NICE National Institute for Health and Care Excellence

NICE guidance

Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

HealthTech guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG18.

1 Recommendation

More research is needed

1.1 The procalcitonin tests (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay) show promise but there is currently insufficient evidence to recommend their routine adoption in the NHS. Further research on procalcitonin tests is recommended for guiding decisions to:

- stop antibiotic treatment in people with confirmed or highly suspected sepsis in the intensive care unit or
- start and stop antibiotic treatment in people with suspected bacterial infection presenting to the emergency department.

Centres currently using procalcitonin tests to guide these decisions are encouraged to participate in research and data collection (see section 6.25).

2 The technologies

2.1 Procalcitonin is involved in maintaining calcium levels in the blood and is an indirect biomarker of infection. It is released into the circulation in response to pro-inflammatory stimuli, especially those originating from bacteria. Procalcitonin testing can be used to help clinicians to diagnose bacterial infection (that can cause sepsis) and guide decisions on starting antibiotic treatment. Procalcitonin levels are usually low in people with viral infections, chronic inflammatory disorders or autoimmune processes.

2.2 Thermo Fisher Scientific has a patent for using procalcitonin as a biomarker for sepsis. However, other companies have also 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 complexes.

2.3 Five procalcitonin assays were identified during scoping as relevant to this assessment: the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific), the VIDAS BRAHMS PCT assay (bioMerieux), the ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics), the Elecsys BRAHMS PCT assay (Roche Diagnostics) and the LIAISON BRAHMS PCT assay (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).

3 Clinical need and practice

The problem addressed

3.1 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic treatment in the following populations:

- Adults and children with confirmed or highly suspected sepsis in intensive care settings.
- Adults and children with suspected bacterial infection presenting to the emergency department.

3.2 Infections, such as pneumonia, may be caused by bacteria or viruses. Bacterial infections can be treated with antibiotics, but antibiotic treatment is inappropriate for viral infections. Many people, especially children, are often treated with antibiotics without the causative agent being known. Common side effects of antibiotics include mild stomach upset and diarrhoea. Less commonly, people may have an allergic reaction to an antibiotic. Furthermore, overuse of broad-spectrum antibiotics contributes to the development and spread of antimicrobial resistance. Therefore, rapid and accurate determination of the presence or absence of bacterial infection is important to reduce unnecessary exposure to antibiotics.

3.3 Sepsis is a common and serious problem among patients being treated in intensive care units. Bacteria are the most common cause of sepsis, but systemic viral and fungal infections can also occur. Symptoms of sepsis include fever or a very low body temperature, rapid breathing and altered mental status, such as reduced alertness or confusion. These symptoms also occur with systemic inflammatory response syndrome, a life-threatening condition that can be caused by the body's overreaction to an infection or a non-infectious event such as trauma or burns. Clinicians must be able to rapidly distinguish between infectious and non-infectious causes of systemic inflammatory response syndrome, as well as between different agents of infection, to guide appropriate therapy.

3.4 Severe sepsis is one of the most common reasons for admission to an intensive care unit. In its most severe form, septic shock, it has a mortality rate of 40% to 60%, which is thought to increase substantially for every hour of delay in starting appropriate antibiotic treatment. Therefore, broad-spectrum, high-potency antibiotics are widely used in intensive care units. It is important for clinicians to be able to monitor the progression of sepsis and the response to antibiotic treatment so that broad-spectrum antibiotic treatment can be narrowed or reduced (de-escalated) as soon as possible.

3.5 The Department of Health and Social Care's UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018 sets out actions to slow the development and spread of antimicrobial resistance. One aim of the strategy is to conserve and steward the effectiveness of existing antimicrobials by ensuring antibiotics are used responsibly and less often. Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate antibiotic therapy and to reduce unnecessary exposure to antibiotics.

The condition

3.6 The most common type of bacterial infection in people attending the emergency department is respiratory tract infection. Lower respiratory tract infection includes: acute bronchitis; acute exacerbations of chronic obstructive pulmonary disease or asthma; and pneumonia. It is a major cause of sepsis in children and adults. In addition to the lungs, the most common sites of bacterial infection leading to sepsis are the urinary tract, abdomen and pelvis. Sepsis can also result from skin infections (such as cellulitis), post-surgical infections and infections of the nervous system (such as meningitis or encephalitis).

3.7 Sepsis is the presence of systemic inflammatory response syndrome in addition to a documented or presumed infection. Untreated sepsis can progress to severe sepsis, resulting in 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. Severe sepsis can progress to multiple organ failure causing septic shock.

3.8 Septic shock is defined as sepsis-induced hypotension (low blood pressure) that

continues despite adequate fluid resuscitation. Septic shock prevents organs from getting enough oxygenated blood. Complications of septic shock can include respiratory failure, heart failure, kidney injury or failure, abnormal blood clotting and death.

The diagnostic and care pathways

3.9 A diagnosis of sepsis, according to the Surviving Sepsis Campaign's guidelines (2012) should be based on infection, documented or suspected, plus some of the following criteria:

- General variables: temperature above 38.3°C or below 36°C; heart rate greater than 90 beats per minute; rapid breathing; altered mental status; significant oedema; and 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 C-reactive protein; and raised plasma procalcitonin.
- Haemodynamic and tissue perfusion variables: low blood pressure; and raised blood lactate (a concentration of equal to or greater than 4 mmol/litre suggests tissue hypoperfusion).
- Organ dysfunction variables: low arterial blood oxygen; reduced urine output; increased creatinine levels (indicating impaired kidney function); coagulation abnormalities; absent bowel sounds; reduced platelet count; and raised plasma bilirubin levels.

