/day, IV 4-hourly), gentamicin (6 mg/kg/day, IV 6-hourly) and carbenicillin (500 mg/kg/day, IV 4-hourly) (KGC)
- granulocytopenia (granulocyte count remaining ≤ 500/mm^3) but no fever on day 7 (according to two separate measurements of fever and granulocyte count during the preceding 24 hours)

Exclusion criteria

Patients with
- documented infection
- resolution of both fever and granulocytopenia on day 7
- resolution of granulocytopenia but not of fever on day 7
- fever and granulocytopenia on day 7

Population

Intervention: N = 16; median age = 15 (range 1-30) years; 9 males; underlying malignancy: leukemia (N = 9), lymphoma (N = 2), solid tumour (N = 5); median duration of granulocytopenia = 12 (range 9-25) days.
Control: N = 17; median age = 14 (range 2-33) years; 13 males; underlying malignancy: leukemia (N = 12), lymphoma (N = 1), solid tumour (N = 4); median duration of granulocytopenia = 14 (range 7-25) days.

Interventions

Aminoglycoside levels were determined within 48 hours of initiating antibiotic therapy and adjusted, if required, to maintain a 15 minute post-infusion peak 4-8 µg/ml. None of the patients in this study received oral nonabsorbable antibiotics or was treated in Laminar airflow rooms.
– On day 7 randomisation to either discontinue antibiotics (control group) or to continue receiving antibiotics until granulocytopenia resolved (i.e., polymorphonuclear leukocytes >5OO/mm^3; intervention group).

Outcomes See below

Results

- Intention to treat analysis showed that 7/17 control patients and 1/16 intervention patients became febrile after implementation of randomised interventions (from day 8 onwards; p = .024). [2 control patients were taken off antibiotic treatment on day 8 due to severe hyponatremia and rising liver transaminase – it was 1 of these 2 control patients who subsequently became febrile].
- 2 control and no intervention patients died.
- Non-infectious complications: Electrolyte abnormalities (control: N = 9; intervention = 10), abnormal liver function tests (control: N = 1; intervention = 4), renal abnormalities (serum creatinine 1.5-3 mg/dl; control: N = 1; intervention = 1), yeast colonisation (control: N = 3; intervention = 5), phlebitis (control: N = 1; intervention = 1), rash (control: N = 1; intervention = 1).

General comments

This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.

References of Included Studies (For systematic reviews):

1

Citation: Santolaya ME, Villarroel M, Avendano LF, Cofre J. Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis 1997 Jul;25(1):92-7.

Design: RCT

Country: Chile

Aim: To examine the safety of stopping antibiotic therapy on day 3 of treatment in children with cancer, non-bacterial fever and neutropenia.

Inclusion criteria

Children hospitalised because of a cancer, fever, and severe neutropenia (ANC ≤ 500/mm^3) with no identifiable focus of bacterial infection, hemodynamic stability, negative admission cultures, and serum CRP levels of ≤ 40 mg/L on days 1 and 2.

Exclusion criteria

Children who had clinical and/or laboratory evidence of bacterial infection and/or a serum CRP level of > 40 mg/L on day 1 or 2 as they were considered potentially bacteremic.
It is not mentioned as an exclusion criterion, but 14 patients were excluded because antimicrobial treatment was administered during the 7 days before admission.

Population *75 episodes in 68 patients were enrolled in the study.*

Intervention: N = 39; mean age = 5.6 (SD = 3.8) years; 21 males; oncological disease: leukemia (N = 18), lymphoma (N = 1), solid tumour (N =20); chemotherapy status: Induction (N = 28), maintenance (N = 11); indwelling catheter (N = 17); mean ANC (/mm^3) on day 1 = 246 (SD = 167).
Control: N = 36; mean age = 6.8 (SD = 4.3) years; 20 males; oncological disease: leukemia (N = 15), lymphoma (N = 2), solid tumour (N =19); chemotherapy status: Induction (N = 27), maintenance (N = 9); indwelling catheter (N = 13); mean ANC (/mm^3) on day 1 = 297 (SD = 181).
There were no statistically significant differences between the two treatment arms on the above variables.

Interventions

Therapy with an antistaphylococcal penicillin and a third-generation cephalosporin or an aminoglycoside was started at admission for all children. On day 3 the children were randomised to one of the following two groups:
Intervention: Antibiotic therapy continued until resolution of the episode of neutropenia and fever.
Control: All antibiotic therapy stopped.
Trimethoprim-sulfamethoxazole prophylaxis was not administered to any of the patients and no child received treatment with colony-stimulating factors.

Outcomes

Detection of clinical focus suggestive of bacterial infection, positive bacterial culture after day 3, reappearance of fever, deterioration of haemodynamic stability not attributable to blood loss, progressive increase in serum CRP levels to > 40mg/L during ≥ 2 consecutive measurements. All these outcomes were considered unfavourable and indicators of restarting antibiotics in the control group and adjusting antibiotic therapy in the intervention group. Outcomes were considered favourable when none of these (unfavourable) variables occurred.

Results

- Mean duration of fever = 2.7 (SD = 1.82) days in the control group and 3.5 (SD = 3.62) days in the intervention group (ns).
- Mean duration of severe neutropenia = 8.3 (SD = 5.42) days in the control group and 9 (SD = 5.83) days in the intervention group (ns).
- Mean hospital stay = 8 (SD = 5.22) days in the control group and 9 (SD = 5.87) days in the intervention group (ns).
- Favourable outcomes occurred in 34/36 control episodes and in 36/39 intervention episodes.
- Antibiotic therapy was stopped in 29 febrile episodes that resolved and in 7 febrile episodes despite continuous fever in the control group.
- Mean duration of antibiotic treatment = 7 (SD = 3.98) days in the intervention group.
- No deaths occurred.
- Discharge diagnoses: adenovirus infection (control: N = 4; Intervention: N = 3), respiratory syncytial virus infection (control: N = 3; Intervention: N = 6), parainfluenza virus infection (control: N = 3; Intervention: N = 3), influenza virus infection (control: N = 0; Intervention: N = 1), clinical upper respiratory tract infection (control:

N = 7; Intervention: N = 5), varicella (control: N = 6; Intervention: N = 8), hepatitis A (control: N = 0; Intervention: N = 1), enterovirus infection (control: N = 1; Intervention: N = 1), mixed infection (control: N = 2; Intervention: N = 1), coagulase-negative staphylococcus infection (control: N = 0; Intervention: N = 2), fever of unknown origin (control: N = 10; Intervention: N = 8).
General comments This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.
References of Included Studies (For systematic reviews): NA

1

2

1 Appendix 1 – literature search strategies

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: How do neutrophil count and temperature relate to the risk of complications of sepsis, in cancer patients with suspected neutropenic sepsis?

Question no: D 1

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-30/11/2010	527	72	30/11/2010
Update Search	1/12/10-7/11/11	133	2	07/11/2011
Premedline	All-06/12/2010	95	14	06/12/2010
Update Search	6/12/10-7/11/11	89	2	07/11/2011
Embase	All-01/12/2010	563	42	01/12/2010
Update Search	1/12/10-7/11/11	201	2	07/11/2011
Cochrane Library	All-06/12/2010	932	12	06/12/2010
Update Search	6/12/10-7/11/11	27	0	07/11/2011
Cinahl	All-06/12/2010	830	10	06/12/2010
Update Search	6/12/10-7/11/11	99	0	07/11/2011
Psychinfo	All-06/12/2010	23	0	06/12/2010
Update Search	6/12/10-7/11/11	1	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-09/12/2010	1651	48	09/12/2010
	9/12/10-	139	1	07/11/2011

Update Search	7/11/11			
Biomed Central	All-09/12/2010	147	2	09/12/2010
Update Search	9/12/10-7/11/11	11	0	07/11/2011
BMI	All-06/12/2010	4	0	06/12/2010
Update Search	9/12/10-7/11/11	5	0	07/11/2011

Total References retrieved (after de-duplication): 221 update search: 6

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutrophils/

2. (neutrophil adj count*).tw.

3. white blood cell count.mp. or exp Leukocyte Count/

4. exp Blood Cell Count/

5. 1 or 2 or 3 or 4

6. exp Fever/di, pa, ph, pp, th [Diagnosis, Pathology, Physiology, Physiopathology, Therapy]

7. exp Body Temperature/

8. (fever* or febrile* or temperature*).tw.

9. 6 or 7 or 8

10. 5 or 9

11. exp Neutropenia/bl, ci, co, di, dt, pa, pp, pc [Blood, Chemically Induced, Complications, Diagnosis, Drug Therapy, Pathology, Physiopathology, Prevention & Control]

12. (neutropen* or neutropaen*).tw.

13. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

14. (neutrop?en* adj (sepsis* or fever*)).tw.

15. (febrile* adj neutrop?en*).tw.

16. exp Agranulocytosis/bl, ci, co, di, dt, pa, ph, pp, pc [Blood, Chemically Induced, Complications, Diagnosis, Drug Therapy, Pathology, Physiology, Physiopathology, Prevention & Control]

17. Antineoplastic Combined Chemotherapy Protocols/ae [Adverse Effects]

18. 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 10 and 18

20. exp Prognosis/

21. exp Risk Assessment/

22. exp Risk Factors/

23. exp "Sensitivity and Specificity"/

24. exp Early Diagnosis/

25. exp Diagnosis/

26. exp Multivariate Analysis/

27. risk index*.tw.

28. (scoring adj system*).tw.

29. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. 19 and 29

31. limit 30 to yr="2000 -Current"

32. exp Neoplasms/

33. cancer*.tw.

34. 32 or 33

35. 30 and 34

36. limit 35 to yr="2000 -Current"

37. neutropenia.ti.

38. neutrop?en*.ti.

39. 37 or 38

40. 10 and 30 and 39

41. limit 40 to yr="2000 -Current"

No search filters were applied.

Health Economics Literature search details

A Health Economics Search was not required.

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: What information and support for patients receiving anti-cancer treatment and their carers reduces the adverse effects of neutropenic sepsis?

Question no: B

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	244	17	12/01/11
Premedline	All	9	1	12/01/11
Embase	All	625	18	12/01/11
Cochrane Library	All	80	2	17/01/11
Cinahl	All	32	4	18/01/11

Psychinfo	All	4	0	12/01/11
Web of Science (SCI & SSCI) and ISI Proceedings	All	827	14	17/01/11
BNI	All	4	2	18/01/11

Total References retrieved (after de-duplication): 29

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2010-2011	30	2	02/11/2011
Premedline	2010-2011	5	0	02/11/2011
Embase	2010-2011	130	3	02/11/2011
Cochrane Library	2010-2011	45	0	02/11/2011
Cinahl	2010-2011	8	0	02/11/2011
Psychinfo	2010-2011	2	1	02/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2010-2011	406	5	02/11/2011
BNI	2010-2011	0	0	02/11/2011

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen$ or neutropaen$).tw.

3. exp Agranulocytosis/

4. (granulocytopen$ or granulocytopaen$ or granulopen$or granulopaen$).tw.

5. (neutrop?en$ adj (sepsis$ or fever$)).tw.

6. (febrile$ adj neutrop?en$).tw.

7. or/1-6

8. Office Visits/

9. Remote Consultation/

10. Self Care/

11. ((patient$ or consumer$) adj2 (decision$ or choice$ or preference$ or support$ or educat$)).tw.

12. ((personal or interpersonal or individual$) adj2 (decision$ or choice$ or preference$ or support$ or educat$)).tw.

13. (information adj2 (aid$ or support$ or need$ or provision)).tw.

14. or/8-13

15. exp Teaching Materials/

16. Pamphlets/

17. (pamphlet$ or leaflet$).tw.

18. ((Alert$ or report$) adj2 card$).tw.

19. ((electronic or email) adj report$).tw.

20. exp Audiovisual Aids/

21. (video$ or dvd$).tw.

22. exp Internet/

23. exp social support/

24. exp Self-Help Groups/

25. exp Patient Education/mt [Methods]

26. exp telephone/

27. exp hotlines/

28. or/15-27

29. ((hot or help$ or tele$ or phone) adj line$).tw.

30. chemotherap$.tw.

31. 29 and 30 32. 14 or 28 or 31 33. 7 and 32
Health Economics Literature search details – NOT REQUIRED
NOTES RCTs were specified in the protocol for this search. RCTs filter was removed as no RCTs were found.

1

NATIONAL COLLABORATING CENTRE FOR CANCER
Clinical Guideline Neutopenic Sepsis Literature search summary
Question title: ***Information and support for patients and carers - SEE TOPIC B (search combined)***
Question no: I

3

4

5

NATIONAL COLLABORATING CENTRE FOR CANCER
Clinical Guideline Neutopenic Sepsis Literature search summary
Question title: Training of all healthcare professionals on the identification and management of neutropenic sepsis
Question no: J

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	244	12	02/02/11
Premedline	All	7	1	02/02/11
Embase	All	370	19	03/02/11
Cochrane Library	All	104	0	02/03/11
Cinahl	All	513	16	03/02/11
Psychinfo	All	3	0	03/02/11
Web of Science (SCI & SSCI) and ISI Proceedings	All	278	9	03/02/11
BNI	All	7	2	03/02/11

Total References retrieved (after de-duplication): 38

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2010-2011	51	2	02/11/2011
Premedline	2010-2011	9	1	02/11/2011
Embase	2010-2011	222	5	02/11/2011
Cochrane Library	2010-2011	49	0	02/11/2011
Cinahl	2010-2011	55	2	02/11/2011
Psychinfo	2010-2011	2	0	02/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2010-2011	52	1	02/11/2011
BNI	2010-2011	11	0	02/11/2011

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Education/

2. Computer-Assisted Instruction/

3. Role Playing/

4. exp Teaching/

5. or/1-4

6. (educat$ or train$ or learn$ or teach$).tw.

7. e-learning.tw.

8. ("role play" or “role playing”).tw.

9. (dvd or internet or intranet).tw.

10. simulat$.tw.

11. or/6-10

12. guideline$.tw.

13. 6 and 12

14. 5 or 11 or 13

15. exp Neutropenia/

16. (neutropen$ or neutropaen$).tw.

17. exp Agranulocytosis/

18. (granulocytopen$ or granulocytopaen$ or granulopen$or granulopaen$).tw.

19. (neutrop?en$ adj (sepsis$ or fever$)).tw.

20. (febrile$ adj neutrop?en$).tw.

21. or/15-20

22. 14 and 21

Health Economics Literature search details – NOT REQUIRED

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Which signs or symptoms experienced by patients in the community predict the development of neutropenic sepsis?

Question no: A

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-20/04/2011	1508	48	20/04/2011
Update search	20/4/11-7/11/11	123	7	07/11/2011
Premedline	All-20/04/2011	97	2	20/04/2011
Update search	20/4/11-7/11/11	13	0	07/11/2011
Embase	All-20/04/2011	374	14	20/04/2011
Update search	20/4/11-7/11/11	25	1	07/11/2011
Cochrane Library	All-02/05/2011	1794	4	02/05/2011
Update search	2/5/11 – 7/11/11	114	0	07/11/2011
BNI	All-20/04/2011	16	3	20/04/2011
Update search	20/4/11-7/11/11	0	0	7/11/11
Cinahl	All-03/05/2011	349	27	03/05/2011
Update search	3/5/11 – 7/11/11	33	1	07/11/2011
Psychinfo	All-20/04/2011	13	2	20/04/2011
Update search	20/4/11-7/11/11	0	0	07/11/2011

Web of Science (SCI & SSCI) and ISI Proceedings	All-20/04/2011	175	1	20/04/2011
Update search	20/4/11-7/11/11	110	1	07/11/2011
Biomed Central	All-03/05/2011	612	0	03/05/2011
Update search	3/5/11 – 7/11/11	50	0	07/11/2011

Total References retrieved (after de-duplication): 105 update search: 7

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. exp "Signs and Symptoms"/

3. sign*.tw.

4. symptom*.tw.

5. perceive*.tw.

6. exp Fever/

7. (fever* or pyrexia* or temperature*).tw.

8. flu*.tw.

9. rigor*.tw.

10. exp Mucositis/

11. mucosit*.tw.

12. exp Diarrhea/

13. diarrh?ea*.tw.

14. exp Vomiting/

15. vomit*.tw.

16. primary infect*.tw.

17. or/2-16

18. exp Drug Therapy/ae, co [Adverse Effects, Complications]

19. chemotherap*.tw.

20. exp Antineoplastic Protocols/

21. (cancer adj2 treatment*).tw.

22. 18 or 19 or 20 or 21

23. exp Diagnostic Errors/

24. exp Diagnosis/

25. (likelihood* or likely*).tw.

26. diagnos*.tw.

27. recogni*.tw.

28. 23 or 24 or 25 or 26 or 27

29. 1 and 22

30. 1 and 17

31. 30 or 29

No search filters were applied.

Health Economics Literature search details

No Health Economics search was required.

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Should additional peripheral blood culture in patients with a central line, CRP (c-reactive protein), urinalysis, chest x-ray, lactate, blood gases be used in the emergency empirical assessment of a person with suspected neutropenic sepsis?

Question no: C

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-13/06/2011	184	39	13/06/2011
Update Search	13/6/11-7/11/11	6	1	07/11/2011
Premedline	All-13/06/2011	71	5	13/06/2011
Update Search	13/6/11-7/11/11	41	2	07/11/2011
Embase	All-13/06/2011	842	36	13/06/2011
Update Search	13/6/11-7/11/11	29	1	07/11/2011
Cochrane Library	All-20/06/2011	234	17	20/06/2011
Update Search	20/6/11-7/11/11	1	0	07/11/2011
Cinahl	All- 20/06/2011	270	44	20/06/2011
Update Search	20/6/11-7/11/11	25	1	07/11/2011
BNI	All-13/06/2011	0	0	13/06/2011
Update Search	13/6/11-7/11/11	0	0	07/11/2011
Psychinfo	All-13/06/2011	0	0	13/06/2011
Update Search	13/6/11-7/11/11	3	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-14/06/2011	98	5	14/06/2011
Update Search	14/6/11-7/11/11	70	9	07/11/2011

Biomed Central	All-27/06/2011	194	9	27/06/2011
Update Search	27/6/11-7/11/11	13	0	07/11/2011

Total References retrieved (after de-duplication): 137 update search: 13

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp Bacteremia/di [Diagnosis]

9. bacterem*.tw.

10. exp Infection/di [Diagnosis]

11. exp Catheterization, Central Venous/ae [Adverse Effects]

12. exp Catheter-Related Infections/di [Diagnosis]

13. exp Sepsis/di [Diagnosis]

14. 8 or 9 or 10 or 11 or 12 or 13

15. exp Neoplasms/dt [Drug Therapy]

16. exp Antineoplastic Agents/ae [Adverse Effects]

17. 15 or 16

18. 7 or 14

19. 17 and 18

20. peripheral blood culture*.tw.

21. exp C-Reactive Protein/

22. exp Urinalysis/

23. chest x-ray*.tw.

24. lactate*.tw.

25. blood gas*.tw.

26. 20 or 21 or 22 or 23 or 24 or 25

27. exp Intensive Care Units/

28. exp Patient Admission/

29. exp Emergency Service, Hospital/

30. exp Triage/

31. 27 or 28 or 29 or 30

32. 7 and 31

33. exp Diagnosis/

34. diagnostic*.tw.

35. standard test*.tw.

36. 33 or 34 or 35

37. 19 and 26

38. 32 and 36

39. 37 or 38

No search filters were applied.

Health Economics Literature search details

A Health Economics search was not required.

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Which tests can predict outcome and response to treatment in patients with neutropenic sepsis?

Question no: D 2

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-2010	522	91	23/12/2010
Update search	01/11-7/11/11	10	0	07/11/2011
Premedline	2000-2010	4	1	05/01/2011
Update search	01/11-7/11/11	17	3	07/11/2011
Embase	2000-2010	1283	149	05/01/2011
Update search	01/11-7/11/11	141	4	07/11/2011
Cochrane Library	2000-2010	209	0	05/01/2011
Update search	01/11-7/11/11	1	0	07/11/2011
Cinahl	2000-2010	757	5	05/01/2011
Update search	01/11-7/11/11	32	3	07/11/2011
Psychinfo	2000-2010	3	0	05/01/2011
Update search	01/11-7/11/11	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2000-2010	402	11	05/01/2011
Update search	01/11-7/11/11	33	3	07/11/2011
Biomed Central	2000-2010	528	1	05/01/2011

Update search	01/11-7/11/11	119	2	07/11/2011
BMI	2000-2010	0	0	05/01/2011
Update search	01/11-7/11/11	0	0	07/11/2011

Total References retrieved (after de-duplication): 223 update search: 9

Medline search strategy *(This search strategy is adapted to each database.)*

Neutropenia AND Tests AND Prosprective Studies

1. exp Neutropenia/

2. (neutrop?en* adj sepsis*).tw.

3. (neutrop?en* adj fever*).tw.

4. exp Blood Cell Count/

5. exp Leukocyte Count/

6. Monocyte count.mp.

7. Lactate*.tw.

8. exp Liver Function Tests/

9. exp Kidney Function Tests/

10. exp Platelet Count/

11. exp C-Reactive Protein/du [Diagnostic Use]

12. exp Calcitonin/du

13. exp Interleukin-6/du [Diagnostic Use]

14. exp Interleukin-8/du [Diagnostic Use]

15. (C-Reactive Protein* or CRP*).tw.

16. exp Bacterial Infections/di [Diagnosis]

17. exp Biological Markers/du [Diagnostic Use]

18. exp "Predictive Value of Tests"/

19. exp Prospective Studies/

20. exp Prognosis/

21. prognos*.tw.

22. predict*.tw.

23. exp Risk Factors/

24. (risk* adj1 score*).tw.

25. (risk* adj1 stratification*).tw.

26. or/18-25

27. or/1-3

28. or/4-17

29. 26 and 27 and 28

No search filters were applied.

Health Economics Literature search details

A Health Economics Search was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Which is the most valid published risk stratification score or algorithm for influencing management and predicting outcome in patients with neutropenic sepsis?

