Royal College of Obstetricians and Gynaecologists

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Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection

August 2012

NICE Clinical Guideline

National Collaborating Centre for Women's and Children's Health

Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection

National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence

August 2012

Update Information:
NICE's original guideline on neonatal infection (early onset): antibiotics for prevention and treatment was published in 2012. It was updated in 2021 and 2024. See the NICE website for the guideline recommendations and the evidence reviews for the 2021 and 2024 guidance. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021 and 2024.

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers

NCC-WCH Editor: Karen Packham

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The appendices are presented in separate files.

1 Guideline summary

1.1 Guideline development group members, NCC-WCH staff and acknowledgements

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1.2 Foreword

Early-onset neonatal bacterial infection (infection with onset within 72 hours of birth) is a significant cause of mortality and morbidity in newborn babies. Parent organisations and the scientific literature

report that there can be unnecessary delays in recognising and treating sick babies. In addition, concern about the possibility of early-onset neonatal infection is common. This concern is an important influence on the care given to pregnant women and newborn babies. There is wide variation in how the risk of early-onset neonatal infection is managed in healthy babies. The approach taken by the NHS needs to:

- prioritise the treatment of sick babies
- minimise the impact of management pathways on healthy women and babies
- use antibiotics wisely to avoid the development of resistance to antibiotics.

These drivers have not always been addressed consistently in the NHS, and this guideline was commissioned to ensure they would be addressed in future.

Five key principles underpin the recommendations in this guideline.

- Unless it is dangerous, families should be offered choice. The guideline includes recommendations to support families in making choices through provision of information and, where appropriate, reassurance.
- Intrapartum antibiotic prophylaxis should be administered in a timely manner to all eligible women who choose it.
- Babies with suspected early-onset neonatal infection should be treated as quickly as possible.
- Antibiotic exposure should be minimised in babies who do not have an early-onset neonatal infection.
- An integrated system of clinical care is needed to allow full implementation of the guideline recommendations.

The guideline will assume that prescribers will use a drug's summary of product characteristics (SPC) to inform their decisions for individual women and babies. Where dosages recommended in the guideline are based on evidence that is not reflected in the SPC, this is indicated in footnotes to the recommendations.

This guideline should be read in conjunction with:

- Caesarean section. NICE clinical guideline 132 (2011).
- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 (2010).
- Induction of labour. NICE clinical guideline 70 (2008).
- Antenatal care. NICE clinical guideline 62 (2008).
- Intrapartum care. NICE clinical guideline 55 (2007).
- Urinary tract infection in children. NICE clinical guideline 54 (2007).
- Feverish illness in children. NICE clinical guideline 47 (2007).
- Postnatal care. NICE clinical guideline 37 (2006).

Unless otherwise indicated, all references to infection in the guideline recommendations refer to early-onset neonatal infection (that is, onset of infection within 72 hours of birth).

1.3 Care pathways

This section was updated in 2021. Please see https://www.nice.org.uk/guidance/cg149/ for the update.

1.4 Key priorities for implementation

The current recommendations can be found at: https://www.nice.org.uk/guidance/cg149

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1.5 Key research recommendations

This section on research recommendations was partially updated in 2021.

Number	Research recommendation	See section
RR 3	This research recommendation has been removed from the 2021 update.	

Number	Research recommendation	See section
RR 4	This research recommendation has been removed from the 2021 update.	

Number	Research recommendation	See section
		6
RR 5	This research recommendation has been removed from the 2021 update.	6
	Investigations during antibiotic treatment	**10**
RR 12	What is the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early-onset neonatal infection in babies receiving antibiotics for suspected infection? Why this is important The systematic reviews conducted for the guideline identified limited evidence relating to investigations used to guide the decision to stop antibiotic treatment in babies receiving antibiotics for suspected early-onset neonatal infection. One study evaluated procalcitonin-guided decision making for identifying babies in whom antibiotic treatment could safely be stopped, but the approach used was at an early stage of development and had not been evaluated fully. The guideline recommendations reflected uncertainty about the diagnostic test accuracy of laboratory investigations used individually or in combination, and further research involving sufficiently powered studies is needed to evaluate this. The ideal study design would be a randomised controlled trial that compares clinical outcomes associated with particular investigation and treatment termination strategies. The next best design would be a	10

Number	Research recommendation	See section
	prospective cohort study to determine the diagnostic test accuracy of an investigation strategy evaluated in a clinically relevant group of babies. The research should examine clinical effectiveness or diagnostic test accuracy in preterm and term babies separately.	
	Duration of antibiotic treatment	**10**
RR 13	What is the optimal duration of treatment (course length) in babies who receive antibiotics for confirmed early-onset neonatal infection? Why this is important The Guideline Development Group identified no evidence to inform the choice of duration of antibiotic treatment (course length) for confirmed early-onset neonatal infection. In the absence of evidence, the Guideline Development Group based its recommendations on its knowledge of current clinical practice. Further research is needed to evaluate different course lengths in the following clinical circumstances: • babies with group B streptococcal bacterial meningitis • babies with group B streptococcal septicaemia • babies with Gram-negative bacterial meningitis (such as *Escherichia coli* meningitis) • babies with Gram-negative septicaemia. The research should ideally take the form of multinational randomised controlled trials. The primary outcome should be relapse within 10 days of stopping treatment. Secondary outcomes should include long-term neurodevelopment.	10

1.6 Research recommendations

This section on research recommendations was partially updated in 2021.

Number	Research recommendation	See section
	Information and support	**4**
RR 1	How does each step in the care pathway for prevention and treatment of early-onset neonatal infection impact on babies and their families? Why this is important Further research is needed to evaluate the impact on babies and their families of each step in the care pathway for the prevention and treatment of early-onset neonatal infection. This is important because family needs will have implications for service delivery in the neonatal period and subsequently. The nature of such needs and the extent to which they vary between families have not been described in the evidence considered for inclusion in the guideline. Future research should focus particularly on the impacts of antibiotic prophylaxis and treatment. Impacts should be assessed in terms of	4

Number	Research recommendation	See section
	short- and long-term outcomes, and include consideration of resource utilisation and costs. Relevant study designs would include randomised controlled trials, observational studies, and qualitative studies to investigate families' views and preferences.	
RR 2	What is the clinical and cost effectiveness of information and support offered to parents and carers of babies who have received antibiotics for suspected or proven early-onset neonatal infection? **Why this is important** Further research is needed to determine the optimal form of information and support to be offered to parents and carers of babies who have received antibiotics for suspected or proven early- onset neonatal infection. This is important because current practice is not of a consistently high standard, and many families feel unsupported, which may have implications for use of health service resources. Future research should include consideration of the timing and format for delivering information and which types of healthcare professional should deliver the information. Relevant study designs would include randomised controlled trials, observational studies, and qualitative studies to investigate parents' and carers' views and preferences.	4
	Risk factors for infection and clinical indicators of possible infection	**5.2**
RR 3	This research recommendation has been removed from the 2021 update.	5.2
		6
RR 5	This research recommendation has been removed from the 2021 update.	6

Number	Research recommendation	See section
RR 6	This research recommendation has been removed from the 2021 update.	6

Routine antibiotics after birth 7

No research recommendations were identified in relation to routine antibiotics after birth.

Investigations before starting antibiotics in the baby 8

No research recommendations were identified in relation to investigations before starting antibiotics in the baby.

Antibiotics for suspected infection 9

RR 7 What is the incidence in England and Wales of resistance to commonly used antibiotics among bacteria that cause early-onset neonatal infection? 9

Why this is important

In developing the guideline recommendations the GDG referred to a number of recently published population-based surveillance studies conducted in the United Kingdom. These studies reported data on the incidence of early-onset neonatal infection, causative microorganisms, and the range of antibiotics used to treat infection. Further population-based surveillance studies are needed to identify the characteristics of bacteria that cause early-onset neonatal infection in England and Wales, including resistance to commonly used antibiotics. The studies should include consideration of

Number	Research recommendation	See section
	invasive and non-invasive isolates from women giving birth and newborn babies.	
RR 8	What is the optimal antibiotic treatment regimen for early-onset neonatal meningitis? **Why this is important** Further research is needed to identify the optimal antibiotic treatment regimen for early-onset neonatal meningitis. This is important because there is uncertainty about the most clinical and cost effective treatment regimen for this condition, which causes death is some babies, and serious illness and long-term disability in others. The research should be conducted using multinational randomised controlled trials and should include consideration of the choice of antibiotic and duration of treatment (course length).	9
RR 9	What is the optimal antibiotic dosage regimen for the treatment of early-onset neonatal infection? **Why this is important** Further research is needed to determine the optimal antibiotic dosage regimen for the treatment of early-onset neonatal infection. This is important because current dosage regimens do not take account of the unique physiology of newborn babies, especially preterm babies. The primary focus of the research should be antibiotic treatment using benzylpenicillin or other betalactam antibiotics (such as cefotaxime). The research should include studies involving population pharmacokinetic modelling and studies that relate pharmacokinetic parameters to clinical and microbiological outcomes.	9
RR 10	What is the incidence and severity of adverse effects with antibiotics used to prevent or treat early-onset neonatal infection? **Why this is important** Further research is needed to investigate the safety of antibiotics used to prevent or treat early-onset neonatal infection. This is important because the risks associated with gentamicin are thought to be low enough to justify using this treatment in newborn babies, but the risks have not been quantified, especially in preterm babies. Exposure to antibiotics early in life could have implications in later life, but any risks associated with early exposure have not been quantified. Future research should consider adverse effects associated with the use of antibiotics in general (for example, the development of abnormal gut flora in the perinatal period and its consequences later in life), and adverse effects specific to particular antibiotics (for example, hearing loss and kidney dysfunction associated with the use of gentamicin). The research should include consideration of the incidence and severity of adverse effects and their relationships with gestational age and postnatal age.	9

Number	Research recommendation	See section
RR 11	What are the core exposures and outcomes that should be used to evaluate clinical effectiveness of antibiotics to prevent or treat early-onset neonatal infection? Why this is important Research is needed to produce consensus definitions of the core exposures and outcomes that should be used as part of primary and secondary research studies (including quantitative meta-analysis) to evaluate the clinical effectiveness of antibiotics for the prevention or treatment of early-onset neonatal infection. This is important because the diverse definitions and combinations of exposures and outcomes examined in the evidence reviewed for the guideline resulted in imprecise and indirect estimates of effectiveness. Future research to agree consensus definitions should cover exposures such as maternal and fetal risk factors for early-onset neonatal infection, and core outcomes should place particular emphasis on patient-important outcomes.	9
	Duration of antibiotic treatment	**10**
RR 12	What is the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early- onset neonatal infection in babies receiving antibiotics for suspected infection? Why this is important The systematic reviews conducted for the guideline identified limited evidence relating to investigations used to guide the decision to stop antibiotic treatment in babies receiving antibiotics for suspected early-onset neonatal infection. One study evaluated procalcitonin- guided decision making for identifying babies in whom antibiotic treatment could safely be stopped, but the approach used was at an early stage of development and had not been evaluated fully. The guideline recommendations reflected uncertainty about the diagnostic test accuracy of laboratory investigations used individually or in combination, and further research involving sufficiently powered studies is needed to evaluate this. The ideal study design would be a randomised controlled trial that compares clinical outcomes associated with particular investigation and treatment termination strategies. The next best design would be a prospective cohort study to determine the diagnostic test accuracy of an investigation strategy evaluated in a clinically relevant group of babies. The research should examine clinical effectiveness or diagnostic test accuracy in preterm and term babies separately.	10
RR 13	What is the optimal duration of treatment (course length) in babies who receive antibiotics for confirmed early-onset neonatal infection? Why this is important The Guideline Development Group identified no evidence to inform	10

Number	Research recommendation	See section
	the choice of duration of antibiotic treatment (course length) for confirmed early-onset neonatal infection. In the absence of evidence, the Guideline Development Group based its recommendations on its knowledge of current clinical practice. Further research is needed to evaluate different course lengths in the following clinical circumstances: • babies with group B streptococcal bacterial meningitis • babies with group B streptococcal septicaemia • babies with Gram-negative bacterial meningitis (such as *Escherichia coli* meningitis) • babies with Gram-negative septicaemia. The research should ideally take the form of multinational randomised controlled trials. The primary outcome should be relapse within 10 days of stopping treatment. Secondary outcomes should include long-term neurodevelopment.	
	Therapeutic drug monitoring for gentamicin No research recommendations were identified in relation to therapeutic drug monitoring for gentamicin.	**11**
	Care setting	**12**
RR 14	What is the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection? Why this is important The systematic reviews conducted for the guideline identified very limited evidence in relation to care setting. Further research is needed to evaluate the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection. This is important because of the need to support informed choice relating to care setting during labour, birth and the postnatal period. The research should include consideration of the competencies required to deliver particular aspects of care (such as intrapartum antibiotic prophylaxis), the implications of transfer between different care settings (such as transfers to or from the woman's home or a stand-alone midwifery unit), and family preferences, including the balance between choice and safety. The models of care should be specified, including exposure to medication. The potential benefits and harms of each component should be considered as part of the evaluation of clinical and cost effectiveness.	12

1.7 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

2 Introduction

2.1 Early-onset neonatal infection

Background and definitions

Early-onset neonatal bacterial infection (infection with onset within 72 hours of birth) is a significant cause of mortality and morbidity in newborn babies. Parent organisations and the scientific literature report that there can be unnecessary delays in recognising and treating sick babies. In addition, concern about the possibility of early-onset neonatal infection is common. This concern is an important influence on the care given to pregnant women and newborn babies. There is wide variation in how the risk of early-onset neonatal infection is managed in healthy babies. The approach taken by the National Health Service (NHS) needs to:

- prioritise the treatment of sick babies
- minimise the impact of management pathways on healthy women and babies
- use antibiotics wisely to avoid the development of resistance to antibiotics.

These drivers have not always been addressed consistently in the NHS, and this guideline was commissioned to ensure they would be addressed in future.

The guideline development group (GDG) interpreted the above concerns and drivers within four key principles that underpinned the group's decisions in formulating recommendations for clinical practice:

- Unless it is dangerous, families should be offered choice. The GDG believed that it was important in this guideline to make recommendations to support families by discussing their individual situations, by providing information to enable their understanding and decision making, and by reassuring them should they have any concerns (see Chapter 4).
- Intrapartum antibiotic prophylaxis should be administered in a timely manner to all eligible women who choose it. The GDG addressed this directly within the guideline by making a recommendation (see Chapter 6).
- Babies with suspected early-onset neonatal infection should be treated as quickly as possible.
- Antibiotic exposure should be limited in babies who do not have an early-onset neonatal infection.

All things being equal, the number of doses of antibiotics and the size of each dose should be minimised. In sick babies, healthcare professionals need to adjust the dose to treat suspected or proven infection. However, the vast majority of newborn babies who are given antibiotics do not have any infection. It has been suggested that antibiotics in the days after birth may increase the risk of illnesses such as eczema and asthma in later life, but these risks cannot be quantified. Widespread antibiotic use may also be associated with a risk of antimicrobial resistance. For these reasons, healthy babies should have minimal exposure to antibiotics.

The GDG recognised that to fulfil its third and fourth principles, it was essential that the recommendations to guide management be part of an integrated system of clinical care. To establish a clinical pathway that would deliver best care for babies and their mothers and support for their families within a cost-effective framework, the GDG acknowledged and agreed a fifth principle:

- An integrated system of clinical care is needed to allow full implementation of the guideline recommendations. To ensure prompt treatment in babies with early-onset

neonatal infection while minimising unnecessary antibiotic exposure the guideline includes recommendations on an integrated system of clinical care (for example, systems to provide early availability of blood culture results). Some of the recommendations in the guideline cannot be followed if the integrated approach is not implemented.

Terminology is important in this topic. To avoid confusion this GDG adopted the following definitions:

- Infection is an illness caused by a micro-organism: for example, bacterial infection is caused by bacteria. The dominant bacterial infection in newborn babies is septicaemia. The operational definition of septicaemia used in the guideline is a positive blood culture.
- Sepsis is a clinical condition that occurs during infection, but which is also seen in the absence of confirmed (or proven) infection.

The GDG chose to use infection as the focus of the guideline because it is an unambiguous gold standard in tests of diagnostic accuracy and in studies of antibiotic efficacy.

The possibility of infection in babies can be described in various ways, including 'suspected infection' and 'suspected sepsis'. The GDG has consistently used 'suspected infection' because some babies who need treatment because of suspected or possible infection do not have any of the features of clinical sepsis.

Another key definition in this area is that of 'early-onset neonatal infection'. The literature uses definitions that range from infection that starts within 48 hours of birth to infection that starts within 1 week of birth. At the time the guideline scope was developed there was no validated definition of early-onset infection, so as part of the scoping process it was agreed that the definition that would be used for early-onset infection was infection arising within 72 hours of birth.

When reviewing the literature the GDG considered all relevant information irrespective of the definition of infection or sepsis used by the study authors, or the study authors' definition of early- onset infection.

Population-based surveillance in the UK

Central to the management of early-onset neonatal infection is an awareness of the causative bacteria. The UK is fortunate to have population-based microbiological surveillance data, and two UK population-based neonatal infection surveillance studies were published during the development of the guideline.

The first study (Muller-Pebody 2011) described bacteria isolated from neonatal blood cultures, and their susceptibilities to antibiotics commonly recommended for empirical treatment of suspected infection, using data from the Health Protection Agency's (HPA) LabBase2 database for the period January 2006 to March 2008. The database captures microbiological results submitted voluntarily by 90% of laboratories in England and Wales. Table 2.1 summarises bacterial isolates associated with early-onset neonatal infection (onset within 48 hours of birth).This table excludes *coagulase-negative staphylococci* (CONS). In the context of early-onset neonatal infection CONS are usually regarded as blood sample contaminants (although true CONS infection can arise from hospital-acquired infection, most commonly as late-onset neonatal infection). The data reported in this study were acquired using the HPA's passive microbiological surveillance scheme, and so the clinical importance of the bacterial isolates cannot be established.

Table 2.1 Bacteria isolated from blood cultures from babies with early-onset neonatal infection (onset within 48 hours of birth) in England and Wales, January 2006 to March 2008[a]

Micro-organism	Number of isolates	Percentage of all isolates
Gram positive	**920**	**77**
Group B streptococcus	477	40
Non-pyogenic streptococci[b]	142	12
Staphylococcus aureus	75	6
Enterococcus species	49	4
Micrococcus species	35	3
Streptococcus pneumoniae	32	3
Diphtheroids	32	3
Beta-haemolytic streptococci	28	2
Listeria monocytogenes	13	1
Bacillus species	10	1
Group A streptococci	5	<1
Propionibacterium species	3	<1
Other[c]	19	2
Gram negative	**270**	**23**
Escherichia coli	137	12
Enterobacteriaceae[d]	35	3
Haemophilus influenzae	34	3
Pseudomonas species	18	2
Acinetobacter species	12	1
Haemophilus parainfluenzae	8	1
Haemophilus species	4	<1
Other[e]	22	2
Total	**1190**	**100**

[a] Source: Muller-Pebody 2011; excludes coagulase-negative staphylococci (a Gram-positive micro-organism), for which there were 326 isolates in the same population and time period

[b] *Streptococci viridans*, *S mitis*, *S oralis*, *S salivarius*, *S sanguinis* group, *S intermedius*, *S milleri*, *S anginosus*, *S acidominimus*, *S gordonii*, *Abiotrophia* species, *Aerococcus* species

[c] *Streptococcus* group G, *Streptococcus* group C, *Streptococcus* group D, *Bacillus* other named, *Bacteroides* species, *Lactococcus cremoris*, *Listeria* species, *Eubacterium* species, *Gardnerella vaginalis*, *S anaerobic*,*S dysgalactiae*, *S equisimilis*

[d] *Klebsiella* species, coliform, *Enterobacter* species, *Morganella* species, *Kluyvera* species, *Citrobacter* species, *Pantoea* species, *Proteus* species, *Salmonella paratyphi*, *Serratia*species

[e] *Moraxella* species, *Stenotrophomonas maltophilia*, *Bacteroides* species, *Neisseria* species, *Sphingomonas paucimobilis*, *Aeromonas* species, *Peptostreptococcus* species, *Burkholderia cepaci*, *Oligella urethralis*, *Roseomonas* species, *Weeksella virosa*

The second study (Vergnano 2011) provided a description of NeonIN, a network of level 2 and level 3 neonatal units in England involved in the prospective collection of clinical and microbiological data on episodes of neonatal infection. The study included a report on micro-organisms isolated from blood, cerebrospinal fluid (CSF) and urine samples in babies with early- or late-onset neonatal infection

(although all urine infections reported were late-onset)and who received antibiotics for at least 5 days; antibiotic susceptibilities of the reported organisms were also reported. The report was compiled from information in the NeonIN database for the 3year period from 1 January 2006 to 31 December 2008, at the end of which 12 neonatal units (two level 2 and 10 level 3) were active participants.

Table 2.2 summarises bacterial isolates associated with each episode of early-onset neonatal infection (onset of infection less than 48 hours after birth), excluding CONS, which were not recorded for the entire study period, and fungal pathogens (*Candida albicans*). The data reported in this study were acquired from neonatal units with an interest in neonatal infection and so they are expected to have a different case mix from other centres (for example more babies in these units undergo surgery).

Table 2.2 Bacteria isolated from blood or cerebrospinal fluid cultures from babies with early-onset neonatal infection (onset within 48 hours of birth) in a network of level 2 and level 3 neonatal units in England, January 2006 to December 2008[a]

Micro-organism	Number of episodes	Percentage of all episodes
Gram positive	**94**	**76**
Group B streptococcus	65	52
Non-pyogenic streptococci[b]	5	4
Staphylococcus aureus	6	5
Enterococcus species	3	2
Micrococcus species	1	<1
Streptococcus pneumoniae	2	2
Diphtheroids	1	<1
Beta-haemolytic streptococci	0	0
Listeria monocytogenes	7	6
Bacillus species	4	3
Group A streptococci	0	0
Propionibacterium species	0	0
Other[c]	0	0
Gram negative	**30**	**24**
Escherichia coli	23	19
Enterobacteriaceae[d]	2	2
Haemophilus influenzae	4	3
Pseudomonas species	1	<1
Acinetobacter species	0	0
Haemophilus parainfluenzae	0	0
Haemophilus species	0	0
Other[e]	0	0
Total	**124**	**100**

[a] Source: Vergnano 2011; excludes coagulase-negative staphylococci (a Gram positive micro-organism), for which the number of episodes in the same population and time period was not reported, and fungal pathogens (one episode was associated with *Candida albicans*)

[b] *Streptococci viridans*, *S miti*, alpha-haemolytic streptococci, other Streptococcus species

[c] *Streptococcus* group G, *Streptococcus* group C, *Streptococcus* group D, *Bacillus* other named, *Bacteroides* species, *Lactococcus cremoris*, *Listeria* species, *Eubacterium* species, *Gardnerella vaginalis*, *S anaerobic*, *S dysgalactiae*, *S equisimilis*

[d] *Morganella* species, *Serratia* spp

[e] *Neisseria* species

Despite the differences in case mix, the two studies reported similar proportions of isolates or episodes of early-onset neonatal infection being caused by Gram-positive bacteria other than CONS and Gram-negative bacteria (about 75% and 25%, respectively). In both studies the most frequent causative Gram-positive and Gram-negative bacteria for early-onset neonatal infection were *Streptococcus agalactiae* (group B streptococcus; GBS) and *Escherichia coli*, respectively. However, *Listeria monocytogenes* accounted for 1% of documented infections in the first study (Muller-Pebody 2011) compared with 6% in the second study (Vergnano 2011).

The first study reported that 97% of all causative bacteria other than CONS for early-onset neonatal infection were susceptible to an antibiotic regimen combining benzylpenicillin with gentamicin, 99% were susceptible to amoxicillin combined with benzylpenicillin, 96% were susceptible to cefotaxime as monotherapy and 100% were susceptible to amoxicillin combined with cefotaxime. The susceptibilities of GBS and *Ecoli* to each of these regimens were in the range 98–100%. However, the proportions of isolates that were tested for susceptibility to the various antibiotic regimens varied considerably (47%, 67%, 16% and 49%, respectively), perhaps because certain isolates were not expected to be susceptible to particular antibiotic regimens. The authors recommended the use of gentamicin-based antibiotic regimens over cefotaxime-based regimens in neonatal units because the frequent use of third-generation cephalosporins, such as cefotaxime, has been linked to increased incidence of resistant bacterial pathogens in these settings.

The second study (Vergnano 2011) reported that 95% of bacterial pathogens other than CONS that cause early-onset neonatal infection were susceptible to an antibiotic regimen combining benzylpenicillin with gentamicin. Susceptibility to antibiotic regimens varies between bacterial organisms, and in this study all isolates of *Staphylococcus aureus* were reported to be resistant to the regimen combining benzylpenicillin and gentamicin. The authors of this study concluded that the NeonIN data did not support the use of an antibiotic regimen combining ampicillin and cefotaxime for empirical treatment of early-onset neonatal infection because it provided lower coverage for the majority of causative organisms and its use encourages the development of antibiotic resistance.

The UK population-based surveillance studies demonstrate that surveillance systems are useful, but they need to be improved. Collaborations between networks such as NeonIN and the HPA will be central to improving the management of early-onset neonatal infection. The GDG recommended further research in this area (see Chapter 9).

2.2 For whom is this guideline intended

This guidance is of relevance to those who work in or use the NHS in England and Wales, in particular:

- healthcare professionals involved in the care of pregnant women in any setting, including obstetricians and midwives
- healthcare professionals involved in the care of newborn babies, including neonatologists, general paediatricians, general practitioners (GPs) and nurses
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners and public health and trust managers
- pregnant women whose babies are known to be at risk of an early-onset neonatal infection, and parents and carers of babies who are at risk of, or have suspected or confirmed, early-onset neonatal infection.

2.3 Related NICE guidance

- Caesarean section. NICE clinical guideline 132 (2011).
- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 (2010).
- Induction of labour. NICE clinical guideline 70 (2008).
- Antenatal care. NICE clinical guideline 62 (2008).
- Intrapartum care. NICE clinical guideline 55 (2007). Update in progress. Publication date to be confirmed
- Urinary tract infection in children. NICE clinical guideline 54 (2007).
- Feverish illness in children. NICE clinical guideline 47 (2007). Update in progress. Publication expected May 2013
- Postnatal care. NICE clinical guideline 37 (2006).

3 Guideline development methodology

3.1 Introduction

This guidance was commissioned by NICE and developed in accordance with the guideline development process outlined in the 2009 edition of The Guidelines Manual.

Information about the clinical areas covered by the guideline (and those that are excluded) is available in the scope of the guideline (reproduced in Appendix A).

All guideline development group (GDG) members' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in Appendix B). None of the interests declared by GDG members constituted a material conflict of interest that would influence recommendations developed by the GDG.

Organisations with interests in the prevention and treatment of early-onset neonatal infection were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process. A list of registered stakeholder organisations for the guideline is presented in Appendix C.

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities were considered by the GDG throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available in NICE's Equality Scheme.

3.2 Developing review questions and protocols and identifying evidence

The GDG formulated review questions based on the scope (see Appendix A) and prepared a protocol for each review question (see Appendix D). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix E) to the following databases: Medline, Medline In-Process, Embase and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using Medline, Embase, the Cochrane Central Register of Controlled Trials, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. Where appropriate, review questions were grouped together for searching. The searches were not limited by countries in which studies were conducted, but studies conducted outside the European Union (EU), the USA, Canada, Australia and New Zealand were excluded manually from the search results because they were viewed to be less relevant to the development of guideline recommendations. In geographical settings other than those listed above, causative organisms, prevalence rates and clinical practice are likely be different to those in the UK. Different virulence factors are likely to alter the nature and timing of the patient response, and prevalence rates need to be homogenous to allow interpretation of statistics such as diagnostic test accuracy (whether to put a particular test into clinical practice); in geographical settings other than those listed above there is significant risk of heterogeneity in prevalence rates.

The initial search for the review of risk factors in the baby (including symptoms and signs of infection) resulted in a very large number of articles for consideration, and so the search was limited to articles published in or after 2000 to ensure a manageable workload for the GDG and the NCC-WCH

technical team. The remaining searches were not limited by date. Animal studies were excluded from Medline and both Medline and Embase were limited to English-language studies only. Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases before 22 September 2011.

3.3 Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In this approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating)
- Limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up; these can reduce the quality rating)
- Inconsistency of effects across studies (this can reduce the quality rating where more than one study is considered for the same outcome)
- Indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating)
- Imprecision (the extent to which the point estimate or its confidence interval [CI] reflects a statistically significant or clinically important difference; this can reduce the quality rating)
- Other considerations (including large magnitude of effect, evidence of a dose–response relationship or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high; this may be downgraded to moderate, low or very low if the factors outlined above are not addressed adequately. For issues of prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study): a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors outlined above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity and likelihood ratios (LRs) for positive and negative test results (LR^+ and LR^-, respectively) were calculated or quoted where possible (see Table 3.1).

Table 3.1 '2 x 2' table for calculation of diagnostic test accuracy parameters

	Reference standard positive	**Reference standard negative**	**Total**
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of test results in study)

Sensitivity = a/(a+c), specificity = d/(b+d), LR^+ = sensitivity/(1–specificity), LR^- = (1–sensitivity)/specificity

The GDG prioritised LRs for evaluating diagnostic test accuracy, where available, because Jaeschke's (1994) rules of thumb provide a recognised and objective system for assessing the usefulness of a given test. (There is no corresponding guide to determining how close to 100% sensitivity and specificity must be for a test to be useful in practice.) The interpretations used for sensitivity, specificity and likelihood ratios for positive and negative test results are:

- The sensitivity of a test represents the proportion of babies with the target condition (early-onset neonatal infection) who have a positive test result.
- The specificity of a test represents the proportion of babies without the target condition who have a negative test result.
- A perfect test (one that classifies all babies with and without the target condition correctly) would have sensitivity and specificity both equal to 100%. A test with a high sensitivity (close to 100%) is good for ruling out the target condition in babies who have a negative test result. A test with a high specificity (close to 100%) is good for ruling in the target condition in babies who have a positive test result.
- The likelihood ratio for a positive test result (positive likelihood ratio; LR^+) indicates how much more likely a baby is to have the target condition given a positive test result, compared with the pretest probability of having the condition.
- The likelihood ratio for a negative test result (negative likelihood ratio; LR^-) indicates how much less likely a baby is to have the target condition given a negative test result, again compared to the pre-test probability of having the condition.
- A 'very useful' diagnostic test would be one for which LR^+ is very large (greater than 10, as a rule of thumb) and LR^- is close to zero (smaller than 0.1, as a rule of thumb; see Jaeschke 1994).
- A 'moderately useful' diagnostic test would be one for which LR^+ is between 5 and 10 and LR^- is between 0.1 and 0.2.
- A likelihood ratio between 0.2 and 5 indicates that a diagnostic test is not particularly useful. A likelihood ratio of 1 indicates that the test is not at all informative.

The GRADE system described above covers studies of treatment effectiveness. It is also being used increasingly for studies reporting diagnostic test accuracy measures, which is relevant to several review questions in this guideline. For such studies, NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QADAS) methodology checklist to assess the quality of individual studies (see the NICE guidelines manual). A body of evidence based on prospective cohort studies would have an initial quality rating of high in the GRADE system, whereas a body of evidence based on retrospective cohort studies or case–control studies would have an initial quality rating of moderate. The QADAS quality assessments for the individual studies contributing to the body of evidence for each outcome would determine the limitations of the evidence in the GRADE quality assessment for that outcome.

The number of studies identified for each review question is summarised in Appendix F. Some studies were excluded from the guideline reviews after obtaining copies of the corresponding publications because they did not meet inclusion criteria specified by the GDG (see Appendix G). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H). Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% CIs, and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs). RRs were prioritised by the GDG for dichotomous outcomes because they have a natural interpretation.

The body of evidence identified for each review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled RRs, pooled ORs or weighted mean differences (MDs). By default, meta-analyses were conducted by fitting random effects models because the study populations and interventions evaluated were viewed by the GDG as being intrinsically heterogeneous and different to the populations and interventions of interest to the GDG (for example, the gestational ages or postnatal ages of babies varied greatly between included studies, as did regimens for administration of antibiotics, even when the same antibiotic was being used).Where quantitative meta-analysis could not be undertaken, the range of effect sizes reported in the included studies was presented. Forest plots for all meta-analyses conducted for the guideline are presented in Appendix I. GRADE findings are presented in full in Appendix J; abbreviated versions (summary of findings without the individual components of the quality assessment) are presented in this document.

Various approaches may be used to assess imprecision in the GRADE framework. In this guideline, dichotomous outcomes in intervention studies were downgraded in terms of imprecision when the total number of events was less than 300 and continuous outcomes were downgraded when the total sample size was less than 400. These are default thresholds used in GRADE for intervention studies. For diagnostic test accuracy studies, evidence was downgraded in terms of imprecision when the width of the 95% CI for either sensitivity or specificity was 40 percentage points or more, or if the CI for any of sensitivity, specificity, LR^+ or LR^- was not reported or not calculable. These thresholds and decision rules have been used in other NICE clinical guidelines (for example Non-invasive ventilation for motor neurone disease, NICE clinical guideline 105, 2010).

3.4 Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to the prevention and treatment of early-onset neonatal infection, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the (very limited) relevant published health economic literature are presented alongside the clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- Reacting to different risk factors, singly or in combination
- Investigations (tests) such as: C-reactive protein (CRP); procalcitonin; full blood count; white blood cell (WBC) count; platelet count; lumbar puncture; polymerase chain reaction (PCR); investigations specific to urinary tract infection (for example suprapubic aspirates); surface swabs; and gastric aspirates

- Intrapartum antibiotic prophylaxis for the prevention of early-onset neonatal infection compared with no treatment
- Antibiotic treatment regimens in babies with:
    - confirmed early-onset neonatal infection (bacterial cause identified)
    - presumed symptomatic infection, but no bacterial cause identified
    - initial clinical suspicion of infection, but no continuing clinical concerns and results of all investigations normal
    - asymptomatic babies receiving prophylactic treatment
- Cost effectiveness of different care settings, taking into account the woman's choice as well as the feasibility of delivering a safe standard of care in different settings.

Details of the health economic analyses conducted for the guideline are presented in Chapter 13.

3.5 Evidence to recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree short clinical and, where appropriate, cost effectiveness evidence statements, which were presented alongside the evidence profiles. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues)
- key conclusions.

In areas where no substantial clinical research evidence was identified, the GDG members considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions, including tests and other investigations) was considered was based on GDG consensus in relation to the likely cost effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified ten 'key priorities for implementation' (key recommendations) and five high-priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on the prevention and treatment of early-onset neonatal infection and outcomes in the NHS as a whole; these were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were also selected using a variant of the nominal group technique.

3.6 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses were reviewed by NICE in accordance with the NICE guideline development process.

4 Information and support

Introduction

The objectives of this review question are to identify the information and support that should be provided for pregnant women whose unborn babies are at sufficiently high risk of an early-onset neonatal infection to affect clinical management, and for parents and carers of babies who are at increased risk of, or have suspected or confirmed, early-onset neonatal infection. In prioritising this review question for inclusion in the guideline, the guideline development group's (GDG's) intention was to include recommendations explaining the rationale for, and possible consequences of, each step in the care pathway derived from the evidence identified for the other review questions. A systematic search for evidence was also conducted, with no restrictions on study design and explicitly seeking to identify qualitative research reporting views and experiences of parents and carers of babies with, or at risk of, early-onset neonatal infection (including expectant mothers offered intrapartum antibiotic prophylaxis to prevent early-onset neonatal infection in their babies, and parents or carers of babies given postnatal antibiotic prophylaxis or treatment). The outcomes prioritised for consideration included parental satisfaction, involvement in decision making, empowerment, anxiety, impact on the baby's family (including subsequent pregnancies) and health-related quality of life in the baby.

Review question

What information and support should be provided for parents and carers?

Existing NICE guidance

Antenatal care (NICE clinical guideline 62, 2008) provides guidance on the care of healthy pregnant women in the antenatal period. The guideline recommends that pregnant women should be offered information about food hygiene, including how to reduce the risk of food-acquired infections, at the first contact with a healthcare professional. The guideline highlights the risks to pregnant women, unborn babies and newborn babies associated with listeriosis, which is caused by listeria (*L monocytogenes)*. The guideline recommends that information offered to pregnant women should include how to reduce the risk of listeriosis by:

- drinking only pasteurised or ultra heat treated (UHT) milk
- not eating ripened soft cheeses, for example camembert, brie and blue-veined cheese (there is no risk with hard cheeses, such as cheddar, or cottage cheese or processed cheese)
- not eating pâté of any kind (including vegetable pâté)
- not eating uncooked or undercooked ready-prepared meals.

Intrapartum care (NICE clinical guideline 55, 2007) provides guidance on the care of healthy women in labour at term (37–42 weeks' gestation). The guideline recommends that women presenting with term prelabour rupture of membranes (PROM) should be informed that the risk of serious neonatal infection is 1% (rather than 0.5% for women with intact membranes). The guideline also recommends that women with term PROM should be asked to inform their healthcare professionals immediately of any concerns they have about their baby's wellbeing in the first 5 days following birth, particularly in

the first 12 hours when the risk of infection is greatest. The guideline reviewed evidence relating to labouring and giving birth in water, and this included consideration of the risks of maternal and neonatal infection. The guideline recommends that women should be informed that there is insufficient high-quality evidence to either support or discourage giving birth in water (whereas the opportunity to labour in water is recommended for pain relief).The guideline also includes the following recommendations that set out principles of care relating to information and support:

- All women in labour should be treated with respect and should be in control of and involved in what is happening to them, and the way in which care is given is key to this. To facilitate this, healthcare professionals and other caregivers should establish a rapport with the labouring woman, ask her about her wants and expectations for labour, and be aware of the importance of tone and demeanour and of the actual words they use. This information should be used to support and guide the woman through her labour.
- To establish communication with the labouring woman, healthcare professionals should involve the woman in any handover of care to another professional, either when additional expertise has been brought in or at the end of a shift.
- Any examination or treatment of the baby should be undertaken with the consent and in the presence of the parents or, if this is not possible, with their knowledge.

Induction of labour (NICE clinical guideline 70, 2008) provides guidance on the care of women who are having or are offered induction of labour, including induction of labour in women with preterm or term PROM. The guideline includes a recommendation that sets out principles of care relating to information and support. Healthcare professionals offering induction of labour should:

- allow the woman time to discuss the information with her partner before coming to a decision
- encourage the woman to look at a variety of sources of information
- invite the woman to ask questions, and encourage her to think about her options
- support the woman in whatever decision she makes.

Postnatal care (NICE clinical guideline 37, 2006) provides guidance on routine care for women and their babies in the first 6–8 weeks after birth. The guideline recommends that parents are offered information and advice at each postnatal contact to allow them to assess their baby's general condition, identify symptoms and signs of common infant health problems, and to contact healthcare professionals or emergency medical services if needed.

Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) provides guidance on the management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care (the guideline excludes babies already receiving care in neonatal units). The guideline includes the following recommendations relating to information and support for parents and carers:

- If the baby is assessed as being at low risk of meningococcal disease (disease associated with *Neisseria meningitidis*, or meningococcus) and is discharged after initial observation, advise parents or carers to return to hospital if the baby appears ill to them.
- Before discharging babies from hospital, consider their requirements for follow-up and discuss potential long-term effects of their condition and likely patterns of recovery with their parents or carers (and provide them with opportunities to discuss issues and ask questions).
- Offer parents and carers information about, and access to, further care immediately after discharge.
- Offer parents and carers contact details of patient support organisations (including meningitis charities) that can offer support, befriending, in-depth information, advocacy, counselling and written information to signpost families to further help.
- Offer parents and carers advice on accessing future care.

Feverish illness in children (NICE clinical guideline 47, 2007) provides guidance on the assessment and initial management of fever in children younger than 5 years. The guideline includes the following recommendation relating to information and support for parents and carers:

- Provide a 'safety net' for babies with an intermediate risk of serious illness and for whom no diagnosis has been made, or offer referral to specialist paediatric care for further assessment (safety netting means giving the baby's parents or carers verbal or written information on warning symptoms and how to access further healthcare, arranging follow-up at a specific time and location, or liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the baby if further assessment is needed).

The guideline recommends home-based care for babies with a low risk of serious illness and offering advice to the baby's parents or carers on when and how to seek further advice and care from healthcare professionals. The guideline also recommends consideration of social and family circumstances and parental anxiety and instinct when deciding whether or not to admit a baby with fever to hospital.

Urinary tract infection in children (NICE clinical guideline 54, 2007) provides guidance on the diagnosis, treatment and long-term management of urinary tract infection in children and young people younger than 16 years. The guideline recommends that healthcare professionals should ensure that when a baby has been identified as having a suspected urinary tract infection (UTI), their parents or carers are given information about the need for treatment, the importance of completing any course of treatment and advice about prevention and possible long-term management.

Medicines adherence (NICE clinical guideline 76, 2009) provides guidance on involving patients in decisions about prescribed medicines and supporting adherence. The guideline focuses on involving patients in decisions about prescribed medicines and supporting adherence. Although the guideline focuses specifically on people aged 16 years and older, some recommendations set out general principles that might also be applied to parents and carers taking decisions about clinical care on behalf of babies; for example, healthcare professionals should:

- adapt their consultation style to the needs of the individual to provide an opportunity to be involved in decision making about prescribed medicines at the level they would like
- ask open-ended questions because these are more likely to reveal concerns
- explain the medical aims of treatment and discuss the pros and cons of proposed medicines openly at the level preferred by the individual
- explain the disease or condition clearly and how the medicine will influence this
- accept that people may have different views from healthcare professionals about the balance of risks, benefits and side effects of medicines
- offer information that is relevant to the individual's personal circumstances, and that is easy to understand and free from jargon
- suggest where to find reliable information and support after the consultation (for example by providing written information or directing people to other resources, such as NHS Choices.

Description of included studies

No studies were identified for inclusion for this review question.

Evidence statements

No evidence specific to prevention and treatment of early-onset neonatal infection was identified relating to information and support that should be provided for parents and carers.

Evidence to recommendations

Relative value placed on the outcomes considered

The priority outcomes specified in the protocol for this review question were:

- parental and carer satisfaction
- parental and carer involvement in decision making
- parental and carer anxiety
- parental and carer empowerment
- impact on the baby's family, including subsequent pregnancies
- health-related quality of life of the baby.

The GDG prioritised the above outcomes with the aim of ensuring that pregnant women whose unborn babies are at sufficient risk of an early-onset neonatal infection to affect clinical management, and parents and carers of babies who are at increased risk of, or have suspected or confirmed, early- onset neonatal infection, are well informed and to promote informed choice. The GDG also aimed to enable parents and carers to understand the short- and long-term implications of antibiotic prophylaxis or treatment for the baby and their family.

Consideration of clinical benefits and harms

The advantage of giving parents and carers timely and specific information about the risks and benefits of administering antibiotics is that such practice should lead to timely assistance where appropriate. Provision of information for parents and carers should include consideration of outcomes associated with not administering antibiotics when they are indicated (for example, a baby at increased risk of an early-onset neonatal infection might become very unwell very quickly if antibiotics are not given). Provision of timely and specific information should allow parents and carers to be better involved in the decision-making process regarding care of their babies. This might also result in better short- and long-term outcomes for the baby, improved parental and carer satisfaction, and reduced parental and carer anxiety. Moreover, well informed and supported parents and carers might have a better understanding of the circumstances surrounding treatment of an early-onset neonatal infection and, therefore, be better prepared for issues such as administration of antibiotics leading to a prolonged hospital stay (thus having an impact on the baby's family), the need for intravenous access (and other invasive procedures or tests) and the possibility of adverse effects of antibiotics on the baby's developing immune system and intestinal flora.

Giving parents and carers information has the potential harm of causing unnecessary anxiety (for example when parents and carers have knowledge of potential serious complications in a baby that is given antibiotic treatment yet does not develop complications). It also might lead to unnecessary worry, such as the fact that the parents or carers might not be able to care for the baby as they would wish (for example raising doubts about the possibility of breastfeeding or holding a baby that is being treated with antibiotics).

Consideration of net health benefits and resource use

The cost of providing information and support is dependent on its quantity and method of delivery, and the cost of providing extra professional participation has resource implications. However, the benefit of giving timely and specific information to parents and carers could result in better use of healthcare resources, for example by helping to distinguish between babies who do and do not require antibiotic treatment, thus avoiding unnecessary antibiotic treatment and hospital stay for babies who do not need antibiotics.

Quality of evidence

No evidence was identified for inclusion for this review question and so the quality of the available evidence did not impact on the strength of the GDG's recommendations. The recommendations were

formulated using the GDG's knowledge and experience (see below), taking account of evidence identified for other review questions and recommendations arising from that evidence.

Other considerations

In the absence of evidence, the GDG based its recommendations on the knowledge and experience of its members, emphasising that the ethos of the entire guideline was to promote informed choice for parents and carers of babies at increased risk of early-onset neonatal infection or with suspected or confirmed early-onset neonatal infection. No specific equalities issues were identified relating to this review question. The GDG was, however, aware of recommendations regarding information and support in related NICE guidelines, including Intrapartum care (NICE clinical guideline 55, 2007) and Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010). The GDG refined or adapted relevant recommendations from other guidelines, tailoring them to the specific considerations of providing information and support for parents and carers of babies at increased risk of, or with, an early-onset neonatal infection.

Key conclusions

The GDG considered the infection pathway and organised its recommendations according to the information and support needed by parents and carers at each stage of the pathway. The GDG considered the type of information needed, and the most effective means of communicating that information to parents and carers.

Information for pregnant woman before the birth of the baby

The GDG agreed that women whose unborn babies are at sufficiently high risk of early-onset neonatal infection to affect clinical management should be made aware of the risk and be provided with information about antibiotic prophylaxis and treatment and support to enable them to make decisions about clinical care. The GDG agreed that the information should cover the risks and benefits of administering antibiotics to the woman and her baby for prevention of early-onset neonatal infection. The GDG also agreed that the woman should be reassured that if she had Group B streptococcus (GBS) colonisation in a previous pregnancy, but without infection in the baby, this would not affect the management of the birth in the current pregnancy.

The GDG believed that discussions with pregnant women should, where possible, be conducted in a timely manner during pregnancy (because some risk factors will not be evident early in pregnancy) to maximise the woman's understanding and promote her engagement in treatment decisions. The risks associated with infection should be discussed as soon as they are identified and revisited close to labour and birth if relevant.

The GDG considered that pregnant women should be made aware of observations, protocols and investigations that might be performed in order to confirm an early-onset neonatal infection. The GDG agreed that healthcare professionals should inform women of the potential benefits and harms of antibiotic prophylaxis and treatment administered to the woman or her baby.

The GDG considered that the impact of the care setting on the baby's family was particularly relevant, and that the woman should understand how long antibiotic treatment would last, how it would be administered, and whether these considerations might affect any care setting, such as the planned place of birth.

During the birth

The GDG recognised the importance of healthcare professionals maintaining communication with women in labour by involving them when additional expertise is required because of the risk of early-onset neonatal infection or, as in Intrapartum care (NICE clinical guideline 55, 2007), at the end of a shift. The GDG considered that the handover of care in both these circumstances should include an update about the presence of any infection because this would ensure continuity of care and minimise the risk of failing to pass on information about the presence of an infection.

After the birth

The GDG agreed that parents and carers of babies in whom there are clinical concerns about possible early-onset neonatal infection have some needs in common with pregnant women whose babies are at risk of infection. Parents and carers should, therefore, be given information about the

risks and benefits of antibiotic treatment, observations, protocols and investigations to confirm early-onset neonatal infection, and the impact on the baby's care setting. The GDG also agreed that parents and carers of babies who are at risk of, or have suspected or confirmed, early-onset neonatal infection should be informed that parental care of the baby (such as holding the baby) can continue during antibiotic prophylaxis and treatment unless the healthcare team considers that the baby is too unwell. The GDG recognised the importance of informing parents and carers about the baby's health condition. If the mother chooses to breastfeed the baby her healthcare team should ensure that every effort is made to facilitate this in accordance with the United Nations Children's Fund (UNICEF) Initiative. Moreover, if a baby is temporarily unable to breastfeed, healthcare professionals should support the mother to express breast milk if she wishes to do so.

The GDG agreed that healthcare professionals should choose the most suitable method of delivery for information and allow sufficient time for parents and carers to discuss the information provided. Healthcare professionals should provide an opportunity for parents and carers to ask questions and support them in their decision-making process.

