NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Diagnosis and monitoring of sepsis: procalcitonin testing (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

Final scope

June 2014

1 Introduction

The BRAHMS PCT Sensitive Kryptor assay is manufactured by Thermo Fisher Scientific. The Medical Technologies Advisory Committee identified the BRAHMS PCT Sensitive Kryptor assay as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by discussions at the scoping workshop held on 28 May 2014 and an assessment subgroup meeting held on 20 June 2014. The following alternative technologies have been included in the scope: the VIDAS BRAHMS PCT assay (BioMérieux); the ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics); the LIAISON BRAHMS PCT (DiaSorin) and the Elecsys BRAHMS PCT assay (Roche Diagnostics). A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Procalcitonin (PCT) is a 116 amino acid peptide which stems from the CALC-I gene, a gene which encodes calcitonin (a peptide hormone which lowers the concentration of calcium in the blood when it rises above the normal value).

Procalcitonin is an indirect marker of infection. It is released into the circulation in response to pro-inflammatory stimuli, especially those that are bacterial in origin. It is claimed that measuring procalcitonin levels in serum or plasma can be used to provide an indication of the severity of a person's response to an infection, including the likelihood of systemic infection and/or sepsis being present (table 1). As such, procalcitonin testing may be used to assist clinicians in making a diagnosis of bacterial infection (which can cause sepsis), and to guide decisions on the initiation of antibiotics. Procalcitonin levels are usually low in people with viral infections, chronic inflammatory disorders or autoimmune processes.

Table 1: Interpretation of procalcitonin results for the differential diagnosis of sepsis

PCT <0.05 ng/ml	• No systemic inflammatory reaction.	• Normal values for healthy individuals.
PCT <0.5 ng/ml	• Measurable but low systemic inflammatory reaction.	• Sepsis is not likely. • Local inflammation and local infection are possible. • Low risk of progression to severe sepsis. • If strong suspicion of sepsis remains, procalcitonin should be reassessed 6-24 hours later.
PCT ≥0.5 to <2.0 ng/ml	• Significant but moderate systemic inflammatory reaction.	• Sepsis is possible, but the elevated procalcitonin level may be caused by a range of other conditions known to induce procalcitonin. • Moderate risk for progression to severe systemic infection. • Patient should be closely monitored and procalcitonin should be reassessed within 6-24 hours.
PCT ≥2 to <10 ng/ml	• Severe systemic inflammatory reaction.	• Sepsis is likely unless other causes are known. • High risk for progression to severe sepsis.
PCT ≥10 ng/ml	• Indicates an important systemic inflammatory response.	• Almost exclusively due to severe bacterial sepsis or septic shock. • High likelihood of severe sepsis or septic shock.

Situations where procalcitonin levels may be elevated in the absence of bacterial infection include:

- physiological elevation in neonates during the first 48 hours of life;
- during the first days after a major trauma, a major surgical intervention, or severe burns;
- during treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines;
- in patients with invasive fungal infections or acute attacks of plasmodium falciparum malaria;
- in patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, severe liver cirrhosis and acute or chronic viral hepatitis;
- in people with small cell lung cancer or medullary C-cell carcinoma of the thyroid.

Procalcitonin can be detected in serum and plasma around 6 hours after an infectious insult, and peak values are reached at around 12 to 48 hours. Circulating procalcitonin has a half-life of around 20 to 35 hours, and as soon as the correct therapy is initiated levels begin to drop. This suggests that procalcitonin testing may also be used as a means of monitoring therapeutic response, to guide the continuation, change or discontinuation of antimicrobial treatment.

Using procalcitonin testing may help to conserve the effectiveness of existing antimicrobials by reducing antibiotic initiation and antibiotic course length. It is reported that pathogenic microorganisms are becoming increasingly resistant to antimicrobial treatments, including antibiotics, antivirals and antifungals. Resistance results in antimicrobial therapy becoming less effective at treating infections and of greatest concern is the rapid development of bacterial resistance to antibiotics. This is particularly relevant for the treatment of sepsis because antibiotic resistant bacteria may be the cause of infections that trigger sepsis. The Department of Health has set out actions to slow the development and spread of antimicrobial resistance in the UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. One of the aims of the strategy is to conserve and steward the effectiveness of existing antimicrobials by ensuring antibiotics are used responsibly and less often.