Question no: E1

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1999-2010	504	79	13/12/10
Premedline	1999-2010	4	2	13/12/10
Embase	1999-2010	736	99	13/12/10
Cochrane Library	1999-2010	184	5	14/12/10
Cinahl	1999-2010	924	32	15/12/10
Web of Science (SCI & SSCI) and ISI Proceedings	1999-2010	505	73	14/12/10
BIOSIS	1999-2010	469	42	14/12/10
Biomed Central	1999-2010	726	51	15/12/10

Total References retrieved (after de-duplication): 157

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2010-2011	122	18	01/11/2011
Premedline	2010-2011	9	5	01/11/2011
Embase	2010-2011	212	34	01/11/2011
Cochrane Library	2010-2011	35	0	02/11/2011
Cinahl	2010-2011	233	12	02/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2010-2011	226	24	02/11/2011
BIOSIS	2010-2011	162	9	02/11/2011

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen$ or neutropaen$).tw.

3. exp Agranulocytosis/

4. (granulocytopen$ or granulocytopaen$ or granulopen$or granulopaen$).tw.

5. (neutrop?en$ adj (sepsis$ or fever$)).tw.

6. (febrile$ adj neutrop?en$).tw.

7. or/1-6

8. exp models, statistical/

9. exp regression analysis/

10. discriminant analysis/

11. Statistics, Nonparametric/

12. ((risk$ or statistic$) adj (score$ or scoring or index$ or indices or algorithm$ or stratif$ or rule$ or classif$ or assess$ or categor$)).tw.

13. ((MASCC or EWS or ASCO or EORTC) adj (score$ or scoring or index$ or indices or algorithm$ or stratif$ or rule$ or classif$ or assess$ or categor$)).tw.

14. (myelotoxic$ adj (score$ or scoring or index$ or indices or algorithm$ or stratif$ or rule$ or classif$ or assess$ or categor$)).tw.

15. ((treatment or therapy) adj algorithm$).tw.

16. (predicti$ adj (score$ or scoring or index$ or indices or algorithm$ or stratif$ or rule$ or classif$ or assess$ or categor$)).tw.

17. nomogra$.tw.

18. or/8-17

19. 7 and 18

20. letter.pt.

21. Letter/

22. letter$/

23. editorial.pt.

24. historical article.pt.

25. Case Report/

26. case reports.pt.

27. Case Study/

28. exp animal/ not human/

29. exp Animal Experimentation/

30. exp Models, Animal/

31. exp rodentia/

32. exp rodent/

33. Animals, Laboratory/

34. or/20-33

35. 19 not 34

36. limit 35 to yr="1999 -Current"

Health Economics Literature search details

This topic was identified as low priority in terms of health economics.

Notes:

A date limit from 1999 onwards was specified by the GDG. A general exclusions filter was applied to the search.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutropenic Sepsis Literature search summary

Question title: Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients receiving anti-cancer treatment?

Question no: F1

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2/2011	490	169	01/03/2011
Update search	3/11-7/11/2011	30	13	07/11/2011
Premedline	All-2/2011	134	23	01/03/2011
Update search	3/11-7/11/2011	1	0	07/11/2011
Embase	All-2/2011	265	142	01/03/2011
Update search	3/11-7/11/2011	36	19	07/11/2011
Cochrane Library	All-2/2011	240	77	01/03/2011
Update search	3/11-7/11/2011	9	0	07/11/2011
Cinahl	All-2/2011	38	33	01/03/2011
Update search	3/11-7/11/2011	0	0	07/11/2011
BNI	All-2/2011	58	9	01/03/2011
Update search	3/11-7/11/2011	1	0	07/11/2011
Psychinfo	All-2/2011	107	0	01/03/2011
Update search	3/11-7/11/2011	8	0	07/11/2011
Web of Science (SCI & SSCI) and ISI	All-2/2011	67	33	01/03/2011

Proceedings				
Update search	3/11-7/11/2011	44	17	07/11/2011
Biomed Central	All-2/2011	71	1	01/03/2011
Update search	3/11-7/11/2011	8	1	07/11/2011

Total References retrieved (after de-duplication): 485 update search: 31

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Granulocyte Colony-Stimulating Factor/

2. exp Granulocyte-Macrophage Colony-Stimulating Factor/

3. G-CSF*.tw.

4. GM-CSF*.tw.

5. exp Filgrastim/

6. lenograstim*.tw.

7. pegfilgrastim*.tw.

8. molgramostim*.tw.

9. sargramostim*.tw.

10. filgrastim*.tw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp Fluoroquinolones/

13. Ciprofloxacin/

14. exp Ofloxacin/

15. levofloxacin*.tw.

16. exp Norfloxacin/

17. moxifloxacin*.tw.

18. Ciprofloxacin*.tw.

19. Ofloxacin*.tw.

20. Norfloxacin*.tw.

21. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. exp Trimethoprim-Sulfamethoxazole Combination/

23. co-trimoxazole*.tw.

24. exp Sulfonamides/

25. 22 or 23 or 24

26. 11 or 21 or 25

27. exp Antibiotic Prophylaxis/

28. prophyla*.tw.

29. prophylactic treatment*.tw.

30. (risk* adj1 infection*).tw.

31. 27 or 28 or 29 or 30

32. exp Neutropenia/

33. (neutropen* or neutropaen*).tw.

34. (neutrop?en* adj (sepsis* or fever*)).tw.

35. (febrile* adj neutrop?en*).tw.

36. 32 or 33 or 34 or 35

37. 26 and 31 and 36

RCT and SR filters were applied to this search strategy.

Health Economics Literature search details

This topic was selected as high priority topic for Health Economics. The Information Specialist was asked to perform a search for Health Economics with the terms for the Neutropenic Sepsis General Search and applied the SIGN Health economics filter to this search. The Literature Search Summary for the Health Economics Search will therefore appear as an own document within the Appendix.

The SCHARR Quality of Life filter was not applied to search.

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NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Health economics broad search

Database name	No of references found	Finish date of search
Medline	428	14/02/2011
Update search	30	07/11/2011
Embase	1305	14/02/2011
Update search	131	07/11/2011

Medline search strategy *(This search strategy is adapted to the EMBASE database.)*

1. exp Neutropenia/

2. exp Agranulocytosis/

3. agranulocyt*.tw.

4. (neutropenia* or neutropaenia*).tw.

5. neutropenic*.tw.

6. (febrile* adj neutropenia*).tw.

7. (neutropenic adj (sepsis* or fever*)).tw.

8. or/1-7

9. (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*).tw.

10. exp Neoplasms/co, dt, th [Complications, Drug Therapy, Therapy]

11. 9 or 10

12. 8 and 11

13. economics/

14. (economic evaluation$ or economic analy$ or pharmacoeconomi$ or health economic$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

15. (cost benefit$ or cost containment$).tw. or cost effective$.mp. or cost minimi$.mp. or cost utilit$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

16. (exp cost/ and cost analysis/) or "costs and cost analysis"/

17. cost-benefit analysis/

18. cost allocation/

19. cost control/

20. cost of illness/

21. cost savings/

22. cost sharing/

23. health care costs/

24. direct service costs/

25. employer health costs/

26. hospital costs/

27. health expenditures/

28. capital expenditures/

29. economic value of life/

30. exp economics, hospital/ or exp economics, medical/

31. exp "fees and charges"/ or exp budgets/

32. (health?care adj cost$).mp.

33. (fiscal or funding or financial).mp.

34. (cost adj estimate$).mp.

35. (cost adj variable$).mp.

36. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

37. or/14-37

38. letter.pt.

39. editorial.pt.

40. historical article.pt.

41. or/38-40

42. 37 not 41

43. 12 and 42

The Information Specialist was asked to perform a search for Health Economics with the terms for the Neutropenic Sepsis General Search and applied the SIGN Health economics filter to this search.

The SCHARR Quality of Life filter was not applied to the search.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients with a prior episode of neutropenic sepsis?

Question no: F 2

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2/2011	378	11	09/03/2011
Update search	3/11-7/11/2011	33	5	07/11/2011
Premedline	All-2/2011	5	4	14/03/2011
Update search	3/11-7/11/2011	2	1	07/11/2011
Embase	All-2/2011	739	14	14/03/2011
Update search	3/11-7/11/2011	8	2	07/11/2011
Cochrane Library	All-2/2011	53	10	14/03/2011
Update search	3/11-7/11/2011	18	0	07/11/2011
Cinahl	All-2/2011	12	7	14/03/2011
Update search	3/11-7/11/2011	0	0	07/11/2011
BNI	All-2/2011	1	0	14/03/2011
Update search	3/11-7/11/2011	1	0	07/11/2011
Psychinfo	All-2/2011	0	0	14/03/2011
Update search	3/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI	All-2/2011	11	3	14/03/2011

Proceedings				
Update search	3/11-7/11/2011	26	0	07/11/2011
Biomed Central	All-2/2011	58	1	14/03/2011
Update search	3/11-7/11/2011	6	1	07/11/2011

Total References retrieved (after de-duplication): 20 update search: 5

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Granulocyte Colony-Stimulating Factor/

2. G-CSF*.tw.

3. Granulocyte infusion*.tw.

4. exp Filgrastim/

5. lenograstim*.tw.

6. pegfilgrastim*.tw.

7. filgrastim*.tw.

8. or/1-7

9. exp Fluoroquinolones/

10. Ciprofloxacin/

11. exp Ofloxacin/

12. levofloxacin*.tw.

13. exp Norfloxacin/

14. moxifloxacin*.tw.

15. Ciprofloxacin*.tw.

16. Ofloxacin*.tw.

17. Norfloxacin*.tw.

18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp Antibiotic Prophylaxis/

20. prophyla*.tw.

21. secondary prophylaxis*.tw.

22. or/19-21

23. exp Neutropenia/

24. (neutropen* or neutropaen*).tw.

25. (neutrop?en* adj sepsis*).tw.

26. or/23-25

27. 22 and 26

28. 8 and 27

29. 18 and 27

30. 28 or 29

31. 27 and 30

RCT and SR were added to this search strategy.

Health Economics Literature search details

A Health Economics search was not required.

Clinical Guideline Neutopenic Sepsis **Literature search summary**

Question title: Does the length of time before empiric antibiotics are given influence patient outcomes?

Question no: E4

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-5/2011	782	38	31/05/2011
Update search	6/11-7/11/2011	12	2	07/11/2011
Premedline	All-5/2011	53	0	31/05/2011
Update search	6/11-7/11/2011	4	2	07/11/2011
Embase	All-5/2011	1386	44	08/06/2011
Update search	6/11-7/11/2011	20	9	07/11/2011
Cochrane Library	All-5/2011	32	1	08/06/2011
Update search	6/11-7/11/2011	22	0	07/11/2011
Cinahl	All-5/2011	13	1	08/06/2011
Update search	6/11-7/11/2011	1	1	07/11/2011
BNI	All-5/2011	1	0	31/05/2011
Update search	6/11-7/11/2011	0	0	07/11/2011
Psychinfo	All-5/2011	5	0	31/05/2011
Update search	6/11-7/11/2011	17	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-5/2011	754	7	08/06/2011
	6/11-	389	0	07/11/2011

Update search	7/11/2011			
Biomed Central	All-5/2011	195	2	08/06/2011
Update search	6/11-7/11/2011	27	1	07/11/2011

Total References retrieved (after de-duplication): 76 update search: 8

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. (neutrop?en* adj (sepsis* or fever*)).tw.

4. (suspect* adj1 neutrop*).tw.

5. (potential* adj1 neutrop*).tw.

6. 1 or 2 or 3 or 4 or 5

7. exp Anti-Bacterial Agents/

8. antibiotic*.tw.

9. ((broad-spectrum* or combination*) adj1 antibiotic*).tw.

10. (empiric* adj1 antibiotic*).tw.

11. 7 or 8 or 9 or 10

12. 6 and 11

13. Patient Admission/

14. (patient* adj2 (admis* or admit*)).tw.

15. ((pre or before or prior or previous) adj2 hospital*).tw.

16. ((previous or prior or before) adj (admit* or admiss*)).tw.

17. (preadmit* or pre admit* or pre-admit* or preadmiss* or pre admiss* or pre-admiss*).tw.

18. (early administr* adj5 antibiotic*).tw.

19. exp Time Factors/

20. needle time*.tw.

21. (time adj1 treatment*).tw.

22. (delay* adj2 treatment*).tw.

23. (onset* adj1 symptom*).tw.

24. (onset* adj1 sign*).tw.

25. exp Intensive Care Units/st [Standards]

26. exp Emergency Service, Hospital/st [Standards]

27. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 12 and 27

A Systematic Review search filter was applied.

Health Economics Literature search details

A Health Economics was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Neutopenic Sepsis	**Literature search summary**
Question title: Is there any difference between the outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients?	
Question no: E2	

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-06/2011	537	64	06/07/2011
Update search	07/11-7/11/2011	9	0	07/11/2011
Premedline	All-06/2011	13	6	06/07/2011
Update search	07/11-7/11/2011	30	7	07/11/2011
Embase	All-06/2011	2079	84	11/07/2011
Update search	07/11-7/11/2011	69	0	07/11/2011
Cochrane Library	All-06/2011	617	25	29/06/2011
Update search	07/11-7/11/2011	44	0	07/11/2011
Cinahl	All-06/2011	120	26	12/07/2011
Update search	07/11-7/11/2011	4	0	07/11/2011
BNI	All-06/2011	2	1	06/07/2011
Update search	07/11-7/11/2011	0	0	07/11/2011
Psychinfo	All-06/2011	3	1	06/07/2011
Update search	07/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-06/2011	71	10	12/07/2011
Update search	07/11-7/11/2011	34	1	07/11/2011
Biomed Central	All-06/2011	23	1	12/07/2011
Update search	07/11-7/11/2011	3	0	07/11/2011

Total References retrieved (after de-duplication): 129 update search: 7

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp Antineoplastic Agents/ae [Adverse Effects]

9. exp Antineoplastic Combined Chemotherapy Protocols/ae [Adverse Effects]

10. exp Anti-Bacterial Agents/ad, tu [Administration & Dosage, Therapeutic Use]

11. 8 or 9 or 10

12. 7 and 11

13. exp Inpatients/

14. (inpatient* or in-patient*).tw.

15. exp Hospitalization/

16. hospital*.tw.

17. exp "Length of Stay"/

18. exp Patient Discharge/

19. exp Infusions, Intravenous/ or exp Infusions, Parenteral/

20. intravenous antibiotic*.tw.

21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. exp Outpatients/

23. outpatient*.tw.

24. exp Ambulatory Care/

25. exp Home Care Services/

26. exp Administration, Oral/

27. oral admin*.tw.

28. exp Aftercare/

29. non-hospital*.tw.

30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31. 12 and 21

32. 12 and 30

33. 31 and 32

RCT filter applied.

Health Economics Literature search details

A Health Economics search was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Neutopenic Sepsis	**Literature search summary**

Question title: Is there a difference in the effectiveness of empiric intravenous antibiotic monotherapy and empiric dual therapy in the treatment of patients with neutropenic sepsis.

Question no: E 3

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006-2010	773	80	23/11/2010
Update search	11/10-7/11/2011	210	9	07/11/2011
Premedline	2006-2010	25	1	23/11/2010
Update search	11/10-7/11/2011	45	8	07/11/2011
Embase	2006-2010	1229	73	23/11/2010
Update search	11/10-7/11/2011	214	10	07/11/2011
Cochrane Library	2006-2010	353	45	23/11/2010
Update search	11/10-7/11/2011	48	1	07/11/2011
Cinahl	2006-2010	211	12	23/11/2010
Update search	11/10-7/11/2011	7	0	07/11/2011
BNI	2006-2010	1	0	23/11/2010
Update search	11/10-7/11/2011	0	0	07/11/2011
Psychinfo	2006-2010	4	2	23/11/2010
Update search	11/10-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2006-2010	105	17	23/11/2010
Update search	11/10-7/11/2011	134	2	07/11/2011
Biomed Central	2006-2010	245	1	23/11/2010
Update search	11/10-7/11/2011	73	0	07/11/2011

Total References retrieved (after de-duplication): 196 update search: 23

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. or/1-6

8. exp Anti-Bacterial Agents/

9. (antibiotic or antibiotic*).tw.

10. exp beta-Lactamases/ or exp beta-Lactams/

11. exp Penicillins/ or penicillin*.tw.

12. Tazobactam*.tw.

13. ureidopenicillin*.tw.

14. exp Ticarcillin/ or ticarcillin*.tw.

15. exp Piperacillin/ or piperacillin*.tw.

16. exp Quinolones/ or quinolone*.tw.

17. exp Ciprofloxacin/ or ciprofloxacin*.tw.

18. exp Ceftazidime/ or ceftazidime*.tw.

19. meropenem*.tw.

20. exp Imipenem/ or imipenem*.tw.

21. exp Aztreonam/ or aztreonam*.tw.

22. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. exp Aminoglycosides/

24. aminoglycoside*.tw.

25. exp Amikacin/ or amikacin*.tw.

26. exp Gentamicins/ or gentam?cin*.tw.

27. exp Tobramycin/ or tobram?cin*.tw.

28. exp Kanamycin/ or kanam?cin*.tw.

29. exp Netilmicin/ or netilm?cin*.tw.

30. 23 or 24 or 25 or 26 or 27 or 28 or 29

31. (beta-lactam* or beta?lactam*).tw

32. 22 or 30

33. 7 and 30

34. 33 or 31

An RCT search filter was applied

Health Economics Literature search details

A Health Economics search was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: In patients with a central venous access device with no external signs of line infection but with suspected neutropenia or neutropenic sepsis, what are the benefits and risks of adding vancomycin, teicoplanin or linezolid to first-line antibiotics?

Question no: G

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2011	209	48	19/07/2011
Update search	7/11-7/11/2011	19	1	07/11/2011

Premedline	All-6/2011	40	10	19/07/2011
Update search	7/11-7/11/2011	20	4	07/11/2011
Embase	All-6/2011	191	41	19/07/2011
Update search	7/11-7/11/2011	35	6	07/11/2011
Cochrane Library	All-6/2011	128	31	18/07/2011
Update search	7/11-7/11/2011	12	2	07/11/2011
Cinahl	All-6/2011	106	17	19/07/2011
Update search	7/11-7/11/2011	6	0	07/11/2011
BNI	All-6/2011	3	1	19/07/2011
Update search	7/11-7/11/2011	0	0	07/11/2011
Psychinfo	All-6/2011	2	0	19/07/2011
Update search	7/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2011	235	17	19/07/2011
Update search	7/11-7/11/2011	7	0	07/11/2011
Biomed Central	All-6/2011	51	4	01/08/2011
Update search	7/11-7/11/2011	3	0	07/11/2011

Total References retrieved (after de-duplication): 138 update search: 10

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. exp Bacteremia/pc [Prevention & Control]

8. exp Bacterial Infections/pc [Prevention & Control]

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp Catheterization, Central Venous/ae [Adverse Effects]

11. exp Catheters, Indwelling/ae [Adverse Effects]

12. (central venous line* or cvl*).tw.

13. (central venous catheter* or cvc*).tw.

14. PICC*.tw.

15. (central venous access device* or cvad*).tw.

16. Hickman*.tw.

17. Port-a-cath*.tw.

18. Lumen*.tw.

19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. exp Anti-Bacterial Agents/

21. antibiotic*.tw.

22. exp Anti-Infective Agents/

23. exp Glycopeptides/ad [Administration & Dosage]

24. Glycopeptide*.tw.

25. exp Vancomycin/ad [Administration & Dosage]

26. vancomycin*.tw.

27. exp Teicoplanin/ad [Administration & Dosage]

28. Teicoplanin*.tw.

29. exp Oxazolidinones/ad [Administration & Dosage]

30. Oxazolidinone*.tw.

31. linezolid*.tw.

32. first line antibiotic*.tw.

33. broad spectrum*.tw.

34. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35. 9 and 19 and 34

RCT filter applied.

Health Economics Literature search details

A Health Economics search was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Neutopenic Sepsis	**Literature search summary**
Question title: Which patients with central venous access devices and neutropenic sepsis will benefit from removal of their central line?	
Question no: H	

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-7/2011	1103	144	03/08/2011
Update serach	8/11-7/11/2011	18	1	07/11/2011
Premedline	All-7/2011	36	5	08/08/2011
Update serach	8/11-7/11/2011	25	1	07/11/2011
Embase	All-7/2011	2745	139	08/08/2011
Update serach	8/11-7/11/2011	108	2	07/11/2011
Cochrane Library	All-7/2011	384	16	08/08/2011
Update serach	8/11-7/11/2011	44	0	07/11/2011
Cinahl	All-7/2011	1679	14	10/08/2011
Update serach	8/11-7/11/2011	59	0	07/11/2011
BNI	All-7/2011	2	0	08/08/2011
Update serach	8/11-7/11/2011	1	0	07/11/2011
Psychinfo	All-7/2011	0	0	08/08/2011
Update serach	8/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-7/2011	261	4	10/08/2011
Update serach	8/11-7/11/2011	39	0	07/11/2011
Biomed Central	All-7/2011	146	3	10/08/2011
Update serach	8/11-7/11/2011	5	0	07/11/2011

Total References retrieved (after de-duplication): 234 update search: 4

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. or/1-6

8. exp Bacterial Infections/pc [Prevention & Control]

9. intra-luminal*.tw.

10. tunnel infection*.tw.

11. pocket infection*.tw.

12. exp Catheterization, Central Venous/ae [Adverse Effects]

13. exp Catheters, Indwelling/ae [Adverse Effects]

14. exp Catheter-Related Infections/pc [Prevention & Control]

15. (central venous line* or cvl*).tw.

16. (central venous catheter* or cvc*).tw.

17. PICC*.tw.

18. (central venous access device* or cvad*).tw.

19. Hickman*.tw.

20. Port-a-cath*.tw.

21. Lumen*.tw.

22. (line adj2 preserv*).tw.

23. exp Equipment Contamination/ae, pc [Adverse Effects, Prevention & Control]

24. catheter related sepsis*.tw.

25. catheter related blood stream infection*.tw.

26. (sign* adj2 thrombosis*).tw.

27. (sign* adj2 thrombophlebitis*).tw.

28. (sign* adj2 sepsis*).tw.