At discharge

To avoid or minimise the risk of complications in future pregnancies, the GDG suggested that before discharging women from hospital, healthcare professionals should inform women about the risk of early-onset neonatal infection in future pregnancies. If the baby has had a GBS infection the mother should be asked to inform her maternity care team if she becomes pregnant again. To ensure that information is passed on for any future pregnancies, healthcare professionals should inform the woman's GP in writing about the increased risk of early-onset neonatal GBS infection in future pregnancies. The GDG also agreed that if the woman was found to be carrying GBS in a previous pregnancy this would not affect the management of the birth for the current pregnancy and the woman should be reassured of this.

The GDG recognised the importance of providing parents and carers with follow up and discharge planning for the baby, which should include verbal or written information on warning signs and how to access further healthcare, arranging follow up at a specific time and location, or liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the baby if further assessment is needed. As in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010), the GDG recommended that information for parents and carers should include details of relevant parent support organisations.

With these recommendations the GDG aimed to empower parents and carers to manage their own concerns. Information about warning signs should be tailored to the initial level of concern about the baby because this will help parents and carers recognise the signs promptly, and it will give them confidence in their ability to make appropriate judgements if the baby appears ill to them. The GDG's view was that parents and carers should seek medical advice if the baby shows any signs of abnormal behaviour (for example inconsolable crying or listlessness), being floppy or developing difficulties with feeding or tolerating feeds, or has a temperature abnormality that cannot be explained by environmental factors. The GDG's consensus view was that a temperature of less than 36°C or more than 38°C would be abnormal.

Recommendations

Number	Recommendation
	Information and support This section was partially updated in 2021. See https://www.nice.org.uk/guidance/cg149/ for the current recommendations.

1 •

- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

Research recommendations

Number	Research recommendation
	Information and support
RR 1	How does each step in the care pathway for prevention and treatment of early-onset neonatal infection impact on babies and their families? Why this is important Further research is needed to evaluate the impact on babies and their families of each step in the care pathway for the prevention and treatment of early-onset neonatal infection. This is important because family needs will have implications for service delivery in the neonatal period and subsequently. The nature of such needs and the extent to which they vary between families have not been described in the evidence considered for inclusion in the guideline. Future research should focus particularly on the impacts of antibiotic prophylaxis and treatment. Impacts should be assessed in terms of short- and long-term outcomes, and include consideration of resource utilisation and costs. Relevant study designs would include randomised controlled trials, observational studies, and qualitative studies to investigate families' views and preferences.

RR 2 What is the clinical and cost effectiveness of information and support offered to parents and carers of babies who have received antibiotics for suspected or proven early-onset neonatal infection?

Why this is important

Further research is needed to determine the optimal form of information and support to be offered to parents and carers of babies who have received antibiotics for suspected or proven early-onset neonatal infection. This is important because current practice is not of a consistently high standard, and many families feel unsupported, which may have implications for use of health service resources. Future research should include consideration of the timing and format for delivering information and which types of healthcare professional should deliver the information. Relevant study designs would include randomised controlled trials, observational studies, and qualitative studies to investigate parents' and carers' views and preferences.

5 Risk factors for infection and clinical indicators of possible infection

This section was updated and replaced in 2021. See https://www.nice.org.uk/guidance/cg149/evidence for the 2021 evidence review on risk factors for early onset infection (RQ 1.1/1.2/1.3)

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

The research recommendations in this section have been removed from the 2021 update.

RR 4

6 Intrapartum antibiotics

This section was updated and replaced in 2021. See https://www.nice.org.uk/guidance/cg149/evidence for the 2021 evidence review on intrapartum antibiotics RQ2.1.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

The research recommendations in this section have been removed from the 2021 update.

7 Routine antibiotics after birth

Introduction

The objectives of this review question are to evaluate the effectiveness of antibiotic prophylaxis administered routinely to all babies after birth, or to well babies in whom maternal or fetal risk factors for early-onset neonatal infection have been identified, to prevent early-onset neonatal infection. Specific issues prioritised by the guideline development group (GDG) for consideration in this question were: potential differences in clinical management, depending on whether intrapartum antibiotics had been administered as prophylaxis to prevent early-onset neonatal infection or for maternal indications; which class of antibiotics to use; timing, route and frequency of antibiotic administration; dosage; and the impact of prematurity on clinical management.

The considerations regarding inclusion of evidence obtained using particular study designs are similar to those in the review question relating to intrapartum antibiotics (see Chapter 6). For the evaluation of clinical outcomes (such as prevention of early-onset neonatal infection) the GDG restricted consideration to evidence from randomised controlled trials (RCTs). For pharmacokinetic outcomes (for example incidence of therapeutic or toxic concentrations of a particular antibiotic) used to evaluate dosage regimens the GDG restricted consideration to evidence from RCTs where such evidence was available. Other comparative or non-comparative pharmacokinetic and pharmacodynamic studies were considered only when no relevant evidence from RCTs was identified. The GDG drew initial conclusions about effectiveness based on clinical outcomes reported in RCTs and then reviewed pharmacokinetic outcomes only for those antibiotics that it was considering recommending. As noted in Chapter 6, the rationale for considering pharmacokinetic outcomes in this guideline is that few antibiotics are licensed for use in pregnancy or in preterm babies; the GDG prioritised consideration of safe and effective dosage regimens in all of the review questions relating to antibiotic treatment.

Review question

In babies with maternal risk factors for early-onset neonatal infection is routine administration of antibiotics to the baby effective in preventing early-onset neonatal infection?

Existing NICE guidance

Intrapartum care (NICE clinical guideline 55, 2007) identified prelabour rupture of membranes (PROM) as a major obstetric risk factor for neonatal infection and evaluated various clinical management strategies following term PROM (although preterm PROM was outside the scope of the guideline). The guideline recommendations covered the clinical management and care of the baby after birth, including criteria for administration of antibiotics to the baby after birth. The guideline noted that babies who are asymptomatic at birth have a lower risk of developing neonatal sepsis. The guideline recommended a risk-based clinical management strategy for women with term PROM, which included the following elements:

- If there are no signs of infection in the woman, do not give antibiotics to the woman or the baby, even if the membranes have been ruptured for over 24 hours.
- Do not perform blood, cerebrospinal fluid or surface culture tests in an asymptomatic baby.

- Observe asymptomatic term babies born to women with term PROM more than 24 hours before labour closely for the first 12 hours of life (at 1 hour, 2 hours and then 2 hourly for 10 hours). The observations should include: general wellbeing; chest movements and nasal flare; skin colour including perfusion, by testing capillary refill; feeding; muscle tone; temperature; heart rate; and respiration.
- Offer immediate referral to a neonatal care specialist for a baby with any symptom of possible sepsis, or born to a woman who has evidence of chorioamnionitis.

Description of included studies

Six studies (all RCTs) were identified for inclusion for this review question (Auriti 2005; Hammerberg 1989; Hammerschlag 1980; Patel 1999; Pyati 1983; Siegel 1982).

Clinical outcomes reported in randomised controlled trials

Four RCTs evaluated the effectiveness of antibiotics in babies with risk factors for early-onset neonatal infection (Pyati 1983; Auriti 2005; Hammerberg 1989; Hammerschlag 1980).

The first study (Pyati 1983) evaluated the effectiveness of benzylpenicillin administered intramuscularly to babies with low birthweight (indicating a high risk of group B streptococcus [GBS] infection) within 60–90 minutes of birth and then every 12 hours for 72 hours compared to no administration of benzylpenicillin within 60–90 minutes of birth, but administration at 12 hours after birth and then every 12 hours for 72 hours.

The second study (Auriti 2005) evaluated the effectiveness of a single bolus of ampicillin plus netilmicin administered intravenously to babies with at least one risk factor for early-onset neonatal infection upon admission to the neonatal intensive care unit (NICU) compared to a 3-day course of ampicillin plus netilmicin administered intravenously in two divided doses. The risk factors for infection were:

- history of prolonged rupture of membranes (more than 24 hours)
- suspected chorioamnionitis (rupture of membranes more than24 hours, stained and foul amniotic fluid, maternal fever or leukocytosis)
- proven maternal urinary tract infection
- leukopenia (less than 5000 cells/mm^3) or neutropenia (less than 1750 cells/mm^3) at birth
- presence on admission to the NICU of a central venous or arterial catheter, an endotracheal tube, pleural drainage or history of invasive resuscitation manoeuvres.

The third study (Hammerberg 1989) evaluated the effectiveness of piperacillin plus placebo versus ampicillin plus amikacin administered to babies with risk factors for sepsis within 7 days of birth. The risk factors for sepsis were:

- prolonged rupture of membranes (more than 18 hours; more than 36% of babies in both treatment groups were born following prolonged rupture of membranes)
- intrapartum maternal fever (more than 38°C)
- foul-smelling amniotic fluid.

The study also included babies with the following clinical signs or laboratory findings consistent with sepsis (these were also described as risk factors for sepsis by the study authors):

- apnoea (cessation of breathing for more than 15 seconds resulting in bradycardia and cyanosis)
- poor perfusion (capillary refill time more than 5 seconds)
- ratio of immature to total neutrophils (I:T ratio) more than 0.2.

The fourth study (Hammerschlag 1980) evaluated the effectiveness of erythromycin eye ointment versus 1% silver nitrate eye drops administered immediately after birth for the prevention of neonatal chlamydial conjunctivitis and respiratory tract infection in babies born to women who tested positive for Chlamydia (*Chlamydia trachomatis*) in the third trimester of pregnancy.

Two further RCTs evaluated the effectiveness of antibiotics given to all babies shortly after birth (Patel 1999; Siegel 1982). The first study (Patel 1999) evaluated the effectiveness of benzylpenicillin administered intramuscularly to babies within 1 hour of birth versus no benzylpenicillin for the prevention of GBS infection. The second study (Siegel 1982) evaluated the effectiveness of benzylpenicillin administered intramuscularly to babies within 1 hour of birth versus topical tetracycline ointment for the prevention of gonococcal eye infections (caused by *N gonorrhoeae*), GBS colonisation and systemic GBS disease.

Pharmacokinetic and pharmacodynamic studies

Based on the GDG's initial consideration of clinical outcomes reported in RCTs, the pharmacokinetics and pharmacodynamics of benzylpenicillin were prioritised for evaluation, but no RCTs or studies of other designs reporting pharmacokinetic outcomes associated with benzylpenicillin treatment were identified for inclusion.

Evidence profiles

The evidence profiles for this review question are presented in Tables 7.1 to 7.6. Tables 7.1 to 7.4 contain evidence relating to the effectiveness of antibiotics in babies with risk factors for early-onset neonatal infection. Tables 7.5 and 7.6 contain evidence relating to the effectiveness of antibiotics given to all babies within 1 hour of birth (universal prophylaxis).

Table 7.1 Evidence profile for intramuscular benzylpenicillin within 60–90 minutes of birth and then every 12 hours for 3 days versus no early treatment (treatment started12 hours after birth and then every 12 hours for 3 days) in babies with low birthweight[a]

Number of studies	Number of babies		Effect		Quality
	Intramuscular benzylpeni-cillin within 60–90 minutes of birth and then every 12 hours for 3 days	No early treatment	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Blood or cerebrospinal fluid culture-proven early-onset group B streptococcal infection					
1 (Pyati 1983)	10/589 (2%)	14/598 (2%)	RR 0.73 (0.32 to 1.62)*	6 fewer per 1000 (from 16 fewer to 15 more)*	Moderate
Mortality (early-onset)[b]					
1 (Pyati 1983)	6/589 (1%)	8/598 (1%)	RR 0.76 (0.27 to 2.18)*	24 fewer per 1000 (from 48 fewer to 12 more)*	Moderate

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Details of no early treatment not reported in the article; it is unclear whether babies received no benzylpenicillin or did receive benzylpenicillin but not within 60-90 minutes of birth; low birthweight was used to indicate a high risk of group B streptococcal infection.

[b] Early-onset infection defined as infection in the first 5 days of life

Table 7.2 Evidence profile for a single bolus dose versus a 3-day course of intravenous ampicillin plus netilmicin in preterm babies (< 32 weeks' gestation) with risk factors for early-onset neonatal infection

Number of studies	Number of babies		Effect		Quality
	Single bolus dose of ampicillin plus netilmicin	3-day course of ampicillin plus netilmicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mortality (early-onset)[a]					
1 (Auriti 2005)	3/14 (21%)	3/16 (19%)	RR 1.14 (0.27 to 4.78)*	26 more per 1000 (from 137 fewer to 709 more)*	Low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 2 days of life

Table 7.3 Evidence profile for piperacillin (50 mg/kg) plus placebo every 12 hours versus ampicillin (50 mg/kg) plus amikacin (7.5 mg/kg) every 12 hours in babies with risk factors for sepsis (including clinical signs and laboratory abnormalities consistent with sepsis) who were aged less than 7 days

Number of studies	Number of babies		Effect		Quality
	Piperacillin plus placebo	Ampicillin plus amikacin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Blood culture proven sepsis[a]					
1 (Hammerberg 1989)	6/200 (3%)	7/196 (4%)	RR 0.84 (0.29 to 2.46)*	6 fewer per 1000 (from 25 fewer to 59 more)*	Low
Mortality during antibiotic treatment or within 1 week after treatment					
1 (Hammerberg 1989)	17/200* (8.5%)	27/200* (13.8%)	RR 0.62 (0.35 to 1.10)*	52 fewer per 1000 (from 90 fewer to 14 more) *	Low
Mortality from infection					
1 (Hammerberg 1989)	3/200 (2%)	2/196 (1%)	RR 1.47 (0.25 to 8.70)*	5 more per 1000 (from 8 fewer to 79 more)*	Low
Renal impairment (serum creatinine >100 micromol/l) among babies treated for >24 hours					
1 (Hammerberg 1989)	NR (25.2%)	NR (21.8%)	NC (*P*>0.05)	NC	Low
Hepatic impairment (total serum bilirubin >20 micromol/l) among babies treated for >24 hours					
1 (Hammerberg 1989)	NR (57.1%)	NR (57.7%)	NC (*P*>0.05)	NC	Low

NC not calculable, NR not reported, P probability, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Blood cultures were obtained before antibiotics were administered

Table 7.4 Evidence profile for erythromycin eye ointment applied immediately after birth versus 1% silver nitrate eye drops instilled immediately after birth to babies born to women who tested positive to Chlamydia

Number of studies	Number of babies		Effect		Quality
	Erythromycin eye ointment	1% silver nitrate eye drops	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Culture-proven chlamydial conjunctivitis					
1 (Hammerschlag 1980)	0/24 (0%)	12/36 (33%)	RR 0.059 (0.004 to 0.955)*	313 fewer per 1000 (from 17 fewer to 333 fewer)*	Low
Culture-proven chlamydial nasopharyngeal infection					
1 (Hammerschlag 1980)	5/24 (21%)	10/36 (28%)	RR 0.75 (0.29 to 1.92)*	69 fewer per 1000 (from 197 fewer to 256 more)*	Low
Culture-proven chlamydial pneumonia					
1 (Hammerschlag 1980)	1/24 (4%)	3/36 (8%)	RR 0.50 (0.06 to 4.53)*	42 fewer per 1000 (from 78 fewer to 294 more)*	Low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 7.5 Evidence profile for intramuscular benzylpenicillin (50,000 IU) administered to all babies within 1 hour of birth versus no benzylpenicillin prophylaxis

Number of studies	Number of babies		Effect		Quality
	Intramuscular benzylpenicillin within 1 hour of birth	No benzylpenicillin prophylaxis	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Clinical sepsis					
All neonates					
1 (Patel 1999)	96/5389 (1.8%)	140/5609 (2.5%)	RR 0.71 (0.55 to 0.92)*	7 fewer per 1000 (from 2 fewer to 11 fewer)	Very low
Preterm neonates					
1 (Patel 1999)	86/1400 (6.1%)	112/1464 (7.7%)	RR 0.8 (0.61 to 1.05)*	15 fewer per 1000 (from 30 fewer to 4 more)	Very low
Term neonates					
1 (Patel 1999)	10/3989 (0.3%)	31/4145 (0.7%)	RR 0.34 (0.16 to 0.68)*	5 fewer per 1000 (from 2 fewer to 6 fewer)	Very low

Number of studies	Number of babies		Effect		Quality
	Intramuscular benzylpenicillin within 1 hour of birth	No benzylpenicillin prophylaxis	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Identified sepsis					
All neonates					
1 (Patel 1999)	35/5389 (0.6%)	67/5609 (1.2%)	RR 0.54 (0.36 to 0.82)*	5 fewer per 1000 (from 2 fewer to 8 fewer)	Very low
Preterm neonates					
1 (Patel 1999)	27/1400 (1.9%)	43/1464 (2.9%)	RR 0.66 (0.41 to 1.06)*	10 fewer per 1000 (from 17 fewer to 2 more)*	Very low
Term neonates					
1 (Patel 1999)	8/3989 (0.2%)	24/4145 (0.6%)	RR 0.35 (0.16 to 0.77)*	4 fewer per 1000 (from 1 fewer to 5 fewer)*	Very low
Group B streptococcus					
All neonates					
1 (Patel 1999)	22/5389 (0.4%)	52/5609 (0.9%)	RR 0.44 (0.27 to 0.72)*	5 fewer per 1000 (from 3 fewer to 7 fewer)*	Very low
Preterm neonates					
1 (Patel 1999)	15/1400 (1.1%)	33/1464 (2.3%)	RR 0.48 (0.26 to 0.87)*	12 fewer per 1000 (from 3 fewer to 17 fewer)*	Very low
Term neonates					
1 (Patel 1999)	7/3989 (0.2%)	19/4145 (0.5%)	RR 0.38 (0.1611 to 0.9097)*	3 fewer per 1000 (from 0.4 fewer to 4 fewer)*	Very low
Group B streptococcus blood culture					
All neonates					
1 (Patel 1999)	6/5389 (0.1%)	58/5609 (1%)	RR 0.5 (0.32 to 0.79)*	3 fewer per 1000 (from 1 fewer to 3 fewer)*	Very low
Preterm neonates					
1 (Patel 1999)	2/1400 (0.1%)	12/1464 (0.8%)	RR 0.17 (0.04 to 0.78)*	7 fewer per 1000 (from 2 fewer to 8 fewer)*	Very low
Term neonates					
1 (Patel 1999)	4/3989 (0.1%)	9/4145 (0.2%)	RR 0.46 (0.14 to 1.5)*	1 fewer per 1000 (from 2 fewer to 1 more)*	Very low
Mortality due to clinical or identifiable sepsis					
All neonates					
1 (Patel 1999)	4/5389 (0.1%)	16/5609 (0.3%)	RR 0.26 (0.09 to 0.78)*	2 fewer per 1000 (from 1 fewer to 3 fewer)*	Very low
Preterm neonates					
1 (Patel 1999)	4/1400 (0.3%)	10/1464 (0.7%)	RR 0.42 (0.13 to 1.33)*	4 fewer per 1000 (from 6 fewer to 2 more)*	Very low

Number of studies	Number of babies		Effect		Quality
	Intramuscular benzylpenicillin within 1 hour of birth	No benzylpenicillin prophylaxis	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Term neonates					
1 (Patel 1999)	0/3989 (0%)	7/4145 (0.2%)	RR 0.07 (0.004 to 1.212)*	2 fewer per 1000 (from 2 fewer to 0.4 more)*	Very low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article; it is not clear whether more than one organism was isolated in any baby

Table 7.6 Evidence profile for a single intramuscular dose of benzylpenicillin[a] within 1 hour of birth versus topical tetracycline ointment in all babies

Number of studies	Number of babies		Effect		Quality
	Single intramuscular dose of benzylpenicillin within 1 hour of birth	Topical tetracycline ointment (applied to the eyes)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Culture proven early-onset benzylpenicillin-susceptible bacterial infection (any body fluid)[b]					
1 (Siegel 1982)	3/16,082 (0.02%)	24/15,976 (0.15%)	RR 0.12 (0.04 to 0.41)*	1 fewer per 1000 (from 1 fewer to 1 fewer)*	Very low
Culture proven early-onset benzylpenicillin-resistant bacterial infection (any body fluid)[b]					
1 (Siegel 1982)	12/16,082 (0.08%)	4/15,976 (0.03%)	RR 2.98 (0.96 to 9.24)*	1 more per 1000 (from 1 fewer to 2 more)*	Very low
Culture proven early-onset group B streptococcal infection (any body fluid)[b]					
1 (Siegel 1982)	3/16,082 (0.02%)	19/15,976 (0.12%)	RR 0.16 (0.05 to 0.53)*	1 fewer per 1000 (from 1 fewer to 1 fewer)*	Very low
Culture proven early-onset benzylpenicillin-susceptible and resistant bacterial infection (any body fluid)[b] and group B streptococcus infection (any body fluid)[b]					
1 (Siegel 1982)	18/16,082 (0.12%)	47/15,976 (0.3%)	RR 0.38 (0.22 to 0.65)*	2 fewer per 1000 (from 1 fewer to 2 fewer)*	Very low
Mortality (early-onset sepsis[c])					
1 (Siegel 1982)	5/16,082 (0.03%)	5/15,976 (0.03%)	RR 0.99 (0.29 to 3.43)*	1 fewer per 1000 (from 1 fewer to 1 more)*	Very low
Meningitis					
1 (Siegel 1982)	2/16082 (0%)	10/15976 (0.1%)	RR 0.2 (0.044 to 0.9066)*	0.5 fewer per 1000 (from 0.06 fewer to 0.6 fewer)*	Very low
Penicillin hypersensitivity					
1 (Siegel 1982)	0/16082 (0%)	0/15976 (0%)	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Single intramuscular dose of benzylpenicill in within 1 hour of birth	Topical tetracycline ointment (applied to the eyes)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Perinatally acquired gonococcal ophthalmia					
1 (Siegel 1982)	0/16082 (0%)	0/15976 (0%)	NC	NC	Very low
Chlamydial conjunctivitis					
1 (Siegel 1982)	34/16082 (0.2%)	45/15976 (0.3%)	RR 0.75 (0.4811 to 1.1711)*	0.7 fewer per 1000 (from 1 fewer to 0.5 more)*	Very low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Dose of benzylpenicillin was 50,000 units in babies with birthweight ≥ 2000 g and 25,000 units in babies with birthweight < 2000 g

[b] Unclear whether blood cultures were taken before or after administration of antibiotics

[c] Early-onset sepsis defined as sepsis in the first 3 days of life

Evidence statements

In babies at risk of early-onset GBS infection(birthweight 501–2000 g) who received intramuscular benzylpenicillin within 60–90 minutes of birth and then every 12 hours for 3 days, there was no difference in the rate of culture-proven early-onset GBS infection or mortality compared with babies who received no early treatment (moderate quality evidence).

In preterm babies (less than 32 weeks' gestation) with risk factors for (or laboratory evidence of) early-onset neonatal infection there was no difference in mortality among those who received a single bolus of ampicillin plus netilmicin compared with those who received a 3-day course of the same antibiotics (low quality evidence).

In babies aged less than 7 days with risk factors for (or clinical signs or laboratory evidence of) sepsis who received piperacillin plus placebo there were no differences in blood culture-proven sepsis, mortality from infection, mortality during antibiotic treatment or up to 1 week after treatment, renal impairment or hepatic impairment compared with babies who received ampicillin plus amikacin (low quality evidence).

In babies born to Chlamydia-positive mothers, application of erythromycin eye ointment immediately after birth was more effective than 1% silver nitrate eye drops in reducing the incidence of culture-proven chlamydial eye infection. There was, however, no difference in the incidence of culture-proven chlamydial nasopharyngeal infection or pneumonia among the two groups (low quality evidence).

Babies who received intramuscular benzylpenicillin prophylaxis within 1 hour of birth for the prevention of GBS infection had lower rates of blood culture-proven early-onset sepsis, but not mortality, compared with babies who received no benzylpenicillin prophylaxis at birth (low quality evidence).

Babies who received intramuscular benzylpenicillin prophylaxis within 1 hour of birth for the prevention of gonococcal eye infections had lower rates of culture-proven early-onset benzylpenicillin- susceptible bacterial infections and culture-proven early-onset GBS infection, but not culture-proven early-onset benzylpenicillin-resistant bacterial infections, nor mortality associated with any early-onset infection, compared with babies who received topical tetracycline eye ointment (low quality evidence).

Health economics profile

The GDG planned to conduct a cost effectiveness analysis comparing different strategies for identifying and treating babies at risk of early-onset neonatal infection or with symptoms and signs of early-onset neonatal infection. However, no published health economic analyses were identified in relation to this review question, and no clinical evidence was identified to inform development of a health economic model specifically for the guideline.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG members prioritised the following clinical outcomes in the baby as they considered these would be reported consistently across study populations and would aid their decision making by most strongly reflecting early-onset neonatal infection:

- failure of prevention of neonatal infection
- mortality (the GDG prioritised this outcome where mortality due to infection was specified)
- duration of hospital stay
- neonatal adverse events
- long-term outcomes in the baby
- resistance among neonatal flora.

Consideration of clinical benefits and harms

The priority outcome for the GDG was the prevention of early-onset neonatal infection and the associated benefit of reduced morbidity and so the GDG made its decisions primarily based upon this outcome. The GDG considered the additional benefits or harms associated with other clinical outcomes where the findings for early-onset neonatal infection were equivocal, where there was evidence of reduced incidence of early-onset neonatal infection following treatment with more than one type of antibiotic and where there was clear evidence of statistically significant harms. The GDG also considered the spectrum of antibiotic activity and the potential broader harm of antibiotic resistance.

Consideration of net health benefits and resource use

The costs associated with intravenous administration of antibiotics to the baby are the cost of the antibiotics themselves, the equipment and staff costs needed to set up and perform the intravenous infusion, and the need for a hospital stay. The GDG noted that, as a general principle, prevention of infection is cost effective. The guideline review of maternal risk factors used to specify indications for maternal intrapartum antibiotic prophylaxis or postnatal antibiotic prophylaxis in the baby reflected the GDG's opinion that the benefits of universal treatment experienced by the few would be outweighed by the potential harms of exposing many women and babies to antibiotics unnecessarily. Such practice would also promote the potential broader harm of promoting antibiotic resistance.

Quality of evidence

The GDG noted that only a few RCTs were identified for inclusion in the guideline review and that only one RCT provided evidence of even moderate quality. The evidence for all other outcomes was of very low or low quality. No evidence was identified at all relating to duration of hospital stay, long- term outcomes in the baby or resistance among neonatal flora.

No pharmacokinetic studies specific to benzylpenicillin in babies with or without risk factors were identified for inclusion.

Neonatal risk factors

Evidence came from only one RCT in which low birthweight was used as an indicator of GBS in a population of predominately black babies. The diagnostic test accuracy of this proxy measure of the risk of GBS infection is unclear, and there were no significant differences in GBS infection or mortality due to early-onset neonatal infection between those babies who received early treatment with benzylpenicillin and those who did not.

Maternal risk factors

Evidence came from only one RCT in which babies with the maternal risk factor of a positive Chlamydia test result were given localised prophylaxis to prevent eye infection immediately after birth; the antibiotic used was either erythromycin (an antibiotic) in the form of eye ointment or 1% silver nitrate (a disinfectant) in the form of eye drops. Significantly fewer babies who received erythromycin eye ointment developed conjunctivitis compared with those who received silver nitrate eye drops. However, there were no significant differences in the incidence of nasopharyngeal or respiratory infections (pneumonia) due to Chlamydia.

Combinations of maternal and neonatal risk factors

Evidence came from two RCTs that examined the effects of different antibiotics or different regimens involving the same combination of antibiotics. The GDG highlighted the absence of evidence with regard to risk factors in placebo-controlled (or no-treatment controlled) studies.

In the first RCT there were no statistically significant differences within 7 days of birth for any sepsis, mortality or toxicity outcome when administration of piperacillin plus placebo was compared with ampicillin plus amikacin in babies with any of six maternal or neonatal risk factors for sepsis.

In the second RCT there was no statistically significant difference in mortality caused by early-onset infection in preterm babies (less than 32 weeks of gestation) who had any of five maternal or neonatal risk factors for infection following prophylaxis with a single intravenous bolus dose of ampicillin plus netilmicin compared to a 3-day course of intravenous ampicillin plus netilmicin.

Universal administration of antibiotics

Two quasi-randomised clinical trials in newborn babies evaluated universal prophylaxis with intramuscular benzylpenicillin within 1 hour of birth compared with no treatment or treatment with tetracycline eye ointment, respectively.

In the first study (comparison with no treatment), statistically significantly fewer babies who received benzylpenicillin had clinical sepsis, identified sepsis, GBS or a positive GBS blood culture, or died due to clinical or identifiable sepsis. In subgroup analyses performed according to gestational age, statistically significantly fewer term babies who received benzylpenicillin had clinical or identified sepsis, but there was no statistically significant difference for preterm babies. However, statistically significantly fewer preterm babies who received benzylpenicillin had a positive GBS blood culture, whereas there was no statistically significant difference for term babies. There were no statistically significant differences in mortality from clinical or identifiable sepsis in either preterm or term babies, although the finding for all babies showed a significant protective effect of benzylpenicillin.

In the second study (comparison with tetracycline eye ointment), significantly fewer babies who received benzylpenicillin developed bacterial infections, benzylpenicillin-susceptible bacterial infections, GBS infection and meningitis.

Other considerations

The GDG did not identify any equalities issues requiring attention in this review question, although the group drew a careful distinction between preterm and term babies.

Recommendations from existing guidelines (including Intrapartum care, NICE clinical guideline 55 [2007], which covers immediate care of babies born to women with term PROM, including indications for antibiotic treatment) were also reviewed, and the GDG discussed the need for recommendations to prevent early-onset neonatal infection in the babies covered by this guideline.

Key conclusions

The GDG defined 'routine' administration of antibiotics as antibiotic administration to every newborn baby. If intrapartum antibiotic prophylaxis was indicated but not received (for example because the baby was born before antibiotics could be administered to the woman) then the GDG considered that the baby would still be regarded as having a risk factor for early-onset neonatal infection.

The GDG noted that risk factors should not be counted twice during assessment of the baby after birth, especially with regard to whether or not intrapartum antibiotic prophylaxis was indicated, and whether or not intrapartum antibiotic prophylaxis was received.

Neonatal risk factors

The GDG chose not to expand its recommendation (in Chapter 6) regarding intrapartum antibiotic prophylaxis for GBS infection to include postnatal administration of antibiotics.

Maternal risk factors

The GDG considered that systemic rather than localised antibiotic prophylaxis would be more effective in preventing chlamydial infections. The GDG noted that current practice is to treat women who test positive for Chlamydia with a single dose of azithromycin, and the group was satisfied that this would provide prophylactic cover for their babies too.

Although no evidence relating to gonococcal infections was identified for inclusion in the guideline review, the GDG noted that current practice is to treat women who test positive for Gonococcus (*N gonorrhoeae*) with a single dose of an appropriate antibiotic, and the group was satisfied that this would provide prophylactic cover for their babies too.

Combinations of maternal or neonatal risk factors

The GDG did not regard either of the RCTs identified for inclusion regarding antibiotic prophylaxis for combinations of maternal and neonatal risk factors as being very relevant to the UK setting. The group noted that piperacillin (which contains ampicillin plus a pharmaceutical agent that is active against *Pseudomonas* species) is currently marketed in the UK only in combination with tazobactum, and so it would be an unlikely choice of antibiotic. Furthermore, all the antibiotics evaluated in the RCT involving piperacillin were broad-spectrum, and the GDG did not wish to recommend the use of broad-spectrum antibiotics unless absolutely necessary because of the risk of promoting antibiotic resistance.

Universal administration of antibiotics

The GDG noted that in the 1980s, when one of the RCTs relating to universal administration of antibiotics was conducted, intrapartum antibiotic prophylaxis may not have been established clinical practice. The GDG chose not to expand its recommendation (in Chapter 6) regarding intrapartum antibiotic prophylaxis to cover postnatal administration of antibiotics for the prevention of early-onset neonatal infection.

Having considered all the evidence identified for inclusion, the GDG concluded that it was important that babies with no maternal or neonatal risk factors should not receive antibiotics routinely. Such practice will avoid exposing babies unnecessarily to potential adverse effects of antibiotics, and it will minimise the risk of antibiotic resistance developing further. Thus, the GDG's recommendation was that antibiotics should not be given routinely to babies without risk factors, clinical indicators or laboratory evidence of possible infection.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

No research recommendations were identified for this review question.

8 Investigations before starting antibiotics in the baby

Introduction

Investigations can contribute to management in babies at risk of early-onset neonatal infection in two ways. Firstly, investigations can be part of the process that decides whether a baby receives antibiotics or does not receive antibiotics. Secondly, investigations can be part of the process of making decisions about when to stop antibiotics. This chapter relates only to the role of investigations in making decisions about whether or not to start antibiotics for early-onset neonatal infection. The role of investigations in making decisions about when to stop antibiotics is dealt with in Chapter 10.

The guideline development group (GDG) formulated two review questions relating to investigations (diagnostic tests) before starting antibiotics, and these were addressed through a single systematic search of the literature.

The first review question focused on investigations in babies who have no symptoms or signs of infection whatsoever but have risk factors for early-onset neonatal infection which are not sufficiently severe to prompt immediate treatment with antibiotics. In this question, the purpose of the investigations is, therefore, to identify babies in whom antibiotic treatment should be started despite the absence of symptoms and signs of early-onset neonatal infection. The emphasis in this question is on determining which investigations are useful for identifying babies who appear well but should, nevertheless, start antibiotic treatment because they are at risk of early-onset neonatal infection. The following index tests were prioritised by the GDG for consideration for this question:

- C-reactive protein (CRP)
- procalcitonin
- peripheral white blood cell (WBC) counts, including total neutrophil count and ratio of immature to total neutrophils (I:T ratio)
- platelet count
- surface swabs(including eye swabs and umbilical cord swabs)
- urine microscopy or culture
- gastric aspirates.

The tests considered for this question tend to be less invasive than some of the tests considered in the second question (for example lumbar puncture is not included in this question) because the babies in whom they will be performed appear well.

Another reason to perform investigations before starting antibiotics is that such investigations may confirm that infection is present or help to rule out infection. Thus the second review question in this chapter focused on the value of investigations to rule in, or rule out, infection. In this question, the purpose of the investigations is to distinguish between babies who require a course of antibiotic treatment because infection is likely or definitely present and those in whom infection can be ruled out (and antibiotics stopped as soon as possible).

The following index tests were prioritised by the GDG for consideration for this question:

- CRP and other acute phase reactants
- procalcitonin
- interleukins
- cytokines
- peripheral WBC counts, including total neutrophil count and I:T ratio
- platelet count
- 'buffy coat' examination (white blood cells and platelets)
- rapid tests, including polymerase chain reaction (PCR), optical immunoassay and latex agglutination test
- surface swabs(including eye swabs and umbilical cord swabs)
- urinalysis
- urine microscopy or culture
- cerebrospinal fluid (CSF) examination (via lumbar puncture)
- gastric aspirates
- chest X-ray.

Across both review questions, diagnostic test accuracy studies in which CSF culture was used as the reference standard were sought for tests based on CSF parameters, while diagnostic test accuracy studies in which blood culture was used as the reference standard were sought for all other index tests. Studies in which the reference standard included clinical diagnosis were, however, considered by the GDG.

The first review question focuses on babies perceived to be at low risk of early-onset neonatal infection. In this case a useful diagnostic test will be one that changes the low pre-test probability (risk) of early-onset neonatal infection to a high post-test probability given a positive test result (see Section 3.3). Thus, the likelihood ratio for a positive test result (LR^+) is of prime importance for the first review question (because the aim is to avoid unnecessary antibiotic treatment). The role of the likelihood ratio for a negative test result (LR^-) is less important for this question because the pre-test probability of infection will already be low, and a moderately small value of LR^- will be sufficient to provide convincing evidence that the baby does not have an infection and does not require treatment with antibiotics. However, without LR^- one cannot determine how long to continue observing babies who remain at risk of becoming ill.

The second review question focuses on babies with symptoms or signs suggesting early-onset neonatal infection and babies perceived to be sufficiently at risk to prompt immediate treatment with antibiotics while investigations are conducted to confirm or rule out infection. In this case a useful diagnostic test will be one that changes the pre-test probability (risk) of early-onset neonatal infection to a high post-test probability given a positive test result, or a low post-test probability given a negative test result. Thus, LR^+ and LR^- are both important for this review question: LR^+ would help to identify babies in whom antibiotics should be continued because a test with a high LR^+ will identify babies who have a high risk of infection and thus should carry on receiving antibiotics (or direct a change in antibiotics to target a specific organism); LR^- would help to identify babies in whom antibiotics can be stopped safely because a test with a low LR^- will identify babies who have a very low risk of infection.

The GDG was aware of the risk of localised infections in newborn babies, particularly affecting the eyes and umbilical area (omphalitis). This chapter includes consideration of the appropriate investigations for babies with signs of these infections.

Review questions

What investigations of asymptomatic babies after birth are useful in identifying those who should/not be treated for early-onset neonatal infection or determining the treatment strategy?

What investigations should be performed prior to commencing treatment in:

- babies with symptoms
- babies with risk factors without symptoms?

Existing NICE guidance

Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102) includes recommendations relating to the diagnosis of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in secondary care. Recommendations relating to investigations in children and young people with petechial rash include:

- In children and young people with an unexplained petechial rash and fever (or history of fever) perform the following investigations:
  - full blood count
  - CRP
  - coagulation screen
  - blood culture
  - whole-blood PCR for meningococcus
  - blood glucose
  - blood gas.
- In children and young people with an unexplained petechial rash and fever (or history of fever) but no high-risk clinical manifestations:
  - treat with intravenous ceftriaxone immediately if the CRP or WBC count (especially neutrophil count) is raised, as this indicates an increased risk of having meningococcal disease
  - be aware that while a normal CRP and normal white blood cell count mean meningococcal disease is less likely, they do not rule it out. The CRP may be normal and the white blood cell count normal or low even in severe meningococcal disease.

Recommendations relating to investigations in children and young people with suspected bacterial meningitis include:

- Perform a CRP and WBC count.
- If the CRP or WBC count is raised and there is a non-specifically abnormal CSF (for example, consistent with viral meningitis), treat as bacterial meningitis.
- Be aware that a normal CRP and WBC count does not rule out bacterial meningitis.
- Regardless of the CRP and WBC, if no CSF is available for examination or if the CSF findings are uninterpretable, manage as if the diagnosis of meningitis is confirmed.

Recommendations relating to PCR tests for bacterial meningitis and meningococcal disease include:

- Perform whole blood real-time PCR testing (ethylenediaminetetraacetic acid [EDTA] sample) for *N meningitidis* to confirm a diagnosis of meningococcal disease.

- Take the PCR blood sample as soon as possible because early samples are more likely to be positive.
- Use PCR testing of blood samples from other hospital laboratories if available, to avoid repeating the test.
- Be aware that a negative blood PCR test result for *N meningitidis* does not rule out meningococcal disease.
- Submit CSF to the laboratory to hold for PCR testing for *N meningitidis* and *Streptococcus pneumoniae*, but only perform the PCR testing if the CSF culture is negative.
- Be aware that CSF samples taken up to 96 hours after admission to hospital may give useful results.

Recommendations relating to performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis include:

- Perform a lumbar puncture as a primary investigation unless this is contraindicated.
- Do not allow lumbar puncture to delay the administration of parenteral antibiotics.
- CSF examination should include WBC count and examination, total protein and glucose concentrations, Gram stain and microbiological culture. A corresponding laboratory-determined blood glucose concentration should be measured.
- In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:
    - signs suggesting raised intracranial pressure (reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more), relative bradycardia and hypertension, focal neurological signs, abnormal posture or posturing, unequal, dilated or poorly responsive pupils, papilloedema, or abnormal 'doll's eye' movements)
    - shock
    - extensive or spreading purpura
    - after convulsions until stabilised
    - coagulation abnormalities (coagulation results [if obtained] outside the normal range, platelet count below 100 x 10^9/litre, or receiving anticoagulant therapy)
    - local superficial infection at the lumbar puncture site
    - respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).
- In children and young people with suspected bacterial meningitis, if contraindications to lumbar puncture exist at presentation consider delaying lumbar puncture until there are no longer contraindications. Delayed lumbar puncture is especially worthwhile if there is diagnostic uncertainty or unsatisfactory clinical progress.
- CSF white cell counts, total protein and glucose concentrations should be made available within 4 hours to support a decision regarding adjunctive steroid therapy (adjunctive steroid therapy is not relevant in this guideline).
- Start antibiotic treatment for bacterial meningitis if the CSF white cell count is abnormal (in neonates at least 20 cells/microlitre; be aware that even if there are fewer than 20 cells/microlitre, bacterial meningitis should still be considered if other symptoms and signs are present).

- Perform a repeat lumbar puncture in neonates with:
  - persistent or re-emergent fever
  - deterioration in clinical condition
  - new clinical findings (especially neurological findings) or
  - persistently abnormal inflammatory markers.
- Do not perform a repeat lumbar puncture in neonates:
  - who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery
  - before stopping antibiotic therapy if they are clinically well.

The guideline also recommends that skin scrapings, skin biopsies, petechial or purpuric lesion aspirates (obtained with a needle and syringe) and throat swabs should not be used when investigating for possible meningococcal disease.

Feverish illness in children (NICE clinical guideline 47, 2007) includes recommendations about investigations in children under 5 years with fever. Recommendations relating to management by non-paediatric practitioners include:

- Children with symptoms and signs suggesting pneumonia who are not admitted to hospital should not routinely have a chest X-ray.
- Urine should be tested on children with fever as recommended in Urinary tract infection in children (NICE clinical guideline 54, 2007).

Recommendations relating to management by paediatric specialists include:

- Babies younger than 3 months with fever should have the following investigations performed:
  - full blood count
  - blood culture
  - CRP
  - urine testing for urinary tract infection
  - chest X-ray only if respiratory signs are present
  - stool culture, if diarrhoea is present.
- Babies younger than 1 month should have a lumbar puncture (unless contraindicated) performed without delay and, whenever possible, before the administration of antibiotics.

Urinary tract infection in children (NICE clinical guideline 54, 2007) includes recommendations about the diagnosis of urinary tract infection in children and young people younger than 16 years, which include the following.

- Babies and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.
- Babies and children with an alternative site of infection should not have a urine sample tested. When babies and children with an alternative site of infection remain unwell, urine testing should be considered after 24 hours at the latest.
- Babies younger than 3 months with a possible or suspected urinary tract infection should be referred immediately to paediatric specialist care and a urine sample should be sent for urgent microscopy and culture. Such babies should be managed in accordance with the recommendations for their age group in Feverish illness in children

(NICE clinical guideline 47, 2007). Management includes treatment with parenteral antibiotics.

Postnatal care (NICE clinical guideline 37, 2006) provides guidance on routine care for women and their babies in the first 6–8 weeks after birth. The guideline recommends that healthcare professionals should perform a complete examination of the baby within 72 hours of birth, including a physical examination involving checking the baby's eyes, skin and umbilical cord. The guideline also recommends that parents should be advised how to keep the umbilical cord clean and dry, and advised that antiseptics should not be used routinely.

Description of included studies

Twenty-six studies (all cohort studies) were identified for inclusion from the searches conducted for these review questions (Ansong 2009; Bender 2008; Benitz 1998; Berger 1995; Berger 2004; Franz 1999; Franz 2001; Garges 2006; Hachey 1992; Hall 1995; Heimler 1995; Hofer 2011; Jackson 2004; Labenne 2011; Laforgia 1997; Newman 2010; Ottolini 2003; Philip 1980; Prabhakar 1999; Reier-Nilsen 2009; Resch 2003; Schwersenski 1991; Selimovic 2010; Tamim 2003; Visser 1979; Williamson 1995).

Two studies were identified for inclusion relating to the question about investigations to identify asymptomatic babies who should receive antibiotics (Newman 2010; Ottolini 2003). Both studies investigated the diagnostic test accuracy of peripheral WBC counts in asymptomatic babies at risk of early-onset neonatal infection. Newman 2010 focused on the accuracy of tests based on peripheral WBC counts, absolute neutrophil counts and I:T ratio, using different thresholds or ranges for each measure and tests conducted at different time points after birth (the study was conducted in babies born at 34 or more weeks of gestation and in many cases tests were carried out because of maternal risk factors, although the risk factors were not reported clearly). Ottolini 2003 focused on the accuracy of a composite measure of abnormal peripheral WBC counts based on total WBC count, absolute neutrophil count and I:T ratio. This study was conducted in babies born at 35 or more weeks of gestation, without other complications and at risk for early-onset neonatal infection, particularly group B streptococcus (GBS) infection, according to the Centers for Disease Control (CDC) criteria (that is, they were born to women with proven or unknown GBS colonisation, prelabour rupture of membranes [PROM], fever of 38°C or more or who had had a previous baby with invasive GBS infection, and who did not receive at least one dose of antibiotics at least 4 hours before birth). No evidence was identified for this question relating to the following index tests: CRP, procalcitonin, platelet count, surface swabs, gastric aspirates or urine microscopy or culture.

Twenty-three studies were identified for inclusion relating to the question about investigations in babies about to start antibiotic treatment (Ansong 2009; Bender 2008; Benitz 1998; Berger 1995; Berger 2004; Franz 1999; Franz 2001; Garges 2006; Hachey 1992; Hall 1995; Heimler 1995; Hofer 2011; Jackson 2004; Labenne 2011; Laforgia 1997; Philip 1980; Prabhakar 1999; Reier-Nilsen 2009; Resch 2003; Schwersenski 1991; Selimovic 2010; Tamim 2003; Visser 1979; Williamson 1995). Eighteen of these studies (Ansong 2009; Bender 2008; Benitz 1998; Berger 1995; Berger 2004; Franz 1999; Franz 2001; Garges 2006; Hachey 1992; Hall 1995; Heimler 1995; Jackson 2004; Laforgia 1997; Philip 1980; Reier-Nilsen 2009; Resch 2003; Visser 1979; Williamson 1995) evaluated the diagnostic test accuracy of the following measures when considered individually:

- CRP (Benitz 1998; Berger 1995; Franz 1999; Franz 2001; Philip 1980; Resch 2003)
- procalcitonin (Bender 2008; Franz 1999; Resch 2003)
- interleukins (Bender 2008; Franz 1999; Franz 2001; Resch 2003)
- peripheral WBC counts (Bender 2008; Berger 1995; Franz 2001; Hachey 1992; Heimler 1995; Jackson 2004; Philip 1980)
- platelet count (Berger 1995)
- PCR (Laforgia 1997; Reier-Nilsen 2009)
- surface swabs (Berger 2004; Hall 1995)

- urine latex agglutination test (Heimler 1995; Williamson 1995)
- urine culture (Visser 1979)
- CSF examination (Ansong 2009; Garges 2006).

Several of these studies focused on the accuracy of tests using different thresholds or ranges of the parameters investigated and tests conducted at different time points after birth. Three of the studies also reported diagnostic accuracy of composite measures based on blood tests such as CRP and interleukins or procalcitonin (Bender 2008; Franz 1999; Franz 2001).

Two further studies evaluated the diagnostic test accuracy of composite measures but did not report diagnostic test accuracy for individual measures (Labenne 2011; Selimovic 2010). Selimovic 2010 focused on the diagnostic test accuracy of a composite measure based on total WBC count, I:T ratio, the ratio of immature to mature neutrophils (I:M ratio) and CRP concentration. Labenne 2011 focused on the predictive accuracy of a scoring system based on biomarkers (interleukins and CRP) and clinical factors (antenatal colonisation before birth, an interval of more than 12 hours between rupture of membranes and birth, and mechanical ventilation at birth).

Three other studies identified for inclusion relating to the question about investigations in babies about to start antibiotic treatment (Prabhakar 1999; Schwersenski 1991; Tamim 2003) reported prevalence data for bacterial meningitis or bacterial urinary tract infection only. No evidence was identified for this question in relation to the following index tests: cytokines, buffy coat examination, gastric aspirates or chest X-ray.

Two of the studies identified for inclusion relating to the question about investigations in babies about to start antibiotic treatment (Benitz 1998; Berger 1995) provided evidence relevant to determining the optimal duration of antibiotic treatment(based on CRP concentrations measured at various intervals after presentation). Evidence relating to CRP concentrations at presentation is discussed in this chapter, whereas the evidence relating to CRP concentrations during the course of antibiotic treatment is discussed in Chapter 10. The remaining study identified through the searches conducted for both review questions considered in this chapter (Hofer 2011) reported diagnostic test accuracy for CRP as an indicator of early-onset neonatal infection in babies who had been hospitalised in the first 72 hours of life. The evidence from this study is relevant to determining the optimal duration of antibiotic treatment and is not, therefore, included in this review, but is discussed in Chapter 10.