The optimal cut-off value ranges used in procalcitonin testing are variable and dependent on a number of factors: the clinical setting (for example, emergency department, intensive care unit, post-operative or trauma patients); the site and extent of the infection (for example, respiratory tract infection, meningitis, abdominal infection); and the co-morbidities of the

patient (for example, immunosuppression). Therefore, procalcitonin test results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

2.2 Product properties

Thermo Fisher Scientific holds a patent for the use of procalcitonin as a biomarker for sepsis. However, several other companies have licensed the use of procalcitonin and its antibodies. All commercial quantitative BRAHMS PCT assays use the same 'sandwich ELISA' principle to quantify procalcitonin by forming antibody-procalcitonin-antibody complexes. The main difference between these assays is the mechanism of detection of these antibody-procalcitonin-antibody complexes.

There are 5 automated quantitative BRAHMS PCT assays available in the UK: the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific), the VIDAS BRAHMS PCT (BioMérieux), the ADVIA Centaur BRAHMS PCT (Siemens Healthcare Diagnostics), the Elecsys BRAHMS PCT (Roche Diagnostics), and the LIAISON BRAHMS PCT (DiaSorin). These assays have all been standardised using the BRAHMS PCT LIA assay (the original manual procalcitonin assay that is not in widespread use in the UK). It is claimed that these assays are technically similar but adapted for use on different analysers. Published data are available which suggest a good correlation between the assays (Schuetz et al. 2009, Hausfater et al. 2010, Lloyd et al. 2012, Sanders et al. 2011, and de Wolf et al. 2009).

2.2.1 BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific)

The BRAHMS PCT Sensitive Kryptor assay is an automated immunofluorescent sandwich assay for the determination of procalcitonin in human serum and plasma. The measurement principle is based on TRACE™ Technology (Time-Resolved Amplified Cryptate Emission), which measures the signal that is emitted from an immunocomplex with time delay. It is indicated for use with the BRAHMS Kryptor, BRAHMS Kryptor compact and BRAHMS Kryptor compact PLUS analysers. The assay has a measuring range of 0.02 to 5000 ng/ml, a functional assay sensitivity of 0.06 ng/ml, and an analytical sensitivity of 0.02 ng/ml. The time to result is 19 minutes.

2.2.2 Elecsys BRAHMS PCT (Roche Diagnostics)

The Elecsys BRAHMS PCT is an automated electrochemiluminescent immunoassay (ECLIA) for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the

detection of light emission by a photomultiplier. The assay is indicated for use on the Elecsys, Modular and Cobas e analysers (Roche). It has a measuring range of 0.02 to100 ng/ml, a functional sensitivity of 0.06 ng/ml and an analytical sensitivity of less than 0.02 ng/ml. The time to result is 18 minutes.

2.2.3 VIDAS BRAHMS PCT (BioMérieux)

The VIDAS BRAHMS PCT is an automated Enzyme-Linked Fluorescent Assay (ELFA) for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with a final fluorescent detection. It is indicated for use with the VIDAS and miniVIDAS analysers (BioMérieux). It has a measuring range of 0.05 to200 ng/ml, a functional detection limit of 0.09 ng/ml and an analytical detection limit of 0.05 ng/ml. The time to result is 20 minutes.

2.2.4 ADVIA Centaur BRAHMS PCT (Siemens Healthcare Diagnostics)

The ADVIA Centaur BRAHMS PCT is an automated chemiluminescent assay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission as the final step. It is indicated for use with the ADVIA Centaur/XP and ADVIA Centaur CP analysers (Siemens). It has a measuring range of 0.02 to75 ng/ml, a functional sensitivity of less than 0.05 ng/ml and an analytical sensitivity of less than 0.02 ng/ml. The time to result is 26 to 29 minutes, depending on the selected analyser.