29. exp Device Removal/

30. central line removal*.tw.

31. or/8 -30

32. 7 and 31

Health Economics Literature search details

A Health Economics was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Neutopenic Sepsis	**Literature search summary**
Question title: When is the optimal time to switch (step down) from intravenous to oral antibiotic therapy?	
Question no: E5	

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	148	41	16/11/10
Premedline	All	0	0	16/11/10
Embase	All	282	45	17/11/10
Cochrane Library	All	125	45	22/11/10
Cinahl	All	328	8	23/11/10
Web of Science (SCI & SSCI) and ISI Proceedings	All	82	36	17/11/10
BIOSIS	All	1	0	17/11/10
Biomed Central	All	114	2	23/11/10

Total References retrieved (after de-duplication): 89

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2010-2011	7	1	02/11/2011
Premedline	2010-2011	1	0	02/11/2011
Embase	2010-2011	11	2	02/11/2011
Cochrane Library	2010-2011	7	1	02/11/2011
Cinahl	2010-2011	10	0	02/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2010-2011	7	2	02/11/2011
BIOSIS	2010-2011	5	1	02/11/2011

Medline search strategy *(This search strategy is adapted to each database.)*

1. Randomized controlled trials as Topic/

2. Randomized controlled trial/

3. Random allocation/

4. Double blind method/

5. Single blind method/

6. Clinical trial/

7. exp Clinical Trials as Topic/

8. or/1-7

9. (clinic$ adj trial$1).tw.

10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

11. Placebos/ antibiotic$ or antimicrob$ or antibacteria$ or anti infective agent$

12. placebo$.tw.

13. randomly allocated.tw.

14. (allocated adj2 random$2).tw.

15. or/9-14

16. 8 or 15

17. case report.tw.

18. Letter/

19. Historical article/

20. review.pt.

21. or/17-20

22. 16 not 21

23. exp Neutropenia/

24. (neutropen$ or neutropaen$).tw.

25. exp Agranulocytosis/

26. (granulocytopen$ or granulocytopaen$ or granulopen$or granulopaen$).tw.

27. (neutrop?en$ adj (sepsis$ or fever$)).tw.

28. (febrile$ adj neutrop?en$).tw.

29. or/23-28

30. letter.pt.

31. Letter/

32. letter$/

33. editorial.pt.

34. historical article.pt.

35. Case Report/

36. case reports.pt.

37. Case Study/

38. exp animal/ not human/

39. exp Animal Experimentation/

40. exp Models, Animal/

41. exp rodentia/

42. exp rodent/

43. Animals, Laboratory/

44. or/30-43

45. 29 not 44

46. 45 and 22

47. exp Anti-Bacterial Agents/

48. Administration, Oral/

49. Infusions, Intravenous/

50. 48 and 49

51. 47 and 50

52. (intravenous$ or parenteral$or par-enteral$ or infusion$).tw.

53. (oral$ or per-os or enteral$).tw.

54. 52 and 53

55. (antibiotic$ or antimicrob$ or antibacteria$ or anti infective agent$).tw.

56. exp Beta-Lactamases/ or exp Beta-Lactams/

57. exp Penicillins/ or penicillin$.tw.

58. Tazobactam$.tw.

59. ureidopenicillin$.tw.

60. (amox?cillin$ or augmentin$ or co-amoxiclav$ or clavulanate$).tw.

61. exp Ticarcillin/ or ticarcillin$.tw.

62. exp Piperacillin/ or piperacillin$.tw.

63. exp Quinolones/ or quinolone$.tw.

64. exp Ciprofloxacin/ or ciprofloxacin$.tw.

65. exp Ceftazidime/ or ceftazidime$.tw.

66. meropenem$.tw.

67. exp Imipenem/ or imipenem$.tw.

68. exp Aztreonam/ or aztreonam$.tw.

69. or/56-68

70. exp Aminoglycosides/ or aminoglycoside$.tw.

71. exp Amikacin/ or amikacin$.tw.

72. exp Gentamicins/ or gentam?cin$.tw.

73. exp Tobramycin/ or tobram?cin$.tw.

74. exp Kanamycin/ or kanamcin.tw.

75. exp Netilmicin/ or netilm?cin$.tw.

76. or/70-75

77. 55 or 69 or 76

78. 54 and 77

79. 51 or 78

80. 46 and 79

Health Economics Literature search details

This topic was identified as low priority in terms of health economics.

Notes

A RCT filter was applied. No date limit was specified

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NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: What is the optimal duration of inpatient care for patients receiving empiric treatment for neutropenic sepsis.

Question no: E8

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-4/2011	453	56	09/05/2011
Update search	5/11-7/11/2011	18	1	07/11/2011
Premedline	All-4/2011	15	2	09/05/2011
Update search	5/11-7/11/2011	5	2	07/11/2011
Embase	All-4/2011	596	61	11/05/2011
Update search	5/11-7/11/2011	48	3	07/11/2011
Cochrane Library	All-4/2011	320	5	16/05/2011
Update search	5/11-7/11/2011	13	1	07/11/2011
Cinahl	All-4/2011	338	8	11/05/2011
Update search	5/11-7/11/2011	18	0	07/11/2011
BNI	All-4/2011	0	0	09/05/2011
Update search	5/11-7/11/2011	0	0	07/11/2011
Psychinfo	All-4/2011	0	0	09/05/2011
Update search	5/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-4/2011	7	1	11/05/2011
Update search	5/11-7/11/2011	20	0	07/11/2011
Biomed Central	All-4/2011	209	1	11/05/2011
Update search	5/11-7/11/2011	26	0	07/11/2011

Total References retrieved (after de-duplication): 93 update search: 4

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. (empiric* adj1 treatment*).tw.

9. antimicrobial*.tw.

10. antibiotic*.tw.

11. antifungal*.tw.

12. (initial* adj1 treatment*).tw.

13. antiviral*.tw.

14. infection control*.tw.

15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16. 7 and 15

17. exp "Length of Stay"/

18. (duration adj1 treatment*).tw.

19. exp Time Factors/

20. optimal duration*.tw.

21. exp Patient Discharge/

22. early discharge*.tw.

23. exp Hospitalization/

24. continu* inpatient care*.tw.

25. discharge criteria*.tw.

26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. 16 and 26

No filters were applied.

Health Economics Literature search details

A Health Economics search was not required.

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NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Neutopenic Sepsis	**Literature search summary**
Question title: What is the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis	
Question no: E7	

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-3/2011	390	38	22/03/2011
Update search	3/11-7/11/2011	23	1	07/11/2011
Premedline	All-3/2011	1	0	23/03/2011
Update search	3/11-7/11/2011	3	0	07/11/2011
Embase	All-3/2011	485	18	22/03/2011
Update search	3/11-7/11/2011	59	10	07/11/2011
Cochrane Library	All-3/2011	408	5	23/03/2011
Update search	3/11-7/11/2011	34	1	07/11/2011
Cinahl	All-3/2011	151	6	23/03/2011
Update search	3/11-7/11/2011	7	0	07/11/2011
Psychinfo	All-3/2011	0	0	23/03/2011
Update search	3/11-7/11/2011	0	0	07/11/2011
BNI	All-3/2011	0	0	23/03/2011
Update search	3/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	All-3/2011	6	1	23/03/2011
Update search	3/11-7/11/2011	21	2	07/11/2011
Biomed Central	All-3/2011	129	1	23/03/2011
Update search	3/11-7/11/2011	11	1	07/11/2011

Total References retrieved (after de-duplication): 59 update search: 12

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/

2. (neutropen* or neutropaen*).tw.

3. exp Agranulocytosis/

4. (granulocytopen* or granulocytopaen* or granulopen*or granulopaen*).tw.

5. (neutrop?en* adj (sepsis* or fever*)).tw.

6. (febrile* adj neutrop?en*).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp Bacterial Infections/th [Therapy]

9. exp Anti-Bacterial Agents/tu, th [Therapeutic Use, Therapy]

10. (antibiotic* or antimicrob* or antibacterial* or anti infective agent*).tw.

11. empiric antibiotic therap*.tw.

12. broad spectrum antibiotic*.tw.

13. exp Amoxicillin/

14. amoxicillin*.tw.

15. exp Penicillins/

16. penicillin*.tw.

17. exp Fluoroquinolones/

18. levofloxacin*.tw.

19. exp Ciprofloxacin/

20. Ciprofloxacin*.tw.

21. exp Ceftazidime/

22. Ceftazidime*.tw.

23. meropenem*.tw.

24. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. 7 and 24

26. exp Neoplasms/

27. (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$).tw.

28. 26 or 27

29. 25 and 28

30. (stop* adj5 treatment*).tw.

31. (discontinu* adj5 treatment*).tw.

32. (stop* adj5 antibiotic*).tw.

33. (discontinu* adj5 antibiotic*).tw.

34. exp Treatment Outcome/

35. (treatment adj2 (duration* or length*)).tw.

36. exp "Length of Stay"/

37. ((duration adj2 fever*) or afebrile*).tw.

38. neutrophil count recover*.tw.

39. or/30-38

40. 29 and 39

RCT, SR and Observational Studies filters have been applied.

Health Economics Literature search details

A Health Economics search was not required.

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Neutopenic Sepsis Literature search summary

Question title: What is the optimal time to change the primary empiric treatment in unresponsive fever?

Question no: E6

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-4/2011	505	115	07/04/2011
Update search	4/11-7/11/2011	21	3	07/11/2011
Premedline	1980-4/2011	55	0	07/04/2011
Update search	4/11-7/11/2011	39	0	07/11/2011
Embase	1980-4/2011	526	26	11/04/2011
Update search	4/11-7/11/2011	21	0	07/11/2011
Cochrane Library	1980-4/2011	574	25	11/04/2011
Update search	4/11-7/11/2011	14	0	07/11/2011
Cinahl	1980-4/2011	47	12	11/04/2011
Update search	4/11-7/11/2011	21	0	07/11/2011
BNI	1980-4/2011	2	0	11/04/2011
Update search	4/11-	0	0	07/11/2011

	7/11/2011			
Psychinfo	1980-4/2011	1	0	11/04/2011
Update search	4/11-7/11/2011	0	0	07/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	1980-4/2011	24	7	11/04/2011
Update search	4/11-7/11/2011	62	3	07/11/2011
Biomed Central	1980-4/2011	220	0	11/04/2011
Update search	4/11-7/11/2011	25	0	07/11/2011

Total References retrieved (after de-duplication): 136 update search: 3

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Neutropenia/dt [Drug Therapy]

2. (neutropen* or neutropaen*).tw.

3. (neutrop?en* adj (sepsis* or fever*)).tw.

4. (febrile* adj neutrop?en*).tw.

5. 1 or 2 or 3 or 4

6. exp Neoplasms/co [Complications]

7. 5 and 6

8. (unresponsive fever* or sustained fever* or permanent fever* or persistent fever* or prolonged fever*).tw.

9. exp Fever/dt [Drug Therapy]

10. 8 or 9

11. 7 and10

12. second line antibiotic*.tw.

13. exp Vancomycin/

14. exp Vancomycin Resistance/

15. exp Teicoplanin/

16. Carbapenems/

17. (carbapen* or Teicoplanin* or Vancomycin*).tw.

18. exp Antifungal Agents/

19. antifungal*.tw.

20. exp Antiviral Agents/

21. antiviral*.tw.

22. (change adj3 treatment*).tw.

23. exp Anti-Bacterial Agents/tu [Therapeutic Use]

24. empiric*.tw.

25. or/12-24

26. 7 and 25

27. 11 or 26

28. limit 27 to yr="1980 -Current"

RCT and SR filters applied.

Health Economics Literature search details

A Health Economics search was not required.

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Appendix 2 – health economics evidence review

1. Inpatient versus ambulatory (non-hospitalised) management strategies.

Review question

Is there any difference between the cost-effectiveness outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients?

Question in PICO format

Patients/population	Interventions	Comparisons	Outcomes
Patients receiving treatment for neutropenic sepsis	In patient care	Ambulatory care (all different forms Community Outpatient Home)	• Incremental cost-effectiveness ratio (ICER) • Results of sensitivity analysis

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). The CRD economic studies filter was applied. Studies published prior to 2000 were excluded as they are unlikely to have relevance to current practice and costs. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

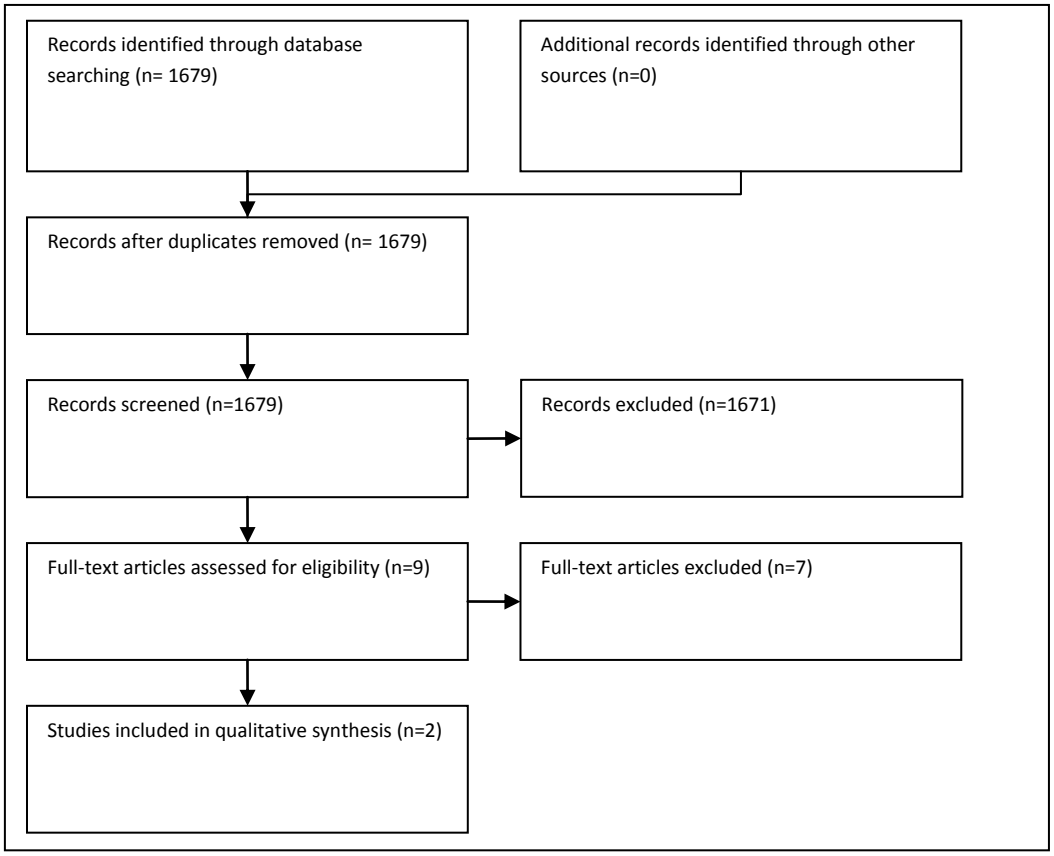
Selection criteria for included evidence:

- Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included (from 2000 to current)
- Studies that were conducted in OECD countries (other than the UK) were included
- Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economist (HJ) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly nine studies and checked against the inclusion criteria.

Results



Characteristics of included studies

Total number of included studies	2 studies
Age group	Adult/elderly (≥18 y): 1 study Paediatric (<18 y): 1 study

Quality and applicability of the included studies

Both papers were deemed partially applicable to the guideline because they are conducted in Canada, not U.K. The utility data of Teuffel 2010 is derived from cancer patients who might don't have direct experience of neutropenic sepsis.

Both papers were deemed to have minor limitations because of two reasons:

1). the estimates of resource use were not derived from a recent well-conducted systematic review (but is similar in magnitude to the best available estimates)

2). Structural sensitivity analysis was not conducted.

Table A1.1 Applicability and limitations of included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		Teuffel 2010 Teuffel 2011
	Potentially serious limitations		
	Very serious limitations		

Evidence statements

Two Canadian studies (Teuffel 2010; Teuffel 2011) were included for this topic. Teuffel 2010 is looking at adult cancer patient with a first episode of low-risk febrile neutropenia; while Teuffel 2011 is looking at paediatric cancer patient with low-risk of febrile neutropenia who were receiving stand-dose chemotherapy.

Both studies are looking at four inventions:

A. Home IV (Entire outpatient management with intravenous antibiotics)

B. HospIV(entire treatment in hospital with intravenous antibiotics)

C. EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intervanous antibiotics, subsequently followed by oral outpatient treatment)

D. HomePO (entire outpatient management with oral antibiotics)

Effectiveness data comes from formal systematic review and meta-analysis. Outcome was reported in terms of ICER or QAFNE (quality-adjusted febrile neutropenia episode). Teuffel 2010 found out that Home IV is more effective and less expensive than all other strategies. Teuffel 2010 found out that Home IV is more effective and less expensive than Home PO and Hosp IV; however is less effective than EarlyDC. The ICER of EarlyDC is £76968.01 per quality-adjusted febrile neutropenia episode, comparing to Home IV.

GRADE table of included studies

Table A1.2. Modified GRADE table of included economic studies

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Teuffel 2010	Minor limitations [1]	Partially applicable [2]	An adult cancer patient with a first episode of low-risk febrile neutropenia.	HospIV(entire treatment in hospital with intravenous antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£6249.85 [3]	-0.011333333 QALYs	Dominated	Results were sensitive to several event probabilities, utilities and costs. Beyond certain thresholds, the best strategy changed from HomeIV to the HomePO strategy. However, HospIV or EarlyDC management were never the preferred strategy in sensitivity analysis.
				EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intervanous antibiotics, subsequently followed by oral outpatient treatment)	Home IV (Entire outpatient management with intravenous antibiotics)	£1930.72 [3]	-0.011083333 QALYs	Dominated	
				HomePO (entire outpatient management with oral antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£98.79 [3]	-0.002833333 QALYs	Dominated	
Teuffel 2011	Minor limitations [4]	Partially applicable [5]	Paediatric cancer patient (hypothetical cohort) with low-risk of febrile neutropenia who	HomePO (entire outpatient management with oral antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£1558.60 [6]	-0.1098 QAFNE (QAFNE=	Dominated	Results were sensitive to costs for a home care nurse per visit, duration of outpatient treatment, utility for HomeIV, and utility for HomePO. Beyond certain

Quality assessment			*Summary of findings*						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
			were receiving stand-dose chemotherapy.				quality-adjusted febrile neutropenia episode)		thresholds, superiority changed from the HomeIV to the HomePO strategy. On the contrary, there was no variable identified that changed the dominance from outpatient management (HomeIV or HomePO) to HospIV or Early DC. PSA shows that at a willingness to pay threshold of $4000 (2010 U.K cost:£ :£ 2261.30) per QAFNE, HomeIV was cost-effective in 57% of the simulations, whereas HOmePO was cost-effective in 35% of the simulations.
				EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intervanous antibiotics, subsequently followed by oral outpatient treatment)	Home IV (Entire outpatient management with intravenous antibiotics)	£3153.95 [6]	0.0209 QAFNE	£76968.01 [6] per QAFNE	
				HospIV(entire treatment in hospital with intravenous antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£8193.27 [6]	-0.0345 QAFNE	Dominated	

1. The estimates of resource use were not derived from a recent well-conducted systematic review, but is similar in magnitude to the best available estimates. Structural sensitivity analysis was not conducted.

2. This study was not conducted in the U.K. Utility data was derived from cancer patients who might don't have direct experience of neutropenic sepsis.

3. Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

4. The estimates of resource use were not derived from a recent well-conducted systematic review, but is similar in magnitude to the best available estimates. Structural sensitivity analysis was not conducted. The value of health effects expressed in terms of quality-adjusted life years (QALYs).

5. This study was not conducted in the U.K. Utility data was derived from parents of children who might don't have direct experience of neutropenic sepsis. 1-(1-VAS) was used instead of EQ-5D.

6. Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx)

References

Teuffel, O., et al. "Treatment strategies for low-risk febrile neutropenia in adult cancer patients: A cost-utility analysis." Journal of Clinical Oncology Conference.var.pagings (2010).

Teuffel, O., et al. "Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer." Pediatrics 127.2 (2011): e279-e286.