Evidence profiles

The evidence profiles for these review questions are presented in Tables 8.1 to 8.13.

Table 8.1 Evidence profile for diagnostic accuracy of tests based on peripheral white blood cell counts in asymptomatic babies at risk of early-onset neonatal infection

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
White blood cell count of 0–4.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	0	NC	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	27.6	NC	Low
At ≥4 hours of age						
1 (Newman 2010)	67,623	NC	NC	80.5	NC	Low
White blood cell count of 5–9.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.4	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	2.4	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	6.4	NC	Low
White blood cell count of 10–14.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.1	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.7	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	1.0	NC	Low
White blood cell count of 15–19.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	0.7	NC	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.6	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.4	NC	Low
White blood cell count of ≥ 20 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.2	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.8	NC	Low
At ≥ 4 hours of						
1 (Newman 2010)	67,623	NC	NC	0.2	NC	Low
Absolute neutrophil count of 0–0.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	7.5	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	33.5	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	115	NC	Low
Absolute neutrophil count of 1–1.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	2.3	NC	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	9.3	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	51.7	NC	Low
Absolute neutrophil count of 2–4.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.0	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	1.1	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	6.9	NC	Low
Absolute neutrophil count of 5–9.99 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	0.9	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010	67,623	NC	NC	0.9	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.6	NC	Low
Absolute neutrophil count of ≥10 ×10^3/microlitre						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	0.9	NC	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.6	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.3	NC	Low
Immature:total neutrophil ratio of 0–0.1499						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	0.4	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.5	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	0.3	NC	Low
Immature:total neutrophil ratio of 0.15–0.299						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.3	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	1.2	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	1.2	NC	Low
Immature:total neutrophil ratio of 0.3–0.4499						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	1.4	NC	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	2.9	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	3.1	NC	Low
Immature:total neutrophil ratio of 0.45–0.599						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	4.8	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	3.3	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	8.8	NC	Low
Immature:total neutrophil ratio of ≥0.6						
At < 1 hour of age						
1 (Newman 2010)	67,623	NC	NC	6.1	NC	Low
At 1–3.99 hours of age						
1 (Newman 2010)	67,623	NC	NC	8.4	NC	Low
At ≥ 4 hours of age						
1 (Newman 2010)	67,623	NC	NC	10.7	NC	Low
Composite measure of abnormal white blood cell count (defined as any of: total white blood cell count ≤ 5,000 or ≥ 30,000/mm^3; absolute neutrophil count < 1,500 mm^3; or immature:mature neutrophil ratio > 0.2)						
1 (Ottolini 2003)	1,655	41 (18 to 65)	73 (71 to 75)	1.5 (0.9 to 2.7)	0.8 (0.5 to 1.2)	Low

NC not calculable, WBC white blood cell

Table 8.2 Evidence profile for C-reactive protein in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
CRP ≥ 2.5 mg/l in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	69	96	17	0.3	Moderate
CRP ≥ 8 mg/l in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	49	100	NC	0.5	Moderate
CRP > 8 mg/l in the prediction of infection in the first week of birth, using culture of bacteria from blood, CSF or urine as reference standard						
1 (Philip 1980)	376	47	86	3	0.6	Moderate
CRP > 10 mg/l in the prediction of infection within the first 3 days of life, using blood culture or clinical infection as reference standard						
1996/1997 data						
1 (Franz 2001)	378	34 (23 to 47)	95 (92 to 97)	8 (4 to 14)	0.7 (0.6 to 0.8)	High
1997/1998 data						
1 (Franz 2001)	331	28 (20 to 38)	98 (94 to 100)	12 (5 to 30)	0.7 (0.7 to 0.8)	High
CRP > 10 mg/l at presentation in the prediction of infection within the first 3 days of life						
Using proven sepsis as reference standard						
1 (Benitz 1998)	1002	35 (30 to 40)	90 (88 to 91)	4 (1 to 8)	0.7 (0.4 to 1.4)	High
Using either proven or probable sepsis as reference standard						
1 (Benitz 1998)	1002	39 (30 to 49)	93 (91 to 94)	5 (3 to 8)	0.7 (0.5 to 0.9)	High
CRP > 10 mg/l in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	28 (16 to 43)	97 (92 to 99)	9	0.7	Moderate

CRP C-reactive protein, NC not calculable

Table 8.3 Evidence profile for procalcitonin in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
PCT > 0.27 ng/ml in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	80 (66 to 91)	53 (44 to 62)	2	0.4	Moderate
PCT > 0.50 ng/ml in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	57 (41 to 71)	66 (57 to 74)	2	0.7	Moderate
PCT ≥ 2 ng/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	83	61	2	0.3	Moderate
PCT > 3.50 ng/ml in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	30 (18 to 46)	91 (84 to 95)	3	0.8	Moderate
PCT > 5.75 ng/ml at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	68	67	2	0.5	Low
PCT ≥ 6 ng/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	77	91	9	0.3	Moderate
PCT ≥ 14 ng/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	63	100	NC	0.4	Moderate

NC not calculable, PCT procalcitonin

Table 8.4 Evidence profile for interleukins in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
IL-6 > 12 pg/ml at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	71	71	2	0.4	Low
IL-6 ≥ 60 pg/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	123	71	71	2	0.4	Low
IL-6 ≥ 10 pg/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	71	65	2	0.5	Moderate
IL-6 ≥ 150 pg/ml in the prediction of infection within 12 hours of birth, using blood culture or clinical infection as reference standard						
1 (Resch 2003)	68	46	100	NC	0.5	Moderate
IL-8 > 130 pg/ml at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	64	70	2	0.5	Low
IL-8 ≥ 70 pg/ml in the prediction of infection within the first 3 days of life, using blood culture or clinical infection as reference standard						
1996/1997 data						
1 (Franz 1999)	378	80 (69 to 89)	76 (71 to 81)	3 (3 to 4)	0.3 (0.2 to 0.4)	High
1997/1998 data						
1 (Franz 2001)	331	82 (73 to 89)	79 (73 to 84)	4 (3 to 5)	0.2 (0.2 to 0.3)	High
IL-8 ≥ 70 pg/ml in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	83 (69 to 92)	76 (67 to 83)	4	0.2	Moderate

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
IL-10 > 15 pg/ml at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	64	79	3	0.5	Moderate

IL interleukin, NC not calculable

Table 8.5 Evidence profile for diagnostic accuracy of tests based on peripheral white blood cell counts in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
WBC < 6000 cells/mm^3 in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	67	90	7	0.4	Low
WBC ≤ 5000 cells/mm^3 in the prediction of infection during the first week of birth, using culture of bacteria from blood or CSF as reference standard						
1 (Hachey 1992)	475	23	96	6	0.8	Low
WBC ≤ 5000 cells/mm^3 in the prediction of infection in the first week of birth, using culture of bacteria from blood, CSF or urine as reference standard						
1 (Philip 1980)	376	50	94	8	0.5	Moderate
WBC ≥ 25,000 cells/mm^3 in the prediction of infection during the first week of birth, using culture of bacteria from blood or CSF as reference standard						
1 (Hachey 1992)	475	0	91	NC	1.1	Low
Neutrophils < 4000 cells/mm^3 in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Hachey 1992)	475	20	93	3	0.9	Low
Immature neutrophils < 4000 cells/mm^3 in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	78	80	4	0.3	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Immature neutrophils < 45% in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	67	36	1	0.9	Low
I:T > 0.2 in the prediction of infection within the first 3 days of life, using blood culture or clinical infection as reference standard						
1996/1997 data						
1 (Franz 2001)	378	81 (69 to 91)	42 (36 to 48)	1 (1 to 2)	0.4 (0.3 to 0.8)	High
1997/1998 data						
1 (Franz 2001)	331	70 (59 to 80)	51 (43 to 59)	1 (1 to 2)	0.6 (0.4 to 0.9)	High
I:T ratio > 0.2 at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	70	75	3	0.4	Low
I:T ratio ≥ 0.20 in the prediction of infection in the first week of birth, using culture of bacteria from blood, CSF or urine as reference standard						
1 (Philip 1980)	376	90	78	4	0.1	Moderate
I:T ratio ≥ 0.20 in the prediction of infection during the first week of birth, using culture of bacteria from blood or CSF as reference standard						
1 (Hachey 1992)	475	100	40	2	NC	Low
I:T ratio ≥ 0.30 in the prediction of infection during the first week of birth, using culture of bacteria from blood or CSF as reference standard						
1 (Hachey 1992)	475	92	60	2	0.1	Low
I:T ratio ≥ 0.40 in the prediction of infection during the first week of birth, using culture of bacteria from blood or CSF as reference standard						
1 (Hachey 1992)	475	72	76	3	0.4	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
I:T ratio > 0.75 in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	78	73	3	0.3	Low
Composite measure based on abnormal white blood cell count (defined as any of: total neutrophil count < 1750 cells/mm^3; absolute immature neutrophil count < 1400 cells/mm^3; or I:T ratio > 0.16) in the prediction of infection during the first 3 days of life, using blood culture as reference standard						
1 (Heimler 1995	219	81	51	2	0.6	Low
Composite measure based on abnormal white blood cell count (defined as any of: total neutrophil count < 1750 cells/mm^3; absolute immature neutrophil count < 1400 cells/mm^3; or I:T ratio > 0.16) in the prediction of infection during the first 3 days of life, using blood culture as reference standard						
1 (Jackson 2004)	856	Range 27 to 76	Range 12 to 95	NC	NC	Moderate

CSF cerebrospinal fluid, I:T ratio of immature to mature neutrophils, NC not calculable, WBC white blood cell

Table 8.6 Evidence profile for platelet count in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Platelets < 220,000 cells/mm^3 in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	66	62	2	0.6	Low

Table 8.7 Evidence profile for polymerase chain reaction tests in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
PCR to predict bacterial infection in asymptomatic babies with risk factors for early-onset neonatal infection, using blood culture as reference standard						
1 (Laforgia 1997)	33	100 (40 to 100)	93 (77 to 99)	15 (5 to 15)	0.0 (0.0 to 0.5)	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
PCR to predict bacterial infection in the first week of life, using blood culture as reference standard						
1 (Reier-Nilsen 2009)	48	67 (30 to 100)	86 (75 to 96)	5 (2 to 12)	0.4 (0.1 to 1.2)	Moderate
PCR to predict bacterial infection in the first week of life, using blood culture or clinical diagnosis of infection as reference standard						
1 (Reier-Nilsen 2009)	48	29 (13 to 45)	94 (82 to 100)	5 (1 to 36)	0.8 (0.6 to 1.0)	Moderate

PCR polymerase chain reaction

Table 8.8 Evidence profile for composite measures in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Composite measure based on CRP (> 10 mg/l) and/or PCT (≥0 .50 ng/ml) in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	63 (48 to 77)	66 (57 to 74)	2	0.6	Moderate
Composite measure based on CRP (> 10 mg/l) and/or IL-8 (≥ 70 pg/ml) in the prediction of infection within the first 3 days of life, using blood culture or clinical infection as reference standard						
1996/1997 data						
1 (Franz 2001)	378	92 (82 to 97)	74 (68 to 79)	4 (3 to 4)	0.2 (0.1 to 0.3)	High
1997/1998 data						
1 (Franz 2001)	331	92 (85 to 96)	77 (71 to 83)	4 (3 to 5)	0.1 (0.1 to 0.2)	High
Composite measure based on CRP (> 10 mg/l) and/or IL-8 (≥ 70 pg/ml) in the prediction of infection within 10 days of birth, using blood culture and/or clinical diagnosis of infection as reference standard						
1 (Franz 1999)	162	91 (79 to 98)	73 (64 to 81)	3	0.1	Moderate
Composite measure based on CRP (> 10 mg/l) and/or I:T ratio (> 0.2) in the prediction of infection within the first 3 days of life, using blood culture or clinical infection as reference standard						
1996/1997 data						
1 (Franz 2001)	378	91 (80 to 97)	41 (35 to 47)	2 (1 to 2)	0.2 (0.1 to 0.5)	High

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
1997/1998 data						
1 (Franz 2001)	331	73 (63 to 83)	49 (41 to 58)	1(1 to 2)	0.6 (0.4 to 0.8)	High
Composite measure based on PCT (> 5.75 ng/ml) and IL-6 (> 12 pg/ml) at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	93	46	2	0.2	Low
Composite measure based on PCT (> 5.75 ng/ml) and IL-8 (> 130 pg/ml) at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	89	44	2	0.3	Low
Composite measure based on PCT (> 5.75 ng/ml) and IL-10 (> 15 pg/ml) at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	93	48	2	0.2	Low
Composite measure based on PCT (> 5.75 ng/ml) and I:T ratio (> 0.2) at presentation in the prediction of infection within 72 hours of birth, using blood culture or clinical infection as reference standard						
1 (Bender 2008)	123	85	60	2	0.3	Low
Composite measure based on Predictive score > 0.503 in the prediction of infection within first 72 hours of life, using clinical findings consistent with sepsis or positive cultures as reference standard Predictive score formula = (WBC × 0.01) + (I:T ratio × 5.7) – (I:M ratio × 2.9) + (CRP × 0.01)						
1 (Selimovic 2010)	341	73	89	NC	NC	Very low
Composite measure based on combination of prenatal maternal colonisation, prolonged rupture of membranes ≥ 12 hours, mechanical ventilation at birth, IL-6 concentration ≥ 300 pg/ml and IL-8 concentration ≥ 200 pg/ml with score ≥ 6.5 predicting infection, using clinical findings consistent with sepsis or positive cultures as reference standard						
1 (Labenne 2011)	213	100(86 - 100)	80 (73 to85)	5.5 (4.1 to 6.8)	0	Low

CRP C-reactive protein, IL interleukin, I:M ratio of immature to mature neutrophils, I:T ratio of immature to total neutrophils, NC not calculable, PCT procalcitonin

Table 8.9 Evidence profile for surface swabs in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Any two of skin, ear or pharynx swabs to detect early-onset infection at birth among babies born by caesarean section at < 34 weeks' gestation, using diagnosis of clinical sepsis as reference standard						
1 (Berger 2004)	221	22 (10 to 34)	83 (77 to 89)	1 (1 to 3)	0.9 (0.8 to 1.1)	Moderate
Nose or ear swab to predict GBS infection in the first 2 days of life, using blood culture as reference standard						
1 (Hall 1995)	2221	93 (87 to 99)	99 (98.5 to 99.4)	88 (58 to 132)	0.1 (0.03 to 0.2)	Moderate

Table 8.10 Evidence profile for urine latex agglutination test for group B streptococcus antigen in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
LA test to predict GBS infection in the first 3 days of life, using blood culture as reference standard						
1 (Heimler 1995)	219	94	92	12	0.1	Low
LA test to predict GBS infection in the first 24 hours of life, using blood culture as reference standard						
1 (Williamson 1995)	236	67	68	2	0.5	Low
LA test to predict GBS infection in the first 24 hours of life, using positive GBS culture from any site as reference standard						
1 (Williamson 1995)	236	90 (71 to 100)	70 (64 to 76)	3 (2 to 4)	0.1 (0.02 to 0.9)	Moderate

GBS group B streptococcus, LA latex agglutination

Table 8.11 Evidence profile for urine culture in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Urine culture to predict bacterial infection within 72 hours of birth, using blood culture as reference standard						
1 (Visser 1979)	188	11(0 to 32)*	99 (97-100)*	33 (0 to 87)*	96 (93 to 97)*	Low

* Calculated by the NCC-WCH technical team from data reported in the article

Table 8.12 Evidence profile for cerebrospinal fluid analysis in babies about to start antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Presence of any WBC in CSF (that is, CSF WBC count >0 cells/mm^3) in the prediction of meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	97 (88 to 99)	11 (10 to 12)	1.09 (1.03 to 1.14)	0.3 (0.08 to 1.22)	Very low
CSF WBC > 21 cells/mm^3 to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	79 (67 to 89)	81 (80 to 82)	4 (4 to 5)	0.3 (0.2 to 0.4)	Very low
Elevated CSF WBC count (defined as WBC ≥ 23 or ≥ 26 cells/mm^3 for babies ≥ 37 or < 37 weeks' gestation, respectively) to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Ansong 2009)	13,495	89	82	5	0.1	Very low
CSF protein of 41–90 mg/dl to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	100 (84 to 100)	2 (1 to 3)	1	1.0	Very low
CSF protein of 90–120 mg/dl to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	84 (71 to 92)	28 (27 to 29)	1	0.9	Very low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Elevated CSF protein (defined as protein ≥ 171 or ≥ 151 mg/dl for babies ≥ 37 or < 37 weeks' gestation, respectively) to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Ansong 2009)	13,495	93	76	4	0.1	Very low
Low CSF glucose (defined as glucose ≤ 33 or ≤ 23 mg/dl for babies ≥ 37 or < 37 weeks' gestation, respectively) to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Ansong 2009)	13,495	61	96	14	0.4	Very low
CSF glucose < 20 mg/dl to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	44 (30 to 58)	98 (97 to 99)	1	0.9	Very low
CSF glucose of 20–60 mg/dl to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	89 (78 to 96)	20 (18 to 21)	1	0.9	Very low
CSF glucose > 120 mg/dl to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Garges 2006)	9,111	76 (63 to 87)	63 (62 to 64)	2	0.5	Very low
Composite measure based on any abnormal CSF value (that is, any of WBC ≥ 23 or ≥ 26 cells/mm^3 or protein ≥ 171 or ≥ 151 mg/dl or glucose ≤ 33 or ≤ 23 mg/dl for babies ≥ 37 or < 37 weeks' gestation, respectively) to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Ansong 2009)	13,495	97	67	3	0.1	Very low
Composite measure based all CSF value being abnormal (that is, all of: WBC ≥ 23 or ≥ 26 cells/mm^3 or protein ≥ 171 or ≥ 151 mg/dl or glucose ≤ 33 or ≤ 23 mg/dl for babies ≥ 37 or < 37 weeks' gestation, respectively) to predict bacterial meningitis in the first week of life, using CSF culture as reference standard						
1 (Ansong 2009)	13,495	58	98	32	0.4	Very low

CSF cerebrospinal fluid, NC not calculable, WBC white blood cell

Table 8.13 Prevalence of bacterial meningitis and bacterial urinary tract infection in babies about to start antibiotic treatment

Study	Country	Population	Prevalence of bacterial meningitis	Prevalence of bacterial UTI
Ansong 2009	USA	Babies with suspected GBS infection who had undergone at least one lumbar puncture	46/13,495 (0.3%)	NR
Garges 2006	USA	Babies with suspected early- or late-onset infection who had undergone lumbar puncture	95/9111 (1.0%)	NR
Hachey 1992	USA	Babies evaluated for suspected infection during the first week of life	4/475 (0.8%)	0/475 (0%)
Hall 1995	USA	Babies with suspected early-onset GBS infection	8/2221 (0.4%)	NR
Heimler 1995	USA	Babies with suspected infection during the first 3 days of life whose mothers had received intrapartum antibiotic treatment	4/219 (1.8%)	NR
Philip 1980	USA	Babies with suspected infection in the first week of life	8/376 (2.1%)	0/376 (0%)
Prabhakar 1999	USA	Babies with suspected infection within the first week of life	0/452 (0%)	NR
Schwersenski 1991	USA	Babies evaluated for suspected infection during the first week of life	9/712 (1.3%) based on positive CSF culture 1/712 (0.1%) based on positive CSF culture and blood culture and clinical course consistent with meningitis	NR
Tamim 2003	USA	Babies with suspected infection in the first 24 hours of life	NR	0/349 (0%)
Visser 1979	USA	Babies with suspected infection within 72 hours of birth	1/188 (0.5%)	3/188 (1.6%)

CSF cerebrospinal fluid, GBS group B streptococcus, NR not reported, UTI urinary tract infection

Evidence statements

Identifying asymptomatic babies who should receive antibiotic treatment

A low peripheral WBC count (4.99×10^3/microlitre or less) is a very useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at 1 hour or more after birth, but it is not a useful test at less than 1 hour after birth(low quality evidence).

A low absolute neutrophil count (0.99×10^3/microlitre or less) is a moderately useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at less than 1 hour after birth and a very useful test at 1 hour or more after birth (low quality evidence). A moderately low absolute neutrophil count ($1–1.99\times10^3$/microlitre) is a very useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at 4 hours or more after birth, but it is not a useful test at less than 4 hours after birth (low quality evidence).

An I:T ratio of 0.6 or more is a moderately useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at less than 4 hours after birth, and a very useful test at 4 hours or more after birth(low quality evidence).

No evidence was identified relating to the accuracy of tests based on peripheral WBC counts for ruling out early-onset neonatal infection.

A composite measure of abnormal WBC count (defined as total WBC count 5000/mm^3 or less or 30,000/mm^3 or more, or absolute neutrophil count less than 1500 mm^3, or immature:mature neutrophil ratio more than 0.2) is not a useful test for ruling in or ruling out early-onset neonatal infection in asymptomatic at-risk babies (low quality evidence).

No evidence was identified relating to tests based on CRP, procalcitonin, platelet count, surface swabs (including eye swabs and umbilical cord swabs), gastric aspirates or urine microscopy or culture.

Babies about to start antibiotic treatment

CRP at presentation is, at best, a very useful test for ruling in early-onset neonatal infection, particularly when serial testing is performed over a period of 2 days following presentation, but it is not a useful test for ruling out early-onset neonatal infection. In some studies, CRP at presentation was not a useful test for ruling in or ruling out early-onset neonatal infection (moderate to high quality evidence).

Procalcitonin at presentation is, at best, a moderately useful test for ruling in early-onset neonatal infection but it is not a useful test for ruling out early-onset neonatal infection. In most studies, procalcitonin at presentation was not a useful test for ruling in or ruling out early-onset neonatal infection (low to moderate quality evidence).

Interleukins 6, 8 and 10 at presentation are not useful tests for ruling in early-onset neonatal infection but, at best, interleukin 8 is a moderately useful test for ruling out early-onset neonatal infection. In most studies, interleukins 6, 8 and 10 at presentation were not useful tests for ruling in or ruling out early-onset neonatal infection (low to high quality evidence).

A low peripheral WBC count (6000 cells/mm^3 or less) at presentation is, at best, a moderately useful test for ruling in early-onset neonatal infection but it is not a useful test for ruling out early-onset neonatal infection (low to moderate quality evidence).

A high peripheral WBC count (25,000 cells/mm^3 or more) at presentation is not a useful test for ruling in or ruling out early-onset neonatal infection (low quality evidence).

A low peripheral neutrophil count (4000 cells/mm^3 or less) at presentation is not a useful test for ruling in or ruling out early-onset neonatal infection (low quality evidence).

An I:T ratio of 0.2 or more at presentation is not a useful test for ruling in early-onset neonatal infection but it is, at best, a moderately useful test for ruling out early-onset neonatal infection (low to high quality evidence).

Platelet count at presentation is not a useful test for ruling in or ruling out early-onset neonatal infection (low quality evidence).

PCR at presentation is, at best, a very useful test for ruling in early-onset neonatal infection and ruling out early-onset neonatal infection (low quality evidence). In most studies, PCR at presentation was a moderately useful test for ruling in early-onset neonatal infection but it was not a useful test for ruling out early-onset neonatal infection (moderate quality evidence).

Composite measures at presentation based on CRP and either interleukins or I:T ratio are not useful for ruling in early-onset neonatal infection but are, at best, moderately useful for ruling out early-onset neonatal infection. In some studies, composite measures at presentation based on CRP and either interleukins or I:T ratio were not useful tests for ruling in or ruling out early-onset neonatal infection (moderate to high quality evidence).

Composite measures at presentation based on procalcitonin and either interleukins or I:T ratio are not useful tests for ruling in early-onset neonatal infection but are, at best at best, moderately useful tests for ruling out early-onset neonatal infection (low quality evidence).

Composite measures at presentation based on WBC count, CRP, I:M ratio and I:T ratio are not useful tests for ruling in early-onset neonatal infection but are, at best at best, moderately useful tests for ruling out early-onset neonatal infection (very low quality evidence).

A composite measure at presentation based on maternal and neonatal clinical factors and interleukins is, at best, a moderately useful test for ruling in early-onset neonatal infection and a very useful test for ruling out early-onset neonatal infection (low quality evidence).

Surface swabs (from the skin, ear, nose or pharynx) are, at best, very useful tests for ruling in and ruling out systemic early-onset neonatal infection. In some studies, surface swabs were not useful tests for ruling in or ruling out early-onset neonatal infection (moderate quality evidence).

Urine latex agglutination testing for GBS antigen is, at best, a very useful test for ruling in and ruling out early-onset neonatal infection. In some studies, urine latex agglutination testing for GBS antigen was not a useful test for ruling in or ruling out early-onset neonatal infection (low to moderate quality evidence).

Urine culture is a very useful test for ruling in early-onset neonatal infection, but it is not a useful test for ruling out early-onset neonatal infection (low quality evidence).

CSF parameters (one or more of white cell count, protein concentration and glucose concentration) are, at best, very useful tests for ruling in early-onset neonatal infection and moderately useful tests for ruling out early-onset neonatal infection. In most studies, CSF parameters were not useful tests for ruling in or ruling out early-onset neonatal infection (very low quality evidence).

Composite measures at presentation based on CSF parameters (one or more of white cell count, protein concentration and glucose concentration) and neonatal clinical factors are not useful tests to rule in bacterial meningitis but are, at best, moderately useful tests to rule out bacterial meningitis. In some studies composite measures at presentation based on CSF parameters (one or more of white cell count, protein concentration and glucose concentration) and neonatal clinical factors were not useful tests for ruling in or ruling out bacterial meningitis (very low quality evidence).

No evidence was identified relating to tests based on cytokines, buffy coat examination, gastric aspirates or chest X-ray. No evidence specific to eye swabs and umbilical cord swabs was identified for inclusion.

Prevalence of bacterial meningitis and bacterial urinary tract infection

Ten studies, all of which were conducted in the USA, reported the prevalence of bacterial meningitis and urinary tract infection. The prevalence of bacterial meningitis ranged from 0% to 2.1% and the prevalence of urinary tract infection ranged from 0% to 1.6%.

Health economics profile

The majority of babies considered to be at risk of early-onset neonatal infection are started on antibiotics immediately. However, for babies who are asymptomatic and have only one risk factor healthcare professionals would prefer to avoid unnecessary treatment. This has to be balanced against the benefits of beginning treatment before symptoms and signs are evident. This can significantly reduce mortality and morbidity associated with infection, and may reduce duration of hospital stay. Diagnostic tests can be used to determine which asymptomatic babies may have an infection.

Two strategies were compared using health economic analysis:

- Strategy 1 – asymptomatic babies with only one risk factor who would not be started on antibiotics immediately are tested for a low peripheral WBC count (4.99×10^3/microlitre or less) and a low absolute neutrophil count (0.99×10^3/microlitre or less) obtained 4or more hours after birth; babies with a low count are started on antibiotics.
- Strategy 2 – asymptomatic babies with only one risk factor who would not be started on antibiotics immediately are observed; babies who develop symptoms or signs of early-onset neonatal infection are started on antibiotics.

Many inputs necessary for the health economic analysis were estimates because no published data were identified in the literature. The population size for this specific group (babies with only one risk factor who would not be started on antibiotics immediately) is unknown. As the testing strategy involves giving blood tests to all babies in this population, knowing the actual population to be tested is important. The true infection rate in this population is also unknown, but it is likely to be low. The diagnostic test accuracy is also unknown. The test has a very high likelihood ratio for a positive result, but it may result in a large number of babies having false positive test results and being treated unnecessarily.

The baseline inputs were:

- 50% of near-term and term babies (more than 34 weeks of gestation)born asymptomatic who have only one risk factor and do not start antibiotics immediately are given a blood test; N= 67,087
- 0.5% will have a true infection; N= 335
- The blood test has a false negative rate of 10%, therefore 34 babies with a true infection will have a negative test result.
- The blood test has a false positive rate of 10%, therefore 6709 babies will start antibiotic treatment unnecessarily.
- The strategy will avoid six deaths per year.

Using these inputs the first strategy (involving testing) costs approximately £400,000 less than the second strategy (observation alone) and it results in fewer deaths and less disability because of more timely treatment.

Even though the first strategy could result in fewer deaths, it significantly increases the number of babies kept in hospital for treatment, and the majority will probably be kept in for treatment unnecessarily due to false positive test results. The model did not include consideration of antibiotic resistance or long-term effects of antibiotic use.

It was also thought that a false negative test result may falsely reassure healthcare professionals and parents, and they may be less likely to identify symptoms and signs of infection even if they develop. Also, this strategy involves a large number of babies being given an additional blood test. The consensus of the GDG was that the evidence for the first strategy (involving diagnostic testing) was not strong enough, and the results of the analysis showed too much uncertainty, to recommend the additional blood test for this group of babies. Full details of the health economic analysis are presented in Chapter 13.

A further health economic model was used to evaluate the cost effectiveness of four strategies for measuring CRP concentrations. Some of the strategies involved measurement of CRP concentration at presentation; however, other measurements performed later were also evaluated with the purpose of identifying well babies in whom antibiotics could be stopped safely and discharged. This second health economic analysis is summarised in Chapter 10, with full details being presented in Chapter 13. The outcome of the analysis was that performing a CRP test at presentation is cost effective.

Evidence to recommendations

Relative value placed on the outcomes considered

Throughout the guideline the GDG prioritised LRs for evaluating diagnostic test accuracy and when these data were not available the group considered sensitivity and specificity (see Section 3.3). The GDG agreed that LR^+ more than 10 indicated a test was very useful to rule in infection, 5–10 that it was moderately useful and less than 5 that it was not particularly useful. The GDG agreed that antibiotic treatment should start at the earliest opportunity when very useful tests (LR^+ more than 10) produce a positive test result in asymptomatic babies.

The GDG also agreed that LR^- less than 0.1 indicated a test was very useful to rule out infection, 0.1–0.2 that it was moderately useful and more than 0.2 that it was not particularly useful. The GDG agreed that antibiotic treatment could be stopped and babies could be discharged early and safely when very useful tests (LR^- less than 0.1) produce a positive test result in asymptomatic babies.

For babies about to start antibiotic treatment, the GDG considered that LR^+ was more important than LR^- because LR^+ would be useful for making the decision whether to switch to antibiotics that cover bacterial meningitis.

Trade-off between clinical benefits and harms

The GDG considered the consequences of accurate and inaccurate diagnoses on the care of babies. The group recognised the importance of treating all babies that really have an early-onset neonatal infection early and adequately, but also that inaccurate diagnoses (corresponding to false positive test results) or overtreatment of babies with infection (those with a true positive result) would cause unnecessary exposure to antibiotics, hospital stays and anxiety for babies' families. The GDG also acknowledged the broader harm of increased antibiotic resistance with over-prescription of antibiotics, but considered that the greatest harm would be delayed or missed identification and treatment of early-onset neonatal infection in those babies that really have such an infection (corresponding to a false negative test result).

The GDG gave special deliberation to lumbar puncture, balancing the clinical imperative for prompt identification of bacterial meningitis to facilitate effective treatment, whether and when CSF tests would be needed in addition to other investigations, and the additional risks and inconvenience associated with lumbar puncture because of the invasive nature of the procedure.

Trade-off between net health benefits and resource use

A health economic analysis conducted for the guideline compared two clinical management strategies in asymptomatic babies with only one risk factor and no clinical indicators of possible infection. In the first strategy, such babies would have a full blood count performed and those with low WBC counts or low absolute neutrophil counts would be given antibiotics. In the second strategy, the babies would not have a full blood count performed, but they would be observed and if clinical indicators of possible infection developed they would be given antibiotics. The consensus of the GDG was that the evidence for cost effectiveness of the first strategy was not strong enough to recommend its use, especially as the results of the analysis showed a large degree of uncertainty. Full details of the health economic analysis are presented in Chapter 13.

A further health economic model was used to evaluate the cost effectiveness of four strategies for measuring CRP concentrations. A strategy that involved measurement of CRP concentration at presentation and another measurement performed 18–24 hours later was shown to be cost effective. This second health economic analysis is summarised in Chapter 10, with full details being presented

in Chapter 13. The recommendation to perform a CRP test at presentation is, however, presented in this section.

Quality of evidence

The GDG considered a blood culture to be the reference standard for identification of bacterial infection and therefore concluded that in babies given antibiotics because of risk factors for infection or clinical indicators of possible infection a blood culture should be performed before starting antibiotic treatment.

The GDG reviewed evidence for the diagnostic test accuracy of investigations other than blood culture to aid decision making during the interval required for the results of the blood culture to be made available.

Identifying asymptomatic babies who should receive antibiotic treatment

In relation to the diagnostic test accuracy of a peripheral WBC count at presentation the GDG concluded that:

- For a test performed at 1 hour or more after birth, a low peripheral WBC count (4.99×10^3/microlitre or less) and a low absolute neutrophil count (0.99×10^3/microlitre or less) are very useful tests for ruling in early-onset neonatal infection.
- For a test performed at 4 hours or more after birth, a low absolute neutrophil count (1–1.99×10^3/microlitre) and an I:T ratio of 0.6 or more are very useful tests for ruling in early-onset neonatal infection.

However, the health economic analysis conducted for the guideline did not provide robust evidence of the cost effectiveness of a peripheral WBC count in asymptomatic babies at presentation, and so the GDG did not recommend its use.

No evidence was identified in relation to tests based on CRP, procalcitonin, platelet count, surface swabs, gastric aspirates or urine microscopy or culture.

Babies about to start antibiotic treatment

In relation to the diagnostic test accuracy of a CRP concentration at presentation, six studies provided evidence of mostly moderate or high quality. The GDG noted that CRP testing in the first 8 hours of life is not useful and the evidence included in the review led the GDG to conclude that measuring CRP at presentation was not useful for ruling infection in or out. The group was particularly interested in whether CRP concentrations were useful for guiding decisions on the duration of antibiotic treatment. Several of the included studies were therefore considered further in relation to the review question on optimal duration of antibiotic treatment (see Chapter 10).

The GDG considered that procalcitonin and interleukin (6, 8 and 10) assessments were insufficiently useful to accurately rule in or rule out early-onset neonatal infection in babies about to start antibiotic treatment and chose not to recommend the use of these tests.

With regard to the diagnostic test accuracy of a peripheral WBC count, the GDG concluded that a low count (5000 cells/mm^3 or less, or 6000 cells/mm^3 or less) is a moderately useful test for ruling in early-onset neonatal infection. However, the evidence identified for inclusion confirmed that peripheral WBC counts were not useful for ruling out early-onset neonatal infection, and therefore this investigation was not recommended for babies about to start antibiotic treatment.

I:T ratios of 0.2 or more or 0.3 or more were found to be moderately useful tests for ruling out early-onset neonatal infection, but because I:T ratio is not useful for ruling in early-onset neonatal infection the GDG did not recommend its use in babies about to start antibiotic treatment.

Platelet count and neutrophil counts (assessed individually or as a composite measure) were found not to be useful for ruling infection in or out and the GDG chose not to make a recommendation on their use.

The GDG concluded that tests based on composite measures (involving CRP concentrations, procalcitonin concentrations or I:T ratios) were not useful for ruling in early-onset neonatal infection and were, at best, moderately useful for ruling out early-onset neonatal infection. The GDG chose,

therefore, not to recommend the use of these tests. A composite measure based on interleukin and clinical risk factors was evaluated in one study and found to be very useful for ruling out early-onset infection, but the GDG did not believe a test based on such a measure would be practicable and so the group chose not to recommend its use.

One of three studies that evaluated the diagnostic test accuracy of PCR found it to be a very useful test for ruling in and ruling out early-onset neonatal infection. The inconsistency of the finding between studies, concerns with the level of PCR in preterm and term babies, and the cost of performing the test led the GDG to conclude that it should not be recommended.

Although some evidence was identified in relation to the diagnostic test accuracy of surface swabs, the GDG noted that the time needed to obtain results from these tests would be the same as that needed to obtain results of a blood culture, and so surface swabs would not aid clinical decision making in the evaluation of early-onset neonatal infection (because blood cultures would be performed routinely according to the GDG's recommendations). The GDG noted, however, that positive culture results obtained from surface swabs may be helpful in cases where blood and CSF cultures are negative (although they would provide only a possible aetiology).

With regard to analysis of CSF samples obtained using lumbar puncture, the GDG identified very low quality evidence that an elevated CSF white cell count was very useful for ruling in and ruling out bacterial meningitis in the first week of life. Elevated CSF protein and a composite measure based on CSF white cell count, protein concentration and glucose concentration were very useful tests for ruling out early-onset neonatal infection.

With regard to urine analysis, the GDG noted evidence to support the use of urine latex agglutination testing to rule in GBS in early-onset neonatal infection. However, no recommendation was made because the test is not used in the UK as it is not available commercially. Isolated urinary tract infections without a positive blood culture are rare and the GDG noted that the overall incidence of urinary tract infections in newborn babies is very low. The GDG believed that if a blood culture was positive, a positive urine culture would not add value clinically, and that babies at risk of developing a urinary tract infection would have received antibiotics before urine culture results were available.

No evidence was identified in relation to tests based on cytokines, buffy coat examination, gastric aspirates or chest X-ray for babies about to start antibiotic treatment

Localised infections of the eyes and umbilical cord

No evidence specific to eye swabs and umbilical cord swabs was identified for inclusion.

Prevalence of bacterial meningitis and bacterial urinary tract infection

The evidence identified by the GDG in relation to the prevalence of early-onset neonatal bacterial meningitis and urinary tract infection indicated that these conditions are of sufficient clinical importance for recommendations to be directed at affected babies. The GDG was aware, however, that bacterial meningitis in babies who are not already receiving treatment in neonatal units is covered by Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010). Similarly, urinary tract infection in babies is covered by Urinary tract infection in children (NICE clinical guideline 54, 2007).

Other considerations

No specific equalities issues were identified in relation to this review question.

Key conclusions

Identifying asymptomatic babies who should receive antibiotic treatment

The GDG considered recommending that a full blood count be performed at least 4 hours after birth before starting antibiotics in asymptomatic babies born at more than 34 weeks of gestation and with at least one risk factor for early-onset neonatal infection. The health economic analysis conducted for the guideline found the test to be cost effective, but there was considerable uncertainty in the evaluation as a number of key inputs were estimates elicited from the GDG. The GDG concluded that a full blood count should not be performed specifically for the purpose of identifying early-onset neonatal infection because of the large number of babies that would be given an extra test if the

recommendation was included in the guideline, and the number of babies who would have false positive test results and, therefore, be given antibiotics unnecessarily.

Babies about to start antibiotic treatment

The GDG considered a blood culture to be the reference standard for identification of bacterial infection and therefore recommended that in babies given antibiotics because of risk factors for infection or clinical indicators of possible infection a blood culture should be performed before starting antibiotic treatment. However, the group concluded that the diagnostic test accuracy of CRP, procalcitonin, interleukins, full blood count and PCR was not sufficiently strong to recommend their use at presentation.

The GDG consensus was that CSF examination adds value in terms of ruling bacterial meningitis in or out, but that explicit guidance was required to minimise the number of babies who would be exposed to the risks of lumbar puncture unnecessarily. The GDG acknowledged that babies with a positive blood culture would receive antibiotic treatment for early-onset neonatal infection. The GDG was aware of the recommendations contained in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) regarding contraindications to lumbar puncture in newborn babies. The GDG recommended that healthcare professionals perform a lumbar puncture in babies in whom any of the following criteria are met:

- a strong clinical suspicion of infection
- clinical symptoms or signs suggesting meningitis.

Although the GDG believed that a lumbar puncture should usually be performed before starting antibiotics in babies with clinically suspected meningitis or in whom there was a strong clinical suspicion of infection, the group was concerned that lumbar puncture should not delay timely administration of antibiotic treatment in these sick babies. Consequently, the group recommended that the lumbar puncture be performed soon after starting antibiotic treatment if necessary.

The GDG further recommended that a lumbar puncture be considered in a baby who is receiving antibiotics if any of the following criteria are met:

- CRP concentration 10 mg/l or more
- a positive blood culture
- the baby is not responding satisfactorily to antibiotic treatment.

The corresponding recommendation is presented in Chapter 10 because it relates to investigations performed during antibiotic treatment.

The GDG consensus was that a recommendation was required to discourage the practice of using urine microscopy or culture routinely as part of the investigation for systemic early-onset neonatal infection because they do not usefully contribute to the diagnosis. Similarly, healthcare professionals should not perform skin swab microscopy or culture as part of the investigation for systemic early- onset neonatal infection in the absence of clinical signs of a localised infection.

Localised infections of the eyes and umbilical cord

The GDG recognised that while minor conjunctivitis with encrusting of the eyelids is common and often benign, a purulent discharge may indicate the presence of a serious infection, for example with Chlamydia or Gonococcus and therefore requires urgent investigation. No evidence specific to the investigation of eye infections was identified for inclusion in the guideline review, but the GDG considered that serious infections were much more likely to be present in babies with a purulent exudate. Both chlamydial and gonococcal eye infections have the potential for causing lasting injury to the eye unless recognised and treated without delay. The GDG recommended, therefore, that in babies with a purulent eye discharge, healthcare professionals should collect swab samples urgently, specifically requesting investigation for Chlamydia and Gonococcus. Given the urgency for treatment of gonococcal conjunctivitis, the GDG recommended that babies with purulent eye discharge should start systemic antibiotic treatment while awaiting the swab results. No specific recommendation was made on the choice of antibiotics. The GDG believed that expert microbiological advice should be sought, ensuring that the chosen antibiotic regimen provides cover for possible gonococcal infection.

No evidence specific to the investigation of umbilical infections was identified for inclusion in the guideline review. Nevertheless, the GDG recommended that in babies with clinical signs of umbilical infection, including a purulent discharge or signs of periumbilical cellulitis (for example redness, increased skin warmth or swelling), healthcare professionals should perform a blood culture and a swab sample for microscopy and culture. Umbilical infections may be caused by a range of bacterial pathogens, including Gram-positive (for example *Staph aureus*) and Gram-negative micro-organisms. Umbilical infections may also lead to systemic bacterial infection. The GDG recommended, therefore, that antibiotic treatment with intravenous flucloxacillin and gentamicin should be started in babies with clinical signs of umbilical infection. The GDG acknowledged that the recommendation was with respect to the initial treatment of umbilical cord infection (omphalitis) and that in severe infection, expert opinion may be required. Regarding the dosage regimen for gentamicin, this should be adequate for the treatment of possible associated septicaemia, and so the GDG recommended the same dosage regimen as for suspected early-onset neonatal infection (see Chapter 9).

The GDG recognised the need for further research in relation to investigations to inform the decision about whether or not to start antibiotic treatment for early-onset neonatal infection. The GDG's recommendation for further research in this area was incorporated into a research recommendation covering which risk factors for early-onset neonatal infection, clinical symptoms and signs of infection, and laboratory investigations should be used to identify babies who should receive antibiotics (see Chapter 5).

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

No research recommendations were identified for this review question.

[††]Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

9 Antibiotics for suspected infection

Introduction

The objectives of this review question are to identify a safe and effective choice of antibiotics (either individual drugs or classes of drugs to be used alone or in combination) and treatment regimens for babies with suspected early-onset neonatal infection. Specific issues prioritised by the guideline development group (GDG) for consideration in this question were: the need to cover the most likely bacterial pathogens (including group B streptococcus [GBS], the most important Gram-positive organism), *E coli* (the most important Gram-negative organism) and possibly other organisms such as listeria (*L monocytogenes*); the use, if possible, of narrow-spectrum antibiotics to reduce the risk of bacterial antibiotic resistance; whether antibiotic blood concentrations need to be monitored; route and frequency of antibiotic administration; dosage; and the impact of prematurity on clinical management.

The considerations regarding inclusion of evidence obtained using particular study designs are similar to those in the review question relating to intrapartum antibiotics (see Chapter 6). For the evaluation of clinical outcomes (such as cure rate for early-onset neonatal infection) the GDG restricted consideration to evidence from randomised controlled trials (RCTs). For pharmacokinetic outcomes (for example incidence of therapeutic or toxic concentrations of a particular antibiotic) used to evaluate dosage regimens, the GDG restricted consideration to evidence from RCTs when such evidence was available. Other comparative or non-comparative pharmacokinetic and pharmacodynamic studies were considered only where no relevant evidence from RCTs was identified. The GDG members drew initial conclusions about effectiveness based on clinical outcomes reported in RCTs and then reviewed pharmacokinetic outcomes only for those antibiotics that they were considering recommending. As noted in Chapter 6, the rationale for considering pharmacokinetic outcomes in this guideline is that few antibiotics are licensed for use in pregnancy or in preterm babies; the GDG prioritised consideration of safe and effective dosage regimens in all of the review questions relating to antibiotic treatment.

Review question

What is the optimal antibiotic treatment regimen for suspected early-onset neonatal infection?

Existing NICE guidance

Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) includes recommendations for antibiotic treatment of suspected, confirmed and unconfirmed but clinically suspected bacterial meningitis and meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia) in children and young people younger than 16 years. Babies who are already receiving care in neonatal units are excluded from the guideline. Recommendations relating to pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia include:

- Give parenteral antibiotics (intramuscular or intravenous benzylpenicillin) to children and young people with suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) at the earliest opportunity (in primary or secondary care) but do not delay urgent transfer to hospital to give the parenteral antibiotics.

Recommendations relating to assessment and diagnosis in secondary care include:

- Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):
    - petechiae start to spread
    - the rash becomes purpuric
    - there are signs of bacterial meningitis
    - there are signs of meningococcal septicaemia
    - the child or young person appears ill to a healthcare professional.
- In a child or young person with an unexplained petechial rash and fever (or history of fever) but no high-risk clinical manifestations treat with intravenous ceftriaxone immediately if the C-reactive protein (CRP) or white blood cell (WBC) count (especially neutrophil count) is raised, as this indicates an increased risk of having meningococcal disease.

Recommendations relating to management of suspected bacterial meningitis or meningococcal disease in secondary care include:

- Treat children younger than 3 months with suspected bacterial meningitis without delay using intravenous cefotaxime plus either amoxicillin or ampicillin.
- Treat suspected meningococcal disease without delay using intravenous ceftriaxone.
- In children younger than 3 months, ceftriaxone may be used as an alternative to cefotaxime (with or without ampicillin or amoxicillin), but be aware that ceftriaxone should not be used in premature babies or in babies with jaundice, hypoalbuminaemia or acidosis as it may exacerbate hyperbilirubinaemia.

Recommendations relating to antibiotic treatment for specific infections in confirmed bacterial meningitis include:

- Treat Group B streptococcus (GBS) meningitis with intravenous cefotaxime for at least 14 days. If the clinical course is complicated consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.
- Treat bacterial meningitis due to *L monocytogenes* with intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first 7 days.
- Treat bacterial meningitis due to Gram-negative bacilli with intravenous cefotaxime for at least 21 days unless directed otherwise by the results of antibiotic susceptibilities. If the clinical course is complicated consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Recommendations relating to antibiotic treatment for confirmed meningococcal disease include treating with intravenous ceftriaxone for 7 days in total unless directed otherwise by the results of antibiotic susceptibilities.

Recommendations relating to antibiotic treatment for unconfirmed bacterial meningitis or meningococcal disease (that is, in children and young people for whom diagnostic test results are negative but clinical suspicion of bacterial meningitis or meningococcal disease remains) include:

- In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. If the clinical course is complicated, consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.
- In children and young people with unconfirmed but clinically suspected meningococcal disease, treat with intravenous ceftriaxone for 7 days in total.

Feverish illness in children (NICE clinical guideline 47, 2007) includes recommendations relating to antibiotic treatment in children younger than 5 years with fever. Recommendations relating to management by non-paediatric practitioners include:

- Oral antibiotics should not be prescribed to children with fever without apparent source.
- Children with suspected meningococcal disease should be given parenteral antibiotics at the earliest opportunity (either benzylpenicillin or a third-generation cephalosporin).