2.2.5 LIAISON BRAHMS PCT (DiaSorin)

The LIAISON BRAHMS PCT is a sandwich chemiluminescent immunoassay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission by a photomultiplier. The assay is indicated for use with the LIAISON analyser (DiaSorin). It has a measuring range of 0.1 to 500 ng/ml, a functional sensitivity of less than 0.24 ng/ml and an analytical sensitivity of less than 0.032 ng/ml.

2.2.6 Other alternative technologies

A point of care test for procalcitonin, the BRAHMS PCT-Q (Thermo Fisher Scientific), is available to the NHS and was considered for inclusion in the scope. Stakeholders at the scoping workshop highlighted that this test is semi-quantitative, and therefore suggested that this test should not be included in the assessment.

3 Target conditions / indications

Systemic inflammatory response syndrome and sepsis

3.1 Background

Systemic inflammatory response syndrome (SIRS) is a life-threatening illness caused by the body overreacting to an infectious or non-infectious insult. Sepsis is the presence of SIRS in addition to a documented or presumed infection. If sepsis is not treated it can progress to severe sepsis or septic shock and can lead to multiple organ failure and death. Severe sepsis occurs when sepsis progresses to sepsis-induced organ dysfunction. That is, when the body's response to infection interferes with the functioning of vital organs, such as the heart, kidneys, lungs or liver.

Septic shock occurs in severe cases of sepsis, and is defined as sepsis-induced hypotension (low blood pressure) persisting despite adequate fluid resuscitation. Septic shock prevents organs from receiving enough oxygenated blood. Complications of septic shock can include:

- respiratory failure
- heart failure
- kidney injury or failure
- abnormal blood clotting.

Definitions of sepsis have been published by the following societies:

- The American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference Committee (Bone et al 1992)
- 2001 SCCM / ESICM / ACCP / ATS / SIS International Sepsis Definitions Conference (Levy et al 2003)
- The German Sepsis Society (Reinhart et al 2010).

In the UK there are estimated to be 30,000 cases of severe sepsis each year, and it is one of the most common reasons for admission to an intensive care unit, accounting for almost one third of all cases. Sepsis, especially when treatment is delayed, has a mortality rate of 40%, rising to approximately 60% if septic shock develops.

Bacterial infections are the most common cause of sepsis; however it can also be caused by viral and fungal infections. The most common sites of infection leading to sepsis are the lungs, urinary tract, abdomen and pelvis. Other sources of infection leading to sepsis include skin infections (such as

cellulitis), post-surgical infections and infections of the nervous system (such as meningitis or encephalitis). Sepsis can also be caused by a condition known as neutropenia, in which the number of white blood cells in the blood is low. This is called neutropenic sepsis and people having anticancer treatment, particularly chemotherapy, can be at risk.

Everybody is potentially at risk of developing sepsis from minor infections, but some people are at higher risk, such as people who:

- are very young or very old
- have a weakened immune system
- have just had surgery, have severe injuries or large burns
- are on mechanical ventilation
- have intravenous drips or catheters.

Sepsis is a particular risk for people already in hospital for another serious illness.

3.2 Care pathway

3.2.1 Diagnosis

The diagnostic work-up of sepsis is described in several guidelines:

- NICE Clinical Guideline 151: prevention and management of neutropenic sepsis in cancer patients (2012)
- The Royal College of Obstetricians and Gynaecologists Green-Top Guideline 64a Bacterial Sepsis in Pregnancy (2012)
- The Royal College of Obstetricians and Gynaecologists Green Top Guideline 64b Bacterial Sepsis following Pregnancy (2012)
- Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock; 2012.

In addition a NICE clinical guideline Sepsis: the recognition, diagnosis and management of severe sepsis is currently in development with an estimated publication date of July 2016.