Evidence tables

Table A1.3. Evidence table of included economic studies

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Teuffel **Year:** 2011 (a) **Country:** Canada	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analytic model **Time horizon:**30 days **Perspective:** health care payer in Ontario/Canada **Source of effectiveness data:** Formal systematic review and meta-analysis	**Base case:** Adult cancer patient (hypothetical cohort) with a first episode of low-risk febrile neutropenia. **Exclusion criteria:** Not reported. **Sample size:** Not reported **Age:** Not reported	**Treatment strategy:** A. Home IV (Entire outpatient management with intravenous antibiotics) B. HospIV(entire treatment in hospital with intravenous antibiotics) C. EarlyDC	**Clinical data:** QALY (Strategy A) Incremental QALY (Strategy B-A) Incremental QALY (Strategy C-A) Incremental QALY (Strategy D-A) **Cost:** Total cost (Strategy A) Incremental cost (Strategy B-A) Incremental cost (Strategy C-A)	0.06642 -0.011333333 -0.011083333 -0.002833333 $2129 (2011 U.K cost: £1245.45) $11388 (2011 U.K cost: £6661.88) $3518 (2011	**Conflict of interest:** None. **Comments:** **Applicability:** Partially applicable **Limitation:** Minor limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of utility data: Obtained from adult cancer patients (a current or previous episode of FN was not mandatory for inclusion). 1-(1-VAS) was used. **Source of cost data:** Not reported **Currency unit:** Canada dollar. **Cost year:** Not reported. **Discounting:** Health effect: not reported. Cost: 0%	**Gender:** **Male:** Not reported **Female:** **Risk of NS:** Low risk **Subgroup analysis:** None	(Early discharge strategy consisting of 48 hours inpatient observation with intervanous antibiotics, subsequently followed by oral outpatient treatment) D. HomePO (entire outpatient management with oral antibiotics)	Incremental cost (Strategy D-A) **ICER per QALY:** B v.s A C v.s A D v.s A **Uncertainty:** Results were sensitive to several event probabilities, utilities and costs. Beyond certain thresholds, the best strategy changed from HomeIV to the HomePO strategy. However, HospIV or EarlyDC management were never the preferred strategy in sensitivity analysis. PSA shows that at a willingness to pay threshold of $4000 (2011 U.K cost:£ 2339.96), HomeIV was cost effective in 54% of the simulations; HomePO was cost effectve in 38% of the simulations; EarlyDC was cost-effective in 8% of the simulations; and the probability for HospIV to become cost-effective was less than 1%.	U.K cost: £2058.00) $180 (2011 U.K cost: £105.30) Dominated Dominated Dominated	
Study 2						
Author: Teuffel **Year:** 2011(b)	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analytic model	**Base case:** Paediatric cancer patient (hypothetical cohort) with low-risk of febrile neutropenia who were receiving stand-dose	**Treatment strategy:** A. Home IV (Entire outpatient management with intravenous	**Clinical data:** (QAFNE= quality-adjusted febrile neutropenia episode) QAFNE (Strategy A) Incremental QAFNE (Strategy B-A) Incremental QAFNE (Strategy C-A)	 0.6632 -0.1098 0.0209	**Conflict of interest:** None. **Comments:** **Applicability:**

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Country: Canada	**Time horizon:** One febrile neutropenia episode **Perspective:** health care payer in Ontario/Canada **Source of effectiveness data:** Formal systematic review and meta-analysis **Source of utility data:** Obtained from 149 parents of children who were receiving active treatment for cancer. A current or previous episode of febrile neutropenia was not mandatory for inclusion. Hypothetical scenarios were presented, and a visual analogue scale (VAS) was used to measure patients' preferences. 1-(1-VAS) was used to derive a stand gamble score from VAS. **Source of cost data:** 1. Ontario health insurance schedule of benefits and fees.	chemotherapy. **Exclusion criteria:** Not reported. **Sample size:** 630 **Age:** Not reported **Gender:** **Male:** Not reported **Female:** **Risk of NS:** Low risk **Subgroup analysis:** None	antibiotics) B. HomePO (entire outpatient management with oral antibiotics) C. EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intervanous antibiotics, subsequently followed by oral outpatient treatment) D. HospIV(entire treatment in hospital with intravenous antibiotics)	Incremental QAFNE (Strategy D-A) **Cost:** Total cost (Strategy A) Incremental cost (Strategy B-A) Incremental cost (Strategy C-A) Incremental cost (Strategy D-A) **ICER per QAFNE:** B v.s A C v.s A D v.s A **Uncertainty:** Results were sensitive to costs for a home care nurse per visit, duration of outpatient treatment, utility for HomeIV, and utility for HomePO. Beyond certain thresholds, superiority changed from the HomeIV to the HomePO strategy. On the contrary, there was no variable identified that changed the dominance from outpatient management (HomeIV or HomePO) to HospIV or Early	-0.0345 $2732 (2011 U.K cost: £1598.19) $2757 (2011 U.K cost: £1612.82) $5579 (2011 U.K cost: £3263.66) $14493 (2011 U.K cost: £8478.27) Dominated $136,148 (2011 U.K cost: £79645.33) Dominated	Partially applicable **Limitation:** Minor limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	2. Local finance offices at the hospital for Sick Children 3. the department of pharmacy at the hospital for Sick Children **Currency unit:** Canada dollar. **Cost year:** 2009 **Discounting:** Health effect: 0% Cost: 0%			DC. PSA shows that at a willingness to pay threshold of $4000 (2011 U.K cost:£ 2339.96) per QAFNE, HomeIV was cost-effective in 57% of the simulations, whereas HOmePO was cost-effective in 35% of the simulations.		

1

2. Empiric intravenous antibiotic monotherapy or empiric intravenous antibiotic dual therapy.

Review question

Is there a difference in the cost-effectiveness of empiric intravenous antibiotic monotherapy and empiric dual therapy in the treatment of patients with neutropenic sepsis.

Question in PICO format

Patients/population	Interventions	Comparisons	Outcomes
Patients with neutropenic sepsis	Intravenous antibiotic monotherapy (Piperacillin/tazobactam Ceftazidime Meropenem Imipenem Aztreonam Ciprofloxacin)	Intravenous antibiotic dual therapy (Monotherapies plus aminoglycosides)	• Incremental cost-effectiveness ratio (ICER) • Results of sensitivity analysis

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). The CRD economic studies filter was applied. Studies published prior to 2000 were excluded as they are unlikely to have relevance to current practice and costs. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

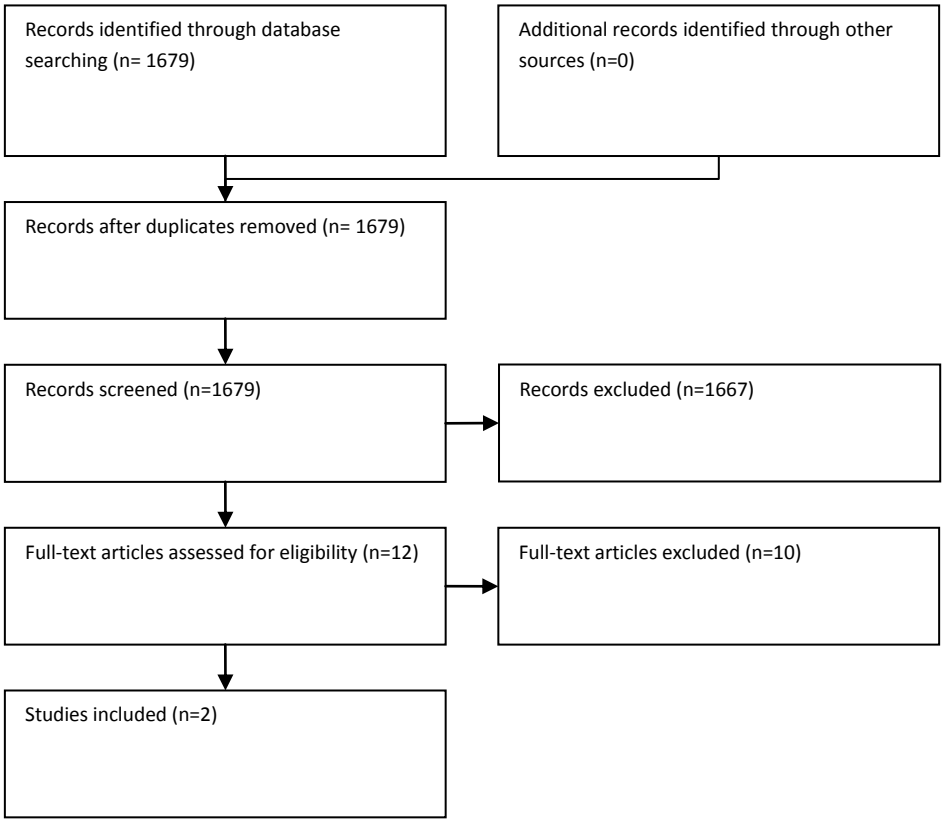
Selection criteria for included evidence:

- Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included (from 2000 to current)
- Studies that were conducted in OECD countries (other than the UK) were included
- Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economist (HJ) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly twelve studies and checked against the inclusion criteria.

Results



Characteristics of included studies

Total number of included studies	2 studies
Age group	≥16 y: 1 study ≤18 y: 1 study

Quality and applicability of the included studies

Two studies were included for this topic. Both papers were deemed partially applicable to the guideline. The most common reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case.

Both papers were deemed to have very serious limitations, because they do not meet one or more aspects of the NICE reference case.

Table A1.1 Applicability and limitations of included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		
	Very serious limitations		Corapcioglu 2005 Paladino 2000

Evidence statements

Two studies were included for this topic. One study (Corapcioglu 2005) was conducted in Turkey in 2005; and the other (Paladino 2000) was conducted in the U.S.A in 2000. The former study shows that monotherapy is more cost-effective than dual therapy; but this conclusion was not tested by sensitivity analysis. The latter study (Paladino 2000) found out that there were no statistically significant differences in cost-effectiveness between monotherapy and dual therapy. However, this conclusion is sensitive to success rates of both interventions. For the majority of the tested range of success rate, monotherapy is more cost effectiveness than dual therapy.

Population

The population of both studies are cancer patients with febrile neutropenia; but study Corapcioglu 2005 is looking at children<18 years while study Paladino 2000 is looking at adults ≥16 years.

Intervention & Comparator

These 2 papers adopted different combination therapy. Corapcioglu 2005 compared cefepime with ceftazidime + amikacin; while Paladino 2000 compared cefepime with gentamicin + ureidopenicillin or mezlocillin.

Outcome

Neither of the two papers quantified health effects in terms of QALYs. Both of them reported health effects in terms of response rate of treatment and median duration of treatment/hospitalization/fever/neutropenia. Paladino 2000 also reported rates of adverse effects.

Source of effectiveness data

Effectiveness data of Corapcioglu 2005 was obtained from a prospective randomised trial; while the effectiveness data of Paladino 2000 was obtained from the pooled result of two prospective randomised trials

GRADE table of included studies

Table A1.2. Modified GRADE table of included economic studies

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Corapcioglu 2005	Serious limitations [1]	Partially applicable [2]	Cancer patients under 18 years with fever and neutropenia	Dual therapy with ceftazidime (150 mg/kg/day (maximum daily dose 6 g) in 3 divided doses) and amikacin (15 mg/kg/day in a single dose)	Monotherapy with cefepime (150 mg/kg/day in 3 divided doses (maximum daily dose 6g))	£4240 [3] per episode of febrile neutropenia	Monotherapy: Duration of fever < 10 days: 13 (52%) ≥ 10 days: 12 (48%) Response without modification: 13 (52%) Infection-related mortality: 0 Dual therapy: Duration of fever < 10 days: 9 (36%) ≥ 10 days: 16 (64%) Response without: 10 (40%)	Can't be calculated	Sensitivity analysis was not conducted.

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost* *(2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
							modification Infection-related mortality: 0		
Paladino 2000	Serious limitations [4]	Partially applicable [5]	Adult cancer patients ≥16 years with febrile neutropenia.	Dual therapy with gentamicin (1.5mg/kg intravenously every 8 hours) and ureidopenicillin (either piperacillin 3g intravenously every 4 hours in 1 trail or mezlocillin 3g intravenously every 4 hours in a second trial)	Monotherapy with cefepime (2g intravenously every 8 hours)	$1127 [6]	Monotherapy: Treatment outcome no. (%) *Cure*: 27 (37%) *failure*: 23 (31%) *indeterminate*: 24 (32%) Patients experiencing adverse effects (no. (%)): 15 (20%) Total adverse effects (no. (%)): 22 (30%) Antibacterial-related length of stay (days (range)): 16 (7-49) Dual therapy:	Can't be calculated	Sensitivity analysis was not conducted.

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost* *(2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
							Treatment outcome no. (%) *Cure* 27 (36%) *failure* 31 (41%) *indeterminate* 17 (23%) Patients experiencing adverse effects (no. (%)) 17 (23%) Total adverse effects (no. (%)) 20 (27%) Antibacterial-related length of stay (days (range)) 17 (7-46)		

1

2 [1] Effectiveness data is based on one single randomised trial conducted in one centre; impact on quality of life was not considered in the analysis; no sensitivity analysis was conducted. Therefore
3 the relevance of these results for informing the current guideline is limited (in the absence of an appropriate willingness to pay threshold).

4 [2] The analysis does not meet one or more aspects of the NICE reference case.

5 [3] Converted from 2004 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 116% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

6

[4] Impact on quality of life was not considered in the analysis; potential conflict of interest: this study was funded in part by an unrestricted grant from Bristol-Myers Squibb Company. Therefore the relevance of these results for informing the current guideline is limited (in the absence of an appropriate willingness to pay threshold).

[5] The analysis does not meet one or more aspects of the NICE reference case.

[6] Converted from 1997 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 132% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

References

Corapcioglu, F. and N. Sarper. "- Cefepime versus ceftazidime + amikacin as empirical therapy for febrile neutropenia in children with cancer: A prospective randomized trial of the treatment efficacy and cost." - Pediatric Hematology and Oncology 22.1 (2005): 59-70.

Paladino, J. A. Cost effectiveness of cephalosporin monotherapy and aminoglycoside/ureidopenicillin combination therapy: for the treatment of febrile episodes in neutropenic patients. PharmacoEconomics 18(4):369-381. 2000.

Evidence tables

Table A1.3. Evidence table of included economic studies

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Corapcioglu **Year:** 2005 **Country:** Turkey	**Type of analysis:** Cost consequence analysis **Time horizon:** Not reported. **Perspective:** Turkish hospital **Source of effectiveness data:** A prospective	**Inclusion criteria:** Cancer patients under 18 years with fever and neutropenia. (Fever was defined as a single axillary temperature ≥38.5 °C or ≥38°C for ≥ 1h. Neutropenia was defined as an absolute neutrophil count (ANC) less than 500 cells/mm3 or a court <1000 cells/ mm3 with a	**Prophylaxis strategy:** A. Monotherapy with cefepime (150 mg/kg/day in 3 divided doses (maximum daily dose 6g)) B. Dual therapy with ceftazidime (150 mg/kg/day (maximum daily	**Clinical data:** **Strategy A** Duration of neutropenia < 10 days Duration of neutropenia ≥ 10 days Response without modification Median duration of treatment Median duration of hospitalization Median duration of defervescence of fever Median duration of neutropenia Infection-related mortality **Strategy B** Duration of neutropenia < 10 days	13 (52%) 12 (48%) 13 (52%) 9.3 ± 3.5 days 8.6 ± 4.0 days 3.8 ± 2.9 days 7.5 ± 4.0 days 0 9 (36%)	**Conflict of interest:** No. **Comments:** **Applicability:** Partially applicable **Limitation:** Serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	randomized study conducted from March 2003 to March 2004 in Pediatric Hematology-Oncology Unit of Kocaeli University Hospital. **Source of utility data:** Utility data was not considered in the analysis. **Source of cost data:** Not reported **Currency unit:** U.S dollar **Cost year:** 2004 **Discounting:** Health effect: 0% Cost: 0%	predicted decrease to <500 cells/ mm3 within 24-48 h.) **Exclusion criteria:** • Inclusion criteria violations (n=5) • Fever attributed to malignancy (n=1) • Death with chemotherapy toxicity (n=1) • Protocol violations (n=3) **Sample size:** A total of 601 episodes of neutropenic sepsis in 29 patients **Subgroup analysis:** None	dose 6 g) in 3 divided doses) and amikacin (15 mg/kg/day in a single dose). Note: Patients were treated for a minimum of 5 days. Treatment could be stopped only after maintained apyrexia had been observed and the neutrophil count had reached 500/ mm3.	Duration of neutropenia ≥ 10 days Response without modification Median duration of treatment Median duration of hospitalization Median duration of defervescence of fever Median duration of neutropenia Infection-related mortality **Utility score:** Not considered **Cost:** Incremental cost (B-A) **ICER per QALY:** Can't be calculated **Uncertainty:** Sensitivity analysis was not conducted.	16 (64%) 10 (40%) 12.2 ± 5.4 days 11.8 ± 5.6 days 6.5 ± 4.6 days 8.1 ± 4.5 days 0 $4240 (2011 UK pounds: £3357.69)	
Study 2						
Author: Paladino **Year:** 2000 **Country:** The U.S.A	**Type of analysis:** Cost consequence study **Time horizon:** One year **Perspective:** American institutional perspective.	**Inclusion criteria:** Adult cancer patients ≥16 years with febrile neutropenia. Fever was defined as oral temperature ≥ 38°C at least twice during a 24-hour period.	**Chemotherapy:** **Prophylaxis strategy:** A: Monotherapy with cefepime (2g intravenously every 8 hours)	**Clinical data:** **Strategy A** Median days of neutropenia (range) Treatment outcome: Cure (no. (%)) Treatment outcome: Failure (no. (%)) Treatment outcome: indeterminate (no. (%)) Patients experiencing adverse effects (no. (%)) Total adverse effects (no. (%)) Antibacterial-related length of stay (range)	 15 (2-85) 27 (37%) 23 (31%) 24 (32%) 15 (20%) 22 (30%) 16 days (7-49)	**Conflict of interest:** Yes. This study was funded in part by an unrestricted grant from Bristol-Myers

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of effectiveness data: **Source of utility data:** Utility data was not considered in the analysis. **Source of cost data:** Published data, reference community hospital etc. **Currency unit:** U.S dollar **Cost year:** 1997 **Discounting:** Health effect: 0% Cost: 0%	Neutropenia was defined as an absolute neutrophil count (ANC) ≤500 cells/µl or ANC between 500 and 1000 cells/ µl that was expected to fall below 500 cells/ µl within 48 hours. **Exclusion criteria:** Not reported. **Sample size:** A total of 169 episodes in 149 patients **Subgroup analysis:** None	B: dual therapy with gentamicin (1.5mg/kg intravenously every 8 hours) and ureidopenicillin (either piperacillin 3g intravenously every 4 hours in 1 trail or mezlocillin 3g intravenously every 4 hours in a second trial)	Deaths due to any cause (no. (%)) Deaths as cause of treatment failure (no. (%)) **Strategy B** Median days of neutropenia (range) Treatment outcome: Cure (no. (%)) Treatment outcome: Failure (no. (%)) Treatment outcome: indeterminate (no. (%)) Patients experiencing adverse effects (no. (%)) Total adverse effects (no. (%)) Antibacterial-related length of stay (range) Deaths due to any cause (no. (%)) Deaths as cause of treatment failure (no. (%)) **Utility score:** Not considered **Cost:** Incremental cost (B-A) **ICER per QALY:** Can't be calculated **Uncertainty:** Sensitivity analysis was not conducted.	4 (5%) 0 (0%) 12 (1-63) 27 (36%) 31 (41%) 17 (23%) 17 (23%) 20 (27%) 17 days (7-46) 4 (5%) 0 (0%) $1127 (2011 U.K pounds: 1021.42)	Squibb Company. **Comments:** **Applicability:** Partially applicable **Limitation:** Serious limitation.

1

3. Primary or secondary prophylaxis with growth factors (for example granulocyte colony stimulating factor) and/or antibiotics (for example fluoroquinolones).

Review question

What is the most cost-effective prophylaxis strategy of Neutropenic Sepsis for patients receiving anti-cancer treatment?

Question in PICO format

Patients/population	Interventions	Comparisons	Outcomes
Patients receiving anti-cancer therapy	• Primary prophylaxis with quinolones • Primary prophylaxis with G-CSF • Primary prophylaxis with G-CSF and quinolones • Primary prophylaxis with PEG-G-CSF • Secondary prophylaxis with quinolones • Secondary prophylaxis with G-CSF • Secondary prophylaxis with G-CSF and quinolones • Secondary prophylaxis with PEG-G-CSF	• Compared with each other, • Compared with placebo or nothing	• Incremental cost-effectiveness ratio (ICER) • Results of sensitivity analysis

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). The CRD economic studies filter was applied. Studies published prior to 2000 were excluded as they are unlikely to have relevance to current practice and costs. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

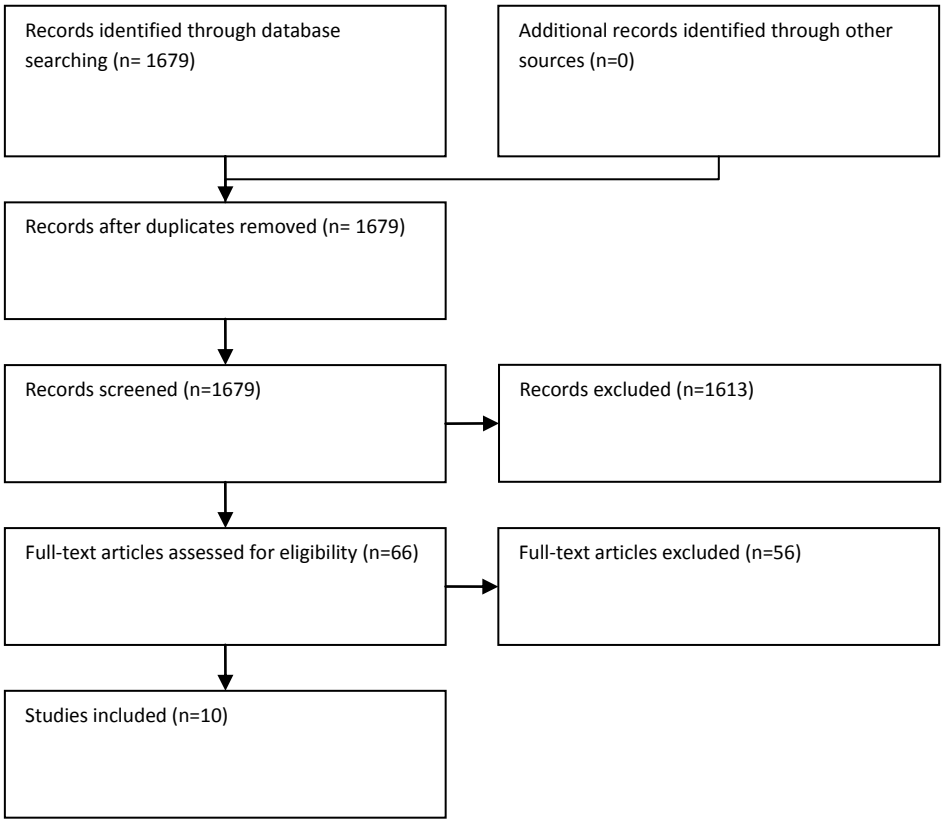
Selection criteria for included evidence:

- Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included (from 2000 to current)
- Studies that were conducted in OECD countries (other than the UK) were included
- Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economist (HJ) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly sixty-six studies and checked against the inclusion criteria.

Results



Characteristics of included studies

Total number of included studies	10 studies
Age group	Adult/elderly: (≥18 y): 10 studies
Treatment category	Solid tumour: 8 studies Non-Hodgkin lymphoma: 2 studies
Colony stimulating factor	G-CSF or PEG-G-CSF

Quality and applicability of the included studies

All included papers were deemed partially applicable to this guideline (Table A1.2). The most common reason for partial applicability was that the analyses did not include all options considered relevant for the topic. For example, most economic studies about G(M)-CSF omit quinoloness. Other reasons for partial applicability included: analysis conducted in countries other than the U.K, health effects not expressed in QALYs etc.