Recommendations relating to management by paediatric specialists include:

- Parenteral antibiotics should be used in babies younger than 1 month.
- When parenteral antibiotics are indicated for babies aged less than 3 months, a third-generation cephalosporin (for example cefotaxime or ceftriaxone) should be given plus an antibiotic active against listeria (for example ampicillin or amoxicillin).
- Children with fever presenting to specialist paediatric care or an emergency department should be given immediate parenteral antibiotics if they are:
    - shocked
    - unrousable
    - showing signs of meningococcal disease.
- Immediate parenteral antibiotics should be considered for children with fever and reduced levels of consciousness. In these cases symptoms and signs of meningitis (and herpes simplex encephalitis) should be sought.
- When parenteral antibiotics are indicated, a third-generation cephalosporin (for example cefotaxime or ceftriaxone) should be given, until culture results are available. For children younger than 3 months, an antibiotic active against listeria (for example ampicillin or amoxicillin) should also be given.
- In a child presenting to hospital with a fever and suspected serious bacterial infection, requiring immediate treatment, antibiotics should be directed against *N meningitidis*, *S pneumoniae*, *E coli*, *Staph aureus* and *Haemophilus influenzae* type b. A third- generation cephalosporin (for example cefotaxime or ceftriaxone) is appropriate, until culture results are available. For babies younger than 3 months of age, an antibiotic active against listeria (for example ampicillin or amoxicillin) should be added.
- Children with suspected meningococcal disease should be given parenteral antibiotics at the earliest opportunity (either benzylpenicillin or a third-generation cephalosporin).

Urinary tract infection in children (NICE clinical guideline 54, 2007) includes the following recommendations relating to acute management of urinary tract infection in children and young people younger than 16 years:

- Babies younger than 3 months with a possible urinary tract infection should be referred immediately to the care of a paediatric specialist. Treatment should be with parenteral antibiotics in line with Feverish illness in children (NICE clinical guideline 47, 2007).
- For babies and children who receive aminoglycoside (gentamicin or amikacin), once daily dosing is recommended.

Description of included studies

Fourteen studies reported in 15 articles were identified for inclusion for this review question (Agarwal 2002; de Alba Romero 1998; Hayani 1997; Isemann 1996; Itsarayoungyuen 1982; Langhendries 1993; Mercado 2004; Metsvaht 2007; Metsvaht 2010; Miall-Allen 1988; Muller 2007; Parm 2010; Rastogi 2002; Skopnik 1992; Snelling 1983).

Clinical outcomes reported in randomised controlled trials

Four RCTs compared the effectiveness of different antibiotics (or combinations of antibiotics) in babies with suspected early-onset neonatal infection:

- One study reported in two articles evaluated the effectiveness of benzylpenicillin plus gentamicin compared to ampicillin plus gentamicin (Metsvaht 2010; Parm 2010).
- One study evaluated the effectiveness of benzylpenicillin plus gentamicin compared with ceftazidime (Snelling 1983).
- One study evaluated the effectiveness of gentamicin compared with tobramycin (Itsarayoungyuen 1982).
- One study evaluated the effectiveness of ticarcillin plus clavulanic acid compared with piperacillin (with or without gentamicin; Miall-Allen 1988).

Seven RCTs evaluated clinical outcomes for different gentamicin dosing regimens in babies with suspected early-onset neonatal infection:

- Four studies evaluated the effectiveness of gentamicin given every 24 hours (4–5 mg/kg/dose) compared with gentamicin given every 12 hours (2–3 mg/kg/dose); babies in both treatment arms also received ampicillin. One study focused on near-term and term babies (birthweight 2500 g or more) with suspected infection in the first 7 days of life (ampicillin dosing schedule not reported; Agarwal 2002). Another study focused on full-term babies with suspected infection in the first 3 days of life (ampicillin dosage 200 mg/kg/day; Skopnik 1992). Another study focused on near-term and term babies (gestational age 34 weeks or more, birthweight 2000 g or more) with suspected infection in the first 24 hours of life (ampicillin dosage regimen not reported; Hayani 1997); the remaining study focused on babies with suspected early-onset neonatal infection (ampicillin dosage regimen not reported; de Alba Romero 1998).
- Two studies evaluated the effectiveness of gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 18–24 hours (2.5–3 mg/kg/dose); babies in both treatment arms also received ampicillin (ampicillin dosing schedules not reported). One study focused specifically on very low birthweight babies (600–1500 g) with suspected neonatal infection in the first 7 days of life (Rastogi 2002) and the other focused specifically on preterm babies (less than 34 weeks of gestation, birthweight 750–2000 g) with suspected neonatal infection in the first 24 hours of life (Mercado 2004).
- One study evaluated the effectiveness of a loading dose of gentamicin (4 mg/kg) compared with the standard initial dose of gentamicin (2.5 mg/kg) in babies with suspected neonatal infection in the first 12 hours of life; babies in both treatment arms received maintenance doses of gentamicin (2.5 mg/kg every 12, 18 or 24 hours depending on gestational age and birthweight) and ampicillin (200–400 mg/kg/day; Isemann 1996).

Six of the studies that reported clinical outcomes associated with gentamicin treatment included therapeutic drug monitoring and individualised dosage adjustment for gentamicin based on thresholds for peak and trough serum gentamicin concentrations, serum creatinine concentrations and urine output (Agarwal 2002; de Alba Romero 1998; Hayani 1997; Isemann 1996; Rastogi 2002; Snelling 1983), but details of the calculations used to determine adjusted dosages were not reported. In the remaining studies involving gentamicin treatment, therapeutic drug monitoring and dosage adjustment for gentamicin was not reported in either treatment arm. Studies that evaluate the effectiveness of strategies for therapeutic drug monitoring and individualised dosage adjustment for gentamicin are discussed in a separate review question (see Chapter 11).

One study evaluated the effectiveness of amikacin given every 24 hours (15 mg/kg/dose) in near-term and term babies (34 weeks or more of gestation) with suspected early-onset neonatal infection compared with amikacin given every 12 hours (7.5 mg/kg/dose); babies in both treatment arms also received ampicillin every 12 hours (Langhendries 1993).

Pharmacokinetic and pharmacodynamic studies

Based on the GDG's initial consideration of clinical outcomes reported in RCTs, the pharmacokinetics and pharmacodynamics of benzylpenicillin and gentamicin were prioritised for evaluation. All seven RCTs that evaluated clinical outcomes for different gentamicin dosing regimens also reported pharmacokinetic outcomes. No further RCTs reporting pharmacokinetic outcomes associated with gentamicin treatment were identified for inclusion.

No RCTs reporting pharmacokinetic or pharmacodynamic outcomes associated with benzylpenicillin treatment were identified for inclusion, but two studies of other designs were identified for inclusion:

- One non-randomised comparative study evaluated the pharmacokinetics of two doses of intravenous benzylpenicillin (25,000 IU/kg every 12 hours and 50,000 IU/kg every 12 hours) in very preterm babies (less than 28 weeks of gestation, birthweight less than 1200 g) with suspected infection in the first 3 days of life; babies in both treatment arms also received gentamicin (5 mg/kg every 48 hours; Metsvaht 2007).
- The other study used Monte Carlo simulation to evaluate the pharmacokinetics of intravenous benzylpenicillin (50,000 IU/kg every 12 hours) in preterm babies (less than 32 weeks' gestation) with suspected infection in the first 3 days of life; babies in both treatment arms also received tobramycin or cefotaxime (dosage regimens not reported; Muller 2007).

Evidence profiles

The evidence profiles for this review question are presented in Tables 9.1 to 9.14. Tables 9.1 to 9.4 contain evidence relating to comparisons between different antibiotics (or combinations of antibiotics). Tables 9.5 to 9.11 contain evidence relating to comparisons between different gentamicin dosing regimens, including pharmacokinetic outcomes. Table 9.12 contains evidence relating to comparisons between different amikacin dosing regimens. Tables 9.13 and 9.14 contain evidence relating to the pharmacokinetics of benzylpenicillin.

Table 9.1 Evidence profile for ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Treatment failure (need for change of antibiotics or death within 7 days)					
1 (Metsvaht 2010)	20/142 (14.1%)	20/141 (14.2%)	RR 0.99 (0.56 to 1.76)*	1 more per 1000 (62 fewer to 108 more)*	Low
Mortality					
7-day mortality					
1 (Metsvaht 2010)	11/142 (7.7%)	14/141 (9.9%)	RR 0.78 (0.37 to 1.66)*	22 fewer per 1000 (63 fewer to 66 more)*	Low
Mortality in the neonatal intensive care unit					
1 (Metsvaht 2010)	13/142 (9.2%)	23/141 (16.3%)	RR 0.56 (0.30 to 1.06)*	72 fewer per 1000 (114 fewer to 10 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mortality in the neonatal intensive care unit in babies < 26 weeks' gestation[b]					
1 (Metsvaht 2010)	6/24 (25.0%)	13/21 (61.9%)	RR 0.40 (0.19 to 0.87)*	371 fewer per 1000 (80 fewer to 501 fewer)*	Low
Colonisation with ampicillin-resistant Gram-negative bacteria					
1 (Metsvaht 2010)	44/142 (30.9%)	44/141 (31.2%)	RR 0.99 (0.70 to 1.40)*	3 fewer per 1000 (94 fewer to 125 more)*	Low
Colonisation with *Staphylococcus haemolyticus*[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.039	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.001	Low
Colonisation with *Klebsiella pneumoniae*[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.107	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.012	Low
Colonisation with *Staphylococcus hominis*[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.003	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.001	Low
Colonisation with *Enterococcus* species[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* < 0.001	Low

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.001	Low
Colonisation with *Staphylococcus aureus*[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.006	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.052	Low
Colonisation with ampicillin-resistant *Acinetobacter* species[c]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.996	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.001	Low
Number of babies colonised with *Acinetobacter species*[c]					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.224	Low
Number of babies colonised with *Enterobacter cloacae*[c]					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.142	Low

NC not calculable, NR not reported, P probability, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 72 hours of life

[b] Mortality in other groups classified by gestational age (< 28 weeks and > 36 weeks) not reported; possibility of selective reporting of statistically significant results

[c] Results of multivariate mixed effect model analysis

[d] Monitoring for colonisation was conducted via rectal swabs on admission to the intensive care unit and twice a week thereafter until discharge from the unit or day 60 if this occurred earlier; colonisation duration represents the ratio of colonising days to 100 intensive care unit days counted from the first to last positive culture with 2 days added to compensate for the sampling interval of 3–4 days

Table 9.2 Evidence profile for ceftazidime compared with benzylpenicillin plus gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Ceftazidime	Gentamicin plus benzylpenicillin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
1 (Snelling 1983)	31/31 (100%)	24/24 (100%)	RR 1.00 (0.93 to 1.07)*	0 fewer per 1000 (70 fewer to 70 more)*	Low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 48 hours of life

Table 9.3 Evidence profile for tobramycin compared with gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Tobramycin	Gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Kidney damage[b] (nephrotoxicity)					
1 (Itsarayoungyuen 1982)	4/30 (13%)	3/20 (15%)	RR 0.89 (0.22 to 3.55)*	17 fewer per 1000 (117 fewer to 383 more)*	Low
Hearing damage[c] (ototoxicity)					
1 (Itsarayoungyuen 1982)	0/30 (0%)	0/20 (0%)	NC	NC	Low

FENa fractional excretion of sodium, NAG N-acetyl glucosamine, NC not calculable, RR relative risk, U:S urine to serum

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 72 hours of life

[b] Babies who had an increase in serum creatinine of ≥0.4 mg% and developed renal abnormalities (such as haematuria, proteinuria, granular casts, decrease in U:S creatinine ratio, increase in NAG enzyme and increase in FENa) were considered to have developed nephrotoxicity. Assessments were made every 3 days during treatment and when treatment was stopped. 4/20 (20%) babies who received gentamicin and 8/30 (27%) babies who received tobramycin also received concurrent treatment with potentially nephrotoxic medications (for example methicillin, furosemide or indomethacin). No baby was suspected to have any renal abnormalities at the time of inclusion to the study. All seven babies who developed nephrotoxicity were judged to be premature and as having hyaline membrane disease

[c] Auditory function was measured by behavioural screening and/or auditory brainstem response. Timings and frequency of assessment was not described by authors

Table 9.4 Evidence profile for ticarcillin plus clavulanic acid compared with piperacillin (with or without gentamicin) in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Ticarcillin plus clavulanic acid	Piperacillin (with or without gentamicin)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rates for neonatal infection					
1 (Miall-Allen 1988)	19/32 (59%)	27/40 (68%)	RR 0.88 (0.61 to 1.26)*	81 fewer per 1000 (263 fewer to 175 more)*	Low
Mortality during treatment					
1 (Miall-Allen 1988)	3/32 (9%)	5/40 (13%)	RR 0.75 (0.19 to 2.90)*	31 fewer per 1000 (101 fewer to 238 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 48 hours of life

Table 9.5 Evidence profile for gentamicin given every 24 hours (4 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in near-term and term babies (birthweight ≥ 2500 g) with suspected infection in the first 7 days of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by a hearing screen test before discharge from hospital)					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics: measurements after the first dose					
Peak concentrations 6–12 microgram/ml after the first dose					
1 (Agarwal 2002)	16/20 (80%)	15/21 (71%)	RR 1.12 (0.79 to 1.59)*	86 more per 1000 (150 fewer to 421 more)*	Low
Peak concentrations 8–12 microgram/ml after the first dose					
1 (Agarwal 2002)	10*/20 (50%)	2*/21 (10%)	RR 5.25 (1.31 to 21.06)*	405 more per 1000 (30 more to 1000 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics: measurements at 24 hours					
Trough concentrations < 0.5 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	2/20 (10%)	0/21 (0%)	RR 5.24 (0.27 to 102.81)	NC	Low
Trough concentrations < 1 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	11/20 (55%)	2/21 (10%)	RR 5.78 (1.46 to 22.88)*	455 more per 1000 (44 more to 1000 more)*	Low
Trough concentrations ≥ 2 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	0/20 (0%)	9/21 (43%)	RR 0.06 (0.00 to 0.89)*	403 fewer per 1000 (47 fewer to 429 fewer)*	Low
Peak concentrations 6–12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	20/20 (100%)	16/21 (76%)	RR 1.30 (1.01 to 1.67)*	229 more per 1000 (8 more to 510 more)*	Low
Peak concentrations 8–12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	16/20 (80%)	6/21 (30%)	RR 2.80 (1.38 to 5.70)*	514 more per 1000 (109 more to 1000 more)*	Low
Peak concentrations > 12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics: measurements at 48 hours					
Trough concentrations < 0.5 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	1/20 (5%)	0/21 (0%)	RR 3.14 (0.14 to 72.92)	NC	Low
Trough concentrations < 1 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	11/20 (55%)	3/21 (14%)	RR 3.85 (1.26 to 11.80)	407 more per 1000 (37 more to 1000 more)*	Low
Trough concentrations ≥ 2 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	0/20 (0%)	6/21 (29%)	RR 0.08 (0.00 to 1.34)	263 fewer per 1000 (286 fewer to 97 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Peak concentrations 6–12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	19/19 (100%)	15/21 (71%)	RR 1.38 (1.05 to 1.83)*	271 more per 1000 (36 more to 593 more)*	Low
Peak concentrations 8–12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	14*/19 (75%)	2*/21 (10%)	RR 7.74 (2.02 to 29.71)*	271 more per 1000 (36 more to 593 more)*	Low
Peak concentration > 12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
All peak concentrations over the 48-hour period					
Peak concentrations of 6–12 microgram/ml after the first, 24-hour and 48-hour doses					
1 (Agarwal 2002)	55/59 (93%)	36/63 (57%)	RR 1.63 (1.30 to 2.04)*	360 more per 1000 (171 more to 594 more)*	Low
Peak concentrations of 8–12 microgram/ml after the first, 24-hour and 48-hour doses					
1 (Agarwal 2002)	41*/59 (70%)	10*/63 (15%)	RR 4.38 (2.42 to 7.92)*	537 more per 1000 (225 more to 1000 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.6 Evidence profile for gentamicin given every 24 hours (4 mg/kg/dose) compared with gentamicin given every 12 hours (2 mg/kg/dose) in full-term babies with suspected infection in the first 3 days of life; all babies also received ampicillin (200 mg/kg/day)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/ dose)	Gentamicin every 12 hours (2 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Kidney impairment (assessed by serum creatinine concentration and glomerular filtration rate)					
1 (Skopnik 1992)	0/10 (0%)	0/10 (0%)	NC	NC	Low
Pharmacokinetics					
Peak concentrations > 12.0 microgram/ml after the dose on the fourth day of treatment					
1 (Skopnik 1992)	0/10 (0%)	0/10 (0%)	NC	NC	Low

NC not calculable

Table 9.7 Evidence profile for gentamicin given every 24 hours (5 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in near-term and term babies (gestational age ≥ 34 weeks, birthweight ≥ 2000 g) with suspected infection in the first 24 hours of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (5 mg/kg/ dose)	Gentamicin every 12 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Kidney impairment (assessed by serum creatinine concentration and glomerular filtration rate)					
1 (Hayani 1997)	0/11 (0%)	0/15 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2.0 microgram/ml before dose on the second or third day					
1 (Hayani 1997)	1/11 (9%)	6/15 (40%)	RR 0.23 (0.03 to 1.63)*	308 fewer per 1000 (388 fewer to 252 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.8 Evidence profile for gentamicin given every 24 hours (5 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in babies with suspected early-onset neonatal infection; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (5 mg/kg/ dose)	Gentamicin every 12 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Kidney impairment (assessed by the N-acetyl-D-glucosaminidase:creatinine ratio)					
1 (de Alba Romero 1998)	0/33 (0%)	0/32 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2.0 microgram/ml before dose on the fourth day of treatment					
1 (de Alba Romero 1998)	4*/33 (12%)	7*/32 (22%)	RR 0.55 (0.18 to 1.71)*	98 fewer per 1000 (179 fewer to 155 more)*	Low
Peak concentrations > 12.0 microgram/ml after dose on the fourth day of treatment					
1 (de Alba Romero1 998)	0/33 (0%)	1/32 (3%)	RR 0.32 (0.01 to 7.66)*	21 fewer per 1000 (31 fewer to 208 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team

Table 9.9 Evidence profile for gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 24 hours (2.5–3 mg/kg/dose) in very low birthweight babies (600–1500 g) with suspected neonatal infection in the first 7 days of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	Gentamicin every 24 hours (2.5–3 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Rastogi 2002)	0/30 (0%)	0/28 (0%)	NC	NC	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	**Gentamicin every 24 hours (2.5–3 mg/kg/ dose)**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**	
Kidney impairment (assessed by a reduction in urine output or an increase in serum creatinine ≥ 0.5 mg/dl)					
1 (Rastogi 2002)	0/30 (0%)	0/28 (0%)	NC	NC	Low
Pharmacokinetics: measurements after the first dose					
Peak concentrations < 5 microgram/ml after the first dose					
1 (Rastogi 2002)	0/29 (0%)	10/28 (36%)	RR 0.05 (0.00 to 0.75)*	339 fewer per 1000 (89 fewer to 357 fewer)*	Low
Peak concentrations of 6–12 microgram/ml after the first dose					
1 (Rastogi 2002)	27/29 (93%)	12/28 (43%)	RR 2.17 (1.40 to 3.37)*	501 more per 1000 (171 more to 1000 more)*	Low
Peak concentrations of 8–12 microgram/ml after the first dose					
1 (Rastogi 2002)	16*/29 (55%)	3*/28 (11%)	RR 5.15 (1.68 to 15.76)*	445 more per 1000 (73 more to 1000 more)*	Low
Peak concentrations >12 microgram/ml after the first dose					
1 (Rastogi 2002)	0/29 (0%)	1/28 (4%)	RR 0.32 (0.01 to 7.59)*	24 fewer per 1000 (35 fewer to 235 more)*	Low
Pharmacokinetics: measurements at 24 hours					
Trough concentrations < 2.0 microgram/ml at 24 hours					
1 (Rastogi 2002)	21/30 (70%)	NR[a]	NC	NC	Low
Trough concentrations < 1 microgram/ml at 24 hours					
1 (Rastogi 2002)	4/30 (13%)	NR[a]	NC	NC	Low
Peak concentrations < 5 microgram/ml after the 24-hour dose					
1 (Rastogi 2002)	-	5/28 (18%)	NC	NC	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	Gentamicin every 24 hours (2.5–3 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics: measurements at 48 hours					
Trough concentrations ≤ 0.5 microgram/ml before the 48-hour dose					
1 (Rastogi 2002)	9/30 (30%)	NR[b]	NC	NC	Low
Peak concentrations < 5 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	0/29 (0%)	5/28 (18%)	RR 0.09 (0.01 to 1.52)*	162 fewer per 1000 (177 fewer to 93 more)*	Low
Peak concentrations of 6–12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	25/29 (86%)	19/28 (68%)	RR 1.27 (0.95 to 1.70)*	183 more per 1000 (34 fewer to 475 more)*	Low
Peak concentrations of 8–12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	15*/29 (52%)	6*/28 (21%)	RR 2.41 (1.09 to 5.33)*	302 more per 1000 (19 more to 928 more)*	Low
Peak concentrations > 12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	2/29 (7%)	0/28 (0%)	RR 4.83 (0.24, to 96.42)*	NC	Low
All peak concentrations over the 48-hour period					
Peak concentrations of 6–12 microgram/ml after the 24-hour and 48-hour doses					
1 (Rastogi 2002)	52/58 (90%)	31/56 (55%)	RR 1.62 (1.26 to 2.08)*	343 more per 1000 (144 more to 598 more)*	Low

NC not calculable, NR not reported, RR relative risk, SD standard deviation

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Actual trough concentrations at 24 hours (mean ± SD, microgram/ml) 4.5–5.0 mg/kg once every 48 hour 1.72 ± 0.6 2.5; 3.0 mg/kg once every 24 hours 1.25±0.4 (P = 0.0013)

[b] Actual trough concentrations at 48 hours (mean ± SD, microgram/ml) 4.5–5.0 mg/kg once every 48 hour 0.70 ± 0.3 2.5; 3.0 mg/kg once every 24 hours 1.32 ± 0.4 (P = 0.00001)

Table 9.10 Evidence profile for gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 18–24 hours (2.5 mg/kg/dose) in preterm babies (< 34 weeks' gestation, birthweight 750–2000 g) with suspected neonatal infection in the first 24 hours of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	Gentamicin every 18-24 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Mercado 2004)	1/19 (5%)	2/21 (10%)	RR 0.55 (0.05 to 5.62)*	43 fewer per 1000 (90 fewer to 440 more)*	Low
Kidney impairment (assessed by a reduction in urine output < 1 ml/kg/hr or an increase in serum creatinine > 1 mg/dl)					
1 (Mercado 2004)	0/19 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2 microgram/ml after the second or third dose					
1 (Mercado 2004)	0/19 (0%)	1/21 (5%)	RR 0.37 (0.02 to 8.50)*	30 fewer per 1000 (47 fewer to 357 more)*	Low
Peak concentrations > 12 microgram/ml after the second or third dose					
1 (Mercado 2004)	2/19 (11%)	0/21 (0%)	RR 5.50 (0.28 to 107.78)*	NC	Low
Peak concentrations < 5 microgram/ml before the second or third dose					
1 (Mercado 2004)	0/19 (0%)	7/21 (33%)	RR 0.07 (0.00 to 1.20)*	310 fewer per 1000 (333 fewer to 67 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.11 Evidence profile for a loading dose of gentamicin (4mg/kg) compared with a standard initial dose of gentamicin (2.5 mg/kg) in babies with suspected neonatal infection in the first 12 hours of life; all babies received maintenance doses of 2.5 mg/kg/dose every 12, 18 or 24 hours depending on gestational age and birthweight; all babies also received ampicillin (200–400 mg/kg/day)

Number of studies	Number of babies		Effect		Quality
	Gentamicin loading dose (4 mg/kg)	Gentamicin standard initial dose (2.5 mg/kg)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Clinical effectiveness					
Mortality					
1 (Isemann 1996)	1/18 (6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)*	NC	Low
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Isemann 1996)	3/12 (25%)	2/10 (20%)	RR 1.25 (0.26 to 6.07)*	50 more per 1000 (148 fewer to 1000 more)*	Low
Kidney impairment (assessed by decrease in urine output and increase in serum creatinine)					
1 (Isemann 1996)	1/18 (6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)*	NC	Low
Pharmacokinetics					
Peak concentrations (> 5 microgram/ml) after the first dose					
1 (Isemann 1996)	17/18 (94%)	1/16 (6%)	RR 15.11 (2.26 to 101.14)*	882 more per 1000 (79 more to 1000 more)*	Low
Peak concentrations > 10 microgram/ml after the first dose					
1 (Isemann 1996)	0/18 (0%)	0/16 (0%)	NC	NC	Low
Trough concentrations > 2 microgram/ml before the second dose (which was administered 12, 18 or 24 hours after the first dose, depending on gestational age and birthweight)					
1 (Isemann 1996)	10/18 (56%)	0/16 (0%)	RR 18.79 (1.19 to 297.03)*	NC	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.12 Evidence profile for amikacin given every 24 hours (15 mg/kg/dose) compared with amikacin given every 12 hours (7.5 mg/kg/dose) in near-term and term babies (≥34 weeks' gestation) with suspected neonatal infection in the first 2 days of life; all babies also received ampicillin every 12 hours[a]

Number of studies	Number of babies		Effect		Quality
	Amikacin every 24 hours (15 mg/kg/ dose)	Amikacin every 12 hours (7.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rates for neonatal infection					
1 (Langhendries 1993)	10/10 (100%)	12/12 (100%)	RR 1.00 (0.84 to 1.18)	0 fewer per 1000 (160 fewer to 180 more)*	Low
Mortality					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low
Kidney damage (nephrotoxicity)[a]					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low
Hearing damage (ototoxicity)[b]					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Urinary levels of four low molecular weight proteins (albumin, beta-2-microglobulin, retinol binding proteins and Clara cell protein) and four kidney-derived enzymes (gamma-glutamyltransferase, alkaline phosphatase, alanine aminopeptidase and N-acetyl-beta-D-glucosaminidase) were used to assess damage to and functional integrity of proximal renal tubules, respectively. Fractional excretion of sodium and levels of phospholipid were also measured

[b] Ototoxicity was assessed using brainstem auditory evoked potentials (BEAPs) performed on day 0 and repeated on days 6 and 9

Table 9.13 Evidence profile for intravenous benzylpenicillin (25,000 IU/kg once every 12 hours compared to 50,000 IU/kg once every 12 hours) in very preterm babies (< 28 weeks' gestation, birthweight < 1200 g) with suspected infection in the first 3 days of life; all babies also received gentamicin (5 mg/kg every 48 hours)

Number of studies	Number of babies		Effect		Quality
	25,000 IU/kg of benzylpenicillin every 12 hours	50,000 IU/kg of benzylpenicillin every 12 hours	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics					
Peak serum penicillin concentration					
1 (Metsvaht 2007)	[a]	[a]	-	-	Very low
Trough serum penicillin concentration[c]					
1 (Metsvaht 2007)	[b]	[b]	-	-	Very low

MIC_{90} minimum inhibitory concentration required to inhibit the growth of 90% of organisms

[a] Dichotomous data not reported; actual peak serum concentrations (median) were: 50,000 IU/kg group (n = 8) 145.5 microgram/ml; 25,000 IU/kg group (n = 9) 58.90 microgram/ml; term babies (n = 23) 22.0 microgram/ml; adults (n = 6) 45 microgram/ml

[b] Dichotomous data not reported; actual trough serum concentrations (median) were: 50,000 IU/kg group (n = 8) 7.1 microgram/ml; 25,000 IU/kg group (n = 9) 3.4 microgram/ml; term babies (n = 23) 2.3 microgram/ml; adults (n = 6) not reported

[c] For a dose of 25,000 IU/kg of benzylpenicillin every 12 hours the median trough concentration was 3.4 microgram/ml. This is well above the MIC_{90} for group B streptococcus (MIC_{90}, 0.062 to 0.094 microgram/ml). This suggests that in this population of very preterm babies < 28 weeks' gestation, a dose of 25 000 IU/kg will be adequate throughout the dosing interval

Table 9.14 Evidence profile for intravenous benzylpenicillin (50,000 IU/kg) every 12 hours in preterm babies (< 32 weeks' gestation) with suspected infection in the first 3 days of life; all babies also received tobramycin or cefotaxime (dosage regimens not reported)

Number of studies	Proportion of simulated babies (n = 10,000 simulations on 167 samples from 20 babies)* receiving 50,000 IU/kg of benzylpenicillin every 12 hours	Effect		Quality
		Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics				
Probability of target attainment for pathogens with MICs of ≤4 mg/l, using Monte Carlo simulation (with the assumption that in preterm babies, at least 50% of the time, the concentration of benzylpenicillin remains above the MIC)[a]				
1 (Muller 2007)	100%	-	-	Very low

MIC minimum inhibitory concentration

[a] The estimates of the pharmacokinetic parameters and measures of dispersion from the study were used to simulate various dosing regimens and obtain the percent fT > MIC as a function of MIC. The simulated subjects were based on 167 data points from 20 patients and reasonable, justified, gestational-age appropriate assumptions about the variability between babies. A Monte Carlo simulation takes repeated samples (n=10,000) from these distributions to give the result reported

Evidence statements

Comparison between different antibiotics or combinations of antibiotics

There were no differences in rates of treatment failure, 7-day mortality, neonatal intensive care unit (NICU) mortality, or colonisation with ampicillin-resistant Gram-negative bacteria between babies treated for suspected early-onset neonatal infection with benzylpenicillin plus gentamicin and those treated with ampicillin plus gentamicin. There was, however, a lower rate of NICU mortality in babies less than 26 weeks of gestation who received ampicillin plus gentamicin compared to those who received benzylpenicillin and gentamicin. Treatment with ampicillin plus gentamicin resulted in more babies being colonised with *Staph haemolyticus* and *Staph hominis*, and longer durations of colonisation, compared with treatment with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin did not affect the number of babies colonised with *Klebsiella pneumoniae*, but those who were colonised had longer durations of colonisation than did babies treated with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin resulted in fewer babies being colonised with *Enterococcus* species and *Staph aureus*, and shorter durations of colonisation, compared to treatment with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin did not affect the number of babies colonised with ampicillin-resistant *Acinetobacter* species, *Acinetobacter* species in general, or *Enterobacter cloacae*, but those colonised with ampicillin-resistant *Acinetobacter* species had shorter durations of colonisation than did babies treated with benzylpenicillin plus gentamicin (low quality evidence).

There was no difference in cure rates between babies who received benzylpenicillin plus gentamicin for suspected early-onset neonatal infection and those who received ceftazidime (low quality evidence).

There were no differences in nephrotoxicity or ototoxicity between babies who received gentamicin for suspected early-onset neonatal infection and those who received tobramycin (low quality evidence).

There were no differences in cure rates or mortality during treatment between babies who received ticarcillin plus clavulanic acid for suspected early-onset neonatal infection and those who received gentamicin and piperacillin (low quality evidence).

Comparison between different dosing regimens of the same antibiotics

No cases of ototoxicity were reported in near-term and term babies who received gentamicin every 24 hours daily for treatment of suspected early-onset neonatal infection, nor in those who received gentamicin every 12 hours (low quality evidence).

No cases of nephrotoxicity were reported in very low birthweight or preterm babies who received gentamicin every 48 hours for suspected early-onset neonatal infection, nor in those who received gentamicin every 18–24 hours (low quality evidence).

No cases of ototoxicity were reported in one study based on very low birthweight babies who received gentamicin every 48 hours for suspected early-onset neonatal infection, nor in those who received gentamicin every 24 hours (low quality evidence). In a separate study based on preterm babies there was no difference in ototoxicity rates between babies who received gentamicin every 48 hours and those who received gentamicin every 18–24 hours (low quality evidence).

There was no difference in cure rates between near-term or term babies who received amikacin every 24 hours for suspected early-onset neonatal infection and those who received amikacin every 12 hours. No cases of mortality, nephrotoxicity or ototoxicity were reported in either treatment arm (low quality evidence).

Pharmacokinetic outcomes

A 12-hourly gentamicin dosing regimen at 2.5 mg/kg/dose is more likely to lead to high trough concentrations of more than 2 microgram/ml compared to 4 mg/kg given at 24-hour intervals (low quality evidence).

In babies who received a 4 mg/kg loading dose of gentamicin compared with babies who received a standard initial dose of 2.5 mg/kg, the evidence relating to trough concentrations is not relevant to clinical practice because some of the trough concentrations were measured at 12 and 18 hours, rather than at 24 hours (low quality evidence).

In term babies, a gentamicin dosage of 2.5 mg/kg 12 hourly was associated with a smaller proportion of babies attaining a useful peak concentration compared to a dose of 4 mg/kg every 24 hours (low quality evidence).

In very low birthweight babies, peak serum gentamicin concentrations of less than 5 microgram/ml were more common in babies receiving 2.5–3 mg/kg/dose every 24 hours than in babies receiving 5 mg/kg/dose every 48 hrs (low quality evidence).

Babies with very low birthweight who received 5 mg/kg/dose of gentamicin every 48 hours were more likely to have a peak concentration in the therapeutic range than were babies who received 2.5–3 mg/kg every 24 hours (low quality evidence).

Babies who received 4.5 mg/kg of gentamicin as the first dose were more likely to attain peak serum concentrations of more than 5 microgram/ml than were babies who received 2.5 mg/kg as the first dose (low quality evidence).

A benzylpenicillin dosage of 25,000 IU/kg is safe and effective in preterm babies (very low quality evidence). No evidence was identified for benzylpenicillin in term babies.

Health economics profile

The GDG planned to conduct a cost effectiveness analysis comparing different strategies for identifying and treating babies at risk of early-onset neonatal infection or with symptoms and signs of early-onset neonatal infection, including different care settings. However, no published health economic analyses were identified in relation to this review question, and no clinical evidence was identified to inform development of a health economic model specifically for the guideline. The costs associated with different antibiotic regimens used in current practice in the UK were explored (see below).

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered that the following clinical outcomes were important when comparing antibiotic treatment regimens:

- cure rates for neonatal infection
- mortality
- duration of hospital stay
- neonatal adverse events
- long-term outcomes
- resistance among neonatal flora.

The priority outcome for the GDG was cure rate because it was most likely to be directly related to the effect of antibiotic treatment. The GDG believed other clinical outcomes might be more subject to the influence of other factors (for example, many factors might influence mortality and duration of hospital stay might depend in part on local policy). Pharmacokinetic outcomes (for example incidence of therapeutic or toxic concentrations) were also considered by the GDG in relation to evaluation of dosage regimens of particular antibiotics.

Consideration of clinical benefits and harms

It is important to choose the optimal antibiotic regimen for empirical treatment of early-onset neonatal infection to be able to target the most likely bacterial organisms responsible. However, drugs that may be considered most effective might have other advantages or disadvantages, for example bacterial resistance. Development of bacterial resistance needs to be considered in relation to the balance between the needs of a baby with early-onset neonatal infection in the present and other babies in the future who might acquire an infection with resistant bacteria. Where the evidence does not indicate a greater clinical effectiveness for any one antibiotic regimen, it is reasonable to use an antibiotic regimen that is associated with a lower potential for the development of antibiotic resistance.

Consideration of net health benefits and resource use

The GDG compared the likely use of healthcare resources for different antibiotic treatment regimens and a summary of the group's considerations is presented in Table 9.15. The group noted that narrow-spectrum antibiotics are less likely to promote (or induce) bacterial resistance, and they are generally less expensive than newer, broad-spectrum antibiotics.

Quality of evidence

All the evidence available from RCTs was of low quality, although this did not prevent the GDG making strong recommendations because there was no evidence to direct a change from the most frequently used antibiotic regimen for empirical treatment of early-onset neonatal infection (see below). No RCT evidence was identified for some antibiotic regimens in current practice, and few of the outcomes prioritised by the GDG were examined for relevant treatment comparisons. The included studies were generally small and evidence was not available comprehensively for babies of different gestational ages. The GDG made research recommendations to address these knowledge gaps, including specification of consensus definitions of core exposures and outcomes required for research to evaluate the clinical and cost effectiveness of antibiotics for the prevention or treatment of early-onset neonatal infection.

Table 9.15 Advantages and disadvantages of antibiotic regimens used for empirical treatment of early-onset neonatal infection in the United Kingdom

	Evidence identified for inclusion in the guideline review		**No evidence identified for inclusion in the guideline but used in clinical practice in the UK**			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
Spectrum	Benzylpenicillin is narrow-spectrum (an advantage in terms of reducing development of antibiotic resistance)	Ampicillin and amoxicillin are broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Ampicillin and amoxicillin are broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Cefotaxime is broad-spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Ampicillin, amoxicillin and cefotaxime are broad-spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Amoxicillin is broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)
Coverage	95–97% coverage based on UK data (excluding CONS)[d] CONS is the major non-susceptible organism, but is not very relevant in early-onset neonatal infection (because it is thought to be due to contamination of blood samples) and, in any case, there will be an opportunity to change to a different antibiotic regimen at 36 hours after presentation if required	Good coverage in the UK Provides optimal cover for listeria Ampicillin or amoxicillin might treat Gram-negative meningitis (such as *Escherichia coli* meningitis)	99% coverage based on UK data (excluding CONS)[e]	96% coverage based on UK data (excluding CONS)[e] Does not cover for listeria or *Enterococcus* species (the UK data did not include many listeria infections) Good CSF penetration, which makes it good for treating bacterial meningitis other than listeria meningitis	100% coverage based on UK data (excluding CONS)[e] Provides cover for listeria and most *Enterococcus* species Good CSF penetration, which makes it good for treating bacterial meningitis other than listeria meningitis	Good coverage in the UK (includes cover for *Staphylococcus aureus*)

	Evidence identified for inclusion in the guideline review		No evidence identified for inclusion in the guideline but used in clinical practice in the UK			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
	Problems with gentamicin resistance may occur in community settings, but less likely in hospital settings If the baby has early-onset *Escherichia coli* meningitis the combination of benzylpenicillin and gentamicin will be inadequate (contrast with ampicillin or amoxicillin plus gentamicin, which will be better as empirical treatment in this situation)					
Need for therapeutic drug monitoring	For gentamicin	For gentamicin	No	No	No	No
Care setting	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU
Cost	Benzylpenicillin net price for 600mg vial is 95p	Ampicillin net price for 500mg vial is £7.83	Benzylpenicillin net price for 600mg vial is 95p	Cefotaxime net price for 500mg vial is £2.14	Ampicillin net price for 500mg vial is £7.83	Co-amoxiclav IV injection 500/100 powder (amoxicillin

	Evidence identified for inclusion in the guideline review		No evidence identified for inclusion in the guideline but used in clinical practice in the UK			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
	Gentamicin IV infusion net price for 10ml (10mg) vial is£1.80 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency; also gentamicin monitoring would require extra blood sampling Infrequent administration of gentamicin is possible if dosage regimen is right Need to follow NPSA guidance on the safe use of gentamicin in neonatal services[f] (because of common prescribing errors) makes gentamicin administration labour intensive (and,	Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Gentamicin IV infusion net price for 10ml (10mg) bottle is £1.80 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency; also gentamicin monitoring would require extra blood sampling Infrequent administration of gentamicin is possible if dosage regimen is right Need to follow NPSA guidance on the safe use of gentamicin in neonatal services[f] (because of common prescribing	Ampicillin net price for 500-mg vial is £7.83 Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency	net price for 1g vial is £4.31 net price for 2g vial is £8.57 The antibiotic would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency Administration of one drug is easier than administration of two drugs (an advantage of monotherapy)	Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Cefotaxime net price for 500mg vial is £2.14 net price for 1g vial is £4.31 net price for 2g vial is £8.57 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses x dose frequency	500 mg as sodium salt, clavulanic acid 100 mg as potassium salt) for reconstitution, net price per vial is £1.21 IV injection 1000/200 powder (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt) for reconstitution, net price per vial is £2.63 The antibiotic would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency Administration of one drug is easier than administration of two drugs (an advantage of monotherapy)

	Evidence identified for inclusion in the guideline review		No evidence identified for inclusion in the guideline but used in clinical practice in the UK			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
	therefore, costly), but some aspects of the NPSA checklist might apply as good practice to all drugs to avoid errors	errors) makes gentamicin administration labour intensive (and, therefore, costly), but some aspects of the NPSA checklist might apply as good practice to all drugs to avoid errors				
Adverse effects	Potential side effects of gentamicin (mainly damage to hearing and kidneys); long-term risks uncertain but probably limited by effective monitoring	Potential side effects of gentamicin (mainly damage to hearing and kidneys); long-term risks uncertain but probably limited by effective monitoring	Unnecessary duplication of treatment (benzylpenicillin may not be needed in addition to ampicillin or amoxicillin)			Concentration of components varies between different parts of the body (uncertain pharmacology)

CONS coagulase-negative Staphylococci, CSF cerebrospinal fluid, IV intravenous, NICU neonatal intensive care unit, NPSA National Patient Safety Agency

[a] An aminoglycoside other than gentamicin (for example, amikacin) might be used in certain settings

[b] Ampicillin and amoxicillin have equivalent roles in each context

[c] The addition of clavulanic acid in this product is to keep amoxicillin active

[d] Data from Muller-Pebody 2011 and Vergnano 2011

[e] Data from Muller-Pebody 2011

[f] NPSA guidance and checklist available at http://www.nrls.npsa.nhs.uk/alerts/?entryid45=66271 and http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=66284&type=full&servicetype=Attachment)

Benzylpenicillin plus gentamicin compared with ampicillin plus gentamicin

In terms of mortality outcomes, the only statistically significant difference between an antibiotic regimen combining benzylpenicillin with gentamicin and a regimen combining ampicillin with gentamicin was a protective effect of ampicillin plus gentamicin for survival of babies under 28 weeks' gestation receiving care in a NICU. The GDG highlighted the small number of babies that were evaluated and the potential for reporting bias (in that results for other gestational age groups were not reported, so the reported finding might have arisen from a *post hoc* analysis rather than preplanned analyses stratified by gestational age). The GDG also considered that the choice of antibiotic regimen would be unlikely to be the only contributing factor to the difference in mortality rates in these preterm babies. Several of the bacteria reported in colonisation results were considered to be atypical of the bacteria that cause early-onset neonatal infection. For example, Staphyloccoccus species and *Acinetobacter* species are possible contaminants, and Enterobacter species might be related to hospital-acquired infections. The GDG believed that even if the excess mortality in the benzylpenicillin plus gentamicin group was due to early-onset neonatal infection, it was plausible that there had been an outbreak of Gram-negative bacteria in the NICU, and that other factors not addressed by the randomisation process might skew the results in this small population (for example, there was a possibility of seasonal effects due to the sequential [cross-over], rather than parallel, study design). The GDG emphasised that for clinically important outcomes, such as 7-day mortality, there was no statistically significant difference between the antibiotic regimens, and so the study did not provide evidence to support a change in practice away from the commonly used narrow-spectrum regimen of benzylpenicillin plus gentamicin. The GDG also noted that the study provided clear evidence of different antibiotic drugs selecting for different micro-organisms. Since none of the colonisation results reported in this study was found by the GDG to be particularly reassuring or worrying, the different selection pressures exerted by the different antibiotic regimens did not prevent the GDG making recommendations for the use of narrow-spectrum antibiotics.

Benzylpenicillin plus gentamicin compared with ceftazidime

Although cure rate was reported in the one RCT that contributed evidence for this treatment comparison, no statistically significant differences were observed. The study authors reported that benzylpenicillin plus gentamicin was the usual first-line antibiotic treatment in the unit where the study was conducted. However, the GDG did not consider the treatment comparison to be relevant to UK practice because ceftazidime is reserved for use against *Pseudomonas* species. The GDG also noted that the source of funding was not reported in the article (the group suspected that healthcare professionals may have been funded by a pharmaceutical company to participate in the study).

Gentamicin compared with tobramycin

Evidence for this comparison came from one small RCT in which no statistically significant differences in nephrotoxicity or ototoxicity between treatment groups were reported. The GDG considered that the evidence for this comparison was drawn from too small a sample size (n=50) to make useful conclusions about adverse effects. The GDG considered further that as neither regimen (gentamicin or tobramycin as monotherapy) covers for GBS, the study was not relevant to the UK setting.

Ticarcillin plus clavulanic acid compared with piperacillin (with or without gentamicin)

Evidence for this comparison came from one RCT in which there were no statistically significant differences between treatment groups in cure rates or mortality. The GDG did not consider that either ticarcillin or piperacillin were useful in the UK setting and would be unlikely choices of antibiotic regimen. Both regimens are used primarily used to cover *Pseudomonas* species. Piperacillin contains ampicillin plus a pharmaceutical agent that is active against *Pseudomonas* species, and it is currently marketed in the UK only in combination with tazobactum.

Comparison of different dosage regimens for gentamicin

The GDG considered that the RCTs comparing clinical outcomes associated with different gentamicin dosage regimens were insufficiently powered to draw clear conclusions about adverse effects. The group considered that it would be equally safe to give antibiotics every 24 or 48 hours (rather than every 12 hours) to allow time for the results of blood cultures to become available before deciding whether or not to continue antibiotic treatment. The group regarded the trough gentamicin concentrations reported in the pharmacokinetic studies as difficult to interpret because they might

have been measured too early. The GDG's view was that the interval between a first and second dose of gentamicin should be at least as long as it would take to obtain a definitive statement regarding the infection status of the baby to prevent unnecessary exposure to antibiotic treatment. The GDG considered that, in terms of early-onset neonatal infection, clinically important micro- organisms would be present (and detectable) by 24 hours at the latest. Adding a 12-hour safety margin, the GDG concluded that blood cultures should be made available to healthcare professionals within 36 hours of presentation to facilitate timely confirmation of infection, or to rule out infection in well babies and expedite their safe discharge from hospital. These issues were considered further in relation to the review question about optimal duration of antibiotic treatment (see Chapter 10).

Comparison of different dosage regimens for amikacin

In the RCT comparing different dosage regimens for amikacin, all babies in both treatment groups were cured and no babies developed renal or hearing impairment. The GDG considered that this study was too small to be used as the basis for a recommendation to give amikacin to babies with suspected early-onset neonatal infection. The group acknowledged, however, that amikacin might be an effective second-line treatment in near-term and term babies where use of gentamicin was not appropriate.

Benzylpenicillin pharmacokinetics

The GDG considered that the evidence from the two non-randomised studies that evaluated the pharmacokinetics of benzylpenicillin in preterm babies was of very low quality. Nevertheless, the GDG's view was that the studies demonstrated that a benzylpenicillin dosage of 25,000 IU/kg every 12 hours is safe and effective in such babies. No evidence was identified for benzylpenicillin pharmacokinetics in term babies.

Other considerations

The GDG considered whether cultural practices associated with particular ethnic groups might influence the incidence of specific early-onset neonatal bacterial infections. For example, the GDG discussed whether increased geographical mobility might increase the prevalence in England and Wales of culinary practices or dietary habits associated with listeriosis, which is caused by listeria (*L monocytogenes*). Antenatal care (NICE clinical guideline 62, 2008) highlights the risks to pregnant women, unborn babies and newborn babies associated with listeriosis, which can be caused by the consumption of unpasteurised milk, ripened soft cheese (such as Camembert, Brie and blue-veined cheese)and pâté. Although the GDG identified no evidence of an increased prevalence of listeriosis in the studies reviewed for the guideline, the GDG's view was that benzylpenicillin and amoxicillin are both suitable for the empirical treatment of suspected early-onset neonatal infection even when listeria is a potential pathogen. The GDG decided to recommend the use of benzylpenicillin plus gentamicin as empirical treatment for early-onset neonatal bacterial infections and not ampicillin plus gentamicin because benzylpenicillin has the advantage of being a narrow-spectrum antibiotic and provides cover for a high percentage of pathogens relevant to the UK, including GBS.

Furthermore, the recommendation to give benzylpenicillin plus gentamicin as empirical treatment for early-onset neonatal infection should not disadvantage any ethnic group in terms of access to appropriate antibiotic treatment. Should listeria be positively identified, however, the GDG recognised that a change of antibiotic regimen to include amoxicillin would be appropriate.

Key conclusions

The GDG considered that the evidence included in the guideline review for the antibiotic regimens involving ceftazidime, ticarcillin plus clavulanic acid, and piperacillin was not relevant to the UK setting and the group chose not make recommendations in relation to these antibiotics. The evidence relating to benzylpenicillin, ampicillin, gentamicin and amikacin was, however, considered to be relevant to clinical practice in the UK.

The GDG was aware that benzylpenicillin and gentamicin are the two most commonly prescribed drugs in UK neonatal units (Turner 2009; this comparison is with all drugs used in neonatal units, not just antibiotics). In terms of antibiotic treatment regimens for early-onset neonatal infection, the GDG identified the following as representing variations in current clinical practice in the UK:

- benzylpenicillin plus gentamicin

- ampicillin (or amoxicillin) plus gentamicin
- benzylpenicillin plus amoxicillin
- cefotaxime monotherapy
- ampicillin (or amoxicillin) plus cefotaxime
- co-amoxiclav monotherapy (amoxicillin plus clavulanic acid).