Diagnostic criteria for sepsis are listed in the Surviving Sepsis Campaign guidelines (adapted from Levy et al. 2003). In summary, regular observations of all vital signs should be taken and recorded, kidney and liver function tests should be performed, inflammatory biomarkers and serum lactate should be

measured. These guidelines state a diagnosis of sepsis should be based on infection, documented or suspected, plus some of the following:

- General variables: temperature of greater than 38.3°C or less than 36°C; heart rate greater than 90 beats per minute; rapid breathing; altered mental status; significant oedema; high blood sugar in the absence of diabetes.

- Inflammatory variables: low or high white blood cell count or more than 10% immature forms; raised plasma CRP; raised plasma procalcitonin.

- Haemodynamic and tissue perfusion variables: low blood pressure; raised blood lactate (a concentration of ≥4 mmol/l suggests tissue hypoperfusion).

- Organ dysfunction variables: low blood oxygen; reduced urine output; increased creatinine levels (indicating impaired kidney function); coagulation abnormalities; absent bowel sounds; reduced platelet count; raised plasma bilirubin levels.

The Surviving Sepsis Campaign guidelines also make the following specific recommendations relating to the diagnosis of sepsis:

- At least 2 sets of blood cultures should be collected (aerobic and anaerobic) before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in the start of antimicrobial administration.

- Cultures of other sites such as urine, cerebrospinal fluid, wounds, respiratory secretions or other body fluids that may be the source of infection should be obtained before initiation of antimicrobial therapy, if doing so does not cause significant delay in the start of antimicrobial administration.

- Imaging studies such as CT or X-ray should be performed in order to confirm a potential source of infection.

- Assays to diagnose systemic fungal infection should be used if available and invasive candidiasis is suspected.

The Surviving Sepsis Campaign guidelines recommend care 'bundles' which should be initiated during the diagnostic work-up of a patient. The 3-hour bundle should be completed within 3 hours:

a. measure lactate levels
b. obtain blood cultures prior to administration of antibiotics
c. administer broad spectrum antibiotics
d. administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L.

The 6-hour bundle should be completed within 6 hours:

e. apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure ≥65 mm Hg
f. in the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L:
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO2)*
g. re-measure lactate if initial lactate was elevated.

The NICE clinical guideline on Feverish illness in children (CG160, 2013) makes a research recommendation relating specifically to procalcitonin. The guideline development group recommended that a UK study of the performance characteristics and cost-effectiveness of procalcitonin versus CRP in identifying serious bacterial infection in children with fever without apparent source be carried out. This research recommendation was made in 2007 and evidence was not updated and reviewed in the 2013 guideline update.

The NICE clinical guideline on Antibiotics for early-onset neonatal infection (CG149, 2012) also makes a research recommendation relating to procalcitonin. The guideline development group recommend further research to provide evidence on 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. During the development of this guideline no evidence was found relating to the use of procalcitonin testing for the identification of asymptomatic babies who should receive antibiotic treatment. Limited low quality evidence was found relating to babies with symptoms about to start antibiotics. The guideline development group considered that procalcitonin 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 this test.

3.2.2 Management/treatment

The treatment of sepsis varies based on the initial infection, the organs affected and the extent of tissue damage. If sepsis is detected early enough it may be possible for patients to be treated with antibiotics in an outpatient setting. If sepsis is severe the patient is normally admitted to the intensive care unit and treated with empiric intravenous antibiotics.

Recommendations on the management of severe sepsis and septic shock are made in the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock; 2012 and are summarised below. All patients with severe sepsis or septic shock will require initial resuscitation, antimicrobial therapy, source control and fluid therapy. Some patients may require additional treatment with vasopressors, inotropic therapy, corticosteroids and other supportive therapy.

Initial resuscitation

Protocol led, quantitative resuscitation (also known as haemodynamic optimisation) of patients with sepsis-induced tissue hypoperfusion should be carried out and within the first 6 hours the following thresholds should be met:

- Central venous pressure: 8 to12 mm Hg
- Mean arterial pressure: greater than or equal to 65 mm Hg
- Urine output: greater than or equal to 0.5 mL/kg/hr
- Central venous or mixed venous oxygen saturation: 70% or 65%, respectively.