Seven papers were deemed to have very serious limitations. The most common reason for serious limitation was that the analyses considered the combined effectiveness of chemotherapy and G(M)-

CSF, but did not count the cost of chemotherapy at all (six studies) or did not count it properly (one study, Whyte 2011). The other three papers were deemed to have potentially serious limitations. The most common reason for potentially serious limitation was that the analyses did not use data from the best available source (ideally data should come from a recently conducted systematic review).

Table A1.1 Applicability and limitations of included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		Lathia 2009; Timmer-Bonte 2008; Timmer-Bonte 2006
	Very serious limitations		Borget 2009; Danova 2008; Liu 2009; Lyman 2009 (a); Lyman 2009 (b); Ramsey 2009; Whyte 2011

Evidence statements

Ten studies were included for this topic: 8 studies for patients with a solid tumour; and 2 studies for patients with non-Hodgkin lymphoma. No economic evidence has been identified for patients with Hodgkin lymphoma.

Solid tumour (adult/elderly)

Six out of the ten included studies looked at female patients with stage II breast cancer. All six studies had conflicts of interest. Four of these papers (Borget 2009; Danova 2008; Liu 2009; Lyman 2009 (b)) compared primary PEG-G-CSF G(M)-CSF with primary PEG-G-CSF; and all four papers found out PEG-G-CSF is more cost-effective than non-peg G(M)-CSF. One paper (Ramsey 2009) compared primary PEG-G-CSF with secondary PEG-G-CSF and found out the latter strategy is more cost-effective. Only one study (Whyte 2011) compared different types of G(M)-CSF with nothing/placebo; and this paper found out that secondary prophylaxis with PEG-G-CSF is the only strategy that is more cost-effective than nothing/placebo.

Two of the 10 papers identified looked at patients with small-cell lung cancer. Both papers compared non-peg G(M)-CSF + quinolones with quinolones alone; one paper (Timmer-Bonte 2006) looked at primary prophylaxis while another (Timmer-Bonte 2008) looked at secondary prophylaxis. Both papers showed that G(M)-CSF + quinolones is more clinically effective than quinolones alone, but is associated with a very high ICER (£0.291 million per febrile neutropenia free cycle (Timmer-Bonte 2008) and £329.282 per percent decrease of the probability of febrile neutropenia (Timmer-Bonte 2006)). No conflicts of interest have been declared for these two papers.

Non-Hodgkin lymphoma (adult/elderly)

Two out of ten included studies looked at elderly patients with non-Hodgkin lymphoma. The base-case analysis for both studies considered a cohort of 64-year-old men and women. Lyman 2009(a) compared primary non-peg G(M)-CSF with PEG-G-CSF, and found out that PEG-G-CSF is more cost-effective. Lathia 2009 compared three prophylaxis strategies: primary non-peg G(M)-CSF, primary

PEG-G-CSF and nothing/placebo, and found out that the ICER associated with non-peg G(M)-CSF and PEG-G-CSF is £0.993 million/QALY and £2.523 million/QALY separately, comparing to nothing/placebo.

Note:

[1] Converted from 2005 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 109% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[2] Converted from 2002 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[3] Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

GRADE table of included studies

1 ***Table A1.2. Modified GRADE table of included economic studies***

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2010 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Borget 2009	Very serious limitations [1]	Partially applicable [2]	A theoretical cohort of women with breast cancer. The base case is a 45-year-old woman with stage II breast cancer receiving four cycles of chemotherapy with a ≥20% risk of febrile neutropenia (FN).	Primary filgrastim (11-day)	Primary PEG-G-CSF	£1282.78 [3]	<0 QALYs	Dominated	Results were also robust to changes in model inputs.
				Primary filgrastim (6-day)	Primary PEG-G-CSF	- £506.69 [3]	-0.106 QALYs	£4770.00 per QALY gained [3]	
Danova 2008	Very serious limitations [4]	Partially applicable [5]	A hypothetical cohort of 45-year-old women with stage II breast cancer receiving 4 cycles of chemotherapy associated with a ≥20% risk of FN.	Primary PEG-G-CSF	Primary filgrastim (6-day)	£36.70 [6]	0.10 QALYs	£349.86 per QALY gained [6]	One-way and two-way sensitivity analysis was conducted but range of ICER was not reported. The paper only reported when the highest PEG-G-CSF and the lowest filgrastim price were used, ICER is still below per £43,522 [6] QALY.
Lathia 2009	Potentially serious limitations [7]	Partially applicable [8]	Patients with diffuse large B-cell lymphoma (the most common subtype of non-Hodgkin Lymphoma) receiving induction chemotherapy. Base-case analysis considered a cohort of 64-year-old men and women	Primary filgrastim (did not report if it is 6 or 11 days)	Nothing	£1992.48 [9]	0.002 QALYs	£0.99 million per QALY gained [9]	All one-way sensitivity analysis yielded ICERs of greater than £0.58 million [9] per QALY gained.
				Primary PEG-G-CSF	Nothing	£5765.08[9]	0.004 QALYs	£2.52million[9] per QALY gained	
Liu 2009	Very serious limitations [10]	Partially applicable [11]	Women aged 30-80 years with early stage (I-III) breast cancer receiving	Primary PEG-G-CSF	Primary filgrastim (6-day)	£505.54[12]	0.052 QALYs depends on scenarios	£ 9773.87 [12] per QALY gained	When the relative risk of FN was ≤1.3 for 6-day filgrastim versus pegfilgastim, the ICER exceeded £34390.80 [12] per
				Primary	Primary	£ 1046.63[12]	-0.028 QALYs	Dominated	

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2010 £)*	*Incremental effects*	*ICER*	*Uncertainty*
			myelosuppressive chemotherapy with an overall FN risk of approximately ≥20%	filgrastim (11-day)	PEG-G-CSF		depends on scenarios		QALY gained. Results were also sensitive to the cost of pegfilgastim, the cost of filgrastim, baselineFN risk, RR of death related to RDI<85% and FN case-fatality. However, when these variables were varied within the plausible ranges, the ICERs did not exceed £13756.32 [12] per QALY gained.
Lyman 2009 (a)	Very serious limitations [13]	Partially applicable [14]	A hypothetical cohort of patients with intermediate- or high-grade non-Hodgkin lymphoma receiving myelosuppressive chemotherapy (e.g, CHOP-21) with an FN risk of approximately ≥20%. A 65-year-old was chosen as base line.	Primary PEG-G-CSF	Primary filgrastim (6-day)	£192.96[15]	Range: 0.042-0.155 QALYs (depends on scenarios)	Range: £1244.61-4594.00 [15] per QALY gained (depends on scenarios)	The probability for PEG-G-CSF to become more cost-effective over filgrastim was 50% with the threshold of £11132.47[15] per QALY gained, 80% for £ 22264.94[15]per QALY gained, and 91% for £37108.23 [15] per QALY gained.
Lyman 2009 (b)	Very serious limitations [16]	Partially applicable [17]	Women 30-80 years with early stage (I to III) breast cancers who were receiving adjuvant myelosuppressive chemotherapy and had an FN risk of ≥20%.	Primary filgrastim (6-day)	Primary PEG-G-CSF	-£ 1005.63 [18]	Range: -(0.043-0.094) QALYs depends on scenarios	Range: -£(10698.30-23386.35) [18] per QALY gained	Probabilistic sensitivity analysis show that the probability that strategy A is cost-effective compared with B was 50% for a threshold value of £14843.29[18] per QALY gained, 80% for a threshold value of £22264.94 [18] per QALY gained, and 90% for a threshold value of £29686.58[18] per QALY gained.
				Primary filgrastim (11-day)	Primary PEG-G-CSF	-£ 4899.77 [18]	-(0.022-0.050) QALYs depends on scenarios	Dominated	
Ramsey 2009	Very serious limitations [19]	Partially applicable [20]	Women aged 30 to 80 years with early stage (I to III) breast cancer receiving myelosuppressive	Primary PEG-G-CSF	Secondary PEG-G-CSF	£6459.06 [21]	0.076 QALYs	£86091.09 [21] per QALY gained	One-way: when FN case fatality was less than 2%, the ICER exceeded £148432.92 [21] per QALY gained.

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2010 £)*	*Incremental effects*	*ICER*	*Uncertainty*
			chemotherapy with an FN risk of approximately 20%. The reference patient was 49 years old with stage II breast cancer receiving six cycles of chemotherapy.						The probability that pegfilgastim primary prophylaxis would be considered cost-effective at the threshold value compared with secondary prophylaxis was 12% for a WTP of £37108.23[21] per QALY gained, 40% of a WTP of £74216.46 [21] per QALY gained, and 75% for a WTP of £148432.92[21] per QALY gained.
Timmer-Bonte 2008	Potentially serious limitations [22]	Partially applicable [23]	Patients with small cell lung cancer at risk of FN defined as 60 years of age or older, extensive disease, a Karnofsky performance stats of 40% to 70%, and/or having received prior chemotherapy. Patients have received primary prhophylaxis with antibiotics or with antibiotics plus G(M)-CSF.	Secondary antibiotics + G(M)-CSF	Secondary antibiotics	£4970.03 [24]	0.02 FN-free cycle	£0.29 million [24] per FN free cycle	Result is robust to probability of FN and treatment cost of FN (although when using higher FN-related costs, the strategies are less distinct in their monetary effects, but still favour antibiotics).
				Secondary sequential approach (Antibiotics after the first episode of FN and antibiotics plus G(M)-CSF after another episode of FN.)	Secondary antibiotics	£1839.87 [24]	-0.11 FN-free cycle	Dominated	
Timmer-Bonte 2006	Potentially serious limitations	Partially applicable [26]	Small-cell lung cancer patients receiving standard dose	Primary antibiotics + G(M)-CSF	Primary antibiotics	First cycle: £611.78[27]	First cycle: 14% decrease of the	First cycle: £44.98 [27] per percent	Sensitivity analysis has only been conducted for cycle 1. G(M)-CSF is cost saving if the

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2010 £)*	*Incremental effects*	*ICER*	*Uncertainty*
	[25]		chemotherapy.			Entire treatment period: £4609.04 [27]	probability of FN Entire treatment period: 23% decrease of the probability of FN	decrease of the probability of FN Entire treatment: £329.28 [27] per percent decrease of the probability of FN	probability of FN is more than 84%, the price of prophylactic G(M)-CSF is less than £421.95 [27] per patient, or the cost of an episode of FN amount to greater than £10366.07 [27]. The acceptability for the willingness to pay was approximately 50%.
Whyte 2011	Very serious limitations [28]	Partially applicable [29]	The base case consisted of a cohort of 52-year-old female patients diagnosed with stage II breast cancer in line with data on presenting characteristics.	Secondary lenograstim (11 days)	Nothing	£968 [30]	0.023 QALYs	Dominated	Results are highly sensitive to baseline FN risk. When willingness to pay is £20,000 per QALY, for a patient with a FN risk level of 11% -37%, secondary PEG-G-CSF is most cost-effective; for patients with a higher risk level, primary PEG-G-CSF is the most cost-effective. Using a WTP threshold of £30,000, primary prophylaxis with PEG-G-CSF was cost-effective for baseline FN risks greater than 29%.
				Secondary lenograstim (6 days)	Nothing	£462	0.023 QALYs	Dominated	
				Secondary filgrastim (11 days)	Nothing	£852	0.024 QALYs	Dominated	
				Secondary filgrastim (6 days)	Nothing	£397	0.024 QALYs	Dominated	
				Secondary PEG-G-CSF	Nothing	If baseline risk =24%: £274 If baseline risk =31%:£253	If baseline risk =24%: 0.042 QALYs If baseline risk =31%: 0.069 QALYs	If baseline risk =24%: £6,500 per QALY gained If baseline risk =31%: £3,651 per QALY gained	

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2010 £)*	*Incremental effects*	*ICER*	*Uncertainty*
				Primary lenograstim (11 days)	Nothing	£8326	0.075 QALYs	Dominated	
				Primary lenograstim (6 days)	Nothing	£4355	0.075 QALYs	Dominated	
				Primary filgrastim (11 days)	Nothing	£7434	0.077 QALYs	Dominated	
				Primary filgrastim (6 days)	Nothing	£3865	0.077 QALYs	Dominated	
				Primary PEG-G-CSF	Nothing	If baseline risk =24%: £3559 If baseline risk =31%:£3252	If baseline risk =24%: 0.128 QALYs If baseline risk =31%:0.181 QALYs	If baseline risk =24%: £38,482 per QALY gained If baseline risk =31%: £26,824 per QALY gained	

[1] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
[2] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study doesn't look at all interventions of interest. Health effects are not discounted at an annual rate of 3.5%.
[3] Uprated from 2006 British Pounds using inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[4] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Have conflicts of interest.
[5] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in Italy, not in the U.K. Doesn't look at all interventions of interest.

[6] Converted from 2008 Italian Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 105% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[7] Only the abstract of this study has been published at the moment, so it is unclear whether all input data of this study come from the best available source.
[8] This study is conducted in Canada, not in the U.K. Doesn't look at all interventions of interest.
[9] Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[10] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. No costs were modelled beyond 1 year; while on the other hand, the effectiveness was modelled for lifetime. Have conflicts of interest.
[11] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study doesn't look at all interventions of interest.
[12] Uprated from 2006 British Pounds using inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[13] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
[14] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the U.K. Doesn't look at all interventions of interest.
[15] Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[16] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
[17] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the U.K. Doesn't look at all interventions of interest.
[18] Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[19] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
[20] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the U.K. Doesn't look at all interventions of interest.
[21] Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[22] Not all estimates of input data come from the best available source (systematic review).
[23] This study is conducted in the Netherlands, not in the U.K. Doesn't look at all interventions of interest. The value of health effects is not expressed in terms of quality-adjusted life years (QALYs).
[24] Converted from 2005 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 109% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[25] Not all estimates of input data come from the best available source (systematic review).
[26] This study is conducted in the Netherlands, not in the U.K. Doesn't look at all interventions of interest. The value of health effects is not expressed in terms of quality-adjusted life years (QALYs).
[27] Converted from 2002 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[28] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF. Part of the effectiveness data (survival rates for breast cancer patients) was obtained from Cancer Research U.K. However it is noted that the survival data of Cancer Research U.K related to breast cancer patients who are receiving all kinds of treatment (chemotherapy, surgery, radiotherapy etc), not only patients who are receiving chemotherapy alone. Therefore this study is likely to significantly over-estimate the effectiveness of chemotherapy and G-CSF.
[29] This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. Didn't look at all interventions of interest.

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Evidence tables

Table A1.3. Evidence table of included economic studies

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Borget. I **Year:** 2009 **Country:** France, U.K (only data of the U.K setting were reported here) **Setting:** Primary prophylaxis	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analytic Model **Time horizon:** Life-time. **Perspective:** French and U.K healthcare payer. **Source of base-line data:** National statistics. **Source of effectiveness data:** Literature review and expert consensus. **Source of utility data:** Literature review and expert consensus. **Source of cost data:** **Drug costs**: the British	**Inclusion criteria:** A theoretical cohort of women with breast cancer. The base case is a 45-year-old woman with stage II breast cancer receiving four cycles of chemotherapy with a ≥20% risk of febrile neutropenia. **Exclusion criteria:** Not reported. **Sample size:** Not reported. **Age:** 45 y **Gender:** **Male:** 0% **Female:** 100% **Risk of NS:** ≥20% **Subgroup analysis:** None	**Chemotherapy:** **Type and dose:** Not reported. **Reduction after NS?** ≥15% dose reduction is possible **No. of cycles:** 4. **Prophylaxis strategy:** E. With pegfilgrastim F. With 11 days of filgrastim G. With 6 days of filgrastim	**Clinical data:** **1. Risk of febrile neutropenia** Baseline risk Strategy A Strategy B Strategy C **2. FN case-fatality among hospitalised FN patients** **3. RDI<85%** Among patients who experience neutropenia Baseline value Among patients who received strategy A Among patients who received strategy B Among patients who received strategy C **4. Impact of RDI<85% on long-term survival** **Utility score:** Breast cancer during chemotherapy FN hospitalisation Breast cancer in years 1-5 Breast cancer after year 5 Incremental QALYs (B-A) Incremental QALYs (C-A)	 24% 7% 12.5% 17.5% 3.4% 40% 9% 11.1% 12.7% 14.2% Hazard ratio: 1.32 0.70 0.33 0.86 0.96 <0 (exact value not reported) -0.106	**Conflict of interest:** Medical writing support (funded by Amgen) was provided by Dawn Batty, from Bioscript Stirling Ltd. Amgen commented on the manuscript. **Comments:** **Applicability:** Partially applicable **Limitation:** Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	National Formulary tariff. **Others:** literature review. **Currency unit:** GBP for the U.K. **Cost year:** U.K: 2006 **Discounting:** Health effect: not reported. Cost: 3%			**Cost:** Incremental cost (B-A) Incremental cost (C-A) **ICER per QALY:** B v.s A C v.s A **Uncertainty:** One-way and multi-way sensitivity analyses have been done; however no detailed outcome were reported. The paper only mentioned that 'these results were also robust to changes in model inputs'.	£1119 (U.K 2011 price: £1282.78) -£442 (U.K 2011 price:-£ 506.69) A dominates. £4161 (U.K 2011 price: £4770.00)	
Study 2						
Author: Danova.M **Year:** 2008 **Country:** Italy **Setting:** Primary prophylaxis in inpatient setting.	**Type of analysis:** Cost-effectiveness analysis. **Model structure:** Markov model **Time horizon:** Life-time **Perspective:** NHS in Italy. **Source of base-line**	**Inclusion criteria:** A hypothetical cohort of 45-year-old women with stage II breast cancer receiving 4 cycles of chemotherapy associated with a ≥20% risk of FN. **Exclusion criteria:** Not reported. **Sample size:** Not reported.	**Chemotherapy:** **Type:** Not reported **Dose:** For pegfilgrastim: RDI<85%:11.1% For filgrastim: RDI<85%: 14.2% **Reduction after NS?** Yes. If a patient survives from a FN, she an also experience a	**Clinical data:** FN risk of strategy A FN risk of strategy B RR of FN (A v.s B) FN case-fatality (among hospitalized FN patients) RR of FN for age≥65 y v.s <65y RR of death for RDI<85% v.s RDI≥85% RR of <85% RDI for age ≥65 v.s <65% y **Utility:** For breast cancer during chemotherapy FN hospitalization Breast cancer in years 1-5	7.0% 17.5% 2.50% 3.4% (0-7%) 1.18 (1-1.76) 1.32 (1-1.8) 1.33 (1.33-1.48) 0.70 (0.50-0.90) 0.33 (0.24-0.42) 0.86 (0.3-0.9)	**Conflict of interest:** Not reported. However, the 2nd author works for Amgen Italy; and the 4th author works for Cerner LifeSciences (consulting company), USA.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	data: Literature review (PubMed 1990-2007). **Source of effectiveness data:** Literature review (PubMed 1990-2007). **Source of utility data:** Literature review of studies either using visual analogue scales or standard gamble methods. **Source of cost data:** Highest price: 'Listed price' of the Italian NHS. Lowest price: minimum observed price in Italy. Hospitalization cost come from literature review. **Currency unit:** Euro. **Cost year:** 2008 **Discounting:** Health effect: Not reported Cost: Not reported	**Age:** >45 y **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** ≥20% **Subgroup analysis:** None.	reduction and/or delay in chemotherapy, leading to a RDI<85% at the end of chemotherapy. **Cycles:** 4 **Prophylaxis strategy:** A. Pegfilgastim B. 6-day filgrastim	Breast cancer in years after year 5 Incremental QALYs (A-B) **Cost:** Incremental cost (A-B) **ICER:** Strategy A v.s B **Uncertainty:** One-way sensitivity analysis shows the results were most sensitive to the RR of FN for 6-day filgrastim v.s pegfilgrastim, moderately sensitive to the costs of pegfilgastim, filgarastim, FN hospitalization, drug administration and the number of chemotherapy cycles. Two-way sensitivity analysis shows the result is insensitive to the costs of filgarstim and pegfilgastim.	0.96 (0.5-1) 0.10 €45/person (2011 UK price: £36.70) € 429 (2011 UK price:£ 349.86)	**Comments:** Patients who have experienced 1 episode of FN are at increased risk of developing FN in subsequent cycles, this paper captured this cost by adding the cost of subsequent care (including additional hospitalizations and outpatient care) to the cost of initial hospitalization. **Applicability:** Partially applicable **Limitation:** Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 3						
Author: Lathia N. **Year:** 2009 **Country:** Canada **Setting:** Primary prophylaxis	**Type of analysis:** Cost-effectiveness (utility) analysis. **Model structure:** Markov model. **Time horizon:** Six cycles (18 weeks) **Perspective:** Hospital **Source of base-line data:** Not reported. **Source of effectiveness data:** Meta-analysis of published studies (for filgrastim) or single study (for pegfilgrastim) **Source of utility data:** Obtained from study conducted at SHSC (Lathia N, Univ of Toronto, 2008) **Source of cost data:** Institutional costs of filgrastim and pegfilgrastim obtained from Sunnybrook Health	**Inclusion criteria:** Patients with diffuse large B-cell lymphoma (the most common subtype of non-Hodgkin Lymphoma) receiving induction chemotherapy. Base-case analysis considered cohort of 64-year-old men and women, reflecting median age of diagnosis **Exclusion criteria:** Not reported. **Sample size:** **Age:** **Gender:** n/N **Male:** Not reported. **Female:** Not reported. **Risk of NS:** Not reported. **Subgroup analysis:** None.	**Chemotherapy:** **Type and dose:** Combination immuno-chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednosone (R-CHOP) **Reduction after NS?** Not reported. **Cycles:** 6 **Prophylaxis strategy:** A. Nothing B. Filgrastim C. Pegfilgrastim	**Clinical data:** **Risk of FN:** Risk of FN (strategy A) Risk of FN (strategy B) Risk of FN (strategy C) **Death rate** **Cost data:** Incremental cost (B-A) Incremental cost (C-A) **Utility:** Decrement due to FN Incremental QALYs (B-A) Incremental QALYs (C-A) **ICER:** B v.s A C v.s A **Uncertainty:** All one-way sensitivity analysis yielded ICERs of greater than $1 millon/QALYs.	 Not reported. 36% 21% Not reported. $3406 (2011 UK price: £1992.48) $9855(2011 UK price: £5765.08) 0.15 0.002 0.004 1.7 million (2011 UK price: £0.99 million) 4.3 million (2011 UK price: £2.52million)	**Conflict of interest:** No relevant conflicts of interest to disclose. Funding for travel to the 51st ASH Annual Meeting was provided by the Toronto Health Economics and Technology. **Comments:** Only abstract of this paper has been published at the moment. The full-text of this paper has been submitted for publication. **Applicability:** Partially applicable **Limitation:** Potentially serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Sciences Centre (SHSC). Cost of hospitalization for FN obtained from study conducted at SHSC (Lathia N, Univ of Toronto, 2008) **Currency unit:** Canadian dollar. **Cost year:** 2009 **Discounting:** Not reported.			(2011 UK price: £0.58 million)		
Study 4						
Author: Liu.Z **Year:** 2009 **Country:** U.K **Setting:** Primary prophylaxis	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision-analytic model **Time horizon:** Life-time. **Perspective:** U.K NHS. **Source of base-line data:** Literature review of PubMed, EmBASE, and the Cochrane database from 1990 to 2007, validated by the experts	**Inclusion criteria:** Women aged 30-80 years with early stage (I-III) breast cancer receiving myelosuppressive chemotherapy with an overall FN risk of approximately 20% or higher. The base case considered 45-year-old patients with stage II breast cancer, each receiving four cycles of chemotherapy. **Exclusion criteria:** Not reported. **Sample size:** Not reported.	**Chemotherapy:** **Type and dose:** Myelosuppressive chemotherapy such as: Docetaxel /doxorubicin/ cyclophosphamide **Reduction after NS?** 15% dose reduction is possible. **Cycles:** 4 **Prophylaxis strategy:** A. Pegfilgrastim B. 6-day filgrastim C. 11-day filgrastim	**Clinical data:** **Risk of FN:** Risk of FN without G-CSF Risk of FN (strategy A) Risk of FN (strategy B) Risk of FN (strategy C) RR of FN: (b v.s a) RR of FN: (c v.s a) **Patients receiving RDI<85%:** Patients receiving RDI<85% (strategy A) Patients receiving RDI<85% (strategy B) Patients receiving RDI<85% (strategy C) **Death rate** FN case-fatality (death among hospitalized FN patients) RR of death (over 30 y) for patients receiving RDI<85% vs ≥85%	 24% 7% 17.5% 12.5% 2.50 1.79 11.1% 14.2% 12.7% 3.4% 1.32	**Conflict of interest:** Funded by Amgen (Europe) GmbH. **Comments:** **Applicability:** Partially applicable **Limitation:** Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of effectiveness data: Literature review of PubMed, EmBASE, and the Cochrane database from 1990 to 2007, validated by the experts. **Source of utility data:** Identified from several studies that applied either visual and analogue scales or Standard Gamble methods, and were all obtained from health professionals rather than being population based. **Source of cost data:** G-CSF cost: British national formulary tariff (2006). Drug administration, FN hospitalization etc were from literature review. **Currency unit:** U.K pounds. **Cost year:** 2006 **Discounting:**	**Age:** 30-80 y **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** ≥20% **Subgroup analysis:** None.		**Impact of age** FF of FN for patients aged≥65y v.s <65y RR of <85% for patients aged≥65 v.s <65y **Cost data:** Incremental Cost (B-A) Incremental Cost (C-A) **Utility data:** Breast cancer during chemotherapy FN hospitalization Breast cancer in years 1-5 Breast cancer in years after year 5 Incremental QALYs (B-A) Incremental QALYs (C-A) **ICER:** B v.s A C v.s A **Uncertainty:** Sensitivity analysis shows that when comparing strategy A v.s strategy B, results were most sensitive to the RR of FN for 6-day filgrastim versus pergilgastim. When the RR of FN was ≤1.3 for 6-day filgrastim versus pegfilgastim, the ICER exceeded £ 30000/QALY (2011 UK Price: £34390.80) gained. Results were also sensitive to the cost of pegfilgastim, the cost of filgrastim,	 1.26 1.38 -£441 (2011 UK Price: -£505.54) £913 (2011 UK Price:£ 1046.63) 0.70 0.33 0.86 0.96 -0.052 -0.028 £ 8526/QALY (2011 UK Price:£ 9773.87) Dominated.	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Health effect: 3%/year Cost: 0%			baselineFN risk, RR of death related to RDI<85% and FN case-fatality. However, when these variables were varied within the plausible ranges, the ICERs did not exceed £ 12000/QALY (2011 UK Price: £13756.32) gained.		
Study 5						
Author: Lyman G. **Year:** 2009 **Country:** The U.S **Setting:** Primary prophylaxis in inpatient or outpatient. This study assumes that 80% of patients with FN were hospitalized, with the other 20% were managed in outpatient setting.	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analytic model **Time horizon:** Life-time horizon (about 35 years) **Perspective:** Payer. **Source of base-line data:** Adjusted from literature review. **Source of effectiveness data:** Literature review. **Source of utility data:** EQ-5D in an NHL (non-Hodgkin's lymphoma) population when available and were used	**Inclusion criteria:** A hypothetical cohort of patients with intermediate- or high-grade NHL receiving myelosuppressive chemotherapy (e.g, CHOP-21) with an FN risk of approximately 20% or higher. A 65-year-old was chosen as base line. **Exclusion criteria:** Not reported. **Sample size:** N/A (hypothetical cohort). **Age:** Not reported. **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** ≥20%	**Chemotherapy:** **Type and dose:** Adjuvant myelosuppressive chemotherapy. **Reduction after NS?** 15% dose reduction is possible **Cycles:** one course of chemotherapy. **Prophylaxis strategy:** A. Pegfilgrastim B. 6-day filgrastim	**Clinical data:** Baseline FN risk FN risk of strategy B RR of FN for strategy A v.s A FN risk of strategy A Inpatient FN case-fatality Outpatient FN case-fatality Impact of RDI<90% on long-term survival (hazard ratio) RR of FN for age≥65y v.s. age <65y RR of ≤90% RDI for ≥65 v.s. <65y **Utility:** NHL during chemotherapy FN hospitalization NHL in year 1 NHL in years after year 1 Incremental QALYs (A-B) **Cost:** Incremental cost (A-B) **ICER:**	27.9% 25.1% 1.92 13.1% 5.8% 0.5% 1.82 1.32 1.42 0.61 0.33 0.79 0.89 (depends on scenarios) 0.042-0.155 $260 (2011 UK Price: £192.96)	**Conflict of interest:** Funded by Amgen, Inc. Dr. Lyman provides consulting services to the pharmaceutical industry. A.L. and R.W.D. are employed by Cerner LifeSciences, which provides consulting services to the pharmaceutical industry. R.B. is an employee of Amgen, Inc. **Comments:** The recurrence risk of FN was indirectly modelled by