The GDG noted that ampicillin and amoxicillin have equivalent roles in each context, and that in certain settings an aminoglycoside other than gentamicin (for example amikacin) might be used. Based solely on the evidence identified for inclusion in the guideline, the GDG's initial view was that there was no reason to direct a change in practice away from the most commonly used antibiotic regimen of benzylpenicillin plus gentamicin. Despite the lack of RCT evidence identified in relation to antibiotic regimens involving amoxicillin, cefotaxime and co-amoxiclav, the GDG considered the potential advantages and disadvantages of each regimen in detail. Specific criteria were:

- the spectrum of antibiotic activity (narrow or broad, with broad-spectrum antibiotics being more likely to exert selective pressure on micro-organisms, thus promoting the development of antibiotic resistance)
- coverage against the most frequent causes of early-onset neonatal infection
- the need for therapeutic drug monitoring
- care setting
- cost
- adverse effects.

The GDG's conclusions in relation to each of these criteria are summarised in Table 9.15. The GDG's overall conclusion was that the combination of benzylpenicillin and gentamicin is the preferred empirical treatment for early-onset neonatal infection. First, the evidence from surveillance data and clinical practice indicates that this combination would successfully treat the vast majority of cases of early-onset neonatal infection. Second, this combination has the major advantage of having a narrow spectrum of activity. The GDG was aware that antibiotic resistance is not commonly induced with gentamicin use. With gentamicin there is a need for therapeutic drug monitoring. However, the dosage interval recommendation in this guideline (usually 36 hours) is such that in many cases only a single dose of gentamicin would be given. This would not only reduce overall antibiotic usage, but would in many cases mean that therapeutic monitoring need not be undertaken as the first monitoring sample would be taken prior to the second dose of gentamicin. Monitoring provides a means of reducing the risk of gentamicin toxicity. The GDG considered the possible concerns regarding an association between gentamicin and ototoxicity.

A prospective birth-cohort study estimated the prevalence of the m.1555A→G mutation to have a prevalence of 1 in 520 (or 0.19%; 95% confidence interval [CI], 0.10 to 0.28) in a population of babies born in 1991–1992 in the UK (Bitner-Glindzicz 2009). This mutation has been associated with a very high risk of deafness following gentamicin administration. The association between gentamicin and deafness may not be relevant to neonates because of pharmacokinetic and pharmacodynamic differences between neonates and older age groups. Gentamicin may not penetrate into the cochlea and the neonatal cochlea may use different metabolic pathways. In support of the suggestion that gentamicin does not pose a similar risk in neonates to older age groups is global experience with aminoglycosides in newborn babies. The GDG noted, however, that benzylpenicilin and gentamicin have been in widespread use in neonatal practice for many years, and very large numbers of babies receive gentamicin every year. Evidence that gentamicin may cause deafness when administered in the neonatal period was lacking. Screening for sensorineural deafness in preterm babies has indicated a very low incidence despite widespread gentamicin usage. Evidence in relation to therapeutic drug monitoring, and the GDG's recommendations on this topic, are presented in Chapter 11.

With respect to the dosage regimen for benzylpenicillin, the GDG noted that the dosages evaluated in the evidence were lower than those commonly used in clinical practice according to the GDG's experience. The GDG members noted further that there was a lack of evidence regarding the

elimination rate of benzylpenicillin in term babies, but based on their knowledge and experience the group believed that there was no risk of toxicity with benzylpenicillin for any baby even if the dosage were to be increased further, and this justified the GDG's recommendation for a more frequent dosing schedule in very ill babies. The evidence presented supports the GDG's position that the recommended dose is likely to be adequate for an uncomplicated septicaemia with a susceptible bacteria. Because the effectiveness of treatment for septicaemia is time dependent, in severe septicaemia increased frequency of antibiotic dosing will improve the antibiotic action. A larger dose of antibiotic might be considered when the infection involves a different compartment of the body (for example inside the blood-brain barrier, as in meningitis). The dosages recommended by the GDG are consistent with those in the summary of product characteristics (SPC; which includes a 'double dose' for babies with meningococcal meningitis). The GDG noted that the double dose is also used in clinical practice to treat GBS meningitis, the rationale being that the MIC for GBS is similar to, or possibly even higher than, that for meningococcus.

With respect to the dosage regimen for gentamicin, the GDG recommended an initial dose of 5 mg/kg to achieve a peak blood gentamicin concentration of 8 mg/l. The GDG's recommendations are strongly supported by evidence reviewed for the guideline showing that an initial dose of 4–5 mg/kg (and no further administration of gentamicin for 48 hours) is effective and safe, even in very low birthweight babies (600–1500 g).Considering the practicality of administering gentamicin (which is often associated with dosing errors in neonatal units), the GDG concluded that a pragmatic approach to the selection of the starting dose for gentamicin within the range 4–5 mg/kg would be 5 mg/kg, since this integer value would be less susceptible to errors when calculating the dose for an individual baby (based on the baby's weight). The GDG's recommendation is in accordance with the SPCs for gentamicin, which for newborn babies recommend 4–7 mg/kg/day administered in a single dose. However, the SPCs do not yet reflect the evidence reviewed for the guideline showing that the lower end of the dosage range recommended in the SPCs is to be preferred. The GDG also noted that current practice varies considerably. A recent survey of gentamicin dosage regimens and approaches to therapeutic monitoring for gentamicin used in 43 UK neonatal units (Kadambari 2011) showed that:

- 24 different combinations of dose, timing of dose and timing of monitoring are currently in use.
- Dosages as low as 2.5–3.5 mg/kg are used in some units, although the vast majority of units (approximately 90% in babies at 24–28 weeks' gestation, and an even higher proportion in babies at more than 28 weeks of gestation) use a dosage of 4.5–5 mg/kg.
- Dosage intervals vary considerably; for example, in babies at 28 weeks of gestation dosage intervals of 12, 18, 24, 36 and 48 hours were being used at the time of drafting this guideline.

Thus, the GDG's recommendations should reduce variations in practice while ensuring the effectiveness and safety of gentamicin dosage regimens for early-onset neonatal infection.

The GDG was aware of the need to document gentamicin administration and therapeutic drug monitoring in accordance with guidance issued by the National Patient Safety Agency (NPSA) in February 2010 on the safe use of gentamicin in neonatal services (see Safer use of intravenous gentamicin for neonates [PDF file]). The GDG believed that such documentation would facilitate decisions regarding any further doses of gentamicin to be given, any changes from empirical treatment to cover specific bacteria confirmed by blood or CSF cultures, and discharge of well babies from hospital. The GDG recognised that expert microbiological advice based on local surveillance data might also need to be considered as part of the decision to change antibiotic regimen. The justification for the GDG's recommended gentamicin dosing interval of 36 hours even in preterm babies (despite no direct evidence being available to support this) was that, on balance, the benefits of treatment would outweigh the risks of not treating. The GDG further recognised that babies with culture-proven Gram-negative infection or who appear to be very ill despite antibiotic treatment having started, would be exceptions to this rule, and that clinical judgment would be required to decide whether the baby needed a second dose of gentamicin before 36 hours had passed. In those babies for whom there is microbiological evidence of Gram-negative bacterial sepsis, this decision would also include whether there was a need to add to the antibiotic regimen an antibiotic providing cover for this pathogen (for example cefotaxime). The GDG's consensus was that if Gram-negative infection was

confirmed, benzylpenicillin should be stopped. The GDG also made a research recommendation to investigate optimal antibiotic dosage regimens and specifically prioritised preterm babies for consideration as part of this research.

In the GDG's view, the evidence included in the guideline review was from studies that were insufficiently powered to examine adverse events of antibiotic treatment, and no long-term outcomes were reported. The GDG therefore made a further research recommendation to address this. The GDG also noted that there was little evidence regarding the optimal antibiotic treatment cover for early-onset neonatal meningitis, and so the group recommended further research on this topic to include consideration of the choice of antibiotic regimen and the duration of antibiotic treatment.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

[‡‡]Benzylpenicillin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 50mg/kg/day in two divided doses in babies under 1 week of age. In babies aged 1–4 weeks the dosage should be increased to 75 mg/kg/day in three divided doses, as recommended in the summary of product characteristics.

[§§]Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

Research recommendations

Number	Research recommendation
	Antibiotics for suspected infection
RR 7	What is the incidence in England and Wales of resistance to commonly used antibiotics among bacteria that cause early-onset neonatal infection? Why this is important In developing the guideline recommendations the GDG referred to a number of recently published population-based surveillance studies conducted in the United Kingdom. These studies reported data on the incidence of early-onset neonatal infection, causative microorganisms, and the range of antibiotics used to treat infection. Further population-based surveillance studies are needed to identify the characteristics of bacteria that cause early-onset neonatal infection in England and Wales, including resistance to commonly used antibiotics. The studies should include consideration of invasive and non-invasive isolates from women giving birth and newborn babies.
RR 8	What is the optimal antibiotic treatment regimen for early-onset neonatal meningitis? Why this is important Further research is needed to identify the optimal antibiotic treatment regimen for early-onset neonatal meningitis. This is important because there is uncertainty about the most clinical and cost effective treatment regimen for this condition, which causes death is some babies, and serious illness and long-term disability in others. The research should be conducted using multinational randomised controlled trials and should include consideration of the choice of antibiotic and duration of treatment (course length).
RR 9	What is the optimal antibiotic dosage regimen for the treatment of early-onset neonatal infection? Why this is important Further research is needed to determine the optimal antibiotic dosage regimen for the treatment of early-onset neonatal infection. This is important because current dosage regimens do not take account of the unique physiology of newborn babies, especially preterm babies. The primary focus of the research should be antibiotic treatment using benzylpenicillin or other betalactam antibiotics (such as cefotaxime). The research should include studies involving population pharmacokinetic modelling and studies that relate pharmacokinetic parameters to clinical and microbiological outcomes.
RR 10	What is the incidence and severity of adverse effects with antibiotics used to prevent or treat early-onset neonatal infection? Why this is important Further research is needed to investigate the safety of antibiotics used to prevent or treat early-onset neonatal infection. This is important because the risks associated with gentamicin are thought to be low enough to justify using this treatment in newborn babies, but the risks have not been quantified, especially in preterm babies. Exposure to antibiotics early in life could have implications in later life, but

any risks associated with early exposure have not been quantified. Future research should consider adverse effects associated with the use of antibiotics in general (for example, the development of abnormal gut flora in the perinatal period and its consequences later in life), and adverse effects specific to particular antibiotics (for example, hearing loss and kidney dysfunction associated with the use of gentamicin). The research should include consideration of the incidence and severity of adverse effects and their relationships with gestational age and postnatal age.

RR 11

What are the core exposures and outcomes that should be used to evaluate clinical effectiveness of antibiotics to prevent or treat early-onset neonatal infection?

Why this is important

Research is needed to produce consensus definitions of the core exposures and outcomes that should be used as part of primary and secondary research studies (including quantitative meta-analysis) to evaluate the clinical effectiveness of antibiotics for the prevention or treatment of early-onset neonatal infection. This is important because the diverse definitions and combinations of exposures and outcomes examined in the evidence reviewed for the guideline resulted in imprecise and indirect estimates of effectiveness. Future research to agree consensus definitions should cover exposures such as maternal and fetal risk factors for early-onset neonatal infection, and core outcomes should place particular emphasis on patient-important outcomes.

10 Duration of antibiotic treatment

Introduction

The objectives of this review question are to determine the optimal duration (or course length) of antibiotics administered to babies for the prevention or treatment of early-onset neonatal infection. In prioritising this question for inclusion in the guideline the guideline development group (GDG) sought to distinguish between course lengths required for babies with confirmed early-onset neonatal infection (that is, where a bacterial cause of the infection has been identified), babies with presumed symptomatic infection but with no bacterial cause identified, babies with initial clinical suspicion of infection but no ongoing clinical concerns and all test results normal, and asymptomatic babies receiving antibiotic prophylaxis. Specific issues prioritised by the GDG for consideration in this question included: choice of antibiotics to provide empirical cover for Gram-positive and Gram- negative bacteria; choice of antibiotics to cover particular Gram-positive and Gram-negative bacteria once identified (for example listeria, methicillin-sensitive *Staph aureus* [MSSA] and methicillin- resistant *Staph aureus* [MRSA]); timing and route of administration; dosage; and potential differences in course length for systemic and localised (site-specific) infections, including meningitis (which usually requires a longer duration of treatment).

At this stage in the care pathway another important consideration is to identify in a timely manner those babies whose antibiotic treatment can safely be stopped. The timely halt of unnecessary antibiotics should reduce the use of healthcare resources, reduce pressure for antimicrobial resistance and demedicalise the postnatal period.

The considerations regarding inclusion of evidence obtained using particular study designs are similar to those in the review question relating to intrapartum antibiotics (see Chapter 6). For the evaluation of clinical outcomes (such as cure rate for early-onset neonatal infection) the GDG restricted consideration to evidence from randomised controlled trials (RCTs). For pharmacokinetic outcomes (for example incidence of therapeutic or toxic concentrations of a particular antibiotic) used to evaluate dosage regimens, the GDG restricted consideration to evidence from RCTs where such evidence was available. Other comparative or non-comparative pharmacokinetic and pharmacodynamic studies were considered only where no relevant evidence from RCTs was identified. The GDG drew initial conclusions about effectiveness based on clinical outcomes reported in RCTs and then reviewed pharmacokinetic outcomes only for those antibiotics that it was considering recommending. As noted in Chapter 6, the rationale for considering pharmacokinetic outcomes in this guideline is that few antibiotics are licensed for use in pregnancy or in preterm babies; the GDG prioritised consideration of safe and effective dosage regimens in all of the review questions relating to antibiotic treatment.

Review question

What is the optimal duration (or course length) of antibiotics for babies:

- with confirmed early-onset neonatal infection (bacterial cause identified)
- with presumed symptomatic infection but no bacterial cause identified
- with initial clinical suspicion of infection but no ongoing clinical concerns and all investigations normal
- asymptomatic babies receiving prophylactic treatment?

Existing NICE guidance

Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) includes recommendations for the duration of antibiotic treatment in children and young people younger than 16 years with suspected, confirmed and unconfirmed but clinically suspected bacterial meningitis and meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia). Babies who are already receiving care in neonatal units are excluded from the guideline. Recommendations relating to duration of antibiotic treatment for specific infections in confirmed bacterial meningitis include:

- Treat group B streptococcus (GBS) meningitis with intravenous cefotaxime for at least 14 days. If the clinical course is complicated consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.
- Treat bacterial meningitis due to listeria with intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first 7 days.
- Treat bacterial meningitis due to Gram-negative bacilli with intravenous cefotaxime for at least 21 days unless directed otherwise by the results of antibiotic susceptibilities. If the clinical course is complicated consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Recommendations relating to duration of antibiotic treatment for confirmed meningococcal disease include treating with intravenous ceftriaxone for 7 days in total unless directed otherwise by the results of antibiotic susceptibilities.

Recommendations relating to duration of antibiotic treatment for unconfirmed bacterial meningitis or meningococcal disease (that is, in children and young people for whom diagnostic test results are negative but clinical suspicion of bacterial meningitis or meningococcal disease remains) include the following.

- In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. If the clinical course is complicated, consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.
- In children and young people with unconfirmed but clinically suspected meningococcal disease, treat with intravenous ceftriaxone for 7 days in total.

Description of included studies

Three studies (all RCTs) were identified for inclusion through the searches conducted specifically for this review question (Engle 2000; Engle 2003; Stocker 2010).

Clinical outcomes reported in randomised controlled trials

The first study (Engle 2000) evaluated the effectiveness of a 4-day course of ampicillin plus gentamicin versus a 7-day course of the same antibiotics in babies receiving treatment for pneumonia that had developed within 75 hours of birth and in whom respiratory signs had resolved within 48 hours of starting antibiotic treatment (that is, randomisation to treatment groups occurred after antibiotic treatment had started). All the babies had received intramuscular benzylpenicillin within 1 hour of birth as part of routine practice to prevent GBS infection.

The second study (Engle 2003) evaluated the effectiveness of a 2-day course of antibiotics (probably ampicillin plus gentamicin, although the type of antibiotics administered was not reported explicitly) versus a 4-day course of the same antibiotics in babies receiving treatment for pneumonia that developed within 54 hours of birth and in whom respiratory signs had resolved within 36 hours of starting antibiotic treatment (again, randomisation to treatment groups occurred after antibiotic treatment had started). All the babies had received intramuscular benzylpenicillin within 1 hour of birth as part of routine practice to prevent GBS infection.

The third study (Stocker 2010) evaluated the effectiveness of procalcitonin-guided decision making relating to duration of empirical antibiotic treatment with ampicillin plus gentamicin in near-term or

term babies with suspected sepsis within 3 days of birth. Procalcitonin-guided decision making was compared with decision making based on conventional laboratory parameters (C-reactive protein [CRP] and ratio of immature to total neutrophils [I:T ratio]).

No therapeutic drug monitoring or individualised dosage adjustment for gentamicin was reported in any of the included studies.

Pharmacokinetic and pharmacodynamic studies

Based on the GDG's initial consideration of clinical outcomes reported in RCTs, the pharmacokinetics and pharmacodynamics of benzylpenicillin and gentamicin were prioritised for evaluation. No RCTs or other study designs reporting pharmacokinetic outcomes associated with benzylpenicillin or gentamicin treatment were identified for inclusion.

Investigations in babies receiving antibiotics

The searches conducted for the review questions covering investigations in babies starting antibiotic treatment (see Chapter 8) contributed further evidence relevant to determining the optimal duration of antibiotic treatment. Three diagnostic test accuracy studies reported CRP concentrations at various intervals after presentation (Benitz 1998; Berger 1995; Hofer 2011) and that evidence is also discussed in this chapter.

Evidence profiles

The evidence profiles for this review question are presented in Tables 10.1 to 10.5. Tables 10.1 and 10.2 contain evidence relating to fixed antibiotic course lengths (2, 4 or 7 days). Tables 10.3 and 10.4 contain evidence relating to CRP-guided decision making in relation to treatment duration. Table 10.5 contains evidence relating to procalcitonin-guided decision making in relation to treatment duration.

Table 10.1 Evidence profile for a 4-day course of ampicillin plus gentamicin versus a 7-day course in babies who developed pneumonia within 75 hours of birth and whose respiratory signs resolved within 48 hours of antibiotic treatment; all the babies had received intramuscular benzylpenicillin within 1 hour of birth as part of routine practice to prevent group B streptococcal infection

Number of studies	Number of babies		Effect		Quality
	4-day course of antibiotics	7-day course of antibiotics	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rate (%)					
1 (Engle 2000)	35	38	≥92% in both groups (NR)	NC	Low
Duration of hospital stay (mean and standard deviation in days)					
1 (Engle 2000)	35	38	6.0 (SD 1.3) versus 8.1 (SD 1.4) (NR) *P*<0.0001	2.1 days less (NR)	Low

NC not calculable, NR not reported, P probability, SD standard deviation

Table 10.2 Evidence profile for a 2-day course of antibiotics (probably ampicillin plus gentamicin) versus a 4-day course of the same antibiotics in babies who developed pneumonia within 54 hours of birth and whose respiratory signs resolved within 36 hours of antibiotic treatment; all the babies had received intramuscular benzylpenicillin within 1 hour of birth as part of routine practice to prevent group B streptococcal infection[a]

Number of studies	Number of babies		Effect		Quality
	2-day course of antibiotics	4-day course of antibiotics	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Relapse rate					
1 (Engle 2003)	3/14 (21%)	0/12 (0%)	RR 6.07 (0.34 to 106.85)*	203 more per 1000 (from 26 fewer to 4234 more)	Low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] The trial was stopped early (to avoid harm) because of the relapse rate in the 2-day treatment arm

Table 10.3 Evidence profile for C-reactive protein in babies receiving antibiotic treatment

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
CRP > 10 mg/l in the prediction of infection within 3 days of birth, using blood culture as reference standard						
1 (Berger 1995)	139	75	86	5	0.3	Low
CRP > 10 mg/l at 8–24 hours after presentation in the prediction of infection within the first 3 days of life						
Using proven sepsis as reference standard						
1 (Benitz 1998)	1002	79 (72 to 86)	78 (76 to 81)	4 (2 to 7)	0.3 (0.1 to 0.8)	High
Using either proven or probable sepsis as reference standard						
1 (Benitz 1998)	1002	93 (88 to 98)	84 (82 to 86)	6 (4 to 8)	0.1 (0.05 to 0.2)	High
CRP > 10 mg/l at any of the next two mornings after presentation in the prediction of infection within the first 3 days of life						
Using proven sepsis as reference standard						
1 (Benitz 1998)	1002	89 (81 to 94)	74 (71 to 77)	3 (2 to 7)	0.2 (0.04 to 0.6)	High
Using either proven or probable sepsis as reference standard						
1 (Benitz 1998)	1002	98 (96 to 99)	79 (77 to 82)	5 (3 to 7)	0.03 (0.008 to 0.1)	High

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
CRP > 10 mg/l at any three readings in the prediction of infection within the first 3 days of life						
Using proven sepsis as reference standard						
1 (Benitz 1998)	1002	89 (81 to 94)	71 (68 to 73)	3 (2 to 6)	0.2 (0.04 to 0.6)	High
Using either proven or probable sepsis as reference standard						
1 (Benitz 1998)	1002	98 (96 to 99)	76 (74 to 79)	4 (3 to 6)	0.03 (0.008 to 0.1)	High

CRP C-reactive protein

Table 10.4 Evidence profile for C-reactive protein in babies hospitalised within the first 72 hours of life

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
CRP > 8 mg/l in the prediction of sepsis within first 72 hours of life in all neonates, using clinical finding of suspected sepsis and positive culture as reference standard						
1 (Hofer 2011)	532	67 (48 to 82)	88 (85 to 91)	NC	NC	Low
CRP > 8 mg/l in the prediction of sepsis within first 72 hours of life in preterm neonates, using clinical finding of suspected sepsis and positive culture as reference standard						
1 (Hofer 2011)	179	53 (29 to 76)	NC	4.6 (3.2 to 6.6)	NC	Low
CRP > 8 mg/l in the prediction of sepsis within first 72 hours of life in term neonates, using clinical finding of suspected sepsis and positive culture as reference standard						
1 (Hofer 2011)	353	86 (57 to 98)	NC	6.1 (3.8 to 9.7)	NC	Low
CRP > 5.5 mg/l in the prediction of sepsis in preterm neonates within first 72 hours of life, using clinical finding of suspected sepsis and positive culture as reference standard						
1 (Hofer 2011)	179	74	86	NC	NC	Very low
CRP > 10.5 mg/l in the prediction of sepsis in term neonates within first 72 hours of life, using clinical finding of suspected sepsis and positive culture as reference standard						
1 (Hofer 2011)	353	86	84	NC	NC	Very low

CRP C-reactive protein, NC not calculable

Table 10.5 Evidence profile for procalcitonin-guided decision making in relation to duration of empirical treatment with ampicillin plus gentamicin in babies with suspected sepsis in the first 3 days of life versus decision making based on conventional laboratory parameters (immature:total (I:T) neutrophil ratio > 0.2 and C-reactive protein > 5 mg/l)

Number of studies	Number of babies		Effect		Quality
	Procalcitonin-guided decision making	Decision making using conventional laboratory parameters	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Duration of antibiotic treatment in hours (all babies)					
1 (Stocker 2010)	60	61	79.1 versus 101.5 (NR) *P*= 0.012	22.4 hours less (NR)	Low
Duration of antibiotic treatment in hours (babies with proven or probable infection)					
1 (Stocker 2010)	9	12	177.8 versus 170.8 (NR) *P*=0.504	7 hours more (NR)	Low
Duration of antibiotic treatment in hours (babies with possible infection)					
1 (Stocker 2010)	21	19	83.4 versus 111.5 (NR) *P*<0.001	28.4 hours less (NR)	Low
Duration of antibiotic treatment in hours (babies with infection unlikely)					
1 (Stocker 2010)	30	30	46.5 versus 67.4 (NR) *P* =0.001	20.9 hours less (NR)	Low

NR not reported, P probability

Evidence statements

In babies who developed pneumonia within 75 hours of birth and whose respiratory signs had resolved within 48 hours of antibiotic treatment there was no difference in cure rate between 4- and 7- day courses of ampicillin plus gentamicin, but duration of hospital stay was shorter in babies who received antibiotics for 4 days (low quality evidence).

In babies who developed pneumonia within 54 hours of birth and whose respiratory signs had resolved within 36 hours of antibiotic treatment there was a higher relapse rate among babies who received a 2-day course of antibiotics (probably ampicillin plus gentamicin) compared with those who received a 4-day course of the same antibiotics. Although the difference was not statistically significant, the trial was stopped early to avoid harm because of the relapse rate in the 2-day treatment arm (low quality evidence).

Measurement of CRP concentrations in babies receiving antibiotics is a very useful test for ruling out early-onset neonatal infection, particularly when serial testing is performed over a period of 2 days following presentation (low to high quality evidence).

Duration of empirical antibiotic treatment with ampicillin plus gentamicin decreased when decisions are based on serial procalcitonin measurements (rather than CRP concentration or I:T ratio) in babies with unlikely or possible infection within 3 days of life, but not in babies with probable or proven infection (low quality evidence).

Health economics profile

Although the clinical evidence did not demonstrate an optimal course length for suspected early-onset neonatal infection, the GDG's view was that the current practice of giving all babies in whom there has been a suspicion of infection a full course (up to 5 days) of antibiotics was unlikely to be a good use of resources. Better diagnosis could reduce the number of babies treated unnecessarily and identify babies who are clinically well after a period of less than 5 days and who no longer need antibiotics and can be discharged from hospital.

Using the review of clinical evidence relating to diagnostic tests in babies with suspected early-onset neonatal infection, the best schedule of tests was determined to be a CRP concentration measured at 8–16 hours after presentation and again with an interval of 18–24 hours between the two samples. If a baby has two negative test results (CRP < 10mg/l), is well and the results of the blood culture are negative (taken at presentation for all babies with suspected sepsis), then antibiotics can be stopped and the baby can be discharged from hospital. Blood culture results should, therefore, be made available within 36 hours to facilitate prompt discharge.

It was also suggested that two CRP tests could be performed more efficiently if the first was at presentation and the second at 24 hours after presentation. As a full blood count is performed at presentation for all babies with suspected sepsis, performing the CRP test at presentation at the same time would reduce workload, and be preferable for parents and carers because blood samples would be taken from the baby twice rather than three times. The sensitivity and specificity of this strategy was calculated using data from Benitz 1998. The serum CRP levels were taken at the initial evaluation and with at least 8 hours between the first two measurements. For this analysis, these results were assumed to approximate to a CRP test at presentation and then again at 24 hours. As Benitz 1998 reported the diagnostic accuracy parameters for a delayed CRP test alone (taken here to represent a test at 24 hours), the strategy of testing at presentation and 24 hours but only using the 24 hour test results for diagnosis was also considered.

Four strategies were considered by the GDG:

- Strategy 1 – CRP is measured three times within the first 3 days. For babies with three negative test results (CRP less than 10 mg/l) and who are considered well by clinicians, antibiotic treatment stops at 3 days and the baby is discharged home. For babies with a positive test result at any of the three tests treatment continues.
- Strategy 2 – CRP measured at 8–16 hours after presentation and again with an interval of 18–24 hours between the two samples. For babies with two negative test results and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test result at either of the two tests treatment continues.
- Strategy 3 – CRP is measured at presentation and again at 24 hours. For babies with two negative test results and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test result at either time treatment continues.
- Strategy 4 – CRP is measured at presentation and again at 24 hours. Only the test result at 24 hours is used for diagnosis, with the test result at presentation used only for comparison. For babies with a negative test result at 24 hours and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test result at 24 hours treatment continues.

For babies who are started on antibiotics immediately because of suspected sepsis, timely and accurate diagnostic tests will identify babies with a true infection for whom treatment should continue and those without an infection for whom treatment should stop. The proportion of babies who are screened for an infection is approximately 10–12% (Bedford Russell 2010). In 2009 (the latest year for which data are available) there were 706,248 live births in England and Wales (Office for National Statistics [ONS] 2010). Using these figures, the number of babies who would be suspected of having sepsis would be 70,625 and only 1002 babies would be expected to have a true infection. More timely diagnosis would allow antibiotics to be stopped promptly in babies who do not have an infection.

Testing only twice and giving 36 hours of antibiotics is cost saving compared to testing three times over 3 days and giving 3 days of antibiotics (strategy 1). As strategy 2 (two CRP tests over two consecutive mornings with 36 hours of antibiotics) is less expensive and more effective than strategy 1 then strategy 1 is said to be dominated and is, therefore, ruled out.

Strategy 3 (CRP tests at presentation and 24 hours with 36 hours of antibiotics) has the fewest quality adjusted life years (QALYs). This strategy has the lowest sensitivity, and so the highest rate of false negative tests. Strategy 4 (CRP tests at presentation and at 24 hours, with only the 24-hour result used for diagnosis, and 36 hours of antibiotics) was slightly more effective and was less expensive than strategy 3. Therefore strategy 3 is dominated by strategy 4.

The comparators left were, therefore, strategy 4 and strategy 2. The incremental cost effectiveness ratio (ICER) of strategy 4 compared to strategy 2 was £1,324,094 per QALY gained. This is much higher than the NICE threshold of £20,000 per QALY and so strategy 2 is not considered cost effective. Strategy 4 had the highest net benefit using the NICE willingness to pay per QALY of £20,000. Therefore the additional cost of performing the CRP tests on subsequent mornings rather than at presentation and at 24hours is not considered to be worth the additional benefit.

The test at 24 hours is likely to have the most diagnostic value and the results of the analysis conducted for the guideline suggest that this test alone can be used for diagnosis. Although the health benefits of strategy 3 and strategy 4 are very similar, the additional cost related to using both test results to diagnose infection suggests that only using the 24-hour test for diagnosis would be cost saving. The full report of this analysis is in Chapter 13.

Local protocols specifying how to treat babies with suspected infection vary nationally; babies are typically kept in hospital for 2–5 days for antibiotic treatment when infection is suspected. The two test strategies with 36 hours of antibiotics rely on all necessary test results being made available within 36 hours, and some hospitals may not have resources to achieve this. Making test results available within the 36-hour timescale may require capital investment and further resources to support pathology services. Cost savings associated with implementing the first strategy will, therefore, vary between hospitals.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered that the following clinical outcomes were important when comparing antibiotic treatment regimens:

- cure rates for neonatal infection
- mortality
- duration of hospital stay
- neonatal adverse events
- long-term outcomes
- resistance among neonatal flora.

The priority outcome for the GDG was cure rate because it was most likely to be directly related to the effect of antibiotic treatment. The GDG believed other clinical outcomes might be more subject to the influence of other factors (for example, many factors might influence mortality and duration of hospital stay might depend in part on local policy).

Consideration of clinical benefits and harms

Specifying the optimal duration of antibiotic treatment will ensure that the bacteria causing an infection have been eliminated. Stopping antibiotic treatment too early (when there is still clinical evidence of infection) can be very harmful for the baby and could lead to a relapse of the disease. However, continuing unnecessary antibiotic treatment may influence the development of the gastrointestinal tract and immune system and promote selection of antibiotic-resistant micro-organisms. In this review

question the GDG aimed to limit any negative effects of a longer duration of antibiotic treatment without compromising cure rates for early-onset neonatal infection.

Consideration of net health benefits and resource use

Duration of antibiotic treatment can have an important impact on the use of healthcare resources. The possibility of stopping antibiotic treatment promptly in babies who do not have an infection would lead to a shorter hospital stay for the baby, freeing up resources for other uses. Moreover, shorter exposure to antibiotics might minimise potential short- and long-term adverse effects of antibiotics on the baby's developing immune system and intestinal flora, and the broader risk of promoting antibiotic resistance.

The CRP testing strategy of a test at presentation and another test 24 hours later was found to be most cost effective in the health economic analysis (see Chapter 13). Although the strategy of two CRP tests on consecutive mornings after presentation had the highest diagnostic value, the incremental benefit was not considered to be good value compared to a test at presentation and another after 24 hours. This strategy will mean babies need to have only two blood tests (rather than three) because the CRP test will be performed at the same time as the blood culture undertaken at presentation. This would be a more efficient use of resources as well as being preferable for parents and carers.

The health benefits of the two strategies giving one test at presentation and another after 24 hours were very similar. The additional cost of using both test results for diagnosis was greater than using only the test at 24 hours for diagnosis. This was because the specificity was lower when using both test results for diagnosis and so fewer babies without an infection would have a negative result and, therefore, be treated unnecessarily. The test at presentation is still considered important as it may prompt a healthcare professional to perform a lumbar puncture for diagnosis of meningitis. Although the GDG's decision to recommend a CRP test at presentation was prompted by the health economic analysis presented in this chapter, the recommendation itself appears in Chapter 8, alongside other tests to be performed at presentation. The recommendation to perform a CRP test at 18–24 hours after presentation is presented in this chapter.

Quality of evidence

Two studies were identified relating to babies with initial clinical suspicion of infection who after 48 hours had no ongoing clinical concerns of infection and the results of all investigations were normal. Both studies evaluated the effectiveness of antibiotics (assumed to be ampicillin plus gentamicin in both studies) given for a specified duration (2 days, 4 days or 7 days) in babies who developed pneumonia within hours of birth (75 hours in one study and 54 hours in the other). Neither study design was ideally suited to answer the GDG's review question for this group of babies because randomisation to treatment duration occurred part way through the course of antibiotics (after respiratory symptoms had resolved). Thus, both studies investigated how long to continue antibiotics once infection had resolved and clinical management was guided partly by resolution of symptoms and signs, and partly by default course lengths. All the babies had received intramuscular benzylpenicillin within 1 hour of birth as part of routine practice to prevent GBS infection which, the GDG highlighted, is not usual practice in the UK. A shorter duration of hospital stay in babies who received a 4-day course of ampicillin plus gentamicin (compared to a 7-day course) is unsurprising. Both studies contributed evidence of low quality and in the absence of clear evidence to direct clinical practice the GDG formulated consensus recommendations regarding default course lengths in babies receiving antibiotics for early-onset neonatal infection (see below).The absence of direct evidence to inform the GDG's recommendations on default course lengths for confirmed early-onset neonatal infection also led the group to recommend further research in this area.

Three diagnostic test accuracy studies identified in relation to the review question covering investigations in babies starting antibiotic treatment (see Chapter 8) contributed evidence of very low to high quality that was relevant to determining the optimal duration of antibiotic treatment. In Chapter 8, the GDG's recommendations focused on whether to give antibiotics to the baby, whereas this review question focuses on when to stop antibiotics in babies for whom the need for antibiotic treatment has been confirmed. All three studies from Chapter 8 that were considered in this chapter reported CRP concentrations at various intervals after presentation. High-quality evidence from one

particular study that reported diagnostic test accuracy measures for serial measurements of CRP concentration at various intervals after presentation was used as the basis for a health economic analysis (see below).

A further study involving babies with presumed symptomatic infection but no bacterial cause identified and babies with confirmed early-onset neonatal infection was identified. This was a pilot study to evaluate the effectiveness of serial procalcitonin measurements in guiding the duration of antibiotic treatment, especially in those babies in whom infection was unlikely and therefore antibiotic treatment could safely be stopped. The quality of evidence in this study was low and the technique is not widely used in the UK. The study reported duration of treatment only, not clinical outcomes of treatment. Clinical outcomes of treatment would be of particular interest in babies in whom infection is unlikely (because of potential adverse effects on the developing immune system and gut flora). Throughout the guideline, the GDG has emphasised the importance of minimising the use of antibiotics in such babies. Moreover, the evidence reviewed in relation to investigations to be performed before starting antibiotics did not support the use of procalcitonin at presentation (see Chapter 8). The GDG did not, therefore, recommend using procalcitonin measurements during antibiotic treatment to guide the duration of treatment, but the group highlighted the need for further research in this area. The GDG was aware that, at the time this guideline was being written, a large RCT designed to evaluate clinical outcomes was being conducted by the same research group that conducted the pilot study reviewed for the guideline.

Other considerations

No specific equalities issues were identified in relation to this review question.

Key conclusions

Due to the lack of high-quality evidence regarding the optimal course length for antibiotic treatment for early-onset neonatal infection the GDG members used their knowledge and experience to formulate recommendations, emphasising that it is important to minimise exposure to antibiotics in babies who do not need them to avoid undesired side effects.

Investigations during antibiotic treatment and decisions 36 hours after starting antibiotic treatment

The view of the GDG was that stopping antibiotics in babies initially suspected of having an early- onset neonatal infection and who are considered to be well would reduce unnecessary exposure to antibiotics in babies who do not have an infection and reduce the duration of hospital stay. This would represent a change in practice that would have a positive impact on the baby's family and result in decreased use of healthcare resources. A health economic model conducted for the guideline demonstrated that the most cost-effective schedule of tests in babies receiving antibiotics for suspected early-onset neonatal infection is to measure the CRP concentration at presentation and again with an interval of 24 hours between the two measurements. This schedule is reflected in the GDG's recommendations for investigations during antibiotic treatment.

Babies who have negative blood culture results no longer need antibiotics. However, the GDG agreed that before stopping antibiotics healthcare professionals should consider how strong the initial suspicion of infection was and whether there were any clinical indicators of infection. The only marker of inflammation recommended by the GDG is CRP concentration, and it was agreed that compared to the baseline measurement value (at presentation), a measurement taken at 18–24 hours that was improving towards the normal range was reassuring and should also be considered as part of the decision to stop treatment at 36 hours. The GDG also noted that good clinical practice would be to take account of the nature of a positive blood culture. If the blood culture shows a mixed growth, or if there is a strong suspicion of contamination, antibiotics can be stopped after 36 hours.

Since the health economic analysis conducted for the guideline showed that stopping antibiotic treatment at 36 hours in the babies listed above will be cost saving, and one of the criteria for stopping treatment depends on the result of blood culture, the cost savings can be realised only if the blood culture results are available within 36 hours. Thus, the GDG emphasised that hospitals should have systems in place to make blood culture results available to healthcare professionals within 36 hours of presentation because this will facilitate timely decisions about stopping antibiotics in well

babies and discharging them from hospital (see Chapter 8). The availability of such systems would support: cost savings; minimisation of exposure to antibiotics; demedicalisation of neonatal care; and shorter durations of hospital stay. The GDG also agreed on the importance of healthcare professionals having access every day to advice from clinical microbiologists or paediatric infectious disease specialists with specific experience in neonatal infection.

The GDG recommended that a lumbar puncture be considered in a baby who is receiving antibiotics if any of the following criteria are met:

- CRP concentration of 10 mg/l or more
- a positive blood culture
- the baby is not responding satisfactorily to antibiotic treatment.

This recommendation arose from the GDG's consideration of the evidence for investigations before starting antibiotic treatment (see Chapter 8, which also includes a recommendation for a lumbar puncture to be performed before starting antibiotic treatment in babies for whom there is a strong clinical suspicion of infection or the baby has clinical signs suggesting meningitis). The GDG considered that both clinical signs and laboratory investigations without lumbar puncture sampling had poor sensitivity for meningitis in this age group. The group acknowledged that it would not always be possible to have blood culture results available before deciding to perform the lumbar puncture. Nonetheless, the GDG agreed that the harm associated with unnecessary lumbar punctures did not outweigh the harms of missing cases of meningitis, nor the benefits of prompt intervention for this condition.

Early-onset neonatal infection without meningitis

In babies with a strong initial clinical suspicion of infection the GDG recommended a default course length of 7 days. Such babies may be clinically well but have risk factors for early-onset neonatal infection, or they may have clinical indicators of possible infection. The GDG considered that for babies in whom there is still clinical concern of infection at 7 days, consideration should be given to continuing antibiotic treatment. The GDG also agreed that laboratory evidence (a positive blood culture) of a pathogen requiring a longer duration of treatment might trigger extension of antibiotic treatment beyond 7 days, but that expert microbiological advice should be sought as necessary when making a decision.

The GDG considered that those babies who, despite a negative blood culture result, continue to receive treatment beyond 36 hours should be reviewed every 24 hours and the decision to stop treatment should be based on the strength of the initial suspicion of infection, the levels and trends of CRP concentration (measured at presentation and at 18–24 hours later) and would be additionally informed by the babies' clinical progress and current condition and by any further CRP results. However, the GDG did not recommend routine measurements of CRP concentration beyond 24 hours. This was because the review of the clinical evidence and the health economic analysis did not cover the timeframe beyond 36 hours. The GDG also noted the associated harms to the baby of additional venepunctures for CRP testing would need to be considered. The GDG recognised, however, that in some units it may be routine practice to measure the CRP concentration at intervals beyond 24 hours in babies in whom there is ongoing clinical concern. If this was done, healthcare professionals would take account of the results from such additional measurements.

Meningitis (babies in neonatal units)

The GDG's view was that in babies in whom meningitis is suspected (for example because the CSF white cell count is elevated) but the causative pathogen cannot be identified because the Gram stain is uninformative, healthcare professionals should provide antibiotic treatment that covers both Gram-negative and Gram-positive pathogens using amoxicillin and cefotaxime. The GDG emphasised that a normal CRP concentration does not exclude bacterial meningitis. The GDG also noted that reference levels (thresholds) for neonates are different to those in older babies and concluded that healthcare professionals should use the CSF glucose or protein thresholds already recommended in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) for neonates who are not already in a neonatal care unit. The GDG agreed that in babies in whom Gram-negative infection has been proven by CSF Gram stain or by CSF culture, cefotaxime should be used alone for

treatment. This may require a change in treatment if a different pathogen had been suspected previously.

The GDG agreed that in babies in whom the CSF culture confirms GBS meningitis, treatment should be continued with benzylpenicillin for at least 14 days and gentamicin for 5 days. The GDG noted that this may require a change in treatment if a different pathogen had been suspected previously.

The GDG noted that combining benzylpenicillin and gentamicin has a synergistic bactericidal effect. This is most beneficial in the early stages of treatment (the first 5 days) and lessens afterwards because gentamicin does not penetrate the CSF as effectively as benzylpenicillin and it is, therefore, less active against bacteria in the central nervous system. After 5 days the beneficial effect of combining gentamicin with benzylpenicillin becomes less relevant because of the toxic effects produced by prolonged exposure to gentamicin. Toxicity associated with gentamicin use is similar to the long-term sequelae of meningitis itself (for example hearing loss) and so the GDG sought to limit the duration of gentamicin use to 5 days to reduce the risk of such effects.

The GDG recognised that the recommendation for GBS meningitis in this guideline is different to that in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010), which recommends intravenous cefotaxime for at least 14 days for babies in the first 3 months of life. The GDG was aware of the more intense selection pressures for the development of resistant bacteria in hospital settings compared to the community settings that are the focus of Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010). In neonatal units narrow-spectrum antibiotics, such as benzylpenicillin combined with gentamicin, are preferred to cefotaxime (Muller-Pebody 2011; Vergnano 2011).

The risks of disrupting the development of gut flora in newborn babies were also considered by the GDG. The evidence reviewed for Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) provided no support for directing the choice of antibiotics to target GBS (benzylpenicillin with or without an aminoglycoside, ampicillin with or without an aminoglycoside, or cefotaxime). The first 72 hours of life are different to the first 3 months of life in terms of the baby's physiology and immune system, and the GDG emphasised that benzylpenicillin is a narrow-spectrum antibiotic that provides adequate cover for all strains of GBS (Muller-Pebody 2011; Vergnano 2001).

With regard to the default course length for antibiotic treatment in babies with meningitis, the GDG considered recommending a course length of 10 or 14 days. An argument in support of a 10-day course is that this would be adequate for GBS meningitis, especially as the aim is to give gentamicin for no longer than absolutely necessary. Counterarguments in favour of a 14-day course for the babies covered by the scope of this guideline are that:

- these babies are more vulnerable to infection (because of the immaturity of their immune systems) than are babies who are not already receiving care in a neonatal unit and who are covered by Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010)
- the small numbers of babies affected (approximately 120 GBS meningitis cases in the first 3 months of life per year, two-thirds of which correspond to late-onset disease)
- the possibility of relapse (this occurs in 5–10% of cases);there is a lack of evidence to evaluate whether a shorter course length is associated with an increased risk of relapse, suggesting that babies with confirmed meningitis need a 'complete' course of antibiotic treatment
- the severity of illness (there is significant mortality and, as described above, long-term sequelae, such as hearing loss, are associated with meningitis)
- the benzylpenicillin dosage recommended in the SPC is higher for babies with meningitis (double the standard dosage of 25 mg/kg every 12 hours)
- parents might prefer to err on side of caution and, therefore, prefer a course length of 14 days.

The GDG concluded that a default course length of 14 days should be recommended, although the group recognised that a shorter course length may be appropriate for some babies. In reaching this

conclusion the GDG highlighted that a 14-day course length ensures consistency with the recommended course length for neonatal meningitis in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102). In neonates with meningitis the GDG recognised that it is common practice to treat for at least 10 days in cases of GBS infection (the most common causative organism) and 14 days in cases caused by any other micro-organism. The GDG recommended that antibiotic treatment be continued beyond 14 days if the baby remains unwell. The GDG also noted that it is not routine practice to repeat lumbar puncture, but this may be helpful if the baby's condition is not improving.

Discharge after antibiotic treatment

The GDG considered the time at which babies who have received antibiotics because of suspected early-onset neonatal infection can be safely discharged from hospital. In particular, the GDG considered whether babies who have received antibiotics should be observed in hospital for a period of time before going home. The GDG considered that relapse, if it occurred at all, would happen after 24 hours, and so the baby could go home after this time provided the parents or carers have adequate support and a contact point through which to seek help and advice. The GDG's discussions focused on the following groups of babies and potential differences between groups in the need for observation after stopping antibiotic treatment:

- babies who are clinically well and in whom the results of investigations are normal at 36 hours after starting antibiotic treatment
- babies who have had a relatively uncomplicated course of treatment, are clinically well, have a CRP concentration heading in the right direction, and may or may not have had a lumbar puncture performed
- babies who have continued antibiotic treatment for more than the default course length of 7 days (14 days in the case of babies with meningitis).

The GDG concluded that babies in all three groups could be discharged from hospital with support immediately after stopping antibiotic treatment.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

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[***]Benzylpenicillin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 100 mg/kg/day in two divided doses in babies under 1 week of age. In babies aged 1–4 weeks the dosage should be increased to 150 mg/kg/day in three divided doses, as recommended in the summary of product characteristics.
[†††]Gentamicin is licensed for use in newborn babies. The summary of product characteristics recommends a dosage of 4–7 mg/kg/day administered in a single dose. The evidence reviewed for the guideline supports a starting dosage of 5 mg/kg every 36 hours administered in a single dose.

Research recommendations

Number	Research recommendations

Duration of antibiotic treatment

RR 12 What is the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early-onset neonatal infection in babies receiving antibiotics for suspected infection?

Why this is important

The systematic reviews conducted for the guideline identified limited evidence relating to investigations used to guide the decision to stop antibiotic treatment in babies receiving antibiotics for suspected early-onset neonatal infection. One study evaluated procalcitonin-guided decision making for identifying babies in whom antibiotic treatment could safely be stopped, but the approach used was at an early stage of development and had not been evaluated fully.

The guideline recommendations reflected uncertainty about the diagnostic test accuracy of laboratory investigations used individually or in combination, and further research involving sufficiently powered studies is needed to evaluate this. The ideal study design would be a randomised controlled trial that compares clinical outcomes associated with particular investigation and treatment termination strategies. The next best design would be a prospective cohort study to determine the diagnostic test accuracy of an investigation strategy evaluated in a clinically relevant group of babies. The research should examine clinical effectiveness or diagnostic test accuracy in preterm and term babies separately.

RR 13 What is the optimal duration of treatment (course length) in babies who receive antibiotics for confirmed early-onset neonatal infection?

Why this is important

The Guideline Development Group identified no evidence to inform the choice of duration of antibiotic treatment (course length) for confirmed early-onset neonatal infection. In the absence of evidence, the Guideline Development Group based its recommendations on its knowledge of current clinical practice. Further research is needed to evaluate different course lengths in the following clinical circumstances:

- babies with group B streptococcal bacterial meningitis
- babies with group B streptococcal septicaemia
- babies with Gram-negative bacterial meningitis (such as *Escherichia coli* meningitis)
- babies with Gram-negative septicaemia.

The research should ideally take the form of multinational randomised controlled trials. The primary outcome should be relapse within 10 days of stopping treatment. Secondary outcomes should include long-term neurodevelopment.