Antimicrobial therapy

Intravenous empiric antimicrobials should be administered within the first hour of recognition of septic shock and severe sepsis. The initial antimicrobial therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis.

Antimicrobials should be reassessed daily for potential de-escalation. Procalcitonin or similar biomarkers can be measured to assist the clinician in deciding whether to stop empiric antimicrobial treatment in patients who were initially suspected of having sepsis but have no subsequent evidence of infection. Empiric combination therapy should not be administered for more than 3 to 5 days and de-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.

The duration of therapy should typically be 7 to 10 days, however longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with *Staphylococcus aureus*, some fungal and viral infections or immunological deficiencies.

Source control

A rapid diagnosis of the specific site of infection should be made and source control measures undertaken (for example, drainage of abscess, removal of infected necrotic tissue, removal of a potentially infected device).

Fluid therapy

Crystalloids should be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock. When patients require substantial amounts of crystalloids then albumin should be used for fluid resuscitation.

Haemodynamic support and adjunctive therapy

Vasopressors should be used to target a mean arterial pressure of 65 mm Hg. Inotropic therapy should be administered if the patient experiences myocardial dysfunction or ongoing signs of hypoperfusion. If haemodynamic stability is not achieved through use of fluid resuscitation and vasopressor therapy, intravenous corticosteroids should be used.

Other supportive therapy

Other supportive therapy may include administration of blood products, mechanical ventilation for sepsis-induced acute respiratory distress syndrome, sedation, analgesia and neuromuscular blockade, glucose control, renal replacement therapy, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, oral or enteral feeding.

Special considerations for paediatric patients

Definitions of sepsis, severe sepsis, and septic shock are similar to adult definitions but depend on age-specific heart rate, respiratory rate and white blood cell count cut-off values. Special considerations for managing sepsis in paediatric patients are described in the Surviving Sepsis Campaign guidelines and in the American College of Critical Care Medicine guidelines on Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock.

3.3 Patient issues and preferences

No specific patient issues relating to procalcitonin testing for the diagnosis and monitoring of sepsis were identified during scoping.

Depression, post-traumatic stress disorder, and functional disability are common in survivors of critical illness (Jackson et al. 2007). Further, older adults who have survived severe sepsis are more likely to develop cognitive and/or physical problems than older adults who are hospitalised for other reasons (Iwashyna et al. 2010).

4 Scope of the evaluation

Table 2: Scope of the evaluation

Decision question	1. Does the use of procalcitonin testing with current clinical practice to guide the initiation and discontinuation of antibiotics in children and adults presenting to the emergency department with suspected bacterial infection represent a clinically- and cost-effective use of NHS resources? 2. Does the use of procalcitonin testing with current clinical practice to guide the initiation and discontinuation of antibiotics in children and adults with suspected or confirmed sepsis in an intensive care unit represent a clinically- and cost-effective use of NHS resources?
Populations	1. Children and adults with suspected bacterial infection 2. Children and adults with suspected or confirmed sepsis
Interventions	• ADVIA Centaur BRAHMS PCT – Siemens Healthcare Diagnostics • BRAHMS PCT Sensitive Kryptor – Thermo Fisher Scientific • Elecsys BRAHMS PCT – Roche Diagnostics • VIDAS BRAHMS PCT – BioMérieux • LIAISON BRAHMS PCT assay - DiaSorin
Comparator	Treatment decisions based on current clinical practice without procalcitonin testing.
Healthcare setting	1. Emergency department 2. Intensive care unit

Outcomes	Clinical outcomes for consideration may include: • Re-admission rate • Duration of ICU/hospital stay • Duration of antibiotic treatment • Adverse effects of antibiotic therapy • Duration of mechanical ventilation • Severity of disease (using scoring systems such as SOFA, SAPS II, APACHE II) • Superinfection rate • Rate of positive fungal cultures • Re-infection rate • Mortality • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs associated with procalcitonin testing • Costs associated with hospital stay • Costs associated with antibiotic treatment
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
	The potential costs and health impacts associated with antibiotic resistance should be discussed.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