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	to calculate QALY. **Source of cost data:** Center for Medicare and Medicaid services or literature review. **Currency unit:** U.S dollar. **Cost year:** 2006 **Discounting:** Health effect: 3%/year Cost: 0%	**Subgroup analysis:** None.		A v.s B **Uncertainty:** One-way sensitivity analysis shows that in scenario 2, the results were sensitive to cost of pegfilgrastim, RR of FN between A and B, FN case-fatality rate, cost of filgrastim, baseline FN risk, cost of administering filgrastim, cost of initial FN hospitalization, and FN RR reduction. Probabilistic sensitivity analyses shows strategy A would be considered cost-effective over strategy B was 50% with the threshold of $15000/QALY (2011 UK Price: £11132.47) gained, 80% for $30000/QALY (2011 UK Price: £ 22264.94) gained, and 91% for $50000/QALY (2011 UK Price: £37108.23) gained.	$1677-6190 (2011 UK Price: £1244.61-4594.00)	taking into account the cost associated with repeated hospitalizations. **Applicability:** Partially applicable **Limitation:** Very serious limitations
Study 6						
Author: Lyman G **Year:** 2009 **Country:** The U.S **Setting:** Primary prophylaxis.	**Type of analysis:** Cost-effectiveness analysis. **Model structure:** Decision analytic model. **Time horizon:** Lifetime. **Perspective:** Health payer.	**Inclusion criteria:** Women 30 to 80 years of age with stage I to III breast cancers who were receiving adjuvant myelosuppressive chemotherapy and had an FN risk of ≥20%. **Exclusion criteria:** Not reported.	**Chemotherapy:** **Type and dose:** Myelosuppressive chemotherapy **Reduction after NS?** 15% dose reduction is possible. **Cycles:** 4 **Prophylaxis**	**Clinical data:** **Risk of FN** Baseline probability of FN Probability of FN with strategy B Probability of FN with strategy C Probability of FN with strategy A RR of FN: B v.s A RR of FN: C v.s A **Percentage of patients with RDI<85%** Strategy B Strategy C	 24% 17.5% 12.5% 7% 2.5 1.79 14.2% 12.7%	**Conflict of interest:** Cerner LifeSciences, Beverly Hills, California.(consulting company) Dr. Lyman has received research grant support and is a

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
This paper assumed that 80% of patients with FN were hospitalized and that 20%were undergoing outpatient management.	**Source of base-line data:** Literature review. **Source of effectiveness data:** Literature review of PubMed, EMBASE, and the Cochrance database from 1990 to 2007. **Source of utility_data:** QALYs were calculated from numeric ratings of the desirability of a particular health outcome. **Source of cost_data:** Centres for Medicare & Medicaid Service, literature review **Currency unit:** U.S dollars. **Cost year:** 2006 **Discounting:** Health effect: 3-5% Cost: 0%	**Sample size:** Not reported. **Age:** 30-80 y **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** ≥20% **Subgroup analysis:** None.	**strategy:** A. Pegfilgrastim B. 6-day filgrastim C. 11-day filgrastim	Strategy A **FN case-fatality** FN case-fatality (in-patient setting) FN case-fatality (out-patient setting) Impact of RDI<85% on long-term survival (hazard ratio or RR) **Age impact** RR of FN for age≥65 y v.s <65 y RR of <85% RDI for age≥65 vs <65 y **Utility:** Breast cancer during chemotherapy FN hospitalization Breast cancer survivors in years 1-5 Breast cancer survivors after years 5 Incremental QALYS (B-A) Incremental QALYS (C-A) **Cost:** Incremental cost (B-A) Incremental cost (C-A) **ICER:** B v.s A	11.1% 3.4% 0.5% 1.32 1.26 1.38 0.70 0.33 0.86 0.96 (depends on scenarios) -(0.043-0.094) -(0.022-0.050) -$1355 (2011 UK Price: -£ 1005.63) -$6602 (2011 UK Price:-£ 4899.77) -$14415-31511 (2011 UK Price:-£ (10698.30-	member of the speakers' bureau of Amgen. Ms. Lalla is an employee of a consulting company that works with pharmaceutical manufacturers. Mr. Barron is an employee of Amgen and owns stock options in Amgen. Dr. Dubois is an employee of a consulting company that works with pharmaceutical manufacturers. **Comments:** Risk of reoccurance of FN was indirectly captured in the model by taking into account the cost associated with repeated

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				C v.s A **Uncertainty:** In the analysis of strategy A v.s B, the results were sensitive to: inpatient FN case-fatality rate, cost of pegfilgrasim and filgrastim, baseline probability of FN< RR of FN between filgrasatim and pegfilgrastim, and cost of administration of filgrastim. Probabilistic sensitivity analysis show that the probability that strategy A is cost-effective compared with B was 50% for a threshold value of $20000 (2011 U.K price: £14843.29) per QALY gained, 80% for a threshold value of $30000 (2011 U.K price: £22264.94) per QALY gained, and 90% for a threshold value of $40000 (2011 U.K price: £29686.58) per QALY gained.	23386.35)) Dominated	hospitalizations. **Applicability:** Partially applicable **Limitation:** Very serious limitations
Study 7						
Author: Ramsey S. **Year:** 2009 **Country:** The U.S.A **Setting:** Primary and secondary prophylaxis	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analysis model **Time horizon:** Lifetime **Perspective:** Health payer **Source of effectiveness data:** Literature review	**Inclusion criteria:** Women aged 30 to 80 years with stage I to III breast cancer receiving myelosuppressive chemotherapy with an FN risk of approximately 20%. The reference patient was 49 years old with stage II breast cancer receiving six cycles of chemotherapy. **Exclusion criteria:**	**Chemotherapy:** **Type and dose:** Docetaxel, doxorubicin/docetaxel, or docetaxel/ doxorubicin/ cyclophosphamide. **Reduction after NS?** 15% dose reduction is possible. **Cycles:** 1	**Clinical data:** **Incidence of FN:** Secondary prophylaxis (no G-CSF) FN RRR: Strategy B v.s Strategy A FN risk with primary prophylaxis **Mortality:** FN case fatality (inpatient) FN case fatality (outpatient) **Utility:** Breast cancer during chemotherapy FN hospitalization Breast cancer in years 1-5 Breast cancer after year 5	 24.6% 73.58% 6.5% 3.4% 0.5% 0.70 0.33 0.86 0.96	**Conflict of interest:** Funded by Amgen Inc., Thousand Oaks, CA, USA. **Comments:** Recurring FN events were indirectly modelled by taking into account the cost associated with

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of utility data: Literature review **Source of cost data:** Literature review and the Current Procedure Terminology codes. **Currency unit:** U.S dollars **Cost year:** 2006 **Discounting:** **Health effect**: Not reported. **Cost:**	Not reported. **Sample size:** Not reported. **Age:** 30-80 years. **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** 20%	**Prophylaxis strategy:** A. Pegfilgrastim (secondary prophylaxis) B. Pegfilgrastim (primary prophylaxis)	Total QALYs (Strategy A) Total QALYs (Strategy B) Incremental QALYs (B-A) **Cost:** Incremental cost (B-A) **ICER:** B v.s A **Uncertainty:** **One way sensitivity analysis:** When FN case fatality was less than 2%, the ICER exceeded $200,000/ QALY (2011 UK price: £148432.92) gained. When varying all other variables within the specified ranges, the ICER did not exceed $200,000/QALY gained except for when the age at diagnosis was near 80years. **Probabilistic sensitivity analysis:** The probability that pegfilgastim primary prophylaxis would be considered cost-effective at the threshold value compared with secondary prophylaxis was 12% for a WTP of $50,000/QALY (2011 U.K Price £37108.23) gained, 40% of a WTP of $100,000/QALY ((2011 U.K Price £74216.46) gained, and 75% for a WTP of	14.487 14.563 0.076 $8703 (2011 UK Price: £6459.06) $116,000 (2011 UK Price: £86091.09)	repeated hospitalizations. **Applicability:** Partially applicable **Limitation:** Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				$200,000/QALY (2011 UK price: £148432.92) gained.		
Study 8						
Author: Timmer-Bonte JN **Year:** 2008 **Country:** The Netherlands **Setting:** Secondary prophylaxis	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Markov model **Time horizon:** five cycles of chemotherapy **Perspective:** Health care payer for the Netherlands **Source of effectiveness data:** Mainly from a randomized phase III study in SCLC (small-cell lung cancer) patients: Timmer-Bonte JN 2005. Data from other published sources were used. **Source of utility data:** Utility data hasn't been used in the model. **Source of cost data:** Mainly from a randomized phase III study in SCLC (small-	**Inclusion criteria:** Patients at risk of FN defined as 60 years of age or older, extensive disease, a Karnofsky performance stats of 40% to 70%, and/or having received prior chemotherapy. Patients have received primary prhophylaxis with antibiotics or with antibiotics plus G-CSF. **Exclusion criteria:** Not reported. **Sample size:** 175 **Age:** ≥60y **Gender:** n/N **Male:** Not reported. **Female:** **Risk of NS:** Not reported. Patients are 60 years of age or older, with extensive disease, a Karnofsky performance stats of 40% to 70%	**Chemotherapy:** **Type and dose:** Cyclophosphamide, doxorubicin, and etoposide every 3 weeks. **Reduction after NS?** An episode of FN without prophylaxis always leads to modification of therapy. **Cycles:** 5 **Prophylaxis strategy:** A. Antibiotics alone (secondary) B. Antibiotics + G-CSF (secondary) C. Antibiotics after the first episode of FN and antibiotics plus G-CSF after another episode of FN. (secondary)	**Clinical data:** **Incidence of FN:** Cycle 1 Cycle 2 Cycle 3 Cycle 4 **Mortality:** No significant difference **Utility:** (Effect was defined as an FN-free cycle, not QALYs) Incremental QALYS (B-A) Incremental QALYS (C-A) **Cost:** Incremental cost (B-A) Incremental cost (C-A) **ICER** (Incremental cost per FN-free cycle): B v.s A C v.s A	A B C 0.23 0.20 0.23 0.15 0.33 0.33 0.13 0.50 0.50 0.08 0.50 0.50 A B C 0.02 -0.11 € 5824 (U.K 2011 price: £4970.03) € 2156 (U.K 2011 price: £1839.87) € 343,110 (U.K 2011 price: £0.29 million) Dominated	**Conflict of interest:** Supported by a research grant from the Dutch Healthcare Insurance Board (OG 99 053). No potential conflicts of interest. **Comments:** **Applicability:** Partially applicable **Limitation:** Potentially serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	cell lung cancer) patients: Timmer-Bonte JN 2005. Data from other published sources were used. **Currency unit:** Euros **Cost year:** 2005 **Discounting:** **Health effect**: Not reported **Cost:** Not reported			**Uncertainty:** This conclusion (Strategy A outweighs B and C) is robust to probability of FN and treatment cost of FN (although when using higher FN-related costs, the strategies are less distinct in their monetary effects, but still favour antibiotics)		
Study 9						
Author: Timmer-Bonte JN **Year:** 2006 **Country:** The Netherlands **Setting:** Primary and secondary prophylaxis	**Type of analysis:** This study has two parts of economic analysis: a). Cost minimization analysis of 1st cycle. b). Cost minimization analysis and cost-effectivness analysis of the entire treatment period. **Model structure:** N/A **Time horizon:** Five cycles of chemotherapy.	**Inclusion criteria:** Small-cell lung cancer patients receiving standard dose chemotherapy. **Exclusion criteria:** Not reported. **Sample size:** 175 **Age:** ≥60 y: 131/175 (74.9%) **Gender:** n/N **Male:** Not reported. **Female:**	**Chemotherapy:** **Type and dose:** Cyclophosphamide 1000 mg/m^2 day 1, Doxorubicin 45 mg/m^2 day 1, Etoposide 100 mg/m^2 day 1,2,3. **Reduction after NS?** **Cycles:** 4 (mean) **Prophylaxis strategy:** A. Primary antibiotics only (Ciprofloxacin	**Clinical data:** **Incidence of FN:** Cycle 1 Strategy A: Strategy B: Decreased incidence of FN (B-A): Entire treatment Strategy A: Strategy B: Decreased incidence of FN (B-A): **FN-related mortality:** Strategy A: Strategy B: **Mean cycle 1 hospitalization for FN:** Strategy A:	**n/N (%)** 20/85 (24%) 9/90 (10%) 14% **n/N (%)** 39/85 (46%) 21/90 (23%) 23% **n/N (%)** 5/85 (6%) 3/90 (2%) **Days** 2.0	**Conflict of interest:** Not reported. But the authors indicated no potential conflicts of interest. **Comments:** **Applicability:** Partially applicable **Limitation:** Potentially serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Perspective: Health care. **Source of base-line data:** A Dutch randomized, phase III trial. **Source of effectiveness data:** A Dutch randomized, phase III trial. **Source of utility_data:** N/A **Source of cost_data:** Available guideline prices, Dutch reimbursement system for pharmaceuticals, and national health tariffs authority. **Currency unit:** Euro. **Cost year:** 2002 **Discounting:** **Health effect:** No. **Cost**: No.	**Risk of NS:** 25%. (Karnofsky score: 40%-70%: 65/175 (37.1%))	+ roxithromycin) B. Primary antibiotics + G-CSF	Strategy B: **Utility:** N/A **Cost:** **Cost items:** Cycle 1 FN-related Chemotherapy Antibiotics^ G-CSF Non-FN hospitalization Transfusions# Entire treatment FN-related Chemotherapy Antibiotics G-CSF Non-FN hospitalization Transfusions **Incremental cost (B-A) (per patient):** First cycle Entire treatment period **Note:** *^: Including administration costs based on a weighted proportion administration methods: 80% self-administration (no cost) and 20% administration by home health*	0.7 **A** **B** 892 339 269 270 79 77 14* 1616 810 459 39 23 **A** **B** 1709 866 1089 1062 319 304 95* 6200 1171 1067 183 192 €680 (U.K 2011 price: £611.78) €5123(U.K 2011 price: £4609.04)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				care. **: Two patients received G-CSF, despite being randomized to group A.* *#: Including red blood cell and platelet transfusions.* **ICER:** (incremental cost per percent decrease of the probability of FN) B v.s A First cycle Entire treatment **Sensitivity analysis:** Sensitivity analysis has only been conducted for cycle 1. Threshold analysis shows that the addition of G-CSF is cost saving if the probability of FN is more than 84%, the price of prophylactic G-CSF is less than 469 euro per patient (U.K 2011 price: £421.95), or the cost of an episode of FN amount to greater than 11522 euro (U.K 2011 price: £10366.07). The acceptability for the willingness to pay was approximately 50%.	 €50 (U.K 2011 price: £44.98) €366 (U.K 2011 price: £329.28)	
Study 10						
Author: Whyte, S **Year:** 2011	**Type of analysis:** Cost-effectiveness analysis	**Inclusion criteria:** The base case consisted of a cohort of 52-year-old female patients	**Chemotherapy:** **Type and dose:** TAC chemotherapy.	**Clinical data:** **FN risk (primary prophylaxis)** RR (Peg v.s Nothing) RR (Filgrastim v.s. Nothing)	 0.30 0.57	**Conflict of interest:** Funded by Amgen Ltd.,