11 Therapeutic drug monitoring for gentamicin

Introduction

The preceding review questions relating to antibiotic treatment (see Chapters 6, 7, 9 and 10) focus on whether particular antibiotics (or classes of antibiotics) are effective and safe in a general sense (that is, in a population of babies receiving antibiotics) and, if so, which dosage regimen is to be preferred. This review question focuses on ensuring effectiveness and safety in individual babies receiving gentamicin. These are important considerations because the effects of gentamicin are concentration-dependent (rather than time-dependent). Too low a peak concentration will be ineffective against the bacteria that the antibiotic is intended to target (see, for example, Touw 2009). Gentamicin has a post-antibiotic effect, whereby a dosage regimen in which a sufficiently high peak serum gentamicin concentration is followed by a period of low serum gentamicin concentrations will be effective. In contrast, adverse effects of gentamicin (particularly in relation to kidney function and hearing) are more closely related to the total amount of the drug in the circulation (as measured by the area under the concentration:time curve). Thus, adjusting the dosage interval provides a means of ensuring sufficiently low trough serum gentamicin concentrations and, therefore, the safety of the dosage regimen (see Touw 2009). Clinically important variability in gentamicin pharmacokinetics occurs even in babies of the same gestational age and postnatal age, and further variability occurs between babies with and without infection; these sources of variability necessitate individualisation of dosage regimens during gentamicin treatment to ensure effectiveness and safety.

Individualising gentamicin dosage regimens involves therapeutic drug monitoring (that is, measuring serum gentamicin concentrations or other parameters linked to the distribution of gentamicin in the body), comparing observed concentrations with target concentrations, and (where necessary) adjusting gentamicin doses or dosing intervals to ensure differences between observed and target concentrations are sufficiently small.

The specific objectives of this review question are to determine which parameters should be monitored (for example peak or trough serum gentamicin concentrations or creatinine clearance) and to identify an effective schedule for monitoring. The question is restricted to consideration of studies focusing specifically on how to perform therapeutic drug monitoring (what to measure and when) and what clinical actions to take based on the results of monitoring. Studies that compare different 'packages' of care, each involving a particular antibiotic drug regimen plus an associated approach to therapeutic drug monitoring, are considered separately under the other review questions relating to antibiotic treatment.

The primary outcome measures for comparing different therapeutic drug monitoring strategies should be clinical outcomes, including clinical cure rate (as in the other antibiotic treatment questions), and incidence of medium- or long-term adverse effects of gentamicin (deafness or kidney dysfunction). The review protocol for this question allowed for consideration of secondary outcomes, including pharmacokinetic and pharmacodynamic parameters (such as time to effective concentration and incidence of toxic concentrations in the blood or urine), and factors associated with the logistics of particular monitoring schedules (such as the number of blood samples collected and the number of doses of gentamicin administered). The guideline development group's (GDG's) view was that preterm birth was likely to be an important consideration in this review question because gentamicin pharmacokinetics are affected by gestational age in addition to postnatal age. Studies of any design were considered for this question.

The review question is restricted to consideration of gentamicin to cover the GDG's recommendations to offer benzylpenicillin plus gentamicin to babies with suspected early-onset neonatal infection (see

Chapter 9). Had the GDG's consideration of the evidence reviewed for the other antibiotic treatment questions led it to recommend the use of other aminoglycosides (such as amikacin) or glycopeptides (such as vancomycin) then this review question would have needed to cover those antibiotics too, whereas therapeutic drug monitoring is not needed for penicillins or cephalosporins (because the risk of adverse effects with these classes of antibiotics is small).

Review question

What is the optimal drug monitoring strategy to achieve effective and safe antibiotic concentrations of gentamicin in the blood in babies with early-onset neonatal infection?

Existing NICE guidance

No relevant NICE guidance was identified for this review question. The GDG is aware, however, of the risk of errors in the prescribing, preparation and administration of gentamicin in neonatal services and of the associated guidance issued by the NPSA in February 2010 on the safe use of gentamicin in neonatal services (see Safer use of intravenous gentamicin for neonates [PDF file]). The NPSA guidance specifies that all NHS organisations responsible for provision of neonatal services should ensure that by 9 February 2011 a local neonatal gentamicin protocol is available (clarifying the initial dose and frequency of administration, blood level monitoring requirements and arrangements for subsequent dosing adjustments based on blood levels) and that local policies and procedures should be developed or revised to state that intravenous gentamicin should be administered to neonates using a 'care bundle' incorporating the following elements:

- When prescribing gentamicin the 24-hour clock format should be used and unused time slots in the prescription administration record should be blocked out at the time of prescribing to prevent errors in the timing of administration.
- Interruptions during preparation and administration of gentamicin should be minimised by the wearing of a disposable coloured apron indicating that staff should not be disturbed.
- Double-checking should be performed during preparation and administration of gentamicin (the NPSA guidance includes a checklist to support this).
- The prescribed dose of gentamicin should be given within 1 hour of the prescribed time.

The guidance also states that neonatal units should implement the care bundle using small cycles of change with a sample group of patients, that compliance with the care bundle should be measured daily for each patient in the sample group until full compliance for all patients receiving gentamicin is achieved, and that all staff involved in prescribing and administration of intravenous gentamicin should receive training relating to its use (training should include interpretation and management of gentamicin blood levels and actions to be taken in relation to dose or frequency following a blood level result).

Description of included studies

Six studies (all observational studies) were identified for inclusion for this review question (Boyle 2006; Edgren 1984; Herngren 1986; Kalenga 1984; Martinkova 2010; Reimche 1987).

Four studies focused on monitoring of plasma or serum gentamicin concentrations as the basis for individualising dosage regimens (Edgren 1984; Herngren 1986; Kalenga 1984; Martinkova 2010).

Martinkova 2010 (a prospective non-comparative study) evaluated clinical and pharmacokinetic outcomes in critically ill babies with suspected sepsis, proven sepsis or pneumonia who were aged up to 1 week at enrolment to the study. Gentamicin was administered by intravenous infusion, with an initial dose of 4 mg/kg and a dosing interval of 24, 36 or 48 hours depending on gestational age. Plasma gentamicin concentrations were determined on four occasions between administration of the first and second infusions, and a two-compartment pharmacokinetic model was used to individualise doses and dosing intervals for the third and fourth infusions. Plasma gentamicin concentrations were

determined using fluorescent polarisation immunoassay. The study included follow-up for ototoxicity and nephrotoxicity for 2 years after the end of gentamicin treatment.

Two older studies (Edgren 1984 and Kalenga 1984) evaluated pharmacokinetic outcomes only in babies who received gentamicin by intravenous infusion. Kalenga (1984; a before-and-after study) focused on critically ill babies aged 1–12 days at enrolment to the study and included comparison with a historical cohort of 'similarly ill' babies who received gentamicin before the introduction of pharmacokinetic monitoring. Edgren (1984; a prospective non-comparative study) focused on babies with suspected sepsis who were aged less than 4 days at enrolment. Both studies used an initial dosage regimen of 2.5 mg/kg every 12 hours. Serum gentamicin concentrations were determined on three occasions between the first and second infusions, and Sawchuk's 1976 method based on a one-compartment pharmacokinetic model was used to individualise doses and dosing intervals for subsequent infusions. Serum gentamicin concentrations were determined using radioimmunoassay.

A further study (Herngren 1986) that reported retrospective comparative data evaluated pharmacokinetic outcomes only in babies aged 1–35 days who received gentamicin by intravenous injection in a neonatal intensive care unit. The initial dosage regimen was 2.5 mg/kg every 12 hours in babies with birthweight less than 2.5 kg and 3.75 mg/kg every 12 hours in babies with birthweight more than 2.5 kg. Serum gentamicin concentrations were determined on one occasion before and three occasions after the second (or third) dose in one group of babies, and on one occasion before and one occasion after the second dose in another group of babies. Gibaldi's 1982 method, which is based on population (rather than individualised) pharmacokinetic modelling, was used to predict steady-state serum gentamicin concentrations after the tenth dose. No changes were made to the dosage regimen in the first group of babies (whether this was because all babies had serum gentamicin concentrations in the target ranges was not reported), whereas doses and dosing intervals were individualised to achieve predicted steady-state concentrations in the target ranges in the second group of babies (all of whom had initial serum gentamicin concentrations outside the target ranges). Serum gentamicin concentrations were determined using homogeneous enzyme immunoassay.

One prospective cohort study (Reimche 1987) focused on monitoring of serum creatinine concentrations as the basis for individualising gentamicin dosage regimens. This study evaluated pharmacokinetic outcomes only in babies aged 3–12 days who received gentamicin by intravenous infusion in a neonatal intensive care unit (NICU). The gentamicin dose was fixed at 2.5 mg/kg throughout the study, and the initial dosing interval was 8, 12 or 18 hours depending on gestational age and postnatal age. Serum creatinine concentrations were determined at least every 72 hours, and used to direct increases in the dosing interval to 24, 36 or 48 hours. Serum gentamicin concentrations were determined by radioimmunoassay on one occasion before and one occasion after a particular dose of gentamicin (which dose the measurements related to varied between babies). Gentamicin pharmacokinetic parameters calculated using the one-compartment pharmacokinetic model used in Sawchuk's 1976 method were compared with serum creatinine concentrations, but no changes were made to the gentamicin dosage regimen on the basis of the gentamicin pharmacokinetic parameters.

The remaining study (Boyle 2006; a diagnostic test accuracy study with a cohort design) evaluated the accuracy of serum gentamicin concentrations obtained by convenience sampling (that is, by timing blood samples to coincide with samples obtained for other clinical tests) as predictors of 24-hour trough serum gentamicin concentrations of 1 mg/l or less. The study focused on babies with increased risk of sepsis, or suspected sepsis or proven sepsis, in the first 4 days of life and included derivation and validation cohorts. The initial gentamicin dosage regimen was 4 mg/kg every 24 hours, and the purpose of predicting 24-hour trough concentrations of 1 mg/l or less was to distinguish between babies in whom the second dose of gentamicin could be administered safely at 24 hours, and those in whom the dosing interval should be extended beyond 24 hours. Serum gentamicin concentrations were determined using fluorescent polarisation immunoassay. The route of administration of gentamicin was not reported in this study.

A further six studies identified for inclusion in relation to the review question about antibiotics for suspected early-onset neonatal infection included therapeutic drug monitoring and individualised dosing for gentamicin as part of a package of care (Agarwal 2002; de Alba Romero 1998; Hayani 1997; Isemann 1996; Rastogi 2002; Snelling 1983; see Chapter 9). Those studies did not evaluate

the effectiveness of therapeutic drug monitoring independently of other aspects of the interventions investigated (such as different dosage regimens), and so they do not provide direct evidence relating to the effectiveness and safety of specific monitoring strategies and schedules.

Evidence profiles

The evidence profiles for this review question are presented in Tables 11.1 to 11.6.

Table 11.1 Evidence profile for clinical outcomes of therapeutic drug monitoring based on plasma gentamicin concentrations and a two-compartment pharmacokinetic model in critically ill babies with suspected sepsis, proven sepsis or pneumonia who received gentamicin by intravenous infusion[a]

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rates					
Cure rate in babies with proven sepsis (those in whom infecting microorganisms were identified)					
1 (Martinkova 2010)	13/13 (100%)	-	NC	NC	Very low
Resolution within 5–10 days of clinical signs and laboratory findings suggesting sepsis in babies with suspected sepsis or pneumonia					
1 (Martinkova 2010)	68/71 (96%)	-	NC	NC	Very low
Adverse effects kidney dysfunction detected during gentamicin treatment					
Gestational age < 34 weeks					
1 (Martinkova 2010)	8/27 (30%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	2/22 (9%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	13/35 (37%)	-	NC	NC	Very low
Normalisation of serum creatinine concentrations before the end of gentamicin treatment					
1 (Martinkova 2010)	13/23 (57%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Normalisation of serum creatinine concentrations within 1 week of the end of gentamicin treatment					
1 (Martinkova 2010)	7/23 (30%)	-	NC	NC	Very low
Adverse effects detected in 2-year follow up after the end of gentamicin treatment					
Hearing impairment detected using transient evoked otoacoustic emission recordings during the first or second year of follow-up (impairment was detected only in babies in with grade 3 or 4 hypoxic-ischaemic encephalopathy)					
1 (Martinkova 2010)	2/46 (4%)	-	NC	NC	Very low
Nephrocalcinosis detected using ultrasound during the first year of follow-up					
1 (Martinkova 2010)	3/68 (4%)	-	NC	NC	Very low
Nephrocalcinosis detected using ultrasound during the second year of follow-up					
1 (Martinkova 2010)	0/46 (0%)	-	NC	NC	Very low

NC not calculable

[a] The initial gentamicin dosage regimen was 4 mg/kg every 24, 36 or 48 hours depending on gestational age

Table 11.2 Evidence profile for pharmacokinetic outcomes of therapeutic drug monitoring based on plasma gentamicin concentrations and a two-compartment pharmacokinetic model in critically ill babies with suspected sepsis, proven sepsis or pneumonia who received gentamicin by intravenous infusion[a]

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Achievement of target ranges for serum gentamicin concentrations: peak concentration after the fourth dose in the target range (6–10 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	11/27 (41%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	11/22 (50%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Gestational age > 38 weeks					
1 (Martinkova 2010)	22/35 (63%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: peak concentration after the fourth dose below the target range (< 6 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	16/27 (59%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	11/22 (50%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	11/35 (31%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: peak concentration after the fourth dose above the target range (> 10 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	0/27 (0%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	0/22 (0%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	2/35 (6%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: trough concentration after the third dose in the target range (0.5–2.0 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	26/27 (96%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Gestational age 34–38 weeks					
1 (Martinkova 2010)	16/22 (73%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	29/35 (83%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: trough concentration after the third dose below the target range (< 0.5 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	1/27 (4%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	6/22 (27%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	5/35 (14%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: trough concentration after the third dose above the target range (> 2.0 mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	0/27 (0%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	0/22 (0%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	1/35 (2%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Bias and precision of predicted peak and trough serum gentamicin concentrations: bias for peak concentration after the fourth dose (mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	27[b]	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	22[c]	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	35[d]	-	NC	NC	Very low
Bias and precision of predicted peak and trough serum gentamicin concentrations: bias for trough concentration after the third dose (mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	27[e]	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	22[f]	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	35[g]	-	NC	NC	Very low
Bias and precision of predicted peak and trough serum gentamicin concentrations: precision for peak concentration after the fourth dose (mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	27[h]	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	22[i]	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Gestational age > 38 weeks					
1 (Martinkova 2010)	35[j]	-	NC	NC	Very low
Bias and precision of predicted peak and trough serum gentamicin concentrations: precision for trough concentration after the third dose (mg/l)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	27[k]	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	22[l]	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	35[m]	-	NC	NC	Very low
Changes to the dosage regimen (changes to dose or dosing interval); decrease in dosing rate (decreased dose with or without increased dosing interval)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	16/27 (59%)	-	NC	NC	Very low
Gestational age 34–38 weeks					
1 (Martinkova 2010)	16/22 (73%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	19/35 (54%)	-	NC	NC	Very low
Changes to the dosage regimen (changes to dose or dosing interval); increase in dosing rate (decreased dosing interval; no babies in any group received an increased dose)					
Gestational age < 34 weeks					
1 (Martinkova 2010)	3/27 (11%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Gestational age 34–38 weeks					
1 (Martinkova 2010)	0/22 (0%)	-	NC	NC	Very low
Gestational age > 38 weeks					
1 (Martinkova 2010)	4/35 (11%)	-	NC	NC	Very low

NC not calculable

[a] The initial gentamicin dosage regimen was 4 mg/kg every 24, 36 or 48 hours depending on gestational age

[b] Mean prediction error 0.83 (95% confidence interval 0.17 to 1.5)

[c] Mean prediction error 1.1 (95% confidence interval 0.25 to 2.0)

[d] Mean prediction error 1.0 (95% confidence interval 0.2 to 1.8)

[e] Mean prediction error 0.33 (95% confidence interval 0.15 to 0.52)

[f] Mean prediction error 0.38 (95% confidence interval 0.10 to 0.67)

[g] Mean prediction error 0.32 (95% confidence interval 0.09 to 0.55)

[h] Mean absolute prediction error 1.5 (95% confidence interval 1.0 to 1.9)

[i] Mean absolute prediction error 1.8 (95% confidence interval 1.2 to 2.4)

[j] Mean absolute prediction error 2.1 (95% confidence interval 1.6 to 2.6)

[k] Mean absolute prediction error 0.45 (95% confidence interval 0.31 to 0.59)

[l] Mean absolute prediction error 0.53 (95% confidence interval 0.31 to 0.76)

[m] Mean absolute prediction error 0.49 (95% confidence interval 0.30 to 0.68)

Table 11.3 Evidence profile for therapeutic drug monitoring based on serum gentamicin concentrations and a one-compartment pharmacokinetic model in critically ill babies or babies with suspected sepsis who received gentamicin by intravenous infusion[a]

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group (before introduction of kinetically guided monitoring)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Achievement of target ranges for serum gentamicin concentrations					
Peak or trough concentration in the therapeutic range (therapeutic ranges not reported clearly; targets for peak and trough were 8 mg/l and < 2 mg/l, respectively)					
1 (Kalenga 1984)	37/44 (84%)	9/45 (20%)	RR 4.20 (2.31 to 7.65)	640 more per 1000 (from 262 more to 1000 more)	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group (before introduction of kinetically guided monitoring)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
At least one peak or trough concentration above the therapeutic range (therapeutic ranges not reported clearly; targets for peak and trough were 8 mg/l and < 2 mg/l, respectively)					
1 (Kalenga 1984)	5/44 (11%)	19/45 (42%)	RR 0.27 (0.11 to 0.66)	308 fewer per 1000 (from 144 fewer to 376 fewer)	Very low
At least one peak below the therapeutic range (therapeutic ranges not reported clearly; targets for peak and trough were 8 mg/l and < 2 mg/l, respectively)					
1 (Kalenga 1984)	2/44 (5%)	9/45 (20%)	RR 0.23 (0.05 to 0.99)	154 fewer per 1000 (from 2 fewer to 190 fewer)	Very low
At least one blood sample unusable or uninterpretable					
1 (Kalenga 1984)	0/44 (0%)	8/45 (18%)	RR 0.06 (0.00 to 1.01)	167 fewer per 1000 (from 178 fewer to 2 more)	Very low
Peak concentration in the target range (4–8 mg/l; follow-up monitoring based on peak concentration only)					
1 (Edgren 1984)	28/30 (93%)	-	NC	NC	Very low
Trough concentration in the target range (< 2 mg/l; follow-up monitoring based on trough concentration only)					
1 (Edgren 1984)	25/30 (83%)	-	NC	NC	Very low
Precision of predicted peak and trough serum gentamicin concentrations					
Precision for peak concentration (absolute difference between observed and predicted peaks ≤ 1 mg/l; follow-up monitoring based on peak concentration only)					
1 (Edgren 1984)	18/30 (60%)[f]	-	NC	NC	Very low
Precision for peak concentration (absolute difference between observed and predicted peaks ≤ 2 mg/l; follow-up monitoring based on peak concentration only)					
1 (Edgren 1984)	28/30 (93%)[c]	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Kinetically guided therapeutic monitoring	Comparison group (before introduction of kinetically guided monitoring)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Precision for trough concentration (absolute difference between observed and predicted peaks ≤ 1 mg/l; follow-up monitoring based on trough concentration only)					
1 (Edgren 1984)	27/30 (90%)[g]	-	NC	NC	Very low

NC not calculable, RR relative risk

[a] The initial gentamicin dosage regimen was 2.5 mg/kg every 12 hours; details of gentamicin dosage regimen and monitoring protocol in historical cohort (Kalenga 1984) not reported

[b] Reported to be due to dehydration at the time of follow-up in some babies who received furosemide (a diuretic) or phototherapy, or to overhydration in other babies

[c] The babies for whom the prediction threshold was not met were born at less than 35 weeks and weighed less than 2 kg at the time of the initial dose of gentamicin

Table 11.4 Evidence profile for therapeutic drug monitoring based on serum gentamicin concentrations and a simplified method for individualising dosage regimens (not dependent on individualised pharmacokinetic modelling) in babies who received gentamicin by intravenous injection in a neonatal intensive care unit[a]

Number of studies	Number of babies		Effect		Quality
	Simplified therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Bias and precision of predicted steady-state peak and trough serum gentamicin concentrations					
Bias for trough concentration (difference between observed and predicted concentrations) in babies who received serum gentamicin before and at 1 hour after the second dose of gentamicin followed by adjustment to the dosage regimen (mg/l)					
1 (Herngren 1986)	15[b]	-	NC	NC	Very low
Precision for trough concentration (absolute difference between observed and predicted trough concentrations) ≤ 1 mg/l in babies who received serum gentamicin before and at 1 hour after the second dose of gentamicin followed by adjustment to the dosage regimen					
1 (Herngren 1986)	15 (73%)[c]	-	NC	NC	Very low
Correlations between observed and predicted steady-state peak and trough concentrations					
Correlation between observed and predicted peak and trough concentrations in babies who received serum gentamicin before and at 1 hour after the second dose of gentamicin followed by adjustment to the dosage regimen (pooled data for peak and trough concentrations)					
1 (Herngren 1986)	15[d]	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Simplified therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Correlation between observed and predicted peak concentrations in babies who received serum gentamicin before and at 1 hour after the second dose of gentamicin followed by adjustment to the dosage regimen					
1 (Herngren 1986)	15[e]	-	NC	NC	Very low
Correlation between observed and predicted trough concentrations in babies who received serum gentamicin before and at 1 hour after the second dose of gentamicin followed by adjustment to the dosage regimen					
1 (Herngren 1986)	15[f]	-	NC	NC	Very low
Correlation between observed and predicted peak and trough concentrations in babies who received serum gentamicin before and at 1, 3 and 5 hours after the second or third dose of gentamicin with no adjustment to the dosage regimen (pooled data for peak and trough concentrations)					
1 (Herngren 1986)	20[g]	-	NC	NC	Very low
Correlation between observed and predicted peak concentrations in babies who received serum gentamicin before and at 1, 3 and 5 hours after the second or third dose of gentamicin with no adjustment to the dosage regimen					
1 (Herngren 1986)	20[h]	-	NC	NC	Very low
Correlation between observed and predicted trough concentrations in babies who received serum gentamicin before and at 1, 3 and 5 hours after the second or third dose of gentamicin with no adjustment to the dosage regimen					
1 (Herngren 1986)	20[i]	-	NC	NC	Very low

NC not calculable

[a] The initial gentamicin dosage regimen was 2.5 mg/kg every 12 hours in babies with birthweight < 2.5 kg and 3.75 mg/kg every 12 hours in babies with birthweight > 2.5 kg

[b] Difference between observed and predicted trough serum gentamicin concentrations 0.7 (95% confidence interval not reported)

[c] Number of babies with precision for trough concentrations ≤ 1 mg/l not reported

[d] Correlation coefficient r = 0.92, *P* not reported

[e] Correlation coefficient r = 0.63, *P* not reported

[f] Correlation coefficient r = 0.21, *P* not reported

[g] Correlation coefficient r = 0.90, *P* not reported

[h] Correlation coefficient r not reported, $P < 0.005$

[i] Correlation coefficient r not reported, $P < 0.005$

Table 11.5 Evidence profile for therapeutic drug monitoring based on serum creatinine concentrations in babies who received gentamicin by intravenous infusion in a neonatal intensive care unit[a]

Number of studies	Number of babies		Effect		Quality
	Serum creatinine guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Achievement of target ranges for serum gentamicin concentrations: peak concentration in the target range (4–10 mg/l)					
All babies					
1 (Reimche 1987)	19/22 (86%)	-	NC	NC	Very low
Gestational age < 34 weeks					
1 (Reimche 1987)	6/8 (75%)	-	NC	NC	Very low
Gestational age ≥ 34 weeks					
1 (Reimche 1987)	13/14 (93%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: peak concentration below the target range (< 4 mg/l)					
All babies					
1 (Reimche 1987)	3/22 (14%)	-	NC	NC	Very low
Gestational age < 34 weeks					
1 (Reimche 1987)	2/8 (25%)	-	NC	NC	Very low
Gestational age ≥ 34 weeks					
1 (Reimche 1987)	1/14 (7%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: peak concentration above the target range (> 10 mg/l)					
All babies					
1 (Reimche 1987)	1/22 (5%)	-	NC	NC	Very low
Gestational age < 34 weeks					
1 (Reimche 1987)	0/8 (0%)	-	NC	NC	Very low

Number of studies	Number of babies		Effect		Quality
	Serum creatinine guided therapeutic monitoring	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Gestational age ≥ 34 weeks					
1 (Reimche 1987)	1/14 (7%)	-	NC	NC	Very low
Achievement of target ranges for serum gentamicin concentrations: trough concentration in the target range (< 0.2 mg/l)					
All babies					
1 (Reimche 1987)	5/22 (23%)	-	NC	NC	Very low
Gestational age < 34 weeks					
1 (Reimche 1987)	1/8 (13%)	-	NC	NC	Very low
Gestational age ≥ 34 weeks					
1 (Reimche 1987)	4/14 (29%)	-	NC	NC	Very low

NC not calculable

[a] The gentamicin dose was fixed at 2.5 mg/kg throughout the study, and the initial dosing interval was 8, 12 or 18 hours depending on gestational age and postnatal age

Table 11.6 Evidence profile for diagnostic test accuracy of serum gentamicin concentrations obtained by convenience sampling as predictors of 24-hour trough concentrations ≤ 1 mg/l in babies with increased risk of sepsis, or suspected or proven sepsis[a]

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Derivation cohort						
Fitted regression model for predicting trough serum gentamicin concentrations ≤ 1 mg/l						
1 (Boyle 2006)	50	71 (52 to 86)	84 (60 to 97)	4.50 (1.66 to 17.36)	0.345 (0.231 to 0.638)	Moderate
Adjusted regression model for predicting trough serum gentamicin concentrations ≤ 1 mg/l						
1 (Boyle 2006)	50	100 (81 to 100)	58 (34 to 80)	2.32 (1.50 to 2.50)	0.027 (0.000 to 0.284)	Low

Number of studies	Number of babies	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality
Validation cohort						
1 (Boyle 2006)	39	92 (74 to 99)	14 (2 to 43)	1.07 (0.88 to 1.34)	0.560 (0.059 to 5.378)	Moderate
Re-analysis of pooled data from derivation and validation cohorts using gestational age > 37 weeks for predicting trough serum gentamicin concentrations ≤ 1 mg/l						
1 (Boyle 2006)	89	94 (85 to 98)	61 (39 to 80)	2.40 (1.56 to 3.49)	0.100 (0.031 to 0.277)	Low

[a] The initial gentamicin dosage regimen was 4 mg/kg every 24 hours

Evidence statements

Clinical outcomes

Cure rates and adverse effects in babies who received kinetically guided monitoring and gentamicin dosage adjustment were investigated in a non-comparative study. The cure rate in babies with culture-proven sepsis was 100%, and resolution of suspected sepsis or pneumonia within 5–10 days of clinical signs or laboratory findings was 95% (very low quality evidence). The same study reported kidney dysfunction during gentamicin treatment in 9–37% of babies, depending on gestational age (very low quality evidence). However, serum creatinine concentrations normalised in 57% of babies before the end of gentamicin treatment, and in a further 30% of babies within 1 week of the end of gentamicin treatment (very low quality evidence). During 2-year follow-up, 4% of babies (n = 2) were reported to have experienced hearing loss, but this was attributed to grade 3 or 4 hypoxic-ischaemic encephalopathy in both babies who were affected (very low quality evidence).

Pharmacokinetic outcomes

A non-comparative study that investigated kinetically guided monitoring and gentamicin dosage adjustment reported that 41–63% of peak plasma gentamicin concentrations were in the target range, with 31–59% below the target range and 0–6% above the target range, depending on gestational age (very low quality evidence). The same study reported that 73–96% of trough plasma gentamicin concentrations were in the target range, with 4–27% below the target range and 0–2% above the target range, depending on gestational age (very low quality evidence). The bias and precision of predicted peak concentrations were higher than those for predicted trough concentrations, but the analysis did not take into account the magnitude of the differences between target peak and trough concentrations (that is, the bias and precision were not expressed as standardised values; very low quality evidence). Decreased dosage rates (achieved using decreased doses, with or without increased dosing intervals) were applied in 54–73% of babies, depending on gestational age, whereas increased dosage rates (achieved using decreased dosing intervals only) were reported in 0–11% of babies (very low quality evidence). Preterm babies (gestational age less than 34 weeks) were more likely to have peak plasma gentamicin concentrations below the target range, and less likely to have an increased dosage rate, compared with term babies (34–38 weeks), although the study did not compare results for babies of different gestational ages systematically (very low quality evidence).

Another study reported achievement of peak or trough serum gentamicin concentrations in the therapeutic ranges in 84% of babies using kinetically guided monitoring and dosage adjustment, compared to 20% in a historical cohort (before introduction of kinetically guided monitoring; very low quality evidence). However, neither the therapeutic ranges in the kinetically guided approach nor the specific details of the gentamicin dosage regimen in the historical cohort were reported. A non-

comparative study that investigated pharmacokinetic outcomes using the same kinetically guided approach to monitoring and dosage adjustment reported that 93% of peak concentrations and 83% of trough concentrations were in the target ranges (very low quality evidence). This study also reported that 93% of observed peak concentrations were within 2 mg/l of the predicted values, and that 90% of observed trough concentrations were within 1 mg/l of predicted values. A further non-comparative study that investigated a simplified approach to monitoring and dosage adjustment (using population rather than individualised pharmacokinetic modelling) reported that 73% of observed trough concentrations were within 1 mg/l of predicted values (very low quality evidence).

A non-comparative study that investigated monitoring and gentamicin dosage adjustment based on serum creatinine concentrations reported that 75–93% of peak serum gentamicin concentrations were in the target range, with 7–25% below the target range and 0–7% above the target range, depending on gestational age (very low quality evidence). This study reported that 13–29% of trough serum gentamicin concentrations were in the target range, depending on gestational age (the proportions of babies in whom serum gentamicin concentrations were below or above the target ranges were not reported in this study; very low quality evidence).

Convenience sampling of serum gentamicin concentrations was not particularly useful as a predictor of 24-hour trough concentrations of 1 mg/l or less in a study that derived a decision rule using a regression model (moderate quality evidence). Similarly, gestational age of more than 37 weeks was not a particularly useful predictor of 24-hour trough concentrations of 1 mg/l or less (low quality evidence).

Evidence to recommendations

Relative value placed on the outcomes considered

The purpose of this review question is to weigh the effectiveness of gentamicin when administered to a population of babies with early-onset neonatal infection with the response to gentamicin treatment in an individual baby, which will depend on physiological factors such as gestational age at birth and postnatal age. For this review question the GDG prioritised consideration of clinical outcomes, including clinical cure rate (as in the other antibiotic treatment questions) and incidence of medium- or long-term adverse effects of gentamicin (hearing loss or kidney dysfunction). The GDG also considered secondary outcomes, namely pharmacokinetic and pharmacodynamic parameters (including time to effective concentration and incidence of subtherapeutic or toxic concentrations in the blood or urine) and factors associated with the logistics of particular monitoring schedules (including the number of blood samples to be collected and the number of doses of gentamicin to be administered). The GDG's view was that preterm birth was likely to be an important consideration in this review question because gentamicin pharmacokinetics are affected by gestational age as well as postnatal age.

Consideration of clinical benefits and harms

This question focuses on the relative weight to be given to the effectiveness of gentamicin treatment (for example in terms of the bactericidal effect of gentamicin against a target micro-organism) and safety considerations, particularly in relation to potential damage to hearing and kidney function. Individualising gentamicin dosage regimens relies on therapeutic drug monitoring, which involves measuring serum gentamicin concentrations or other parameters linked to the distribution of gentamicin in the body, comparing observed concentrations with target concentrations, and (where necessary) adjusting gentamicin doses or dosage intervals to ensure differences between observed and target concentrations are sufficiently small. Target concentrations may be specified for various stages in the absorption and activity profiles of gentamicin, with monitoring schedules typically being based on measurement of peak concentrations (obtained shortly after administration of the drug) to examine whether concentrations are within a specified therapeutic range, or trough concentrations (obtained shortly before administration of a dose of gentamicin) to determine whether the residual concentration of gentamicin is likely to cause toxicity. Other parameters that might be measured include creatinine clearance (as an indicator of kidney function). The specific objectives of this review question were to determine which pharmacokinetic parameters should be monitored and to identify an effective schedule for monitoring. Although the summary of product characteristics (SPC) for

gentamicin recommends various forms of monitoring before, during or after administration, the recommended approaches may not be appropriate or feasible in newborn babies. The approaches outlined in the SPC include measurement of serum gentamicin concentrations and measurement of kidney function in terms of serum creatinine concentrations and creatinine clearance (or glomerular filtration rate [GFR]). Maximum peak concentrations (for example at 1 hour after administration) and minimum trough concentrations (for example at 1 hour before the next administration) are also specified in some SPCs. The GDG's consideration of the evidence identified for inclusion included specific consideration of safe monitoring protocols for preterm babies, since these are least likely to be covered by the provisions of SPCs.

Consideration of net health benefits and resource use

Although this review question was not prioritised for health economic analysis, the potential benefits of therapeutic drug monitoring in terms of reducing clinically important and long-term disabilities such as deafness or impaired kidney function following gentamicin treatment are likely to lead to cost savings compared to no therapeutic monitoring. Despite the SPC for gentamicin stipulating that therapeutic drug monitoring should be undertaken in every person who receives gentamicin, the GDG is aware that errors in gentamicin administration (including the precise timing of administration) occur in practice (see NPSA 2010 guidance on the services and Safer use of intravenous gentamicin for neonates [PDF file]). Specification of, and adherence to, clear protocols for gentamicin administration, monitoring and dosage adjustment should, therefore, lead to cost savings.

Quality of evidence

The evidence identified for inclusion varied considerably in terms of approaches used for monitoring and dosage adjustment, with different studies evaluating clinical and pharmacokinetic outcomes based on different pharmacokinetic parameters, different monitoring schedules and different levels of complexity in the models used to describe the pharmacokinetic properties of gentamicin in the body and to predict gentamicin concentrations in the blood given particular dosage regimens. The quality of the evidence was mostly very low, although evidence for a few outcomes in one study was assessed as being of low or moderate quality. No single study provided strong evidence to support a particular approach to monitoring and dosage adjustment. Only one study incorporated measurement of clinical outcomes, the remaining studies focusing on secondary outcomes specified in the GDG's review protocol. None of the study designs or approaches to pharmacokinetic monitoring was sufficiently similar for the GDG to evaluate the degree of consistency in outcomes when similar approaches were applied in slightly different clinical circumstances (for example to allow comparison between preterm and term babies).

The GDG considered a number of specific issues relating to the evidence identified for inclusion. Firstly, in the only study that reported clinical outcomes low peak serum gentamicin concentrations were observed, despite the gentamicin dose being higher than in the other included studies, and the pharmacokinetic modelling in that study did not adjust the dose to overcome this problem. Similar issues occurred with trough concentrations (quite a few babies missed the target dose, suggesting that the pharmacokinetic model was not as precise as the study authors thought it would be).

Another study suggested that using a pharmacokinetic model for individualised dosage adjustments might be helpful, but the study did not guide the GDG as to what form of pharmacokinetic modelling(for example one or two compartments) should be used. The GDG noted that the complexity of a pharmacokinetic model was not in itself a guarantee of success (because the most complex model was used in the study described above in which a proportion of babies did not receive a therapeutic dose). The GDG noted that even if pharmacokinetic guided monitoring was not to be recommended, some form of monitoring should be used during gentamicin treatment because the SPCs advise this.

A further study used measurement of serum creatinine concentrations as the basis for monitoring and adjustment of gentamicin dosage. The GDG noted that creatinine is a late marker of renal damage due to gentamicin; it does not reflect immediate effects of gentamicin toxicity, and it can be affected by many other factors, including infection itself and common diseases, such as hypoxic-ischaemic encephalopathy. For these reasons the GDG concluded that monitoring and dosage adjustment

based on serum creatinine concentrations should not be recommended in babies receiving gentamicin for early-onset neonatal infection.

A study that examined the predictive accuracy of opportunistic (or convenience) sampling of serum gentamicin concentrations (that is, measuring gentamicin concentrations in blood samples obtained for other clinical reasons) was not clinically useful in the form evaluated in the study. The approach used in the study was naïve in that regression analysis was used to derive a decision rule; this approach ignores the subtleties of pharmacokinetic modelling. The GDG also noted that the decision rule was derived using a sample of only 50 babies, and so the external validity (or generalisability of the rule and its predictive accuracy) was not sufficiently robust to recommend its use in clinical practice. The GDG noted, however, that the study did not demonstrate that opportunistic sampling would never be useful (for example, a different decision rule, perhaps based on pharmacokinetic modelling, could not be ruled out as being useful on the basis of this study).

Other considerations

The GDG was aware of variations in current clinical practice with regard to therapeutic drug monitoring for gentamicin. At least one centre in the UK was known to use individualised pharmacokinetic modelling to determine safe and effective dosage regimens, but this practice was not widespread. A recent survey of gentamicin dosage regimens and approaches to therapeutic monitoring for gentamicin used in 43 UK neonatal units (Kadambari 2011) showed that:

- 24 different combinations of dose, timing of dose and timing of monitoring are currently in use.
- 23% of units measure trough blood gentamicin concentrations before a second dose, 40% before a third dose, 9% before a second or third dose, while the remaining 30% have no written policy for monitoring.
- 27% of units use a target of less than 1 mg/l for trough concentrations, whereas 73% use a target of less than 2 mg/l.
- 36% of units measure peak blood gentamicin concentrations in addition to trough concentrations, and 5% of units measure peak concentrations instead of trough concentrations.
- Only three units reported target peak concentrations (two units use a target of 5–10 mg/l and the other uses 5–8 mg/l).

In formulating its recommendations, the GDG aimed to reduce variations in practice while ensuring the effectiveness and safety of gentamicin dosage regimens for early-onset neonatal infection.

The GDG also noted variations in the approaches to monitoring in the included studies, including whether the timing of blood samples from which to measure gentamicin concentrations was relative to the start or end of an intravenous infusion of gentamicin(since infusion typically takes 30 minutes to 1 hour). The GDG noted that monitoring protocols should be appropriate for the recommended route of administration of gentamicin (because a bolus intravenous injection would result in a sharper peak than an intravenous infusion).

Key conclusions

The GDG recommended that therapeutic drug monitoring be performed for all babies receiving gentamicin, in accordance with the SPC for gentamicin. The GDG agreed the following general principles for local practice regarding therapeutic drug monitoring and dosage adjustment for gentamicin and were guided by them in formulating recommendations for national practice.

- All units should have a policy that considers peak and/or trough gentamicin concentrations, with the possibility of individualised pharmacokinetic modelling, because these approaches appear to be safer than doing nothing.
- The policy should:
    - include a method to provide assurance that there is no unsafe or excessive accumulation of gentamicin by specifying when to measure blood gentamicin

concentrations (for example by measuring trough concentrations; other possibilities would be measurements at other times in the concentration:time curve if using individualised pharmacokinetic modelling)

- consider adapting the dosage regimen in the light of the minimum inhibitory concentration (MIC)in confirmed sepsis (that is, in the presence of a positive culture for a specific micro-organism) or failure to respond to gentamicin treatment (because the purpose of the peak concentration is to assure a sufficiently high concentration to kill the relevant micro-organism and the purpose of the trough concentration is to assure that enough of the drug has cleared [been eliminated from the body] to justify the next dose)
- specify when to measure trough gentamicin concentrations and specify the circumstances in which peak gentamicin concentrations should also be measured
- specify tolerances for peak and/or trough concentrations, and tolerances for the times at which samples are to be obtained.

The GDG agreed that trough gentamicin concentrations in the blood should be measured in all babies receiving gentamicin for suspected or confirmed early-onset neonatal infection. The first trough concentration should be measured immediately before giving a second dose of gentamicin and, as a minimum, further measurements should be considered before every subsequent third dose of gentamicin (that is, monitoring should be performed before the second dose, and considered before the fifth dose, the eighth dose, and so on, if treatment is continued).Since the interval between the second and third doses of gentamicin (if given) will be 36 hours, the GDG agreed that hospital services should make blood gentamicin concentrations available to healthcare professionals in time to inform the next dosage decision.

The GDG agreed that peak gentamicin concentrations need not be monitored routinely, but they should be monitored in carefully selected babies, for example those with oedema or macrosomia (abdominal circumference above the 70th percentile), those who are not responding to gentamicin treatment, and those with a Gram-negative infection. It is normally assumed that recommended regimens are adequate in terms of delivering a therapeutic dose of gentamicin, and so measurement of peak gentamicin concentrations is usually unnecessary. Routine measurement of peak concentrations is not usually recommended because the general literature suggests that adequate peak concentrations can be achieved with a dose ten times the MIC in people with normal body composition. Oedema and large body size may, however, be associated with low peak concentrations. Since gentamicin is water soluble it will distribute away from the circulating volume in babies with oedema, and this will lead to increased volume of distribution and lower peak concentrations. Macrosomia is associated with altered relative volumes of body compartments, which could also affect the volume of distribution and peak gentamicin concentrations.

Although the GDG's discussions highlighted difficulties in specifying target peak and trough gentamicin concentrations in the absence of knowledge about the causative micro-organism of an early-onset neonatal infection, the consensus view was that healthcare professionals should aim initially for a peak concentration of 8mg/l in babies with a Gram negative or staphylococcal infection. The GDG also agreed that peak concentrations should be measured within 1 hour of starting the gentamicin infusion. The GDG consensus was that the target trough concentration for initial dosing should be less than 2 mg/l. The GDG noted that with a longer dosing interval a lower target trough gentamicin concentration may be reasonable, but specifying a target of less than 1 mg/l for all babies could pose practical problems for babies with trough concentrations of 1–2 mg/l. Noting that levels of less than 1 mg/l may be safer, the GDG agreed that this should be the target for trough concentrations during prolonged gentamicin treatment (more than three doses of gentamicin).

The GDG agreed that, in the absence of evidence of renal dysfunction (see below), healthcare professionals should not withhold a dose of gentamicin if monitoring has not been performed. The balance of clinical risks and harms lies in favour of giving gentamicin and establishing afterwards whether the dosage regimen should be adjusted to achieve target peak and/or trough concentrations. The GDG agreed that the dosage interval should be extended for babies in whom the trough gentamicin concentration is above the target concentration, whereas the dose should be reduced for babies in whom the peak gentamicin concentration exceeds the target concentration.

The GDG considered whether renal function should be monitored (for example by measuring serum creatinine concentrations) in babies receiving gentamicin for a suspected or confirmed early-onset neonatal infection. Although the GDG did not recommend routine monitoring of renal function, the group recognised that such monitoring may be performed incidentally in babies receiving gentamicin for early-onset neonatal infection (for example if the baby is preterm). If renal function is a cause of concern, healthcare professionals should consider increasing the frequency of measurement of trough concentrations. Evidence of renal dysfunction (for example an elevated serum urea or creatinine concentration, or anuria) might justify withholding further gentamicin treatment until a trough concentration is available.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

No research recommendations were identified for this review question.

12 Care setting

Introduction

The objectives of this review question are to evaluate the impact of care setting on the clinical management of early-onset neonatal infection. The guideline development group's (GDG's) considerations in relation to this question were intended to encompass the woman's choice of care setting, subject to constraints imposed by the guideline scope, existing NICE guidance for maternity care (see below) and the feasibility of delivering a safe standard of care in different settings (predominantly primary care, including community care, or secondary care). A systematic search for evidence was conducted with no restrictions on study design and explicitly seeking to identify qualitative research reporting views and experiences of parents and carers of babies with or at risk of early-onset neonatal infection and discrete choice experiments to elicit their preferences in relation to options for clinical management. The GDG drew on evidence identified for other review questions in terms of settings where care was delivered. Additionally, the GDG considered competencies needed to deliver the level of care specified in recommendations in other sections of the guideline.

Review question

How does the choice of care setting impact on the clinical management of early-onset neonatal infection?

Existing NICE guidance

Intrapartum care (NICE clinical guideline 55, 2007) includes review questions and recommendations relating to place of care. In particular, it includes a review question on risk factors to be included in assessment to determine the most appropriate place of birth for women during pregnancy. The guideline recommendations identify several groups of women with medical conditions indicating increased risk that suggests planned birth at an obstetric unit: one such group is women with risk factors associated with GBS such that antibiotics in labour would be recommended.

The guideline identified prelabour rupture of membranes (PROM) as a major obstetric risk factor for neonatal infection (although preterm PROM was excluded from the scope of the guideline). The guideline evaluated various clinical management strategies following term PROM, including consideration of the following issues:

- place of care before and during labour and birth
- routine admission to a neonatal unit after birth.

Expectant management at home (rather than expectant management as a hospital inpatient) was identified as a risk factor for neonatal infection after term PROM. The guideline recommended a risk-based clinical management strategy for women with term PROM, which included the following elements.

- Induction of labour is appropriate approximately 24 hours after rupture of the membranes.
- Advise women that, if labour has not started 24 hours after rupture of the membranes, they should give birth in a healthcare setting with access to neonatal services and stay in hospital for at least 12 hours after the birth so that the baby can be observed.
- Offer immediate referral to a neonatal care specialist for a baby with any symptom of possible sepsis, or born to a woman who has evidence of chorioamnionitis.

The guideline also includes review questions on labouring and giving birth in water, and these questions specifically consider the risk of maternal and neonatal infections (meaning that consideration of these issues is outside the scope of this guideline).

Induction of labour (NICE clinical guideline 70, 2008) recommends that if a woman has preterm PROM after 34 weeks, the maternity team should discuss the local availability of neonatal intensive care facilities with her before a decision is made about whether to induce labour.

Postnatal care (NICE clinical guideline 37, 2006) includes the following recommendations relating to care setting:

- Length of stay in a maternity unit should be discussed between the individual woman and her healthcare professional, taking account of the health and wellbeing of the woman and her baby and the level of support available after discharge.
- Local protocols for written communication, particularly in relation to transfer of care between clinical sectors and healthcare professionals, should be available and audited.
- Breastfeeding support should be made available regardless of the location of care.
- Offer parents information and advice at each postnatal contact to allow them to assess their baby's general condition, identify symptoms and signs of common infant health problems, and contact healthcare professionals or emergency medical services if needed.

Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) includes the following recommendations relating to care setting (although babies who are already receiving care in neonatal units are excluded from the guideline):

- Recognise shock in babies who present with symptoms and signs of bacterial meningitis or meningococcal septicaemia and manage urgently in secondary care.
- Transfer babies with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.
- Transfer to tertiary care should be undertaken by an experienced paediatric intensive care retrieval team comprising medical and nursing staff.
- Before discharging babies from hospital consider their requirements for follow-up and discuss potential long-term effects of their condition and likely patterns of recovery with their parents or carers.
- Inform the baby's health visitor about their bacterial meningitis or meningococcal septicaemia.

Feverish illness in children (NICE clinical guideline 47, 2007) includes the following recommendations about care setting:

- Offer immediate referral for emergency medical care using the most appropriate means of transport (usually 999 ambulance) for babies with an immediately life-threatening illness (this recommendation is reiterated in Urinary tract infection in children, NICE clinical guideline 54, 2007).
- Offer urgent referral to a paediatric specialist for babies with a high risk of serious illness but no immediately life-threatening illness (this recommendation is reiterated in Urinary tract infection in children, NICE clinical guideline 54, 2007).
- Offer urgent review by an experienced paediatrician for babies with fever and shock who cannot be roused or show clinical signs of meningococcal disease and consider offering referral to paediatric intensive care.
- Provide a 'safety net' for babies with an intermediate risk of serious illness and for whom no diagnosis has been made, or offer referral to specialist paediatric care for further assessment (safety netting means giving the baby's parent or carers verbal or written information on warning symptoms and how to access further health care, arranging

follow-up at a specific time and location, or liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the baby if further assessment is needed).

The guideline recommends home-based care for babies with a low risk of serious illness and offering the baby's parents or carers advice on when and how to seek further advice and care from healthcare professionals. The guideline also recommends consideration of social and family circumstances and parental anxiety and instinct when deciding whether or not to admit a baby with fever to hospital.

Description of included studies

One prospective, non-comparative observational study was identified for inclusion for this review question (Wagner 2000). The study reported cure rate and other infant outcomes in babies who had received antibiotics in hospital for early-onset neonatal sepsis and who were considered suitable for early discharge with continuation of parenteral antibiotics as outpatients. Early discharge was defined as discharge after at least 4 days of inpatient antibiotic treatment for babies with suspected or proven sepsis or pneumonia (n=83) and after at least 10 days of inpatient antibiotic treatment for babies with meningitis (n=1): in both groups of babies clinical status had to have normalised for at least 48 hours before discharge. All babies included in the study had been prescribed at least a 7–10 day course of antibiotics, implying that completion of the course after early discharge would typically require at least another 3–6 days of outpatient antibiotic treatment. Outpatient administration of antibiotics was performed at the baby's home or in the primary care doctor's surgery by a nurse with paediatric training. Consideration for outpatient treatment was contingent on the parents having access to a telephone at home and transport being readily available in case of emergency.