5 Modelling approach

5.1 Existing models

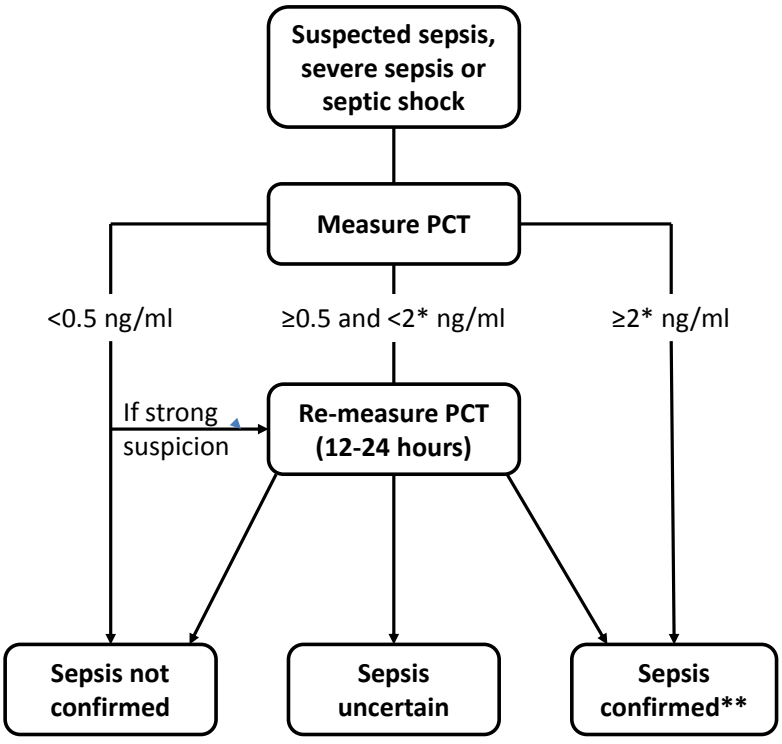
One economic evaluation relating to the use of procalcitonin was identified (Hohn et al. 2013). The study included adults with severe sepsis and septic shock in a surgical intensive care unit in Germany. Procalcitonin was monitored daily and results were fed into an algorithm used to inform decisions about when to discontinue antibiotics. The analysis was based on a retrospective review of records from an intensive care unit database. The mean annual changes were: a decrease of 2.7 intensive care unit days; a decrease of 42 ventilation hours; a decrease of 1.0 antibiotic day; a decrease

of 35.1% in reinfection; and a decrease of 22.4% in 28-day mortality. The annual costs of antibiotic use decreased on average by €14.3 per patient per year. The authors concluded that the procalcitonin algorithm was associated with decreased antibiotic use, without compromising clinical or economic outcomes, but further research was necessary.

5.2 Modelling possibilities

Procalcitonin testing is indicated for use in two separate positions in the care pathway; to diagnose bacterial infection or sepsis before the initiation of antibiotics (figure 1), and to monitor patients with confirmed sepsis in order to guide discontinuation of antibiotics (figure 2). Therefore, two models will be necessary; one to look at the diagnostic indication and one to look at the monitoring indication. Separate models may also be needed for children and for adults.