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Country: U.K **Setting:** Primary and secondary prophylaxis.	**Model structure:** Markov model. **Time horizon:** Lifetime. **Perspective:** U.K NHS **Source of effectiveness data:** Systematic review **Source of utility data:** Literature review. **Source of cost data:** UK databases. **Currency unit:** Pounds. **Cost year:** 2007 **Discounting:** Health effect: 3.5%/year Cost: 3.5%/year	diagnosed with stage 2 breast cancer in line with data on presenting characteristics. **Exclusion criteria:** Not reported. **Sample size:** N/A **Age:** 52 years **Gender:** n/N **Male:** 0% **Female:** 100% **Risk of NS:** 24% or 31%	**Reduction after NS?** 15% (or higher) dose-reduction is possible. **Cycles:** 6 **Prophylaxis strategy:** A. Nothing B. Secondary prophylaxis with lenograstim (11 days) C. Secondary prophylaxis with lenograstim (6 days) D. Secondary prophylaxis with filgrastim (11 days) E. Secondary prophylaxis with filgrastim (6 days) F. Secondary prophylaxis with pegfilgrastim G. Primary prophylaxis with lenograstim (11 days) H. Primary prophylaxis with lenograstim (6	RR (Lenograstim v.s. Nothing) **FN risk (secondary prophylaxis)** RR (if patients has already has an FN event) RR (Cycles 2-6 v.s. Cycle 1) **RDI and mortality** Probability of dying from an FN event Risk of RDI<85% if <65 y and no FN OR for RDI<85% if patient>65 y OR of having RDI 85% if previous FN Hazard ratio if low RDI (<85%) **Utility:** Breast cancer undergoing chemotherapy Breast cancer undergoing chemotherapy (age adjusted for 52y) FN event hospitalization FN event hospitalization (age adjusted for 52y) 1st year after chemo and subsequent year 2-5 Cancer survivors after year 5 Year 20 onward (from diagnosis), utility multiplier for disease-free survival Utility multiplier for local regional breast cancer Utility multiplier for metastatic breast cancer **If baseline risk =24%** Incremental QALYs (Strategy B-A) Incremental QALYs (Strategy C-A) Incremental QALYs (Strategy D-A) Incremental QALYs (Strategy E-A) Incremental QALYs (Strategy F-A) Incremental QALYs (Strategy G-A)	0.62 9.089 0.213 0.036 0.247 1.51 1.58 1.73 0.7 0.843 0.33 0.398 0.855 0.879 0.94 0.74 0.5 0.023 0.023 0.024 0.024 0.042 0.075	and a research grant from Amgen (EUROPE) GmbH was provided to support the production of the article. Amgen staff reviewed and suggested edits, but the final content, authorship, and right to publication remained with the research team. **Comments:** **Applicability:** Partially applicable **Limitation:** Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
			days) I. Primary prophylaxis with filgrastim (11 days) J. Primary prophylaxis with filgrastim (6 days) K. Primary prophylaxis with pegfilgrastim	Incremental QALYs (Strategy H-A) Incremental QALYs (Strategy I-A) Incremental QALYs (Strategy J-A) Incremental QALYs (Strategy K-A) **If baseline risk =31%** Incremental QALYs (Strategy F-A) Incremental QALYs (Strategy K-A) **Cost:** Three G-CSFs were considered: filgrastim, lenograstim and pegfilgastim. Pegfilgastim per injection Filgrastim per injection Lenograstim per injection Administrating a G-CSF injection TAC chemo per cycle Hospitalization per day I.V antibiotics during hospitalization Daily investigation Once-per-FN investigation Average duration of hospitalization for an FN event **If baseline risk =24%** Incremental cost (Strategy B-A) Incremental cost (Strategy C-A) Incremental cost (Strategy D-A) Incremental cost (Strategy E-A) Incremental cost (Strategy F-A) Incremental cost (Strategy G-A) Incremental cost (Strategy H-A) Incremental cost (Strategy I-A)	0.075 0.077 0.077 0.128 0.069 0.181 £686.38 £98.39 £111.83 £21.00 £1,234.00 £235.00 £47.23 £9.27 £47.886 £8 £968 £462 £852 £397 £274 £8326 £4355 £7434	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				Incremental cost (Strategy J-A) Incremental cost (Strategy K-A) **If baseline risk =31%** Incremental cost (Strategy F-A) Incremental cost (Strategy K-A) **ICER:** **If baseline risk =24%** Strategy B v.s Strategy A Strategy C v.s Strategy A Strategy D v.s Strategy A Strategy E v.s Strategy A Strategy F v.s Strategy A Strategy G v.s Strategy A Strategy H v.s Strategy A Strategy I v.s Strategy A Strategy J v.s Strategy A Strategy K v.s Strategy A **If baseline risk =31%** Strategy F v.s Strategy A Strategy K v.s Strategy A **Sensitivity analysis:** Results are highly sensitive to baseline FN risk. When WTP is £20,000 per QALY, for patient with an FN risk level of 11% -37%, secondary pegfilgrastim is most cost-effective; for patients with higher risk level, primary pegfilgrastim is the most cost-effective. Using a WTP threshold of £30,000, primary prophylaxis with pegfilgrastim was cost-effective for baseline FN risks	£3865 £3559 £253 £3252 Dominated Dominated Dominated Dominated £6,500 Dominated Dominated Dominated Dominated £38,482 £3,651 £26,824	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				greater than 29%.		

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Appendix 3 – health economics plan

National Institute for Health and Clinical Excellence

Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 7.1.3 of the Guidelines Manual (2009).

Guideline

Full title of guideline: **Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients** (short: Neutropenic sepsis)

Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on 23/03/2011 by the following people [a]:

For the NCC and GDG:

NCC economist: Huajie Jin

NCC representative(s) [b]: John Graham, Lianne Black, Nathan Bromham

GDG representative(s) [c]: Barry Hancock, Bob Phillips

For NICE (completed by NICE):

CCP lead: Sharon Summers-Ma

Commissioning manager: Claire Turner

Economic lead: Prashanth Kandaswamy

Costing lead:

Proposals for any changes to the agreed priorities will be circulated by email to this group. If substansive revisions are agreed, they will require to be recorded as addenda to this document (section 7) or as an updated version of the document[d].

[a] This may be done by face-to-face meeting, teleconference, or email as convenient.

[b] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

[c] May be GDG chair, clinical lead and/or other members as appropriate.

[d] In case clinical questions are changed, for example, section 4 requires updating as well as other sections if modelling priorities are affected.

Topic priorities identified in the Scope

This section contains all topics covered by the scope. These topics usually reflect selected clinical issues. Please indicate if an area is relevant for economic consideration and if modelling is deemed appropriate to address it.

Area[d]	Relevant?[e]	Appropriate for modelling?[f]
Topic A: Signs and symptoms in people with suspected neutropenic sepsis in the community that necessitate referral to secondary/tertiary care.	Not applicable This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes).	N/A
Topic B: Education and support for patients and carers on the identification of neutropenic sepsis.	Not applicable This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes).	N/A
Topic C: Emergency assessment in secondary/tertiary care of a person with suspected	Medium This question is about patients in secondary or tertiary care with suspected neutropenic sepsis There is uncertainty over the usefulness of emergency	The feasibility of building a model on this topic is hampered by • unclear definition of 'treatment' • lack of data about over-treatment

d This corresponds to the "Key clinical issues that will be covered " section in the scope

[e] Please state if this area is deemed relevant for considering opportunity costs and likely disinvestments. Areas might pose a decision problem directly or implicitly infomr the choice between options. Categories should include information on relevance and if of high or low priority for health economic work (see below).

[f] Health economic work comprises literature reviews, qualitative consideration of expected costs and effects and/or formal decision modelling. Decision modelling is particularly useful where it can reduce uncertainty over cost effectiveness and/or where a recommendation is likely to result in considerable changes in health and/or costs. For further details please see section 7.1 of the Guidelines Manual (2009). It may not be feasible or efficient to address every relevant decision problem by de novo work. There rationale for choosing areas for cost effectiveness modelling should be discussed in detail in Section 5.

neutropenic sepsis.	assessment before treatment. Doing an assessment first could avoid over-treatment and guide the subsequent treatment strategy; but it may also cause a delay in treatment and thus increase the risk to the patients. Despite the importance of this topic, it would be impossible to measure the cost of treatments because there is no clear definition of 'treatment'. The GDG thinks that the choice of treatment will depend on each patient's individual health status so it would be difficult to define a standard treatment for all patients. Therefore no economic analysis will be done for this topic. A cost impact analysis will be conducted at the completion of this guideline. Unit data cost will be presented during the GDG meeting if appropriate.	
Topic D: Appropriate initial investigations of suspected infection in a neutropenic patient in secondary care	D1: Not applicable D2: Low This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes).	D1: This topic is about the definition of neutropenic sepsis and does not lend itself to economic evaluation (no comparative analysis of cost and outcomes). D2: This topic is about identification of patients who are at high risk of an adverse outcome. Patients with poor prognosis outcome will be provided with more aggressive management and intensive monitoring. However, management of high-risk patients by intensive/critical

		care units is beyond the remit of this guideline. Therefore no economic analysis will be conducted for this topic. Unit cost of each test will be presented during GDG meeting if appropriate.
Topic E: Risk stratification and management of suspected bacterial infection	Medium Topic E covers a range of clinical questions related to the management of neutropenic sepsis. Many of the specific clinical questions within this topic are unlikely to be answered by existing economic studies in the literature. Question E1 on the use of risk stratification algorithms is one such example. While it may be possible to evaluate different risk stratification algorithms based on ease of use in clinical practice and accuracy of predicting patient prognosis, a comparative analysis of the impact of choosing one risk stratification algorithm on actual patient outcomes (such as mortality or QALYs) would require data not only on the accuracy of the risk stratification algorithm, but also on the case-mix of patients and their long-term health outcomes. This type of analysis is of questionable relevance as well as feasibility for de novo modelling. Several clinical questions within Topic E relate specifically to optimal timing of a change in management strategy (E4, E5, E6). The difference between strategies being compared in each of these	A preliminary search of the economic literature suggested a small number of economic evaluations have been published for E2 and E8, but not all may be relevant to the UK healthcare setting. Few papers have been identified for other questions within topic E. Therefore the feasibility of doing any models for topic E will be hampered by lack of evidence. Summary of approach for Topic E: • No de novo economic modelling will be undertaken for Topic E. • Published economic evaluations may help inform Question E2 and E8 will be reviewed if deemed relevant.

questions are unlikely to lead to large differences in cost, but rather may be guided by differences in patient outcomes and other considerations such as service configuration that may be difficult to accurately capture using economic modelling.

The questions within Topic E that were considered to have the most relevance for cost and healthcare resource use are those related to alternative management strategies involving inpatient care (E2, E3 and E8). There was considerable discussion with the GDG about the potential for undertaking economic modelling for E2 and E8. Importantly, it was noted that such studies examine different definitions of what constitutes inpatient care or duration of care, making it difficult to generalise findings across studies. As there is no definition of what constitutes a specific inpatient management strategy for this question, costing and evaluating health outcomes using economic modelling will not be feasible. Rather, the GDG anticipated that the different management strategies are unlikely to result in large differences in terms of patient outcomes and those strategies that minimise or reduce the duration of inpatient care will generally be less costly, therefore the level of uncertainty surrounding this question is low and may be adequately answered by a simple cost impact analysis rather than formal economic modelling.

There is uncertainty over the use of monotherapy or combination therapy for patients with neutropenic sepsis. Monotherapy has potential advantages over

	combination therapy. These could include cost, avoidance of the side effects and need for monitoring of drug levels associated with aminoglycosides (aminoglycosides is one important component of combination therapy, and is associated with kidney or inner ear toxicity). Despite this, combination regimens are still widely employed. There are additional reasons why aminoglycosides may still be used, including concerns about secondary infection with clostridium difficile and emerging forms of antibiotic resistance. In addition, particular subgroups of patients may fare better with combination therapy and local knowledge of microbiological flora may also affect treatment choices.There is relatively small difference in cost between the competing alternatives. Therefore on balance, this topic is considered a medium priority for economic analysis. Unit data cost of relevant topics of E will be presented during the GDG meeting if appropriate.	
Topic F: Primary and secondary prophylaxis with GCSF	High There is great uncertainty over the use of G-CSF and/or antibiotics in the prevention of neutropenic sepsis. G-CSF is used to raise neutrophil counts, and shorten the duration of neutropaenia, by stimulating the bone marrow to produce neutrophils. However, adverse effects include diarrhoea, weakness, a flu-like syndrome, and rarely more serious complications such	Separate models will be built for F1 (primary) and F2 (secondary) prophylaxis, as the GDG think the targeted population and interventions of interest are different for these two questions; and the primary strategy prophylaxis won't affect the choice of secondary prophylaxis strategy. Many economic analyses have been identified for both primary and secondary prophylaxis. However the validity of applicability of those analyses would need to be confirmed with the GDG. If the GDG thinks none

	as clotting disorders and capillary leak syndrome. What's more, GCSF must be given by injection, and this may lead to local reactions at the site of administration, and repeated injections may not be desired by patients. Depot formulations are available but expensive. Pre-emptive use of oral antibiotics could reduce the likelihood of infection, but may incur patient-related risks of gut disturbance, allergy, etc and more general risks related to the development of antibiotic resistance in populations. Patients with a prior episode of significant neutropaenia are likely to become more neutropaenic with repeated doses of chemotherapy, putting them at greater risk of neutropaenic sepsis than patients who have never experienced this complication. The trade-off of using G-CSF and antibiotics as secondary prophylaxis is similar to primary prophylaxis. Considering the overall importance of this topic, characterized by a large patient group and potentially significant difference in cost, this topic is highlighted as high priority.	of them could be directly used/adapted to the NHS setting, then a de novo decision tree will be developed for this topic.
Topic G: Empiric glycopeptides antibiotics	High Central venous catheter (central line) is commonly used in cancer patients, but may introduce bacteria	For topic G, no economic or clinical evidence has been identified from a cursory search. The GDG is not aware of any direct relevant economic or clinical evidence either.

	into the bloodstream and thus cause potentially life-threatening infection. The difficult question for the clinician is: for cancer patients with central line who are suspicious of/ diagnosed as neutropenic sepsis with unknown bacteria, should empiric antibiotics be added in addition to first line antibiotics? Trade off could be important because there are monitoring costs and toxicities associated with glycopeptides antibiotics. Considering the overall importance of this topic, characterized by a large patient subgroup and potentially significant difference in cost, this topic is highlighted as high priority.	In the absence of direct relevant evidence, the GDG has been asked if they feel confident to make assumptions of key parameters; or can we 'borrow' data from similar settings. Their answers to both questions are 'No'. Therefore despite the importance of topic G, no economic models will be built for this topic due to paucity of data.
Topic H: Indications for removing central line	Not applicable This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes).	N/A
Topic I: Information for patients and carers	Not applicable This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes).	N/A
Topic J: Training of healthcare professionals	Low Whilst there are potential implications for health benefits from the interventions of interest, these are likely to be small and will be difficult to attribute to the training of healthcare professionals. Economic	N/A

	analysis is therefore not appropriate for this question.

List of clinical questions

Insert a list of all clinical questions in a 'PICO' format that are covered by the guideline.[g]

#	Clinical questions by scope area
	Area 1 (Diagnosis of neutropenic sepsis)
1	Question A Which symptoms and/or signs experienced by patients in the community predict neutropenic sepsis?
	Area 2 (Education and support for reducing adverse effects)
2	Question B What information and support for patients receiving anti-cancer treatment and their carers reduces the adverse effects of neutropenic sepsis?
	Area C (Emergency assessment)
3	Question C Which test should be used in the emergency empirical assessment of a person with suspected neutropenic sepsis?
	Area D (Risk of complications)
4	Question D1 How do neutrophil count and temperature relate to the risk of complications of sepsis, in cancer patients with suspected neutropenic sepsis?
5	Question D2 Which tests predict outcome and response to treatment in patients with suspected neutropenic sepsis?
	Area E (Management of neutropenic sepsis)
7	Question E1 Which is the most valid published risk stratification score or algorithm for influencing management and predicting outcome in patients with neutropenic sepsis?

[g]This is the list of clinical questions to be covered by the guideline.

Question E2

Is there any difference between the outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients?

Question E3

Is there a difference in the effectiveness of empiric intravenous antibiotic monotherapy and empiric dual therapy in the treatment of patients with neutropenic sepsis.

Question E4

Does the length of time before empiric antibiotics are given influence patient outcomes?

Question E5

When is the optimal time to switch (step down) from intravenous to oral antibiotic therapy?

Question E6

What is the optimal time to change the primary empiric treatment in unresponsive fever?

Question E7

What is the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis?

Question E8

What is the optimal duration of inpatient care for patients receiving empiric treatment for neutropenic sepsis?

Area F (Prophylaxis of neutropenic sepsis)

15 Question F1

Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients receiving anti-cancer treatment?

16 Question F2

Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients with a prior episode of neutropenic sepsis?

Area G (Empirical antibiotic for patients with central line)

17 Question G

In patients with a central venous access device with no external signs of line infection but with suspected neutropenia or neutropenic sepsis, what are the benefits and risks of adding vancomycin, teicoplanin or linezolid to first-line antibiotics?

Area H (Removal of central line)

18 Question H

Which patients with central venous access devices and neutropenic sepsis will benefit from removal of their central line?

Area I (General support and information)

19 Question I

What types of support and information have patients with neutropenic sepsis (and their carers) have found useful or requested?

Area J (Training of healthcare professionals)

Question J

Does training healthcare professionals on the identification and management of neutropenic sepsis improve outcomes for patients receiving anti-cancer treatment?

Planned de novo modelling

This section will specify modelling work prioritised by the GDG. It will provide details on how cost effectiveness will be considered for relevant, prioritised clinical areas/decision problems. Proposed modelling work should be listed in chronological order. For each decision model, please state the proposed analytical methods, relevant references and any comments on, for example, possible diversions from the reference case.

Scope area[h] (clinical question(s) [i])	*Outline proposed analysis*
Topic F1 and F2	**Background:** **F1:** There is great uncertainty over the use of Granulocyte colony-stimulating factor (G-CSF), and/or antibiotics in the prevention of neutropenic sepsis. G-CSF is used to raise neutrophil counts, and shorten the duration of neutropenia, by stimulating the bone marrow to produce neutrophils. However, adverse effects include diarrhoea, weakness, a flu-like syndrome, and rarely more serious complications such as clotting disorders and capillary leak syndrome. What's more, G-CSF must be given by injection, and this may lead to local reactions at the site of administration, and repeated injections may not be desired by patients. Depot formulations are available but expensive. Pre-emptive use of oral antibiotics could reduce the likelihood of infection, but may incur patient-related risks of gut disturbance, allergy, etc and more general risks related to the development of antibiotic resistance in populations. Therefore the question is whether the use of growth factors and/or antibiotics in patients on chemotherapy may improve patient overall outcomes within a reasonable cost. **F2:** Patients with a prior episode of significant neutropenia are likely to become more neutropenic with repeated doses of chemotherapy, putting them at greater risk of neutropenic sepsis than patients who have never experienced this complication. The trade-off of using G-CSF and antibiotics are similar to F1.

[h] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[i] Two or more questions may be addressed by a single analysis if appropriate.

Scope area[h] (clinical question(s) [i])	*Outline proposed analysis*
	Separate models will be built for F1 (primary) and F2 (secondary) prophylaxis, as the GDG think the targeted population and interventions of interest are different for these two questions; and the primary strategy prophylaxis won't affect the choice of secondary prophylaxis strategy. **Aim of analysis:** To assess the cost effectiveness of several primary and secondary prophylaxis strategies to prevent first and secondary neutropenic sepsis for cancer patients undergoing anti-cancer therapy. **Patient population:** F1: All patients receiving anti-cancer therapy F2: Patients receiving anti-cancer therapy, with a prior episode of neutropenic sepsis. **Intervention:** F1: • G-CSF (with or without fluroquinolones or co-trimoxale)• Fluoroquinolones alone (Ciprofloxacin, Levofloxacin) • Co-trimoxazole alone F2: • GCSF (with or without fluoroquinolones),• Fluoroquinolones alone (Ciprofloxacin, Levofloxacin) • Co-trimoxazole alone • Granulocyte infusion **Comparison:** Same for both F1 and F2. • Compared to each other. • Placebo or nothing

Scope area[h] (clinical question(s) [i])	*Outline proposed analysis*
	Outcomes: Same for both F1 and F2. • Incidence of neutropenic sepsis • Secondary infection • Death rate • Critical care • Length of stay • Quality of life **Time horizon:** Same for both F1 and F2: Within one course of chemotherapy. (The length of chemotherapy course may differ for different types of cancer, ranged from 5-12 cycles) The GDG are not interested in long-term outcomes, such as overall death rate caused by cancer/chemotherapy. The GDG are aware of long-term impacts of using different prophylaxis strategy, such as delay/dose deduction of chemotherapy, long-term complications from both GCSF and more widespread use of prophylactic antibiotics, etc. However the GDG don't think these long-term impacts could be captured in the model due to data paucity.Sensitivity analysis will be conducted to explore if the final result is sensitive to reoccurrence risk of NS, expected years of life etc. **Analysis methods:** A decision tree approach will be adopted to model the clinical pathway and a cost-utility analysis will be performed using QALYs as the measure of health outcomes. **Clinical evidence:** The clinical data used to populate the model will be mainly derived from the systematic reviews conducted to identify clinical

Scope area[h] (clinical question(s) [i])	*Outline proposed analysis*
	and cost-effectiveness evidence for the topic. To populate the model the following data will be required: (for both primary and secondary prophylaxis) • Prevalence of neutropenic sepsis in each group of patients with or without prophylaxis • Probability of death from neutropenic sepsis • Proportion of patients who will receive extensive chemotherapy (Relative dose intensity (RDI) ≥85%) • Probability of death for patients surviving neutropenic sepsis undergoing extensive or standard chemotherapy • Probability of death for patients from cancer • Probability of death for patients from other causes • Estimate of QALY for cancer patients who experience or do not experience neutropenic sepsis • Estimate of QALY lost associated with neutropenic sepsis-caused hospitalization • Estimate of QALY for cancer patients during extensive or standard chemotherapy • Estimate of QALY for cancer patients after year X. (depends on the length of time horizon) **Costs evidence:** To populate the model the following data will be required: • Costs associated with each primary and secondary prophylaxis strategy. • Costs associated with treatment of neutropenic sepsis, such as hospital stay, critical care etc. NB. The cost of the chemotherapy is excluded because it relate to the treatment of cancer. National reference costs of PbR tariff will be used as sources of unit costs. **Feasibility issues:** F1:

Scope area[h] (clinical question(s) [i])	*Outline proposed analysis*
	A cursory search of NHS EED and HTA has identified many economic studies on this topic; five of them were conducted in the U.K. The most commonly used model is a decision-analytic model that was developed to assess the relative clinical outcomes and costs of primary prophylaxis with pegfilgrastim compared with filgrastim. The base case was for a 45-year-old woman with Stage II breast cancer receiving four cycles of chemotherapy with a ≥20% risk of neutropenic sepsis. The model simulated clinical outcomes and life expectancy in a cohort of women with breast cancer and follows them until death (either from cancer or other causes). The model also included the probability of receiving standard or extensive chemotherapy based upon the RDI. The problems of this model are: firstly, it only looks at patients with breast cancer. The GDG need to make a decision about whether the clinical pathway for women with breast cancer could represent the pathways for patients with various kinds of cancer. Secondly, this model takes the death rate caused by cancer into consideration. The GDG have confirmed that they are not interested in the death rate caused by cancer. Thirdly, this model didn't take reoccurrence of neutropenic sepsis within one course of chemotherapy into consideration. Therefore the overall survival rate of each prophylaxis strategy will be falsely increased, while the total cost associated with neutropenic sepsis will be falsely decreased. F2: Several economic papers have been identified for topic F2. All of them take re-occurrence of neutropenic sepsis into consideration. Two of the papers also provided decision-tree. The assumptions of the model built by Timmer-Bonte are: 1. The passage of time is divided into intervals representing a complete chemotherapy cycle. A patient could go through a maximum of five chemotherapy cycles. 2. After each chemotherapy cycle, the patient may be in one of three different states: 'Stop' (no more chemotherapy), 'no FN' (the patient will experience another round of chemotherapy without previous neutropenic sepsis), and 'FN' (the patient will experience another round of chemotherapy with previous neutropenic sepsis). 3. An episode of neutropenic sepsis without prophylaxis always leads to modification of therapy and that, in all subsequent cycles, prophylaxis was administered.