Before discharge parents were given information on care of the intravenous site (for example, how to evaluate the patency of an intravenous catheter and how to flush the catheter with heparin or saline every 8 hours) and how to recognise symptoms and signs of septic shock, anaphylaxis and change in respiratory status. Each baby was examined daily by the visiting nurse or primary care doctor to check for changes in clinical course, and an anaphylaxis epinephrine kit was placed at the baby's bedside by the visiting nurse at the first home visit. Most (56%) of the babies received ampicillin plus gentamicin: other antibiotic regimens involved ceftriaxone (21%), ampicillin alone (11%), benzylpenicillin alone (9%), gentamicin alone (1%) or nafcillin (2%). When ceftriaxone was prescribed before discharge the first dose was given as an inpatient to monitor for allergic reactions. Four babies who were prescribed intravenous ampicillin plus gentamicin before discharge had their antibiotic regimen changed to intramuscular ceftriaxone after discharge because of loss of intravenous access; in such cases the visiting nurse observed the baby for 1 hour after administration of the first dose of ceftriaxone. For babies prescribed gentamicin, peak and trough levels were measured before discharge and follow-up levels were measured if necessary to ensure blood serum levels were in the therapeutic range.

Evidence profiles

The evidence profile for this review question is presented in Table 12.1.

Table 12.1 Evidence profile for parenteral antibiotic treatment at home after hospital inpatient treatment in babies with suspected or confirmed early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Continued antibiotic treatment at home	Comparison group	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rate for early-onset neonatal infection[b]					
1 (Wagner 2000)	95	-	-	-	Very low
Re-admission to hospital during home treatment due to worsening clinical course[c]					
1 (Wagner 2000)	95	-	-	-	Very low
Re-admission to hospital during home treatment due to hyperbilirubinaemia[d]					
1 (Wagner 2000)	70	-	-	-	Very low
Re-admission to hospital during home antibiotic treatment due to problems unrelated to clinical course[e]					
1 (Wagner 2000)	95	-	-	-	Very low
Re-admission to hospital within 6 months of completing the course of antibiotics[f]					
1 (Wagner 2000)	95	-	-	-	Very low

* Calculated by the NCC-WCH technical team from data reported in the article

[a] The study population comprised babies with positive blood culture with susceptible organisms, clinical sepsis (negative blood culture) with initial presentation of hypotension, tachypnoea or poor perfusion with an abnormal immature:total neutrophil ratio), pneumonia (defined by the attending radiologist's reading of an infiltrate on chest X-ray and clinical signs such as tachypnoea or need for supplemental oxygen), or culture-proven meningitis with negative follow-up culture or suspected meningitis (negative blood culture); babies were discharged to home antibiotic treatment only after their clinical status had normalised for at least 48 hours (vital signs normal, on all oral feedings, in-room air) and they had received parenteral antibiotics in hospital for at least 4 days in the case of culture-proven sepsis, clinical sepsis and pneumonia, or at least 10 days in the case of meningitis; the average age at discharge was 5.2 days (range 4 to 12 days)

[b] Incidence of readmission in the study group (home antibiotic treatment) was 2/95 (2%);* one baby was re-admitted because the primary care doctor felt uncomfortable with home antibiotic treatment despite having previously agreed to participate; another baby was re-admitted because the mother felt uncomfortable with the home health company delivering care

[c] Incidence of readmission in the study group (home antibiotic treatment) was 0/95 (0%)*

[d] Incidence of readmission in the study group (home antibiotic treatment) was 0/70 (0%);* 70 babies had bilirubin levels drawn before discharge

[e] Incidence of readmission in the study group (home antibiotic treatment) was 2/95 (2%);* one baby was re-admitted because the primary care doctor felt uncomfortable with home antibiotic treatment despite having previously agreed to participate; another baby was re-admitted because the mother felt uncomfortable with the home health company delivering care

[f] Incidence of readmission in the study group (home antibiotic treatment) was 2/95 (2%);* one baby was re-admitted at age 2 weeks because of unspecified abdominal pain and again at age 5 weeks for an unspecified acute viral infection; the other baby was diagnosed with viral enteritis at age 6 weeks

Evidence statements

No cases of treatment failure or re-admission to hospital during home antibiotic treatment because of worsening clinical course or hyperbilirubinaemia were reported in babies with early-onset neonatal infection who were discharged to parenteral (intravenous or intramuscular) antibiotic treatment after their clinical status had normalised for at least 48 hours and they had received antibiotics in hospital for at least 4 days in the case of culture-proven sepsis, clinical sepsis and pneumonia, or at least 10 days in the case of meningitis (very low quality evidence). Two babies were, however, re-admitted to hospital during home antibiotic treatment because the mother or primary care doctor withdrew from the study (very low quality evidence). A further two babies were re-admitted to hospital within 6months of completing the course of antibiotics at home (one because of unspecified abdominal pain at age 2 weeks and an unspecified acute viral infection at age 5 weeks, and the other because of a diagnosis of viral enteritis at age 6 weeks; very low quality evidence).

Health economics profile

The GDG planned to conduct a cost effectiveness analysis comparing different strategies for identifying and treating babies at risk of early-onset neonatal infection or with symptoms and signs of early-onset neonatal infection, including different care settings. However, no published health economic analyses were identified relating to this review question, and no clinical evidence was identified to inform development of a health economic model specifically for the guideline.

Evidence to recommendations

Relative value placed on the outcomes considered

All the outcomes specified in the review protocol for this question (cure rates for neonatal infection, mortality, duration of hospital stay, neonatal adverse events, long-term outcomes and resistance among neonatal flora), were considered by the GDG to be influential in the formulation of recommendations. While mortality and long-term outcomes were recognised as being critical to the formulation of recommendations, the GDG did not formally agree an order of priority for the remaining outcomes.

The GDG considered various definitions of cure rate that might be relevant, and agreed that the following would all be relevant:

- mortality
- culture-positive cases that become culture-negative
- culture-positive cases who have recovered (clinically better or resolution of laboratory abnormalities) without need for changing antibiotics
- composite of culture-positive and culture-negative cases who have been treated for at least 5 days and have recovered (clinically better or resolution of laboratory abnormalities) without need for changing antibiotics.

Consideration of clinical benefits and harms

The potential benefit identified by the GDG in delivering care outside the hospital setting (while maintaining a safe standard of care) would be to give more choice in terms of care setting to pregnant women whose unborn babies are at risk of an early-onset neonatal infection and their families (for example home birth attended by community midwives or birth in a midwife-led unit). Similar considerations could result in shorter hospital stays for babies at risk of early-onset neonatal infection if they could safely be observed at home, and for babies with suspected or confirmed early-onset neonatal infection for whom antibiotic treatment can safely be concluded at home. Both scenarios would be beneficial, especially for those parents and carers who might live far from a hospital where their baby is being treated, and it would avoid separating families for long periods.

The GDG was aware that in the UK there is an increasing tendency for children and adults with infection to be discharged from hospital before the end of antibiotic treatment, allowing treatment to

be completed at home (in the community antibiotics can be administered by a community nurse).The GDG emphasised as a potential harm the fact that some community services might not be able to provide a necessarily safe standard level of care. Moreover, some parents and carers might not be able to care for a baby at home, or they might feel more reassured if the baby received care in a hospital setting.

Consideration of net health benefits and resource use

The GDG planned to conduct a cost effectiveness analysis to evaluate the impact of care setting on resource use in the management of early-onset neonatal infection. However, no published health economic analyses were identified, and no clinical evidence was identified to inform the development of a health economic model for this question. The GDG recommended further research to evaluate the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection.

Quality of evidence

Only one study was identified for inclusion and the evidence it contributed was of very low quality. The GDG therefore included a weak recommendation stating that healthcare professionals should consider completing a course of antibiotics outside hospital (for example at home or through visits to a standalone midwifery-led unit) in carefully selected babies depending on the support available locally. In the absence of any evidence at all to direct recommendations with regard to other aspects of care according to the healthcare setting in which it is delivered, the GDG used consensus based on the group members' experience as clinicians or parents or carers.

Other considerations

The GDG agreed that it is important that parents and carers be given appropriate information before the woman and/or baby is discharged from hospital, and that they should have the opportunity to discuss with their healthcare professionals the setting in which care of the baby is delivered before making decisions (see Chapter 1). Another issue discussed by the GDG was the fact that if babies continue antibiotic treatment at home there might be the need for recannulation and the GDG highlighted the risks associated with this procedure.

Key conclusions

As outlined above, the GDG's considerations regarding the very low quality evidence for completing a course of antibiotics outside hospital led to a weak recommendation to consider completing a course of antibiotics outside hospital (for example at home or through visits to a standalone midwifery-led unit) in carefully selected babies (specifically in well babies with no ongoing concerns) provided appropriate support is available locally. The GDG discussed the fact that some babies might also need blood tests to be performed as part of therapeutic drug monitoring and that this should be taken into consideration when completion of a course of antibiotics at home is being considered.

Due to the lack of other evidence identified for this review question, the GDG agreed that the setting where care of the baby is delivered should be determined by the baby's clinical needs and the competencies needed to deliver the care recommended elsewhere in the guideline. The GDG proposed that specific competencies should be established for the following groups of babies, although no direct evidence to inform the specification of relevant competencies was identified:

- babies with no risk factors for infection
- babies who have risk factors for infection but have not yet received antibiotics (including babies whose mothers had intrapartum antibiotics and those in whom intrapartum antibiotics were indicated but not received)
- babies who are asymptomatic at the time of starting antibiotics
- babies who have symptoms or signs of infection at the time of starting antibiotics
- critically ill babies (that is, those requiring organ support, such as ventilation, and those in critical care settings [babies in intensive care and high dependency care, rather than those in special care or transitional care])

- clinically well babies who are still receiving antibiotics
- babies who are being observed after completion of antibiotics.

The GDG recognised that care setting for the woman in terms of planning place of birth is covered by Intrapartum care, (NICE clinical guideline 55, 2007) and is therefore outside the scope of this guideline.

Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/cg149/.

Research recommendations

Number	Research recommendation
	Care setting
RR 14	What is the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection? Why this is important The systematic reviews conducted for the guideline identified very limited evidence in relation to care setting. Further research is needed to evaluate the clinical and cost effectiveness of different models of care for the prevention and treatment of early-onset neonatal infection. This is important because of the need to support informed choice relating to care setting during labour, birth and the postnatal period. The research should include consideration of the competencies required to deliver particular aspects of care (such as intrapartum antibiotic prophylaxis), the implications of transfer between different care settings (such as transfers to or from the woman's home or a stand-alone midwifery unit), and family preferences, including the balance between choice and safety. The models of care should be specified, including exposure to medication. The potential benefits and harms of each component should be considered as part of the evaluation of clinical and cost effectiveness.

13 Health economics

13.1 Introduction

Health economic analysis in a clinical guideline can support and strengthen recommendations by making explicit comparisons between different treatment strategies in terms of their costs and effectiveness. Where an alternative treatment or testing strategy costs more but has better outcomes than the status quo or next best alternative, economic evaluation can provide guidance as to whether the additional cost represents good value to the NHS compared with all possible other uses for those same resources. The results of cost effectiveness analyses can be used to maximise health gain from the resources available and make decisions about NHS resource use more transparent and defendable.

Cost effectiveness analysis, with the units of effectiveness expressed in quality adjusted life years (QALYs), is widely recognised as a useful approach for measuring and comparing different health interventions. Using the QALY as the final outcome allows measurement of the impact of health care in terms of how it extends life as well as how it affects health-related quality of life. Using this generic outcome allows different treatments to be compared using the same threshold for decision making.

Ideally a cost effectiveness analysis would be based on data from a random sample of the patient population (Drummond 2001). The evidence available for analysis in this guideline is derived from clinical trials, observational studies and case studies. Economic models should be underpinned by the highest quality clinical evidence available. Where these data are completely lacking, a model can still be developed using the best available evidence, such as clinical opinion or consensus, and subjecting the model assumptions to a sensitivity analysis. This is done by identifying the most appropriate inputs for a 'base case' and varying the inputs to see how they impact the cost effectiveness results. Sensitivity analysis assesses how important a particular assumption or model parameter is in determining whether an intervention is cost effective compared to the next best alternative.

The perspective of the analyses conducted for this guideline is the NHS. Therefore, only costs and benefits to the NHS are considered. There may be further costs to parents due to lost productivity if a baby remains in hospital unnecessarily, but these will not be included in the guideline analyses because the costs are not incurred by the NHS. This allows decision making to be consistent for different treatments and different patient populations.

The following areas were prioritised for health economic analysis at the beginning of the guideline development process:

- reacting to different risk factors, singly or in combination
- investigations (tests) such as C-reactive protein (CRP), procalcitonin, white blood cell (WBC) count, platelet count, full blood count, lumbar puncture, polymerase chain reaction (PCR), investigations specific to urinary tract infection (for example suprapubic aspirates), surface swabs and gastric aspirates
- intrapartum antibiotic prophylaxis for prevention of early-onset neonatal infection compared with no treatment
- antibiotic treatment regimens in babies with:
    - confirmed early-onset neonatal infection (bacterial cause identified)
    - presumed symptomatic infection but no bacterial cause identified
    - initial clinical suspicion of infection, but no ongoing clinical concerns and all investigations normal
    - asymptomatic babies receiving prophylactic treatment.

- cost effectiveness of different care settings, taking into account the woman's choice as well as the feasibility of delivering a safe standard of care in different settings.

The evidence relating to risk factors (singly or in combination) was limited and the guideline development group (GDG) made recommendations based on consensus. Without evidence on the likelihood of infection according to the presence of individual risk factors or groups of risk factors, it was not possible to develop a model to compare factors for identifying infection that would have reduced the uncertainty in the clinical evidence.

The clinical evidence relating to diagnostic tests highlighted CRP in symptomatic babies as a useful test for both ruling in and ruling out infection. Therefore a health economic analysis was conducted to compare various strategies involving CRP tests. For asymptomatic babies low peripheral WBC count (4.99×10^3/microlitre or less) and a low absolute neutrophil count (0.99×10^3/microlitre or less) obtained at least 4 hours after birth had a significantly higher positive likelihood ratio than measurements obtained at other times. Uncertainty arose as to whether or not testing should be performed in asymptomatic babies, and a health economic analysis that addresses this is presented in this chapter.

Two published health technology assessment reports (HTAs) that considered intrapartum antibiotic prophylaxis by risk groups were identified in the literature (see Section 13.2).

The evidence comparing different antibiotics, dosages and duration of treatment was limited. Therefore it was not possible to develop health economic models to aid decision making which compared antibiotics, their benefits and associated adverse events. A health economic analysis was conducted to consider the duration of antibiotic treatment in babies with suspected sepsis who are found to have no infection.

The clinical evidence available regarding cost effectiveness of different care settings was extremely limited, and so a health economic model focusing specifically on this review question would not have helped decision making. Different settings are discussed in the other health economic evaluations presented in this chapter.

13.2 Review of published health economic evidence

Evidence summary

Two HTAs were identified in the literature review for intrapartum prophylaxis (Colbourn 2007; Daniels 2009). Although neither HTA directly answered the review question on intrapartum prophylaxis for the prevention of early-onset neonatal infection, the HTAs provide useful cost effectiveness evidence to support decision making. Antibiotic prophylaxis is used to prevent both early- and late-onset neonatal infection. As this guideline is concerned only with early-onset neonatal infection Colbourn 2007 was excluded from the review of clinical effectiveness (because it included both early- and late-onset neonatal infection) and it was, therefore, excluded from this health economics review too. The primary outcome in Daniels 2009 was avoidance of deaths associated with early-onset group B streptococcus (GBS), with early-onset GBS disease avoided as the secondary outcome. The Daniels 2009 HTA is reviewed below.

Evidence review – Daniels 2009

This HTA (Daniels 2009) determined the accuracy, acceptability and cost effectiveness of PCR and optical immunoassay (OIA) rapid tests for maternal GBS colonisation in labour. All results from this HTA are reported here for completeness, but rapid tests were not evaluated as part of this guideline, and so the GDG disregarded the results from these strategies in terms of its decision making and formulation of recommendations.

The study involved two large obstetric units in the UK, including all women booked for delivery at the participating units other than for elective caesarean section. Swabs for PCR or OIA were tested on the antenatal ward or labour ward by trained midwifery assistants or by research staff.

Apart from collection of swabs from women and their babies, all other aspects of patient management were entirely at the discretion of the local doctors. Treatment decisions were made solely according to established local guidelines, based on presence of risk factors:

- an incidental finding of GBS colonisation or GBS bacteriuria during pregnancy (GBS in the midstream urine specimen or vaginal swab tested opportunistically)
- previous baby with GBS disease
- maternal fever (more than 38°C)
- chorioamnionitis
- prelabour rupture of membranes (PROM) at term for at least 18 hours
- prematurity (less than 37 weeks).

Current practice in the UK was prophylaxis on the basis of risk factors present at the time of labour. Prophylactic agents and dosage regimens were given in accordance with the RCOG guideline for the prevention of early-onset GBS disease (RCOG 2003): intravenous (IV) benzylpenicillin (3 g) given as soon as possible after the onset of labour and 1.5 g given 4-hourly until delivery. Clindamycin 900 mg 8-hourly was used for women who were allergic to penicillin. These antibiotic schedules have not been changed in the updated RCOG guideline (RCOG 2012).

From March 2005 to January 2007 1400 women were recruited to the study, of whom 308 (22.1%) had risk factors. Maternal colonisation, as defined by a positive enriched culture result, was 15.5% from vaginal swabs, 19.2% from rectal swabs and 21.2% if either result was positive. Of 122 women included in the final analysis who received antibiotics, none had any adverse reactions.

Infant colonisation status was determined by 1291 baby ear cultures, of which 109 were culture positive. Ninety-nine babies were born to GBS colonised mothers (as determined by either vaginal or rectal positive culture results).

Cost effectiveness analysis

A decision model was constructed to analyse the following intervention strategies:

- Strategy 1 – routine untargeted prophylaxis to all (treat all)
- Strategy 2 – no screening and no antibiotic prophylaxis (do nothing)
- Strategy 3 – culture of vaginal and rectal swabs taken at 35–37 weeks' gestation
- Strategy 4 – rapid testing during labour using PCR (test 1)
- Strategy 5 – rapid testing during labour using OIA (test 2)
- Strategy 6 – screening using one or more of five risk factors
- Strategy 7 – risk factors and PCR; only test if mother has risk factors
- Strategy 8 – risk factors and PCR; only test if mother has no risk factors
- Strategy 9 – risk factors and OIA; only test if mother has risk factors
- Strategy 10 – risk factors and OIA; only test if mother has no risk factors.

The perspective of the analysis was from the NHS, only including costs relating to the NHS, and the discount rate used was 3.5%. All cost data were reported in UK 2005/2006 prices. The outcomes were cost per case of early-onset GBS disease or associated infant death avoided.

Resource use data associated with risk factor based screening, culture-based screening and carrying out the PCR and OIA rapid tests were collected prospectively alongside the study. Resource use was assessed only in Birmingham because it was the largest centre. Cross-checks were made to confirm that practice or resource use in the different centres did not differ significantly.

Costs attached to the resource use were taken from standard sources: Health Resource Group data, NHS prices, Personal Social Services Research Unit and the Birmingham Women's Hospital.

Accuracy of culture tests at 35 weeks was based on an estimate from literature. Population prevalence of early-onset GBS and infant mortality were sourced from literature.

The overall neonatal colonisation rate was calculated from the new empirical data estimated by the study as it was considered more accurate than estimates from other sources. The calibrated prevalence of early-onset GBS disease, given neonatal colonisation to obtain the 'correct' value of the population incidence of early-onset GBS disease in the absence of systematic screening or widespread prophylaxis, was 0.00518 given colonisation.

Additional mortality due to early-onset GBS disease alone was estimated to be 0.0746.

Two analyses were undertaken:

- All ten alternative strategies for identifying and treating women at risk of GBS were considered.
- A restricted analysis considered only nine strategies (routine prophylaxis was excluded).

It was assumed that all women presenting in labour before 35–37 weeks' gestation would receive intrapartum prophylaxis due to the high risk of early-onset GBS disease associated with preterm birth. This was tested in a sensitivity analysis. This approach was taken from the Public Health Laboratory Service (PHLS) Group B Streptococcal Working Group (PHLS 2001).

The HTA found no primary studies that measured quality of life in children who had experienced and survived early-onset GBS disease.

Probabilistic sensitivity analysis was carried out for the base-case analysis.

Results

If an incremental cost effectiveness ratio (ICER) of £57,038 (Daniels 2009) per additional case of early-onset GBS avoided is considered acceptable, then adopting a strategy of screening based on risk factors as opposed to doing nothing would be the preferred strategy. The ICER of £6,414 per case of early-onset GBS avoided providing routine untargeted antibiotics to all would be the preferred strategy. This result was reported to hold for the majority of sensitivity analyses.

The results were also presented as a cost per early-onset GBS infant death avoided. Screening based on risk factors compared with a strategy of doing nothing resulted in £746,579 per death avoided, and routine untargeted prophylaxis £533,683 per early-onset GBS death avoided.

The ICER of £533,683 per early-onset GBS associated death avoided was converted to a utility on the basis that a life in full health discounted at the rate of 3.5% recommended by NICE is worth approximately 27 discounted QALYS, giving an ICER of £19,766 per QALY.

Representativeness

The study included approximately 10% of the total number of women delivering in the two centres. Proportionally more white women were recruited. Only 2.7% of pregnancies included in the study were premature, lower than the national average of 7.1% of all live births in England and Wales. A greater proportion of women in the study were undergoing induction of labour than the population average (45% versus 18%). Emergency caesarean section was over-represented in the study sample, making up 21.6% of deliveries compared with a national rate of 13.5%. A lower proportion of study participants had risk factors than in other reported studies (22% compared with 28.9%).

Limitations

The full cost associated with prophylaxis was underestimated in the HTA. No costs related to potential resistance to antibiotics or side effects in this population were considered. Prophylaxis would require more women to give birth in hospitals or birthing centres equipped to provide IV antibiotics. The additional demand and its impact on costs to hospitals and delivery units were not incorporated into the HTA analysis. Also, the strategy would not be acceptable to the majority of women who are anxious and resist further medicalisation of childbirth.

In the second analysis, with prophylaxis excluded, the culture test at 35–37 weeks' gestation for all women was shown to be the most cost-effective option, although the ICER was £27,500 per QALY, which is above the NICE threshold for cost effectiveness. It was assumed that women who went into

labour before undergoing this test would receive routine antibiotics. When this assumption was removed the strategy of screening based on risk factors became the most cost-effective option. Also, when the cost of the culture test was increased from £10.63 to £11.50 the strategy based on risk factors became the most cost-effective option.

The costs associated with the strategy of a culture test at 35–37 weeks of gestation were also underestimated as this strategy will impinge on the way that women have traditionally been cared for. For this strategy to be implemented, it would be necessary for large numbers of midwives to be trained in the prescribing and administration of IV antibiotics.

There were limited data on survival and quality of life for babies who experienced early-onset GBS disease and, given the currently available lifesaving techniques to assist preterm babies and those who experience early-onset GBS disease, there was no evidence on quality of life experienced by babies who do survive. Therefore, it was assumed that all babies who survived experienced full health; this assumption is likely to lead to an overestimation of the QALYs gained because a proportion of babies are likely to experience disability due to the infection.

The HTA was unable to determine exactly what constituted current practice for prevention of early-onset GBS disease in babies in the UK. Current practice was thought likely to be heterogeneous with regard to the application of risk factors in terms of whether screening is based on one risk factor, more than one risk factor, or any at all (Cromwell 2007).

Conclusion

The most cost-effective option reported in the HTA was to provide routine antibiotic prophylaxis to all women without screening. As this was thought unlikely to be acceptable to most women and midwives, this option was discarded and the next best alternative was considered; this was screening, based on a culture test at 35–37 weeks' gestation, with the provision of antibiotics to all women who screen positive, assuming that all women in preterm labour would receive prophylaxis.

The results were very sensitive to very small increases in costs and changes in other assumptions.

An article based on the HTA was published in 2010 (Kaambwa 2010). The economic analysis reported similar results. Routine untargeted intrapartum antibiotics prophylaxis was the most cost- effective strategy, with an ICER of £15,815 per QALY when compared with no screening and no intrapartum antibiotic prophylaxis (all other strategies were removed by simple dominance and extended dominance). Tables 13.1 and 13.2 present the results relevant to risk factors and intrapartum prophylaxis.

Table 13.1 Results of the cost effectiveness analysis reported by Kaambwa 2010 for doing nothing, risk factor screening and routine intrapartum prophylaxis to all women, reporting cost per case of early-onset neonatal group B streptococcal disease avoided

Test/treatment combination	Mean cost per woman	% of early-onset neonatal group B streptococcal disease avoided (effect)	Incremental cost	Incremental effect	ICER
No screening and no intrapartum antibiotic prophylaxis	£1058.53	99.952			
Risk factors	£1063.80	99.963	£5.27	0.000107	£49,252
Routine intrapartum antibiotic prophylaxis to all	£1069.93	99.988	£11.40	0.000353	£32,295

ICER incremental cost effectiveness ratio

Table 13.2 Results of the cost effectiveness analysis reported in Kaambwa 2010 for doing nothing, risk factor screening and routine intrapartum prophylaxis to all women, reporting cost per death associated with early-onset group B streptococcal disease avoided

Test/treatment combination	Mean cost per woman	% of early-onset group B streptococcal disease deaths avoided (effect)	Incremental cost	Incremental effect	ICER
No screening and no intrapartum antibiotic prophylaxis	£1058.53	99.996			
Risk factors	£1063.80	99.997	£5.27	0.0000080	£658,750
Routine intrapartum antibiotic prophylaxis to all	£1069.93	99.999	£11.40	0.0000270	£422,222

ICER incremental cost effectiveness ratio

The PHLS 2001 interim guideline was referenced for the assumption that all women presenting in labour before 35–37 weeks of gestation would receive intrapartum prophylaxis. This was based on US data (in the absence of available UK data) and the RCOG report that they have not been widely adopted in the UK (RCOG 2003). The first edition of the RCOG guideline (RCOG 2003) recommended that antibiotic prophylaxis for GBS was unnecessary for women with preterm rupture of membranes unless they were in established labour. The second edition of the RCOG guideline (RCOG 2012) recommends that women presenting in established preterm labour with intact membranes and no other risk factors for GBS should not routinely be offered intrapartum antibiotic prophylaxis unless they are known to be colonised with GBS.

13.3 Health economic analysis

The clinical review of symptoms, signs and risk factors in newborn babies as predictors of early-onset neonatal infection did not identify evidence that demonstrated that any single symptom or sign would be useful for predicting infection. In the absence of evidence, the GDG consensus was that specific risk factors, symptoms and signs identified in isolation were effective 'red flags' for the immediate initiation of antibiotic treatment. In addition, the GDG view was that the identification of more than one risk factor, symptom or sign was suggestive of infection, and antibiotics should be started immediately before testing for sepsis. Diagnostic tests would then be undertaken to determine which babies should continue to receive antibiotic treatment (that is, to determine which babies have confirmed infection). These tests can also determine whether and when to stop antibiotic treatment in babies who have no infection.

The remaining group of babies have only one risk factor which is not considered to be a 'red flag'. The GDG's view was that immediate antibiotic treatment in this group was not necessary. Diagnostic tests can be undertaken to determine which asymptomatic babies may have an infection, and such babies could then begin antibiotic treatment given the increased effectiveness of antibiotics started early in neonates with sepsis who have not yet developed symptoms or signs.

Although this approach was proposed by the GDG based on consensus on clinical effectiveness, the cost effectiveness of alternative strategies for asymptomatic babies with risk factors for sepsis required further health economic evaluation. In addition, the GDG required a health economic analysis to determine the optimal strategy of CRP testing for babies with suspected sepsis.

What is the most cost effective strategy of C-reactive protein testing to rule out early-onset neonatal infection in babies with suspected sepsis?

What duration of antibiotic treatment should be given to babies with suspected sepsis?

After review of the evidence relating to diagnostic tests for babies with suspected sepsis, the following schedules of CRP tests were chosen for analysis:

- Strategy 1 – CRP is measured three times within the first 3 days. For babies with three negative test results (CRP less than 10 mg/l) and who are considered well by clinicians, antibiotic treatment stops at 3 days and the baby is discharged home. For babies with a positive test result at any of the three tests treatment continues.
- Strategy 2 – CRP measured at 8–16 hours after presentation and again with an interval of 18–24 hours between the two samples. For babies with two negative tests and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test result at any of the two tests treatment continues.
- Strategy 3 – CRP is measured at presentation and again at 24 hours. For babies with two negative test results and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test result at either time treatment continues.
- Strategy 4 – CRP is measured at presentation and again at 24 hours. Only the test result at 24 hours is used for diagnosis, with the test result at presentation used only for comparison. For babies with a negative test result at 24 hours and who are considered well by clinicians, antibiotic treatment stops at 36 hours and the baby is discharged home. For babies with a positive test at 24 hours treatment continues.

Better diagnosis could reduce the number of babies treated unnecessarily. More timely diagnosis would allow antibiotics to be stopped promptly in babies who do not have an infection. The following analysis was developed as the GDG felt that current diagnostic testing and treatment strategies vary considerably in the UK. The GDG considered that strategy 1 was a good representation of current practice. Babies with suspected infection are kept in hospital for 2–5 days for antibiotic treatment when sepsis is suspected. The CRP test at presentation is used to prompt a lumbar puncture where meningitis is suspected and is likely to lead to a quicker diagnosis.

Methods

A model was developed in Microsoft Excel©. The perspective of the analysis was the NHS; only costs and benefits to the NHS were considered. The discount rate used was 3.5% and the cost year was 2010.

Population

The population in the model was all live births: 706,248 in England and Wales in 2009 (ONS 2010). Although the actual infection rate is low, at 1,002 cases per year (Table 13.3), the number of babies who are screened for an infection is approximately 10–12% of all live births (Bedford Russell 2010; Luck 2003). The number of babies suspected of having sepsis in the model is calculated as 70,625.

The suspected sepsis rate was taken from a study in a south London hospital over 1 year. The view of the GDG was that this seemed high, but no further evidence was identified and so the baseline in the model was 10% with a range from 7% to 12% tested.

The incidence of early-onset neonatal infection is taken from an HTA (Colbourn 2007) which used systematic reviews and analyses of primary data to populate an economic analysis in a UK setting (Table 13.3). The incidence of GBS and non-GBS infections was presented for term and preterm babies. The incidence of infection is higher in preterm babies, although only 6.8% of live births are preterm (HSCIC 2011). Meningitis is often a more serious infection and requires longer treatment. The proportions of infections that are due to meningitis are shown in Table 13.3.

Table 13.3 Clinical inputs

Input	Mean	Lower 95% CI	Upper 95% CI	Source
Population				
Number of live births	706,248			ONS 2010
Rate of suspected sepsis	10%	7% (estimate)	12% (estimate)	Bedford Russell 2010; Luck 2003
Term babies	93.2%			HSCIC 2011
Incidence of infection				
Term incidence of early-onset GBS	0.38 per 1000 live births	0.33	0.42	Colbourn 2007
Preterm incidence of early-onset GBS	1.84 per 1000 live births	1.53	2.19	Colbourn 2007
Term incidence of early-onset non GBS	0.5 per 1000 live births	0.36	0.65	Colbourn 2007
Preterm incidence of early-onset non GBS	6.97 per 1000 live births	5.19	9.01	Colbourn 2007
Early-onset GBS preterm meningitis	10.1%	5.6%	15.6%	Colbourn 2007
Early-onset GBS term meningitis	11.9%	8.1%	16.4%	Colbourn 2007
Early-onset non-GBS preterm meningitis	4.5%	1.8%	9.4%	Colbourn 2007
Early-onset non-GBS term meningitis	20.1%	9.3%	39.8%	Colbourn 2007
Diagnostic tests				
CRP > 10 mg/l at either presentation or 24 hours - sensitivity	92.6%			Calculated
CRP > 10 mg/l at either presentation or 24 hours - specificity	80.9%			Calculated
CRP > 10 mg/l at 24 hours - sensitivity	92.9%	87.5%	98.4%	Benitz 1998
CRP > 10 mg/l at 24 hours -specificity	83.9%	81.5%	86.3%	Benitz 1998
CRP > 10 mg/l At any of the next two mornings after presentation in the prediction of infection within the first 3 days of life - sensitivity	97.6%	95.8%	98.8%	Benitz 1998
CRP > 10 mg/l At any of the next two mornings after presentation in the prediction of infection within the first 3 days of life - specificity	79.0%	76.3%	81.7%	Benitz 1998
CRP > 10 mg/l At any three readings in the prediction of infection within the first 3 days of life - sensitivity	97.8%	96.2%	98.9%	Benitz 1998

Input	Mean	Lower 95% CI	Upper 95% CI	Source
CRP > 10 mg/l At any three readings in the prediction of infection within the first 3 days of life - specificity	76.3%	73.5%	79.1%	Benitz 1998
Mortality				
Mortality - term early-onset GBS with meningitis	11.1%	3.9%	28.1%	Colbourn 2007; BPSU database 2005
Mortality - term early-onset GBS bacteraemia alone	5.0%	2.7%	9.0%	Colbourn 2007; BPSU database 2005
Mortality - term early-onset non-GBS	15.2%	5.2%	34.4%	Colbourn 2007; BPSU database 2005
Mortality - preterm ly-onset with meningitis	23.1%	8.2%	50.3%	Colbourn 2007; BPSU database 2005
Mortality - preterm early-onset GBS bacteraemia alone	17.2%	11.5%	25.1%	Colbourn 2007; BPSU database 2005
Mortality - preterm early-onset non-GBS	15.1%	6.8%	29.3%	Colbourn 2007; BPSU database 2005
Disability due to infection				
No disability - bacteraemia	74.6%	64.1%	83.8%	Colbourn 2007
Mild disability - bacteraemia	4.5%	1.1%	10.0%	Colbourn 2007
Moderate disability - bacteraemia	13.9%	7.2%	22.2%	Colbourn 2007
Severe disability - bacteraemia	7.0%	2.3%	13.8%	Colbourn 2007
No disability - meningitis	61.5%	53.5%	68.9%	Colbourn 2007
Mild disability - meningitis	19.6%	14.0%	26.7%	Colbourn 2007
Moderate disability - meningitis	12.8%	8.4%	19.2%	Colbourn 2007
Severe disability - meningitis	6.1%	3.2%	11.2%	Colbourn 2007
Life expectancy				
Life expectancy - no disability or mild disability	78.5	78.4	78.5	Colbourn 2007
Life expectancy - Moderate disability	67.8	38.1	78.5	Colbourn 2007
Life expectancy - Severe disability	26.1	14.5	38.8	Colbourn 2007

CI confidence interval, CRP C-reactive protein, GBS group B streptococcus

Diagnostic tests

Evidence was presented in the review of clinical evidence for a number of diagnostic tests for babies with suspected sepsis who are receiving antibiotics (see Chapter 10). The test strategy that was found to give the best positive and negative likelihood ratios (LRs) in the prediction of infection within

the first 3 days of life was CRP of more than 10 mg/l at any of the next two mornings after presentation.

It was suggested that two CRP tests could be given more efficiently if the first was at presentation and the second at 24 hours. As a full blood count is performed at presentation for all babies with suspected sepsis, measuring the CRP concentration at presentation (that is, from the same blood sample used to perform the full blood count) would reduce workload, and be preferable for parents and carers because blood samples would be taken from the baby twice rather than three times. The sensitivity and specificity of this strategy was calculated using data from Benitz 1998. The serum CRP levels were taken at the initial evaluation and with at least 8 hours between the first two measurements. For this analysis, these results were assumed to approximate to a CRP test at presentation and then again at 24 hours. As Benitz 1998 reported the diagnostic value of a delayed CRP test alone (taken here to represent a test at 24 hours), the strategy of testing at presentation and at 24 hours, but only using the 24-hour test results for diagnosis was also considered.

The comparator for the model was three readings of CRP more than 10mg/l within the first 3 days of life to reflect the length of antibiotic treatment given for suspected sepsis as the baseline (Table 13.3).

Costs

The costs of the CRP tests were assumed to be the same as a blood test. Blood is taken from a baby by a band 6 nurse and this takes 10 minutes. There is also a cost for the pathology services of haematology at £3 per test (DH 2011); see Table 13.4. The total cost of a test is £11.69.

Staffing costs are taken from the Personal Social Services Research Unit publication Unit costs of health and social care (Curtis 2011) which is published annually. These are nationally-applicable unit costs for health services. They include long-term components such as costs of qualifications for health service workers and so provide a complete picture of the opportunity costs of staff time.

Table 13.4 Cost inputs (except costs of consumables for blood tests and antibiotics, see Table 13.5)

Cost category	Input	Unit cost	Source	
Costs related to blood test				
Band 6 nurse 10minutes	£8.33	£50 per hour (including qualifications)	Curtis 2011	
Haematology - pathology	£3	£3	DH 2011	
Costs related to hospital stay				
Average cost of an excess bed day linked to birth[a]	£452		Calculated DH 2011	
Incremental cost of neonatal critical care above the cost of a bed day related to birth for first 2 days of stay	£468 - £452 = £16		Calculated	
Additional cost for hospital stay for a premature baby with infection	£300		Estimate	
Costs related to antibiotics				
Benzylpenicillin	£0.95 600 mg vial	50 mg/kg in 2 divided doses	RPSGB http://www.medicines.org.uk/emc/ (accessed July 2011)	2011

Cost category	Input	Unit cost	Source
Gentamicin	£1.80 10 mg/ml 2 ml vial	4–7 mg/kg per day as a single dose, given once every 36 hours	RPSGB 2011 http://www.medicines.org.uk/emc/ (accessed July 2011)
Band 5 nurse 10 minutes	£6.67	£40 per hour (including qualifications)	Curtis 2011
Registrar 10 minutes	£10.33	£62 per hour (including qualifications)	Curtis 2011
Number of days of antibiotics – bacteraemia	7		GDG recommendation
Number of days of antibiotics – meningitis	10		GDG recommendation
Monitoring costs for gentamicin	£11.69		As for blood test Monitoring after second dose and every third subsequent dose – GDG recommendation
Long-term costs related to disability per year[b]			
Mild/moderate disability	£29,389		Colbourn 2007, Trotter and Edmunds 2002
Severe disability	£740		Colbourn 2007; Trotter and Edmunds 2002

[a] This is the weighted average cost of an excess bed day linked to birth health resource groups from the NHS reference costs for 2009-10

[b] 2000 costs uplifted to 2010 prices using Hospital and community health services index (Curtis 2011)

Antibiotic treatment

All babies with suspected sepsis are given benzylpenicillin and gentamicin. As each dose requires a new vial to be opened the costs were calculated per vial (Table 13.4). The dose reported in the summary of product characteristics (SPC) is used in the model. The frequency of benzylpenicillin administration was taken from the SPC and the frequency of gentamicin administration is from the GDG's recommendation.

The antibiotics are administered intravenously by infusion. A cannula is inserted at the beginning of treatment by a registrar; this is estimated to take 10 minutes. A new cannula needs to be inserted every 72 hours (NCC-WCH 2010). Administering each dose requires 10 minutes of time of a band 5 and a band 6 nurse; one to administer the dose and one to supervise (Table 13.5). As well as staffing costs there are consumables needed to prepare the antibiotics, insert the cannula and give the treatment. The consumables needed were identified in a recent analysis (NCC-WCH 2010) and the costs have been updated for this guideline (Table 13.5).

Table 13.5 Unit costs for consumables for cannula insertion, antibiotic dose preparation, infusion, and blood test (updated from NCC-WCH 2010)

Item	Quantity	Cost	Unit cost	Anti-biotic dose	Cannula insertion	Infu-sion	Blood test	Source
Normal saline flush: 10ml ampoule	1	£0.46	£0.46	Y	Y	Y	N	RPSGB 2011
10 ml leur lock syringe	1	£27 per 100	£0.27	N	N	Y	N	medisave.co.uk[a]
Manometer extension line (50 cm)	1	£1.71	£1.71	N	N	Y	N	NHS supply chain 2007[b]
Heparin sodium solution flush: 5ml ampoule	1	£1.00	£1.00	Y	Y	N	N	RPSGB 2011[c]
5 ml syringe	1	£7.79 per 100	£0.08	Y	N	N	N	firstaidwarehouse.co.uk[a]
2 ml syringe	1	£22.08 per 100	£0.22	Y	N	N	Y	As above
Needle	1	£4.90 per 100	£0.05	Y	N	N	Y	As above
Non-sterile gloves	1	£5.58 per 100	£0.06	N	Y	N	Y	As above
Clinell wipe	1	£6.67 per 200	£0.03	N	Y	N	Y	spservices.co.uk[a]
IV giving set-single	1	£1.75	£1.75	N	Y	N	N	As above
500ml bag of dextrose/saline	1	£1.15	£1.15	N	Y	N	N	Baxter[d]
Cannula t-piece extension (t-connector)	1	£1.50	£1.50	N	Y	N	N	NHS supply chain 2007[e]
Splint	1	1	£1.00	N	Y	N	N	NCC-WCH 2010[f]
Mediplast tape	0.01	£0.30	£0.30	N	Y	N	N	RPSGB 2011[g]
Bandage to secure splint	0.01	£0.30	£0.30	N	Y	N	N	RPSGB 2011[h]
Sterile occlusive dressing	0.01	£1.36	£1.36	N	Y	N	N	RPSGB 2011[i]
Total cost per dose/ insertion/infusion				**£1.06**	**£6.22**	**£2.49**	**£0.36**	

IV intravenous, N no, Y yes

RPSGB 2011 (British National Formulary for Children 2011–12)

[a] Accessed July 2011

[b] Price if bought in a box of 50: £1.56; updated to 2009/10 prices using HCHS index (Curtis 2010)

[c] Heparin Sodium solution 10 units/ml, 5 ml amp = £1

[d] Accessed February 2010

[e] IV accessory: T connector £1.37 each for 50 box order; updated to 2009/10 prices using HCHS index (Curtis 2010)

[f] This price was an estimate from a GDG member of the meningitis guideline

[g] Mediplast 5 m, 1.25 cm = 30p, assume 5 cm per cannula

[h] System 4 #1 padding, absorbent, 3.5 m unstretched, 10 cm = 60p, assume 5 cm needed

[i] Water-impermeable plastic film spread with an adhesive film 2.5 cm x 3 m = £1.36

Giving antibiotics as an infusion also requires a syringe driver. The initial cost of this equipment is high, but it can be used for a number of years before the equipment needs to be replaced. There are two elements to the capital cost: the opportunity cost and the depreciation cost. The opportunity cost is the money spent on the equipment that could have been invested in some other venture, yielding positive benefits. This is calculated by applying an interest rate to the sum invested in the equipment. The depreciation cost also has to be included as the equipment has a certain lifespan and depreciates over time, and eventually, the equipment has to be replaced.

To obtain a cost as an input to the health economic model the initial capital outlay is annuitised over the expected life of the equipment. This gives an 'equivalent annual cost' which can then be apportioned to the procedure on a pro rata basis based on the typical equipment use over the course of the year in order to derive a unit cost of using that equipment. Calculating the equivalent annual cost means making an allowance for the differential timing of costs by discounting.

The formula for calculating the equivalent annual cost is

$$E = (K - [S \div \{1 + r\}n]) \div A(n, r)$$

where:

E = equivalent annual cost

K = purchase price of equipment

S = resale value

r = discount (interest rate)

n = equipment lifespan

A(n, r) = annuity factor (n years at interest rate r).

The calculations used in Bacterial meningitis and meningococcal septicaemia (NICE clinical guideline 102, 2010) were recalculated using the 2011 price for a syringe driver. The cost per infusion for the syringe driver is £0.04 (see Table 13.6).

Table 13.6 Inputs to calculate annual equivalent cost of equipment for infusions

Equipment costs	Unit cost[a]	Total cost	Resale value	Life years	Discount rate	Infusion time (minutes)
Infusion pump	£960	£960	£0	3	3.50%	30

[a] Grasely MS16A hourly rate syringe driver (30 to 60 minutes) www.medisave.co.uk (accessed November 2011)

Additional blood tests are needed when giving gentamicin because the effects of gentamicin are dependent on concentration. Adverse effects of gentamicin (particularly in relation to kidney function and hearing) are closely related to the total amount of the drug in the circulation (as measured by the area under the concentration:time curve). The clinical evidence was limited for this question and the GDG recommended giving a blood test to monitor gentamicin concentrations after the second dose if

antibiotic treatment was to continue, and every third subsequent dose. The cost of the blood test for monitoring is the same as the cost for a diagnostic test: £11.69 (Table 13.4).

Antibiotics are given to all babies with suspected sepsis for 3 days as a baseline (where three CRP test are performed) and for 36 hours in the comparator arms (where only two CRP tests are performed). Babies who have positive test results will continue antibiotic treatment to receive a total of 7 days of antibiotics for bacteraemia and 10 days for meningitis (as recommended by the GDG). It is assumed that these babies would be treated in neonatal special care as they are being given intravenous antibiotics.

NHS reference costs present aggregated cost and activity data from all provider organisations in the UK (DH 2011). Health resource groups (HRGs) are defined by clinicians and reflect clinical practice in the UK, and they provide standard groupings of similar treatments that use similar resources. The unit costs include:

- direct costs associated with a particular activity (for example staff costs)
- indirect costs shared among a number of activities (for example, laundry and lighting)
- overheads relating to the overall running of the organisation (for example finance and human resources).

The reference cost chosen to represent 1 day in hospital relates to the neonatal special care description that had the most activity in the year 2009–2010 (Table 13.5). Babies born after 37 weeks of gestation would have been discharged after an average of 2.67 days (this is the weighted average length of stay for all HRGs for births in the NHS reference costs 2009–10) and so may require an additional stay in hospital. Therefore, for the first 2 days the incremental cost of neonatal special care above the cost of 1 day of postnatal care in hospital linked to the birth is used (Table 13.4) and the full bed day costs for neonatal special care is applied after the first 2 days.

Babies born prematurely are generally kept in hospital after birth for reasons unrelated to infection, so the cost of a bed day is not included for premature babies, but a cost to reflect the increased resource use for treating an infection is included (Table 13.4). This cost is applied as soon as the baby is suspected of having an infection.

Long-term costs related to disability are also included (Table 13.4).Trotter and Edmunds 2002 reported an annual cost of care for mild or moderate disability and severe disability following meningococcal disease. These costs were applied to both bacteraemia and meningitis in the model.

Outcomes of treatment

Babies can die from an early-onset neonatal infection. The mortality rate varies depending on the type of infection and whether the baby was term or preterm (Table 13.3). Meningitis is a more serious infection and has a greater mortality risk. Premature babies are less able to successfully fight an infection even with appropriate treatment. With a perfect diagnostic test where all cases are identified accurately, the number of deaths, given 1002 cases of true infection, would be approximately 123 per year: 61 would be term babies (N=658,223 live term births) and 62 preterm (N= 48,025 live preterm births).

For babies who are treated successfully with antibiotics there is a risk of disability due to the infection (see Table 13.3). As with mortality the risk of morbidity is higher with meningitis than with bacteraemia. The same rate of disability was applied to term and preterm babies.

For false negative cases it is assumed that a baby is discharged after the initial period of antibiotics (at either 36 hours or 3 days) but is readmitted because illness recurs. No mortality or morbidity data were identified for this group. The GDG reported that mortality decreases significantly if antibiotic treatment can be started before symptoms and signs develop. In the readmitted group, all babies were initially treated with antibiotics as they were suspected of having an infection. Therefore, mortality and morbidity was assumed to be only slightly increased in this group as it was assumed that babies would be readmitted promptly if further symptoms and signs develop after discharge. The estimated base case increase in the relative rate of mortality is 2% to reflect the impact of delayed treatment, and this can be changed in the model. This increase was applied to the rates of mild, moderate and severe disability as well as mortality. Hence, in strategies where more babies with a

true infection are falsely diagnosed as uninfected they are discharged too early and are then readmitted for further treatment, but this interruption of treatment results in increased mortality and morbidity.