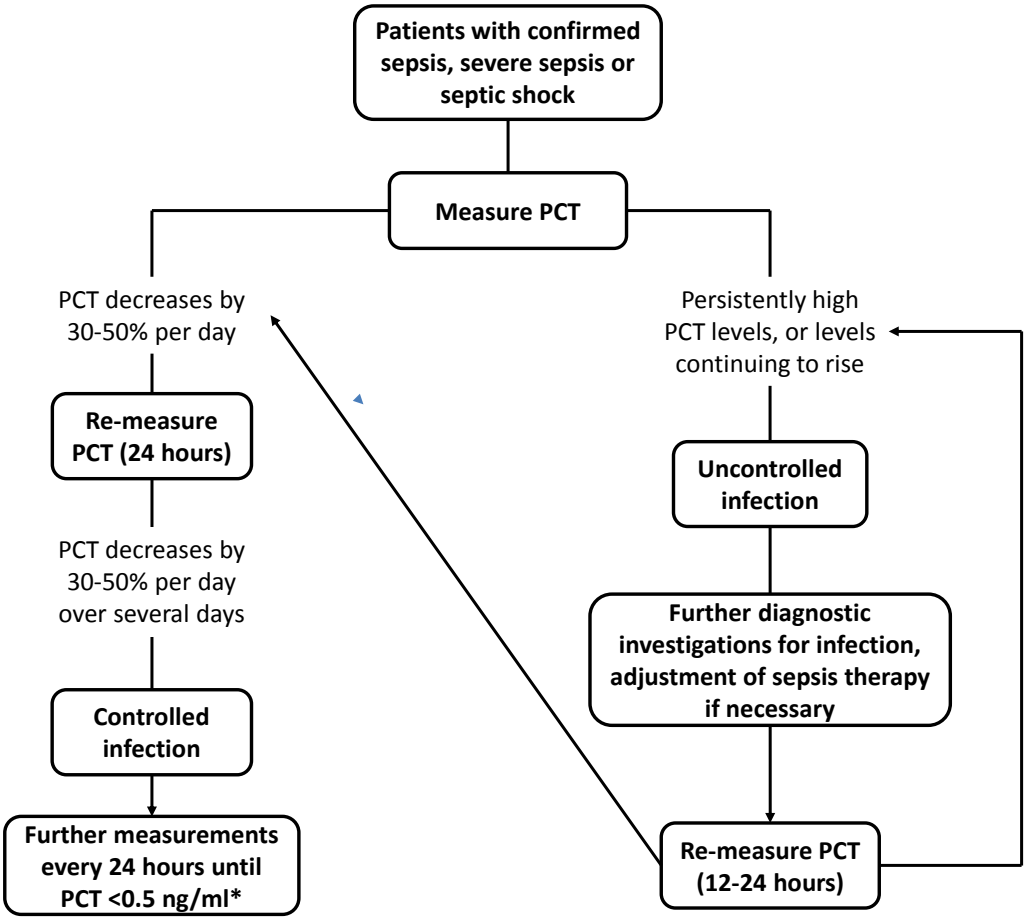
Figure 1: Diagnosis of sepsis using procalcitonin



* The limit of 2 ng/ml is a guide only. The interpretation of the limit values must be adapted to the patient's individual situation.

** In the absence of non-infectious causes of induction of procalcitonin.

Figure 2: Monitoring of patients with sepsis using procalcitonin



* Lower cut off levels may be used to guide antibiotic treatment

6 Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Bacterial sepsis may be more difficult to identify in pregnant women, young children, older people and people with a mental health problem. People with cancer are at risk of neutropenic sepsis.

7 Implementation issues

Due to the time critical nature of diagnosing and initiating treatment of sepsis and bacterial infections, results from procalcitonin testing would need to be available quickly, therefore laboratories would need to analyse samples immediately rather than waiting to run a batch of samples. In addition, the use of the procalcitonin assay may require the implementation of local protocols to aid clinicians with the interpretation of procalcitonin results.

Appendix A Glossary of terms

C-reactive protein
A protein which is produced by the liver and rises when there is inflammation throughout the body

Empiric antibiotic
An antibiotic given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

Immunoassay
A technique or test used to detect the presence or quantity of a protein such as a hormone or an enzyme, based on its ability to act as an antigen a chemical reaction.

Proinflammatory stimuli
Stimuli that can trigger the process of inflammation in the body. Examples of stimuli include toxins, infectious pathogens and foreign bodies.

Sepsis
A life-threatening systematic inflammatory response caused by the presence of an infectious agent (i.e. bacterial, viral, fungal or parasitic).