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References

1. Borget, I. "Pegfilgrastim: a health economic model to assess overall cost-effectiveness." 15(5) (2009): 58-61.

2. Timmer-Bonte Jn, Adang E. M. T. "Modeling the cost effectiveness of secondary febrile neutropenia prophylaxis during standard-dose chemotherapy." 26(2) (2008): 290-96.

Addenda to economic plan

Please state any changes that have been made to the above agreed plan, together with date. If clinical questions have changed since the economic plan was signed off, include a new list with all clinical questions as part of the addenda, together with a comment where questions were inserted, deleted or altered and an explanation.

Scope area[10] (clinical question(s) [11])	*Proposed changes*	*Date agreed*
Topic F1 and F2	Granulocyte infusion was taken out from the protocol. So the inventions of interest for topic F1 and F2 become the same.	7th Feb 2011
Topic F1 and F2	Topic F1 and F2 were combined into one topic. Therefore instead of building two separate economic models for primary and secondary prophylaxis, only one economic model will be built to cover both primary and secondary prophylaxis.	29th March 2011
Topic F	Two decision trees were built: Model A assumes patients will continue to receive full-dose chemotherapy regardless of previous episodes of neutropenic sepsis. Model B assumes that if patients develop one episode of neutropenic sepsis, they will then receive dose-reduction chemotherapy; if they develop two episodes of neutropenic sepsis chemotherapy will be discontinued.	26th May 2011
Topic F	Co-trimoxazole was taken out form PICO.	9th Sep 2011
Topic F	1. The economic analysis won't cover paediatric cancer patients and patients with planned inpatient treatment of greater than 10-days post- chemotherapy.	18th Nov 2011

[10] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[11] Two or more questions may be addressed by a single analysis if appropriate.

	2. Subgroup analysis will be conducted for: • Adult patients with solid tumour (Model B) • Adult patients with non-Hodgkin lymphoma (Model A) • Adult patients with non-Hodgkin lymphoma (Model A) For each patient subgroup, two different scenarios were considered: • Scenario 1 (base-case analysis). This assumed that the overall mortality would be the same for each prophylactic strategy, and only looked at the efficacy of each strategy in terms of preventing neutropenic sepsis. • Scenario 2 (explorative analysis). This assumed there was a survival difference between different prophylactic strategies, and looked at the efficacy of both preventing neutropenic sepsis and improving overall mortality. The overall mortality data used in the explorative analysis were obtained from the clinical evidence review of this topic.	

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Appendix 4. The source of the clinical effectiveness data used for the economic model of primary prophylaxis

The clinical data used to estimate the effectiveness of primary prophylaxis in the economic model in the full guideline is given in Table A4.1 below. Studies fitting our inclusion criteria (main diagnosis either solid tumour, hodgkin lymphoma, non hodgkin lymphoma or leukaemia; primary prophylaxis with G(M)-CSF, pegfilgrastim, ciprofloxacin, levofloxacin, oflaxcin alone or in combination) were extracted from systematic reviews by Gafter et al (2005), Sung et al (2007), Bohlius et al (2008) and Cooper et al (2011). We excluded studies solely in paediatric populations. The full text of the original studies was checked whenever there was insufficient information given in the systematic review (for example to determine the type of antibiotic used for prophylaxis). Meta-analysis of risk ratios, rate ratios and proportions was done using the metafor package in R (Viechtbauer, 2010). The random effects model was used in all cases, using the restricted maximum-likelihood estimator (REML) for residual hetereogeneity.

Key to column headings in table A4.1

study: study identifier
source: the systematic the systematic review from which the data are drawn (see references).
age: the age-group of the patients in the study
proph.class the type of primary prophylaxis given (gcsf – non pegylated G(M)-CSF; peg – pegfilgrastim; gcsf-abx - non pegylated G(M)-CSF plus quinolone antibiotic; abx – quinolone antibiotic.
main.diag: the main diagnostic category of the patients in the study (solid – solid tumours; **hodgkins** – hodgkin lymphoma; non-hd – non-hodgkin lymphoma; leuakaemia)
alloc: whether the study used adequate allocation concealment
dblind: whether the study used double blinding
mort.p: number of mortalities in the primary prophylaxis group
nmort.p: the number of patients in the primary prophylaxis group for whom mortality data were available
mort.c: number of mortalities in the control (no primary prophylaxis) group
nmort.c: the number of patients in the control group for whom mortality data were available
imort.p: the number of infectious mortalities in the primary prophylaxis group
nimort.p: the number of patients in the primary prophylaxis group for whom infectious mortality data were available
imort.c: the number of infectious mortalities in the control group
nimort.c: the number of patients in the control for whom infectious mortality data were available
fn.p: the number of febrile neutropenic events in the primary prophylaxis group
cycles.p: the number of chemotherapy cycles given in the primary prophylaxis group
fn.c: the number of febrile neutropenic events in the control group
cycles.c: the number of chemotherapy cycles given in the control group

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Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. (2008) Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev. Oct 8;(4):CD003189.

Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. (2011). Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. Sep 23;11:404.

Gafter-Gvili, A., Fraser, A., Paul, M., van de Wetering, M., Kremer, L., & Leibovici, L. (2005). Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database of Systematic Reviews.(4):CD004386, 2005., CD004386.

Sung, L., Nathan, P. C., Alibhai, S. M., Tomlinson, G. A., & Beyene, J. (2007). Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine, 147, 400-411.

Viechtbauer, W. (2010). Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software, 36(3), 1-48

Table A4.1 Source of clinical data used for the economic model of primary prophylaxis

study	source	age	proph.class	main.diag	alloc	dblind	mort.p	nmort.p	mort.c	nmort.c	imort.p	nimort.p	imort.c	nimort.c	fn.p	cycles.p	fn.c	cycles.c
Agiletta 2000	BOHLIUS	Adult	gcsf	hodgkins	NA	NA	1	30	2	26	1	30	0	26	NA	NA	NA	NA
Dunlop et al., 1998 (1)	SUNG-BOHLIUS	Adult	gcsf	hodgkins	Adequate	No	0	13	1	12	0	13	0	12	1	12	4	11
Dunlop et al., 1998 (2)	SUNG-BOHLIUS	Adult	gcsf	hodgkins	Adequate	No	1	14	0	11	1	14	0	11	6	11	5	10
Pfreundschuh et al., 2001	SUNG	Adult	gcsf	hodgkins	Unclear	Yes	3	30	5	30	1	30	2	30	NA	NA	NA	NA
Dekker 1981	GAFTER	Adult	abx	leukaemia	Adequate	No	8	26	7	26	4	26	5	26	13	26	23	26
Lew 1991	GAFTER	Adult	abx	leukaemia	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	7	7	11	11
Martino 1984	GAFTER	Adult	abx	leukaemia	Unclear	No	2	30	11	33	2	30	11	33	23	30	33	33
Tsutani 1992	GAFTER	Adult	abx	leukaemia	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	8	25	20	25
Harousseau et al., 2000	SUNG	Adult	gcsf	leukaemia	Adequate	No	5	100	5	94	NA	NA	NA	NA	NA	NA	NA	NA
Holowiecki et al., 2002	SUNG	Adult	gcsf	leukaemia	Unclear	No	1	33	2	31	1	33	0	31	NA	NA	NA	NA
Ifrah et al., 1999	SUNG	Adult	gcsf	leukaemia	Adequate	Yes	0	35	0	29	0	35	0	29	NA	NA	NA	NA
Lowenberg et al., 1997	SUNG	Adult	gcsf	leukaemia	Unclear	No	1	60	3	63	NA	NA	NA	NA	NA	NA	NA	NA
Moreau et al., 1997	SUNG	Adult	gcsf	leukaemia	Unclear	Yes	6	69	2	32	6	69	2	33	NA	NA	NA	NA
Ohno et al., 1993	SUNG	Adult	gcsf	leukaemia	Adequate	No	NA	NA	NA	NA	NA	NA	NA	NA	20	79	9	28
Ohno et al., 1999	SUNG	Adult	gcsf	leukaemia	Unclear	No	0	46	1	21	0	46	0	21	15	46	8	21
Thomas et al., 1999	SUNG	Adult	gcsf	leukaemia	Unclear	Yes	5	95	8	97	NA	NA	NA	NA	NA	NA	NA	NA
Thomas et al., 2004	SUNG	Adult	gcsf	leukaemia	Adequate	No	3	162	3	74	3	162	2	74	NA	NA	NA	NA
Thomas et al., 2007	SUNG	Adult	gcsf	leukaemia	Unclear	No	4	124	10	135	NA	NA	NA	NA	NA	NA	NA	NA
Zittoun et al., 1996	SUNG	Adult	gcsf	leukaemia	Adequate	No	1	27	2	26	NA	NA	NA	NA	NA	NA	NA	NA
Bernasconi et al., 1998	SUNG	Adult,elderly	gcsf	leukaemia	Unclear	No	3	53	8	52	NA	NA	NA	NA	NA	NA	NA	NA
Larson et al., 1998	SUNG	Adult,elderly	gcsf	leukaemia	Adequate	No	12	97	15	88	NA	NA	NA	NA	NA	NA	NA	NA
Milligan et al., 2006	SUNG	Adult,elderly	gcsf	leukaemia	Adequate	No	8	178	9	178	NA	NA	NA	NA	NA	NA	NA	NA
Takeshita et al., 1995	SUNG	Adult,elderly	gcsf	leukaemia	Unclear	Yes	1	57	0	64	1	57	0	64	33	57	53	64
Usuki and Urabe, 2000	SUNG	Adult,elderly	gcsf	leukaemia	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

study	source	age	proph.class	main.diag	alloc	dblind	mort.p	nmort.p	mort.c	nmort.c	imort.p	nimort.p	imort.c	nimort.c	fn.p	cycles.p	fn.c	cycles.c
Usuki et al., 2002	SUNG	Adult,elderly	gcsf	leukaemia	Adequate	No	7	120	5	125	3	120	3	125	NA	NA	NA	NA
Zwierzina et al., 2005	SUNG	Adult,elderly	gcsf	leukaemia	Adequate	No	8	59	5	59	NA	NA	NA	NA	NA	NA	NA	NA
Heil et al., 1997	SUNG	Adult,elderly	gcsf-quin	leukaemia	Adequate	Yes	21	259	25	262	9	259	18	262	NA	NA	NA	NA
Amadori et al., 2005	SUNG	Elderly	gcsf	leukaemia	Adequate	No	53	360	45	362	23	350	23	350	NA	NA	NA	NA
Dombret et al., 1995	SUNG	Elderly	gcsf	leukaemia	Unclear	Yes	20	88	23	85	15	88	17	85	NA	NA	NA	NA
Godwin et al., 1998	SUNG	Elderly	gcsf	leukaemia	Unclear	Yes	21	104	20	103	20	104	14	103	NA	NA	NA	NA
Goldstone et al., 2001	SUNG	Elderly	gcsf	leukaemia	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rowe et al., 1995	SUNG	Elderly	gcsf	leukaemia	Unclear	Yes	3	52	7	47	NA	NA	NA	NA	NA	NA	NA	NA
Stone et al., 1995	SUNG	Elderly	gcsf	leukaemia	Adequate	Yes	52	193	45	195	NA	NA	NA	NA	NA	NA	NA	NA
Witz et al., 1998	SUNG	Elderly	gcsf	leukaemia	Unclear	Yes	20	110	19	122	NA	NA	NA	NA	NA	NA	NA	NA
Channa and Hashmi, 2002	SUNG	Paediatric,adult	gcsf	leukaemia	Unclear	Yes	1	11	6	11	1	11	4	11	NA	NA	NA	NA
Ohno et al., 1990	SUNG	Paediatric,adult	gcsf	leukaemia	Adequate	No	4	48	7	50	2	48	6	50	NA	NA	NA	NA
Aviles et al., 1994	SUNG	Adult	gcsf	non-hd	Unclear	No	0	20	0	22	0	20	0	22	NA	NA	NA	NA
Bastion 1993	BOHLIUS	Adult	gcsf	non-hd	NA	NA	7	59	6	60	NA	NA	NA	NA	NA	NA	NA	NA
Cunningham	BOHLIUS	Adult	gcsf	non-hd	NA	NA	0	18	0	21	0	18	0	21	NA	NA	NA	NA
Gisselbrecht et al., 1997	SUNG-BOHLIUS	Adult	gcsf	non-hd	Unclear	Yes	3	82	3	80	2	81	2	80	52	82	62	80
Kaplan et al., 1991	SUNG	Adult	gcsf	non-hd	Unclear	No	1	16	1	10	1	16	2	14	22	58	28	42
Liberati et al., 1991	SUNG	Adult	gcsf	non-hd	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yau et al., 1996	SUNG	Adult	gcsf-quin	non-hd	Unclear	Yes	0	28	4	28	0	28	3	28	32	64	32	57
Bergmann et al., 1995	SUNG	Adult,elderly	gcsf	non-hd	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Engelhard et al., 1994	SUNG	Adult,elderly	gcsf	non-hd	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fridrik et al., 1997	SUNG-BOHLIUS	Adult,elderly	gcsf	non-hd	Unclear	No	6	42	2	43	6	42	1	43	16	38	21	36
Gerhartz et al., 1993	SUNG	Adult,elderly	gcsf	non-hd	Adequate	Yes	2	89	3	87	NA	NA	NA	NA	NA	NA	NA	NA
Kaku et al., 1993	SUNG	Adult,elderly	gcsf	non-hd	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Oyama et al., 1990	SUNG	Adult,elderly	gcsf	non-hd	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

study	source	age	proph.class	main.diag	alloc	dblind	mort.p	nmort.p	mort.c	nmort.c	imort.p	nimort.p	imort.c	nimort.c	fn.p	cycles.p	fn.c	cycles.c
Rao et al., 2005	SUNG	Adult,elderly	gcsf	non-hd	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	3	22	1	12
Doorduijn et al., 2003	SUNG	Elderly	gcsf	non-hd	Unclear	No	11	197	18	192	4	197	6	192	72	197	86	192
Osby et al., 2002	SUNG	Elderly	gcsf	non-hd	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	2	8	2	6
Grigg et al., 2003	SUNG	Elderly	peg	non-hd	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Balducci et. al, 2007 (2)	COOPER	Elderly	peg	non-hd	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11	73	27	73
Magrath et al., 1996	SUNG	Paediatric,adult	gcsf	non-hd	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Carlson 1997	GAFTER	Adult	abx	solid	Adequate	No	0	45	1	45	0	45	0	45	12	45	15	45
Cullen 2005	GAFTER	Adult	abx	solid	Adequate	Yes	12	781	18	784	4	781	4	784	109	781	152	784
Hartlapp 1987	GAFTER	Adult	abx	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	3	21	16	21
Schoeder 1992	GAFTER	Adult	abx	solid	Unclear	Yes	0	40	2	35	0	40	2	35	2	40	11	35
Bajorin et al., 1995	SUNG	Adult	gcsf	solid	Unclear	No	0	55	1	49	0	55	1	49	19	103	32	92
Chevallier et al., 1995	SUNG	Adult	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	0	61	0	59	NA	NA	NA	NA
Chi et al., 1995	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Feng and Zhou, 1998	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fosså et al., 1998	SUNG	Adult	gcsf	solid	Unclear	No	3	129	10	130	3	129	9	130	25	128	38	129
Gebbia et al., 1993	SUNG	Adult	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	5	43	14	43
Hansen et al., 1995	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	8	39	10	31
Katano et al., 1995	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Muhonen et al., 1996	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Papaldo et al., 2003	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	3	254	16	243
Rampling et al., 1994	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	0	19	0	19	NA	NA	NA	NA
Shi et al., 1994	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Shi et al., 1996	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Steward et al., 1998	SUNG	Adult	gcsf	solid	Adequate	Yes	17	150	13	150	6	150	4	150	81	150	80	150
Stoger et al., 1998	SUNG	Adult	gcsf	solid	Adequate	No	NA	NA	NA	NA	NA	NA	NA	NA	5	24	3	24

study	source	age	proph.class	main.diag	alloc	dblind	mort.p	nmort.p	mort.c	nmort.c	imort.p	nimort.p	imort.c	nimort.c	fn.p	cycles.p	fn.c	cycles.c
Wang et al., 2004	SUNG	Adult	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ardizzoni et al., 1994	SUNG	Adult	gcsf-quin	solid	Adequate	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Timmer-Bonte et al., 2005	SUNG	Adult	gcsf-quin	solid	Unclear	No	NA	NA	NA	NA	3	90	5	85	21	368	39	353
Hecht et al., 2010	COOPER	adult	peg	solid	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3	123	9	118
Anderson et al., 1991	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bui et al., 1995	SUNG	Adult,elderly	gcsf	solid	Adequate	Yes	0	22	0	26	0	22	0	26	5	22	15	26
Bunn et al., 1995	SUNG	Adult,elderly	gcsf	solid	Adequate	No	9	107	1	108	3	107	0	108	NA	NA	NA	NA
Crawford et al., 1991	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	8	101	9	110	3	101	3	110	26	92	58	102
de Vries et al., 1991	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Eguchi et al., 1994	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	0	22	0	23	NA	NA	NA	NA
Eguchi et al., 1994	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fukuoka et al., 1997	SUNG	Adult,elderly	gcsf	solid	Unclear	No	4	32	5	32	3	32	4	32	14	32	24	31
Gebbia et al., 1994	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	5	23	18	28
Hamm et al., 1994	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Havemann et al., 1991	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hidalgo et al., 1998	SUNG	Adult,elderly	gcsf	solid	Adequate	No	2	40	0	40	0	40	0	40	6	220	10	202
Jost et al., 1990	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kotake et al., 1991	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	2	10	1	4
Logothetis et al., 1995	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	11	72	5	64
Long et al., 2002	SUNG	Adult,elderly	gcsf	solid	Adequate	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Paterakis et al., 1996	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Seymour et al., 1995	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	2	53	0	13	1	53	0	13	NA	NA	NA	NA
Shaffer et al., 1993	SUNG	Adult,elderly	gcsf	solid	Unclear	No	1	10	0	11	1	10	0	11	2.5	10.5	0.5	11.5
Shi et al., 1994	SUNG	Adult,elderly	gcsf	solid	Unclear	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Trillet-Lenoir et al., 1993	SUNG	Adult,elderly	gcsf	solid	Unclear	Yes	NA	NA	NA	NA	1	65	3	64	17	65	34	64

study	source	age	proph.class	main.diag	alloc	dblind	mort.p	nmort.p	mort.c	nmort.c	imort.p	nimort.p	imort.c	nimort.c	fn.p	cycles.p	fn.c	cycles.c
Weiss et al., 1996	SUNG	Adult,elderly	gcsf	solid	Unclear	No	2	16	1	7	2	16	1	7	2	16	1	7
Woll et al., 1995	SUNG	Adult,elderly	gcsf	solid	Unclear	No	6	34	1	31	NA	NA	NA	NA	22	34	21	31
Miles et al., 1994	SUNG	Adult,elderly	gcsf-quin	solid	Unclear	No	0	23	2	17	0	23	2	17	NA	NA	NA	NA
Vogel et al., 2005	SUNG	Adult,elderly	peg	solid	Adequate	Yes	5	463	14	465	0	463	2	465	6	463	78	465
Balducci et. al, 2007 (1)	COOPER	Elderly	peg	solid	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15	373	37	373
Romieu et. al, 2007	COOPER	Elderly	peg	solid	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	30	5	29
Wexler et al., 1996	SUNG	Paediatric,adult	gcsf	solid	Unclear	No	0	18	0	18	0	18	0	18	67	167	134	303