Quality adjusted life years

Utility values related to disability were taken from EQ-5D reference values (Colbourn 2007; see Tables 13.7 and 13.8). Utility values can range from 0 to 1, with 0 being death and 1 being full health. The health-related quality of life of a baby who develops a severe disability due to infection was half that for a baby with no disability. The utility values are of the long-term consequences of meningitis or sepsis such as deafness, epilepsy and mild mental 'retardation'. These utility values have been questioned in more recent evaluations (Kaambwa 2010) and so these values were tested in the model. The reduction in quality of life over time was reported for babies with no disability and the rate of reduction was applied to moderate and severe disability as the reduction over time was not reported in the literature.

Table 13.7 Utility values over time for babies with no disability (Colbourn 2007; Kind 1999; Oostenbrinka 2002)

No disability at age (years)	Mean	Standard deviation
< 25	0.94	0.12
25–34	0.93	0.15
35–44	0.91	0.16
45–54	0.85	0.25
55–64	0.80	0.26
65–74	0.78	0.26
> 75	0.73	0.26

Table 13.8 Utility values for babies with a disability (Colbourn 2007; Kind 1999; Oostenbrinka 2002)

Level of disability	Mean (years)
Moderate disability	0.67
Severe disability	0.47

The utility values were applied to each year of life based on the life expectancy related to disability (see Table 13.3). As these are effects that occur in the future these values were discounted by the NICE recommended rate of 3.5% to reflect time preference. Future health gains were discounted to reflect the fact that people would typically place more value on health gain in the present than health gain delayed until some time in the future.

Results

Of the 706,248 live births in England and Wales, 70,298 babies will be suspected of having an infection and will be started on antibiotics immediately. The sensitivity of the CRP tests increases over time (see Table 10.3). Tests conducted at 24 hours and later are better at detecting babies who have an infection than the CRP test performed at presentation. The specificity decreases over time, and babies without an infection are more likely to have a negative test result at presentation than from CRP tests performed later.

Testing only twice and giving 36 hours of antibiotics is cost saving compared to testing three times over 3 days and giving 3 days of antibiotics (Table 13.9).

Strategy 3 (CRP tests at presentation and 24 hours with 36 hours of antibiotics) has the fewest QALYs. This is strategy has the lowest sensitivity and so the highest rate of false negative test results.

Strategy 4 (CRP tests at presentation and at 24 hours, with only the 24 hour result used for diagnosis, and 36 hours of antibiotics), was slightly more effective and was less expensive than strategy 3. Strategy 3 is said to be dominated by strategy 4 and is, therefore, ruled out.

Strategy 2 (two CRP tests over two consecutive mornings with 36 hours of antibiotics) is less expensive and more effective than strategy 1, and so strategy 1 is dominated and, therefore, ruled out.

The comparators left are strategies 2 and 4. The ICER of strategy 4 compared with strategy 2 was £1,324,094 per QALY gained. This is much higher than the NICE threshold of £20,000 per QALY and so strategy 2 is not considered cost effective. As shown in Table 13.10, strategy 4 has the highest net benefit with a willingness to pay per QALY of £20,000. Therefore, the additional cost of doing the CRP tests on subsequent mornings rather than at presentation and at 24 hours is not considered to be worth the additional benefit (see Tables 13.9 and 13.10).

Table 13.9 Results for baseline comparison of testing and treatment strategies for suspected sepsis; the strategies are ranked by increasing cost.

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,269,464	20,183.85	£48,936,232	–3.00	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,333,233	20,186.85	£9,910,464	7.48	£1,324,094
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,952,467	20,178.74	£5,529,698	–0.62	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,422,769	20,179.37	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

Table 13.10 Results for baseline comparison of testing and treatment strategies for suspected sepsis presented as net benefits; the willingness to pay for a quality adjusted life year is £20,000

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Net benefits
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,269,464	20,183.85	£265,407,556
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,333,233	20,186.85	£314,403,769
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,952,467	20,178.74	£318,622,424
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,422,769	20,179.37	£324,164,538

CRP C-reactive protein, QALY quality adjusted life year
Net benefit = (total QALYS × £20,000) – total cost

If the three-test strategy with 3 days of antibiotics had 100% specificity and sensitivity it would be more expensive than two CRP tests on the subsequent mornings with 36 hours of antibiotics (strategy 2) and would increase the health benefit by 3.81 QALYs (see Table 13.11). This increase would result in an ICER of £4,995,030 per QALY gained which would not be considered to be cost effective using the NICE threshold. This test accuracy may reflect that keeping a baby who is suspected of having an infection in hospital for 3 days rather than 36 hours would allow clinicians to better observe the baby and be sure of the diagnosis before discharging babies considered well.

Table 13.11 Results of testing and treatment strategies for suspected sepsis assuming 100% sensitivity and specificity for strategy 1: three tests over 3 days

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£108,209,831	20,190.66	£18,876,599	3.81	£4,955,030
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,333,233	20,186.85	£9,910,464	7.48	£1,324,094
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,952,467	20,178.74	£9,910,464	7.48	£1,324,094
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,422,769	20,179.37	£5,529,698	–0.62	Dominated

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

The upper 95% confidence limit for specificity is 81.9%: using this value, strategy 4 would remain the most cost-effective strategy. If the specificity of strategy 2 is increased to 85% then strategy 2 dominates all other strategies (see Table 13.12).

Table 13.12 Results of testing and treatment strategies for suspected sepsis assuming 85% specificity for strategy 2: C-reactive protein tests on 2 consecutive days.

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,269,464	20,183.85	£60,019,603	–3.00	Dominated
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,952,467	20,178.74	£6,702,606	–8.11	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,422,769	20,179.37	£1,172,908	–7.48	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£78,249,862	20,186.85	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the sensitivity of strategy 4 is increased to 98.4% (the upper 95% confidence limit for the estimate), then it becomes the dominating strategy (see Table 13.13).

Table 13.13 Results of testing and treatment strategies for suspected sepsis assuming 98.4% sensitivity for strategy 4: C-reactive protein tests at presentation and at 24 hours; only 24-hour result used for diagnosis

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,269,464	20,183.85	£48,936,232	–3.00	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,333,233	20,186.85	£9,978,237	–1.25	Dominated
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,952,467	20,178.74	£5,597,472	–9.36	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,354,996	20,188.10	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the rate of suspected sepsis is lower, at 7%, the direction of the results does not change with strategy 4 remaining the most cost- effective strategy. The benefits remain the same because the rate of true infection does not change. There is no health-related quality of life decrement for having treatment unnecessarily because of false positive tests results. The costs are lower because the number of babies treated would be lower.

Table 13.14 Results of testing and treatment strategies for suspected sepsis assuming 7% of live births are suspected of having sepsis.

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£107,533,522	20,183.85	£34,072,524	–3.00	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£73,460,998	20,186.85	£6,884,155	7.48	£919,762
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£70,427,476	20,178.74	£3,850,633	–0.62	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£66,576,843	20,179.37	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the rate of suspected sepsis is higher, at 12%, again the direction of the results does not change, with strategy 4 remaining the most cost effective strategy. The costs increase in this analysis because more babies will be treated.

Table 13.15 Results of testing and treatment strategies for suspected sepsis assuming 12% of live births are suspected of having sepsis.

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3consecutive days with 3 days of antibiotics	£158,760,092	20,183.85	£58,845,370	–3.00	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£99,914,722	20,186.85	£11,928,002	7.48	£1,593,649
Strategy 3: CRP tests at presentation and at 24hours, with 36 hours of antibiotics	£94,635,795	20,178.74	£6,649,075	–0.62	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£87,986,720	20,179.37	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the relative increase of morbidity and mortality associated with infection is only 1%, rather than 2%, then the increase in health benefits of strategy 2 is reduced and the ICER increases to £1,884,567 per QALY gained (see Table 13.16).

Table 13.16 Results of testing and treatment strategies for suspected sepsis assuming a 1% relative increase in morbidity and mortality if the baby is readmitted because of false negative test results

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,256,984	20,185.87	£48,930,734	–2.11	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,326,250	20,187.98	£9,924,184	5.27	£1,884,576
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,930,626	20,182.28	£5,528,560	–0.44	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,402,066	20,182.71	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the relative increase of morbidity and mortality associated with infection is higher, at 4%, then the increase in health benefits of strategy 2 is increased, but the ICER is still much greater than the NICE threshold of £20,000 per QALY (see Table 13.17).

Table 13.17 Results of testing and treatment strategies for suspected sepsis assuming a 4% relative increase in morbidity and mortality if the baby is readmitted because of false negative test results

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,294,309	20,179.82	£48,947,175	–4.77	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,347,134	20,184.60	£9,883,152	11.91	£829,706
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£84,995,945	20,171.70	£5,531,963	–0.99	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,463,982	20,172.69	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the incidence of true infection is actually the lower 95% confidence limit for early-onset GBS infection and non-GBS infection (see Table 13.3) then the health benefits are reduced for all strategies. Strategy 4 remains the most cost-effective option.

Table 13.18 Results of testing and treatment strategies for suspected sepsis assuming the rate of true infection is the lower 95% confidence limit

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£130,296,975	15,688.18	£49,072,955	–2.28	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£81,224,020	15,690.46	£9,949,745	5.70	£1,745,440
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£76,819,008	15,684.29	£5,544,733	–0.47	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£71,274,275	15,684.76	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the incidence of true infection is actually the upper 95% confidence limit for early-onset GBS infection and non-GBS infection (Table 13.3) then the health benefits are increased for all strategies. Strategy 3 has greater health benefits than strategy 4, but the additional benefit is only 0.22 and so the increased cost would not be considered to be worth the additional benefit. Strategy 4 remains the most cost effective option.

Table 13.19 Results of testing and treatment strategies for suspected sepsis assuming the rate of true infection is the upper 95% confidence limit

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£146,715,688	24,948.96	£48,791,418	–3.78	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£97,924,269	24,952.73	£9,869,284	9.43	£1,047,086
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£93,568,828	24,942.53	£5,513,842	–0.78	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£88,054,986	24,943.31	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the mortality rate is increased for all infections to the upper 95% confidence limit (see Table 13.3) then strategy 2 becomes more cost effective, but is still not considered cost effective by the NICE threshold (see Table 13.20).

Table 13.20 Results of testing and treatment strategies for suspected sepsis assuming the mortality rate for all infections is the upper 95% confidence limit

Testing and treatment strategy for suspected sepsis	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£133,619,185	17,624.15	£48,927,153	–7.28	Dominated
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£84,692,031	17,631.43	£9,933,115	18.17	£546,580
Strategy 3: CRP tests at presentation and at 2 4hours, with 36 hours of antibiotics	£80,286,736	17,611.75	£5,527,819	–1.51	Dominated
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£74,758,917	17,613.26	-	-	-

CRP C-reactive protein, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

Probabilistic sensitivity analysis

The base-case analysis used point estimates for the input parameters. The effects of uncertainty in point estimates can be addressed through the use of sensitivity analysis in which each parameter value is varied to see how it affects the results. When there are many input parameters, NICE recommends using probabilistic sensitivity analysis (PSA) to characterise uncertainty. This allows several parameters to be varied simultaneously, rather than one at time as in one-way sensitivity analysis. In a PSA each input is assigned a probability distribution which is defined by measures of variability, such as standard deviations (SDs) or confidence intervals (CIs). A Monte Carlo simulation is then set up to sample inputs at random from their assumed distributions. The simulation is run a large number of times (1000 times for this PSA).

Beta distributions were assumed for adverse events related to early-onset neonatal infection. The parameters for the beta distribution are the number of events and the number of non-events. The diagnostic test accuracies of CRP measurements were also assumed to have beta distributions. As sensitivity and specificity are statistically dependent, the beta distribution was applied to the specificity using the numbers of true negative and false positive results as the parameters. The sensitivity was then obtained as a function of specificity using the diagnostic odds ratio (DOR):

sensitivity = 1 – specificity ÷ (specificity + [1 – specificity] × DOR)

Where:

DOR = (TP ÷ FN) × (TN ÷ FP)

TP = true positives

FN= false negatives

TN= true negatives

FP = false positives

NHS reference costs for hospital stay were defined by a normal distribution for neonatal critical care, and a lognormal distribution for bed days linked to the birth, as these distributions provided the best fit to the data. The costs relating to giving antibiotics (drug costs, consumables and the cost of staff required to administer the drugs) and long-term costs of disability remained deterministic because no data were available to define probability distributions.

Parameter estimates based on the GDG's knowledge and experience in the absence of published evidence from clinical studies (for example the proportion of babies with suspected early-onset neonatal infection) have no measures of variability attached that can be used to define useful probability distributions. Not having probability distributions to determine how GDG inputs vary may add uncertainty to the analysis and these inputs remained fixed in this PSA.

The simulation was run and strategy 4 (CRP tests at presentation and at 24 hours, with only the 24hours result used for diagnosis, with 36 hours of antibiotics) was found to have the highest net benefit (see calculation below) in over 90% of simulations when compared to the other strategies.

Net benefit = total cost of strategy – (total QALYs gained by strategy × willingness to pay per QALY).

Across 1000 simulations, strategy 4 had the highest mean net benefit, strategy 1 had the highest mean cost and strategy 2 had the highest health benefit (see Table 13.21).

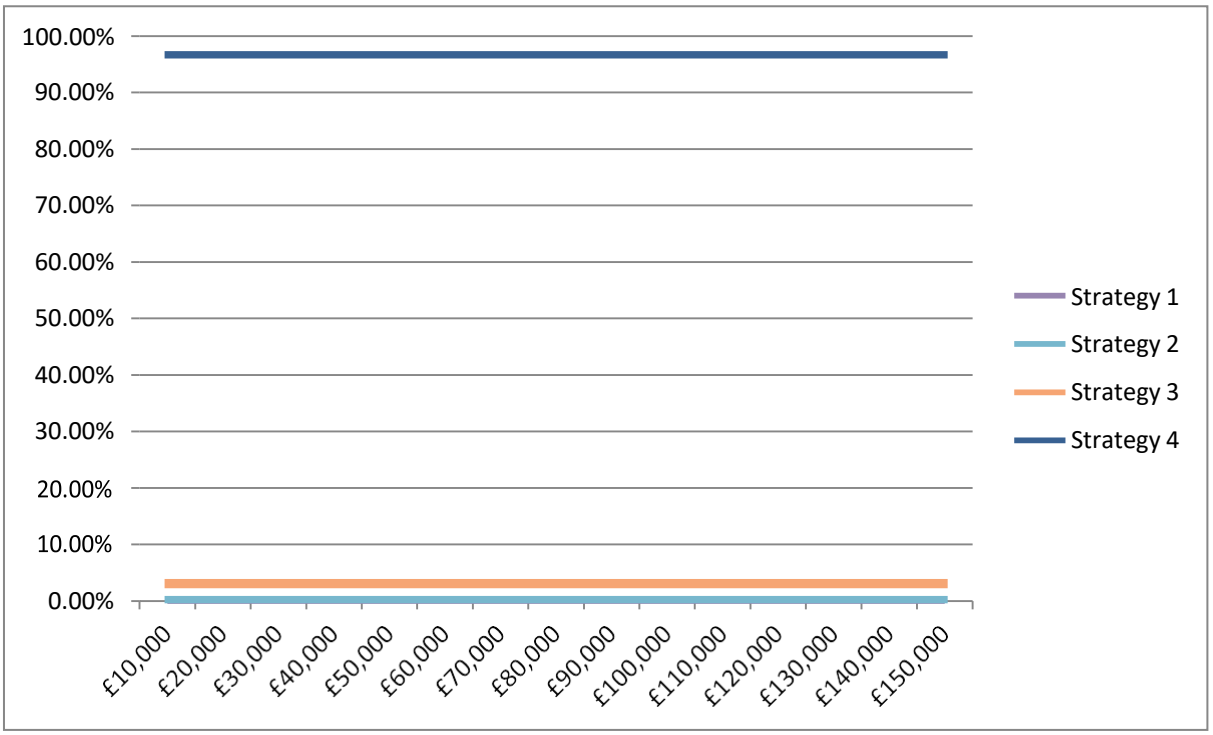
Table 13.21 Mean costs, quality adjusted life years and net benefits from 1000 simulations in the probabilistic sensitivity analysis

Testing and treatment strategy for suspected sepsis	Total cost	Total QALYs	Net benefits
Strategy 1: CRP tests on 3 consecutive days with 3 days of antibiotics	£138,499,738	20,251.27	£266,525,587
Strategy 2: CRP tests on 2 consecutive days with 36 hours of antibiotics	£89,396,794	20,254.18	£315,686,725
Strategy 3: CRP tests at presentation and at 24 hours, with 36 hours of antibiotics	£85,154,020	20,246.24	£319,770,684
Strategy 4: CRP tests at presentation and at 24 hours, only 24 hours result used for diagnosis, with 36 hours of antibiotics	£79,560,943	20,246.81	£325,375,291

CRP C-reactive protein, QALY quality adjusted life year

Varying the willingness to pay per QALY from the NICE recommended value of £20,000 per QALY to £150,000 per QALY did not alter the results, and in 90% of the simulations strategy 4 still produced the highest net benefit. The results of the PSA reflect those seen in the one-way sensitivity analyses where strategy 4 remained the most cost-effective strategy even though in some cases strategy 2 and strategy 3 had higher health benefits (see Figure 13.1).

Figure 13.1 Threshold analysis: probability that a strategy is cost effective by willingness to pay for a quality adjusted life year, ranging from £10,000 to £150,000 per quality adjusted life year



Discussion

Doing a CRP test at presentation alongside the initial blood test, and then again at 24 hours is the most cost-effective strategy. The test at 24 hours is likely to have the most diagnostic value and the results of this analysis suggest that this test alone can be used for diagnosis. Although the health benefits of strategy 3 and 4 are very similar, the additional cost relating to using both test results to diagnose infection suggests that only using the 24 hour test for diagnosis would save costs. In Benitz 1998 the sensitivity of using the test at presentation only was 39.4% compared to over 90% for all other test strategies. However, the test at presentation is still considered important as it may prompt a clinician to perform a lumbar puncture to diagnose meningitis.

The potential cost savings from reducing antibiotic use in suspected sepsis to 36 hours will depend on current practice, which in this model is assumed to be 3 days of antibiotics. Having the tests performed earlier may require additional resources for pathology services and capital costs if more equipment is needed to obtain results within 36 hours. However, reducing the amount of time uninfected babies spend in hospital is likely to save costs.

Key inputs for the model, the sensitivity and specificity of the test and the likelihood a baby would be treated for suspected sepsis were taken from single studies. These parameter values were varied in the model to test the impact of the uncertainty due to limited data.

This analysis includes only mortality and morbidity related to infection, and not hospital stay or antibiotic use. Long-term adverse effects have been reported for intrapartum antibiotic prophylaxis (see Chapter 6). As this model relates to administration of antibiotics to the baby, the long-term adverse effects of intrapartum exposure to antibiotics were not included. It has been recommended that babies are observed daily to allow unnecessary antibiotic treatment to be stopped and therefore the adverse impact of antibiotic treatments should be minimised.

The analysis does not include consideration of antibiotic resistance, but given that the false positive rate is lower for the strategy with two tests and 36-hour treatment than keeping babies in hospital for 3 days, then fewer babies should be treated unnecessarily. Thus, the strategy would be unlikely to increase the development of antibiotic resistance compared to current practice.

Treatment for infection is 7 days for bacteraemia and 10 days for meningitis. Consideration of increased duration of treatment due to more severe infection has not been included in this model. It is unlikely that babies with severe infection would be falsely discharged with either testing strategy.

Conclusion

A testing strategy of two CRP tests (at presentation with suspected infection and 24 hours afterwards), with 36 hours of antibiotics, is likely to be cost saving compared to current practice where more than 36 hours of antibiotics are given for suspected sepsis and more than two CRP tests are performed. This strategy will allow babies who have no infection to be discharged earlier than is currently the case.

Is it cost effective to test and treat asymptomatic babies with only one risk factor (compared to observation with treatment given only when symptoms and signs develop)?

The majority of babies considered at risk are started on antibiotics immediately. However, for babies who are asymptomatic but have only one risk factor clinicians would prefer to avoid unnecessary treatment. This has to be balanced against the benefits of beginning treatment before symptoms and signs are evident. This can significantly reduce mortality and morbidity associated with infection, and may reduce the duration of hospital stay.

The strategies to be compared in this model are:

- Strategy 1 – Asymptomatic babies with only one risk factor would not be started on antibiotics immediately and are tested for a low peripheral WBC count (4.99×10^3/microlitre or less) and a low absolute neutrophil count (0.99×10^3/microlitre or less) obtained 4 or more hours after birth. Babies with a low count are started on antibiotics.

- Strategy 2 – Asymptomatic babies with only one risk factor would not be started on antibiotics immediately and are observed. Babies who develop signs or symptoms are started on antibiotics.

Methods

The Microsoft Excel© model developed for the analysis of treatment of suspected sepsis was adapted for asymptomatic babies. The model population relates to term or near-term babies (born at or after 34 weeks of gestation) to reflect the clinical evidence in the review of diagnostic tests for asymptomatic babies.

Population

The population considered in this analysis was term or near-term babies with a risk factor for infection that was not a 'red flag', meaning that the baby would not be started on antibiotics immediately. Approximately 80% of term babies have no risk factors (Colbourn 2007). Therefore approximately 134,174 term and near-term babies have a risk factor and they are included in this model (see Table 13.22). Data were not identified for the number of asymptomatic babies with only one risk factor, or the proportion of asymptomatic babies who have risk factors but are not treated immediately with antibiotics.

Table 13.22 Clinical inputs

Input	N	%	Source
Population			
Number of live births	706,248		ONS 2010
Term and near term babies ≥ 34 weeks of gestation		96%	HSCIC 2011
With risk factors		80%	
Number of term and near term babies with risk factors	134,174		Calculated
Asymptomatic babies with only one risk who are not immediately started on antibiotics	50%	67,087	Estimate
Infection rate	0.5%	335	Estimate
False negative rate of diagnostic test	10%	34	Estimate
False positive rate of diagnostic test	10%	6709	Estimate
False positive rate of observation for symptoms and signs	5%	3354	Estimate
Mortality rate when treatment starts after symptoms and signs develop			
Early-onset GBS	5.73%		Colbourn 2007; BPSU 2005
Non-GBS	15.2%		Colbourn 2007; BPSU 2005
Mortality rate when treatment starts before symptoms and signs develop			
Relative risk reduction	20%		Estimate
Early-onset GBS	4.58%		Calculated
Non-GBS	12.2%		Calculated

Input	N	%		Source
Disability due to infection				
No disability – bacteraemia	74.6%	64.1%	83.8%	Colbourn 2007
Mild disability – bacteraemia	4.5%	1.1%	10.0%	Colbourn 2007
Moderate disability – bacteraemia	13.9%	7.2%	22.2%	Colbourn 2007
Severe disability – bacteraemia	7.0%	2.3%	13.8%	Colbourn 2007
No disability – meningitis	61.5%	53.5%	68.9%	Colbourn 2007
Mild disability – meningitis	19.6%	14.0%	26.7%	Colbourn 2007
Moderate disability – meningitis	12.8%	8.4%	19.2%	Colbourn 2007
Severe disability – meningitis	6.1%	3.2%	11.2%	Colbourn 2007
Life expectancy				
Life expectancy – no disability or mild disability	78.5	78.4	78.5	Colbourn 2007
Life expectancy – Moderate disability	67.8	38.1	78.5	Colbourn 2007
Life expectancy – Severe disability	26.1	14.5	38.8	Colbourn 2007

GBS group B streptococcus

If 50% of term and near-term babies with risk factors were asymptomatic and had only one risk factor and would not be treated immediately that would equate to a population of N=67,087. All 67,087 babies would be given an additional blood test 4 hours after birth.

Diagnostic test

The most accurate diagnostic test identified for asymptomatic babies was a low peripheral WBC count (4.99×10^3/microlitre or less) and a low absolute neutrophil count (0.99×10^3/microlitre or less) obtained 4or more hours after birth. This had a LR^+ of 115, which is interpreted as how much more likely a baby is to have early-onset neonatal infection given a positive test result compared with the pretest probability of having such an infection. The sensitivity and specificity were not reported in the article from which the LR was extracted, nor could they be calculated from any data reported in the article. Hence it is unknown how likely it is that a baby without an infection will have a positive test result and be treated unnecessarily.

The incidence of infection is known for all live births (see Tables 13.1 and 13.2) but it is not known by risk factor. Therefore the likelihood of true infection in asymptomatic babies with only one risk factor is unknown. The baseline was estimated to be 0.5% (N=335 babies would have a true infection in this group).

The baseline estimates are a 10% false positive rate and 10% false negative rate. The false negative rate will include babies born to women who had intrapartum antibiotic prophylaxis which caused the test result to be negative when an infection is, in fact, present in the baby.

There is also a false positive rate associated with observation, as babies may be mistakenly thought to have symptoms or signs. This again is an unknown input; the baseline estimate is 5%.

The costs of the additional blood test are shown in Table 13.4.

Antibiotic treatment

The treatment costs are as in the previous analysis (see Table 13.4).

It is assumed that these babies would go on to have further tests and treatment will stop once the correct diagnosis has been made (assumed to stop after 36 hours if there is no true infection, thus reflecting guideline recommendations).

For babies who had a true infection identified before symptoms and signs developed it was possible to reduce the duration of treatment and, therefore, hospital stay. Using a conservative assumption, duration of stay for treatment is taken to be the same as for babies who are treated after symptoms and signs develop (see Table 13.4)

Outcomes of treatment

Mortality and disability related to infection are presented in Table 13.22. The mortality and morbidity rates decrease significantly if antibiotic treatment can be started before symptoms and signs develop. The baseline estimate was a relative risk reduction of 20% (see Table 13.24).

Results

The testing strategy costs approximately £1.5 million more than observation, but results in fewer deaths (six deaths prevented per year) and reduces disability due to more timely treatment. This results in testing babies with a risk factor being less expensive and more effective (see Table 13.23).

Table 13.23 Incremental cost effectiveness results with baseline inputs

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£12,846,726	6896	-	-	-
Test all babies with a risk factor within 8 hours	£12,442,816	7159	–£403,910	263.1	Dominant

ICER incremental cost effectiveness ration, QALY quality adjusted life year
Dominant = more effective and less expensive than the comparator

Table 13.24 Net benefit results with baseline inputs (willingness to pay for a quality-adjusted life year £20,000)

Test strategy	Cost	QALYs	Net benefit
Test only if symptoms and signs develop	£12,846,726	6896	£125,063,328
Test all babies with a risk factor within 8 hours	£12,442,816	7159	£130,729,374

QALY quality adjusted life year
Net benefit = total cost of strategy – (total QALYs gained by strategy × willingness to pay per QALY)

The number of babies who would be tested and treated is shown in Table 13.25. Using the baseline inputs would result in 67,087 babies having an additional blood test, of whom 335 would have a true infection. Of babies with a true infection, 301 would have a positive test result and benefit from earlier treatment but 6709 babies would be treated unnecessarily due to a false positive test result.

Table 13.25 Outputs of the model based on estimated inputs for population and for diagnostic test accuracy (see Table 13.3)

Population	N
Asymptomatic babies with only one risk factor who are not immediately started on antibiotics	67,087
Number of babies with a true infection	335
Number of babies with a true infection who will have a false negative test result	34
Number of babies with no infection who would have a false positive test result and start treatment unnecessarily	6709

Changing the true infection rate has a significant impact on the results. If the true infection rate in this population is increased to 1%, then testing becomes more cost saving (Table 13.26). This infection

rate means that 671 cases of infection would be found in this population. This seems unlikely as the number of true infections in all live births in England and Wales was calculated to be 974 and this would mean about 70% of infections occur in babies with only risk factor who would not generally be considered high risk.

Table 13.26 Incremental cost effectiveness results with true infection rate of 1%

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£25,379,698	13,791	-	-	-
Test all babies with a risk factor within 8 hours	£23,050,560	14,317	–£2,329,138	526.2	Dominant

ICER incremental cost effectiveness ratio, QALY quality adjusted life year
Dominant = more effective and less expensive than the comparator

If the true infection rate is reduced to 0.2% of this population, then the ICER increases significantly (see Table 13.27). The same number of babies will be tested and the same number will have a false positive test result, but the number of actual infections that can be identified is lower.

Table 13.27 Incremental cost effectiveness results with true infection rate of 0.2%

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£5,326,943	2758	-	-	-
Test all babies with a risk factor within 8 hours	£6,078,169	2863	£751,226	105.2	£7138

ICER incremental cost effectiveness ratio, QALY quality adjusted life year

Testing all babies remains cost effective according to the NICE threshold if the relative risk reduction in mortality and morbidity is greater than 5%. If the risk reduction is 4% or less, then the incremental cost per QALY is greater than £20,000 (see Table 13.28).

Table 13.28 Incremental cost effectiveness results with the relative risk reduction in mortality and morbidity of 4%

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£12,846,726	6896	-	-	-
Test all babies with a risk factor within 8 hours	£13,984,321	6947	£1,137,595	51.9	£21,899

ICER incremental cost effectiveness ratio, QALY quality adjusted life year

If the utility values associated with disability are varied with the value associated with disability increased, moderate disability having a utility value of 0.77 compared with 0.67 and severe disability having a utility value of 0.57 compared to 0.47, then the ICER increases as the QALY gain is less with testing (see Table 13.27).

Table 13.29 Incremental cost effectiveness results with increased utility associated with moderate and severe disability

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£12,846,726	7039	-	-	-
Test all babies with a risk factor within 8 hours	£12,442,816	7278	–£403,910	239.6	Dominant

ICER incremental cost effectiveness ratio, QALY quality adjusted life year
Dominant = more effective and less expensive than the comparator

Clinicians would prefer to avoid unnecessary treatment for babies who are asymptomatic but have only one risk factor, so the strategy of treating all asymptomatic babies with only one risk factor without testing was not considered in the base case model. The model was run with this treating strategy added. The results of this analysis show that the cost of treating all babies would outweigh the benefits and this strategy has a net loss when compared to testing all babies with a risk factor within 8 hours (see Table 13.30).

Table 13.30 Incremental cost effectiveness results including a strategy of treating all babies with only one risk factor

Test strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Test only if symptoms and signs develop	£12,846,726	6896	-	-	-
Test all babies with a risk factor within 8 hours	£12,442,816	7159	–£403,910	263.1	Dominant
Treat all babies with a risk factor	£16,596,630	7188	£4,153,815	29.2	£142,088

ICER incremental cost effectiveness ratio, QALY quality adjusted life year
Dominant = more effective and less expensive than the comparator

In this strategy all 67,087 babies who are asymptomatic at birth and have only one risk factor would be kept in hospital and started on antibiotics.

Discussion

There is considerable uncertainty in this analysis because a number of inputs are estimated rather than being based on reported data. The population size for this specific group (babies with only one risk factor who would not be started on antibiotics immediately) is unknown. As the testing strategy involves giving blood tests to all babies in this population, knowing the size of the population to be tested is important. The true infection rate in this population is unknown, but is likely to be low. The accuracy of the diagnostic test is also unknown; the LR^+ is very high, but it may result in a large number of babies having false positive test results and being treated unnecessarily.

The model does not take into account place of care as more women may need to give birth in hospital, more hospital beds may be needed and more transfers may be needed to neonatal special care. It also increases the medicalisation of birth which is unlikely to be preferred by pregnant women. This model does not take into account antibiotic resistance from increased antibiotic use or morbidity and mortality caused by the antibiotics. The long-term effects and potential for antibiotic resistance would be most significant if the test has a high false positive rate meaning that more babies would be treated than necessary. The strategy of treating all asymptomatic babies who have a risk factor would be most influenced by these factors making it even less cost effective. Even though this strategy could result in fewer deaths, it significantly increases the number of babies kept in hospital for antibiotic treatment, and the majority will be probably kept in for treatment unnecessarily due to false

positive test results. It was thought that a false negative test result may falsely reassure clinicians and parents and they may be less likely to identify symptoms and signs if they do develop.

The GDG agreed that unnecessary exposure to antibiotics should be avoided. Giving antibiotic prophylaxis would require babies to be in hospital to have intravenous antibiotics for at least 36hours, and the three tests (one blood test and two CRP tests) recommended in the guideline for ruling out infection. The GDG felt that the evidence was not strong enough to recommend testing on this group of babies as a large number of babies would need to have an invasive test for a small number of babies to potentially benefit.

The GDG considered whether a PSA could be conducted to explore the effects of uncertainty in the model inputs. However, as a large number of the key inputs were GDG point estimates (rather than being derived from reported evidence and accompanied by confidence intervals), such an analysis would not be informative and so a PSA was not undertaken.

Conclusion

The consensus of the GDG was that the evidence for the diagnostic test was not strong enough, and the results of the analysis showed too much uncertainty to recommend the additional blood test for this group of babies. Further research in this area is needed.

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15 Abbreviations and glossary

15.1 Abbreviations

CDC	Centers for Disease Control
CI	Confidence interval
CMACE	Centre for Maternal and Child Enquiries
CONS	Coagulase-negative staphylococci
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DH	Department of Health
DOR	Diagnostic odds ratio
E coli	*Escherichia coli*
EU	European Union
FENa	Fractional excretion of sodium
GBS	Group B streptococcus
GDG	Guideline development group
GFR	Glomerular filtration rate
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPA	Health Protection Agency
HRG	Health resource group
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
IL	Interleukin
I:M	Ratio of immature to mature neutrophils
I:T	Ratio of immature to total neutrophils
IU	International unit
IUGR	Intrauterine growth restriction
IV	Intravenous
L monocytogenes	*Listeria monocytogenes*
LA	Latex agglutination
LR	Likelihood ratio

LR^+	Likelihood ratio for a positive test result
LR^-	Likelihood ratio for a negative test result
MD	Mean difference
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
N gonorrhoeae	*Neisseria gonorrhoeae*
N meningitidis	*Neisseria meningitidis*
NAG	N-acetyl glucosamine
NC	Not calculable
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NeonIN	Neonatal Infection Surveillance Network
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal intensive care unit
NPSA	National Patient Safety Agency
NR	Not reported
NS	Not statistically significant
OIA	Optical immunoassay
ONS	Office for National Statistics
OR	Odds ratio
PCR	Polymerase chain reaction
PCT	Procalcitonin
PROM	Prelabour rupture of membranes
PSA	Probabilistic sensitivity analysis
QADAS	Quality Assessment of Studies of Diagnostic Accuracy
QALY	Quality adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RPSGB	Royal Pharmaceutical Society of Great Britain
RR	Relative risk
S pneumoniae	*Streptococcus pneumoniae*
SCBU	Special care baby unit
SD	Standard deviation
SPC	Summary of product characteristics
Staph aureus	*Staphylococcus aureus*
Staph haemolyticus	*Staphylococcus haemolyticus*

Staph hominis	*Staphylococcus hominis*
UNICEF	United Nations Children's Fund
U:S	urine to serum (creatinine) ratio
UTI	Urinary tract infection
WBC	White blood cell

15.2 Glossary

Amniotic fluid	The fluid that bathes the fetus before birth.
Antigen	Any substance that may be specifically bound by any antibody molecule.
Antimicrobial resistance	The ability of micro-organisms to withstand an antibiotic to which they were once sensitive.
Antimicrobial resistance testing	Tests performed on micro-organisms isolated from patients to determine which antibiotics will treat the micro-organisms successfully.
Apnoea	A temporary pause or interruption to breathing.
Bacteria	A type of micro-organism that can cause illness and that can respond to antibiotics.
Bacterial meningitis	Meningitis due to bacteria (see Meningitis).
Bacteriuria	The presence of bacteria in the urine.
Blood culture	A test to look for infection in the bloodstream. A needle is placed in a baby's vein and a small amount of blood (one tenth of a teaspoon) is taken. The blood is put in a special bottle that detects whether any bacteria are present in the blood.
Bolus	A volume of fluid given quickly into a vein.
Bradycardia	An abnormally slow heart rate.
Capillary refill time	A test performed during physical examination. The clinician presses the skin until it is white. The time taken for the skin to return to its previous colour is measured. Capillary refill time can be measured peripherally (on the extremities) or centrally (on the chest wall). A prolonged capillary refill time may be a sign of circulatory insufficiency (such as shock) or dehydration.
Cerebrospinal fluid	The watery fluid that surrounds the brain and spinal cord. Samples of cerebrospinal fluid can be obtained by lumbar puncture.
Chorioamnionitis	Infection of the fetal membranes.
Clinical chorioamnionitis	Symptoms and signs that suggest there is infection of the fetal membranes.
Clinical concern	A judgement made by a healthcare professional that a baby is not behaving as expected. The concern may be mild or severe. The concern is usually based on direct observation, but may be influenced by risk factors or the results of blood tests.
Clinical judgement	The process by which a healthcare professional weighs up the information available to them and makes a decision about whether or not to treat a baby for infection. This is usually done using clinical indicators.
Clinical indicator	Information that is available to clinicians by observing a baby. This includes symptoms such as crying, signs such as jaundice or cyanosis, and features such as heart rate that can be measured at the bedside. Clinical indicators can be assessed every hour without disturbing the baby. This is in contrast to laboratory tests that involve blood sampling.

Coagulopathy	A condition in which the body does not make blood clots properly and the person can bleed much more than usual.
Colonisation	The condition in which a bacteria is found but when the bacteria is not causing infection. Examples include the presence of group B streptococcus on the skin of a baby or the presence of group B streptococcus in the vagina of a pregnant woman.
Confirmed infection	A case in which a bacteria that causes infection has been found in a particular baby with suspected infection.
Conjunctivitis	Redness of the whites of the eyes. Can be due to viruses or bacteria. Some cases due to bacteria are caused by sexually transmitted infections.
C-reactive protein	A plasma protein that circulates in increased amounts during inflammation and after tissue damage. Measurement of C-reactive protein in blood samples is widely used as a marker of infection or inflammation.
Cyanosis	A blue discolouration that suggests the blood contains low levels of oxygen. Peripheral cyanosis affects the hands and feet and is usually due to cold or poor inflammation. Central cyanosis affects the lips and is a sign of significant illness.
Cytokine	A member of a large family of proteins that are important for immunity and inflammation and that act on the effector cells of the immune system.
Disseminated intravascular coagulation	A particular type of coagulopathy.
Early-onset neonatal infection	A condition in which a baby within 72 hours of birth has an illness caused by a micro-organism. This guideline relates to illnesses caused by bacteria. Suspected early-onset neonatal infection is the condition that occurs when the illness is similar to a confirmed infection but a bacteria has not been isolated from the baby.
Empirical antibiotic	An antibiotic that treats a wide spectrum of micro-organisms. Empirical antibiotics are used before the specific organism is known. Once this is known, a more specific antibiotic can be given.
External validity	The degree to which the results of a study hold true in non-study situations, such as in routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Fetal bradycardia	An abnormally slow heart rate in the fetus. This is detected by listening to the fetal heart or measuring it. Measurements are done with a cardiotocograph or electrically using a fetal scalp electrode.
Fetal distress	A condition that indicates that the fetus is at risk of brain injury due to low oxygen levels. Fetal distress is usually detected using a cardiotocograph. Most babies with fetal distress are born quickly and come to no harm. A few babies with fetal distress need neonatal intensive care.
Fetal membranes	Skin-like tissue that forms a sac around the fetus and which contains the amniotic fluid that surrounds the fetus.
Fetal scalp electrode	A device that is attached to the fetal scalp through the birth canal. The fetal heart rate is measured more reliably this way than with a detector placed on the woman's tummy.
Fetal tachycardia	An abnormally fast heart rate in the fetus.
Focal neurological deficit	A finding on physical examination. A deficiency or impairment of the nervous system that is restricted to a particular part of the body or a particular activity. A focal neurological deficit is caused by a lesion in a particular area of the central

	nervous system. Examples include weakness of a limb or cranial nerve palsy. These signs suggest that a given disease is affecting one part of the brain or spinal cord rather than the whole nervous system.
Fontanelle	The membrane-covered gap or soft spot between the skull bones on the top of a baby's skull near the front. A bulging fontanelle can be a sign of meningitis.
Foul-smelling amniotic fluid	Amniotic fluid that is smelly. Some people suggest it may be associated with infection. However, it is a very poor way to predict infection in the baby.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Group B streptococcus	A type of bacteria. It is found in 20% of adults. If transferred to the baby during labour it can cause a life-threatening infection. This infection can be treated with antibiotics. Not all babies who are exposed to group B streptococcus develop an infection.
Hypereflexia	Reflexes that are much easier to detect than usual.
Hyperglycaemia	An abnormally high blood sugar level.
Hypertonia	Stiffness in the body, arms or legs.
Hypoglycaemia	An abnormally low blood sugar level.
Hypotension	Low blood pressure.
Hypothermia	Low temperature.
Hypotonia	Floppiness in the body, arms or legs.
Hypoxia	Low oxygen levels in the blood.
Ileus	A lack of the contractions usually seen in the intestines. Ileus can be due to infection or prematurity. Ileus can show up as a large belly (or distended abdomen).
Ill appearance	When presented with a baby, an assessing healthcare professional can get an impression that the baby looks ill. This impression is formed not only from objective measurements but also from subjective feelings about how the baby looks and reacts. If a healthcare professional's subjective instinct is to describe the baby as 'ill-looking' then the baby is most likely at high risk of serious illness. Healthcare professionals should be confident to follow their impressions of a baby's wellbeing.
Infection	Illness caused by a micro-organism.
Inflammation	The body's response to infection or other attacks. In the skin, inflammation shows as a hot part of the body that is red and swollen. This is accompanied by an increase in some types of blood cells and high levels of chemicals that control the blood cells. In the bloodstream inflammation involves the same blood cells and chemicals.
Intrapartum	During labour.
Intrapartum antibiotic prophylaxis	Antibiotics given during labour to prevent or reduce the harm caused by group B streptococcal infection.
Intrapartum fever	Temperature developed during labour equal to or higher than 38.0°C on one occasion during labour or equal to or higher than 37.5°C on two occasions 2 hours apart.

Invasive bacterial disease	Illness caused by bacteria in a part of the body that is usually sterile (free from bacteria). An example is blood poisoning (septicaemia). This is in contrast to colonisation.
Jaundice	A yellow discolouration of the skin.
Lumbar puncture	A procedure in which cerebrospinal fluid is obtained by inserting a thin, hollow needle into the space between vertebrae in the lumbar region of the spine. The procedure is used to diagnose meningitis and encephalitis.
Macrosomia	A baby with a birthweight that is more than would be expected for their gestational age.
Mechanical ventilation	The process of using a machine (a ventilator or life-support machine) to breathe for a person during an illness.
Meconium-stained amniotic fluid	One sign of fetal distress. About 10% of babies open their bowels before they are born. A few of these babies do this because their oxygen levels are low.
Meningitis	Inflammation of the meninges, the membranes that lie between the surface of the brain and the inside of the skull. Meningitis is usually caused by infection with bacteria or viruses. Bacterial meningitis is a serious condition associated with appreciable mortality and significant neurological complications.
Metabolic acidosis	A high level of acid in the bloodstream that is caused by an increased production of acid by the body. It is detected using a blood test (a blood gas) and is measured in a variable called 'base excess'.
Microbial culture	A test that take a sample to determine whether micro-organisms (viruses, bacteria or fungi) are present by seeing whether micro-organisms can grow in the laboratory.
Minimum inhibitory concentration	The lowest concentration of an antimicrobial agent that will inhibit the visible growth of a micro-organism after overnight incubation in the laboratory. This is an important measure in a diagnostic laboratory as it shows whether the organism in question is resistant to an antimicrobial agent.
Moribund state	A condition where the individual is close to death.
Neonate	A newly born baby aged less than 28 days.
Neutrophil	A type of white blood cell, also called polymorphonuclear leucocytes. These cells are commonly seen during inflammation.
Oliguria	Less urine than usual. This can be caused by a range of illnesses, including infection.
Oxygen desaturation	A sign that oxygen levels in the blood are low. One way to measure oxygen levels uses a probe on a baby's hands or feet to measure how much haemoglobin in the blood is carrying oxygen. If a lot of haemoglobin is carrying oxygen it is saturated. If less haemoglobin is carrying oxygen it is desaturated.
Parenteral antibiotic	An antibiotic given by a route that gets the antibiotic into the circulation, but avoids the digestive tract, usually by intravenous or intramuscular injection.).
Peak gentamicin concentration	The level of gentamicin in the baby's bloodstream shortly after administration. The blood sample is usually taken about 1 hour after giving the drug. High peak concentrations of gentamicin are necessary to kill bacteria.
Persistent fetal circulation	A condition in which blood flow in the heart and lungs does not change after birth. Before birth most blood bypasses the lungs. After birth the blood flow to the lungs normally increases. If the blood flow to the lungs does not increase then it is difficult to get oxygen into the baby's blood. This condition can sometimes be caused by infection.

Petechiae	These are small pinprick-sized (less than 2 mm diameter) and pinprick- appearing purple spots on the skin. They do not go away when you press on them.
Polymerase chain reaction	Polymerase chain reaction is a method of creating copies of specific fragments of DNA. The polymerase chain reaction rapidly amplifies a single DNA molecule into many DNA molecules so that further tests can be carried out.
Preterm labour	Labour that occurs before 37 weeks of gestation.
Preterm prelabour rupture of membranes	Rupture of membranes that occurs before labour starts in women who go on to give birth at less than 37 weeks of gestation.
Procalcitonin	A precursor of the hormone calcitonin that is released into the bloodstream in response to infection or inflammation. Procalcitonin can be measured in blood samples and it is currently under development as a potential test for the detection of serious infections.
Prolonged prelabour rupture of membranes	Rupture of membranes that occurs more than 18 hours before the start of labour.
Purpura	Large petechiae (2 mm or more diameter).
Purulent	Containing pus.
Purulent eye discharge	Copious flow of pus from the eye.
Pustule	A blister that contains yellow fluid. Some pustules contain pus (a sign of inflammation) but some neonatal pustules are not a sign of illness.
Real-time polymerase chain reaction	A laboratory technique that amplifies and measures the quantity of DNA produced.
Red flag	A risk factor or clinical feature that is so commonly seen in infection that it mandates immediate treatment for infection.
Respiratory distress	Clinical features that indicate lung disease, including an increased number of breaths each minute and signs that breathing is more difficult than usual (the skin between the ribs is sucked in).
Risk factor	A feature that means that infection is more likely than average. Risk factors in themselves do not confirm that a baby will have infection. Risk factors indicate that a baby needs more observation than other babies.
Rupture of membranes	A hole appears, or is made, in the fetal membranes. Amniotic fluid leaves the sac around the baby and comes out through the birth canal. This usually happens during labour.
Seizure	A fit.
Sepsis	A condition that looks like an infection. It can be caused by infection (although a micro-organism many not be detected) or by other illnesses.
Shock	A condition in which the circulatory system fails such that the blood pressure is too low to provide adequate blood supply to the tissues.
Sign	A finding on physical examination of a patient that provides the clinician with an objective indication of a particular diagnosis or disorder (see also Symptom).
Skin swab	A test done to determine whether bacteria are present on someone's skin.
Suspected infection	When a baby's condition, observations or risk factors raise the possibility that the baby has an infection. The possibility is great enough for a healthcare professional to do tests looking for bacteria and to start treatment with antibiotics.
Symptom	A patient's report of an abnormal feeling or sensation that provides the clinician with a subjective indication of a particular diagnosis or disorder (see also Sign).

Systemic antibiotic treatment	An antibiotic given by a route that gets the antibiotic into the circulation, for example orally or by intravenous or intramuscular injection
Tachycardia	An abnormally fast heart rate.
Tachypnoea	An abnormally fast breathing rate.
Therapeutic monitoring	A process of measuring the concentration of a drug in the bloodstream, to avoid excessive levels that might be associated with adverse effects or to ensure adequate levels for therapeutic effect.
Thrombocytopenia	Low levels of platelets in the bloodstream. Thrombocytopenia can be caused by infection.
Trough gentamicin concentration	The level of gentamicin in the baby's bloodstream shortly before a further dose is given. High trough gentamicin concentrations may be associated with an increased risk of adverse effects.
Umbilical flare (omphalitis)	A red area (inflammation) around the navel. If it spreads beyond the navel it needs to be treated as an infection.
Vital signs	Observations of heart rate, breathing rate and temperature that can be done easily on a newborn baby. In intensive care settings vital signs can also include blood pressure.

Appendices

The appendices are presented in separate files:

- Appendix A: Scope
- Appendix B: Declarations of interest
- Appendix C: Stakeholders
- Appendix D: Review protocols
- Appendix E: Search strategies
- Appendix F: Summary of identified studies
- Appendix G: Excluded studies
- Appendix H: Evidence tables
- Appendix I: Forest plots
- Appendix J: GRADE tables.