Severe sepsis
A septic infection that is associated with signs of organ dysfunction, damage and altered cerebral function leading to septic shock. Most patients with severe sepsis require treatment in intensive care units and severe sepsis can lead to death.

Septic shock
Sepsis-induced hypotension persisting despite adequate fluid resuscitation

Serum lactate
A laboratory test to measure the amount of lactate in the blood; high levels indicate lactic acidosis, a marker of hypoxia

Superinfection
A new infection occurring in a patient with a pre-existing infection

Systemic Inflammatory Response Syndrome
A life-threatening condition which arises from a severe systemic response to either an infectious or non-infectious insult

Appendix B Abbreviations

CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
ICU	Intensive care unit
PCT	Procalcitonin
SIRS	Systemic inflammatory response syndrome

Appendix C Related NICE guidance and pathways

Related NICE guidance: published guidance

Intravenous fluid therapy in adults in hospital NICE Clinical Guideline CG174 (December 2013) Available from: http://guidance.nice.org.uk/CG174 Date for review: TBC

Feverish illness in children: Assessment and initial management in children younger than 5 years. NICE Clinical Guideline CG160 (May 2013) Available from: http://guidance.nice.org.uk/CG160 Date for review: TBC

Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. NICE Clinical Guideline CG151 (September 2012) Available from: www.nice.org.uk/guidance/CG151 Date for review: TBC

Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection. NICE Clinical Guideline CG149 (August 2012) Available from: http://guidance.nice.org.uk/CG149 Date for review: TBC

Prevention and control of healthcare-associated infections: Quality improvement guide. NICE Public health guidance PH36 (November 2011) Available from http://guidance.nice.org.uk/PH36

The management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guideline CG102 (June 2010) Available from; http://guidance.nice.org.uk/CG102 Date for review: June 2013

Management of acute diarrhoea and vomiting due to gastroenteritis in children under 5. NICE clinical guideline 84 (April 2009) Available from: http://guidance.nice.org.uk/CG84 Date for review: June 2012 – decided not to review at this time

Prevention and treatment of surgical site infection. NICE clinical guideline 74 (October 2008) Available from: http://guidance.nice.org.uk/CG74 Date for review: August 2014

Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children. NICE clinical guideline 54 (August 2007) Available from: http://guidance.nice.org.uk/CG54 Date for review: August 2013

Related NICE guidance: under development

Pneumonia (including community acquired pneumonia). NICE clinical guideline. Expected publication: December 2014

Intravenous fluids therapy in children. NICE clinical guideline. Expected publication: October 2015

Sepsis: the recognition, diagnosis and management of severe sepsis NICE clinical guideline. Expected publication: July 2016

Antimicrobial resistance - changing risk-related behaviours NICE public health guidance. Expected publication: TBC

Acute Medical Emergency. NICE clinical guideline. Expected publication: TBC

Related pathways

The Diagnosis and monitoring of sepsis guidance may be included in several NICE pathways, for example: Neutropenic sepsis pathway, Feverish illness in children, and Antibiotics for early-onset neonatal infection.

In some of these pathways, it may be appropriate to include the full recommendations of the guidance, in others it will only be necessary to give a link to the guidance.

Relevant guidance from other organisations

Scottish Intercollegiate Guidelines Network (2014) Care of deteriorating patients - Consensus recommendations

The College of Emergency Medicine (2013) Clinical standards for emergency departments

Royal College of Obstetricians and Gynaecologists (2012) Bacterial Sepsis in Pregnancy

Royal College of Obstetricians and Gynaecologists (2012) Bacterial Sepsis following Pregnancy

Surviving Sepsis Campaign (2012) International Guidelines for Management of Severe Sepsis and Septic Shock

Department of Health (2011) Antimicrobial stewardship: Start smart - then focus

American College of Critical Care Medicine (2009) Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock

The Intensive Care Society (2007) Investigation of suspected infection in critically ill patients

Appendix D References

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