3.10 The Surviving Sepsis Campaign's guidelines (2012) make the following additional recommendations for diagnosing sepsis:

- Collect at least 2 sets of blood cultures (aerobic and anaerobic) before antimicrobial treatment if such cultures do not cause significant delay (more than 45 minutes) in starting antimicrobial treatment.
- Collect cultures from other sites that may be the source of infection, such as wounds, urine, cerebrospinal fluid, respiratory secretions or other body fluids, before antimicrobial treatment, if doing so does not cause significant delay in

starting antimicrobial treatment.

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

3.11 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 usually admitted to the intensive care unit and treated with empiric intravenous antibiotics (antibiotics are selected based on experience without specific microbial information to support the decision).

3.12 The Surviving Sepsis Campaign's guidelines (2012) make the following recommendations for managing sepsis:

- Initial resuscitation: carry out quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion and meet target thresholds within the first 6 hours.
- Antimicrobial therapy: administer intravenous empiric antimicrobials within the first hour of diagnosing septic shock and severe sepsis. Assess antimicrobial treatment daily for potential de-escalation.
- Source control: make a rapid diagnosis of the specific site of infection and carry out source control measures.
- Other supportive therapy: may include intravenous fluid therapy, vasopressors and inotropes for prevention or correction of low blood pressure; 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; and oral or enteral feeding.

3.13 NICE has published a guideline on pneumonia.

4 The diagnostic tests

The interventions

ADVIA Centaur BRAHMS PCT assay

4.1 The ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics) 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 for use with the ADVIA Centaur/XP and ADVIA Centaur CP analysers. It has a measuring range of 0.02 to 75 nanograms per millilitre, a functional sensitivity of less than 0.05 nanograms per millilitre and an analytical sensitivity of less than 0.02 nanograms per millilitre. The time to result is 26 to 29 minutes, depending on the selected analyser.

BRAHMS PCT Sensitive Kryptor assay

4.2 The BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific) 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 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 nanograms per millilitre, a functional assay sensitivity of 0.06 nanograms per millilitre, and an analytical sensitivity of 0.02 nanograms per millilitre. The time to result is 19 minutes.

Elecsys BRAHMS PCT assay

4.3 The Elecsys BRAHMS PCT assay (Roche Diagnostics) is an automated

electrochemiluminescent 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 for use on the Elecsys, Modular and Cobas e analysers. It has a measuring range of 0.02 to 100 nanograms per millilitre, a functional sensitivity of 0.06 nanograms per millilitre and an analytical sensitivity of less than 0.02 nanograms per millilitre. The time to result is 18 minutes.

LIAISON BRAHMS PCT assay

4.4 The LIAISON BRAHMS PCT assay (DiaSorin) 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 for use with the LIAISON analyser. It has a measuring range of 0.1 to 500 nanograms per millilitre, a functional sensitivity of less than 0.24 nanograms per millilitre and an analytical sensitivity of less than 0.03 nanograms per millilitre.

VIDAS BRAHMS PCT assay

4.5 The VIDAS BRAHMS PCT assay (bioMerieux UK) is an automated enzyme-linked fluorescent assay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with a final fluorescent detection. It is used with the VIDAS and miniVIDAS analysers. It has a measuring range of 0.05 to 200 nanograms per millilitre, a functional detection limit of 0.09 nanograms per millilitre and an analytical detection limit of 0.05 nanograms per millilitre. The time to result is 20 minutes.

The comparator

4.6 The comparator used in this assessment is treatment decisions based on standard clinical practice without procalcitonin testing.

5 Outcomes

The Diagnostics Advisory Committee considered evidence from a number of sources. Full details are in the project documents for this guidance.

How outcomes were assessed

5.1 The External Assessment Group did a systematic review of the evidence on the clinical effectiveness of the use of procalcitonin testing with standard clinical practice to guide antibiotic therapy for:

- patients with confirmed or highly suspected sepsis in intensive care settings
- people presenting to the emergency department with suspected bacterial infection.

5.2 Studies were included in the review if they contained information on the following:

- Adults or children with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in intensive care units; or, adults or children presenting to the emergency department with suspected bacterial infection.
- Treatment decisions based on standard clinical practice with laboratory procalcitonin testing (using any of the 5 tests described in sections 4.1 to 4.5) compared with treatment decisions based on standard clinical practice without procalcitonin testing.
- At least 1 of the following outcomes:
  - antibiotic exposure (initiation or duration of antibiotic therapy)
  - resource use (number of hospital admissions, length of hospital or intensive care unit stay, costs)
  - adverse clinical outcomes (such as in-hospital mortality, condition-specific outcomes, antibiotic-related adverse events).

Overview of included studies

5.3 In summary, 18 studies were included in the review; 8 studies were done in intensive care unit settings and 10 studies were done in emergency department settings.

5.4 Most of the included studies measured procalcitonin levels using the BRAHMS PCT Sensitive Kryptor assay. Two studies measured procalcitonin levels using the VIDAS BRAHMS PCT assay. The remaining 4 studies used quantitative procalcitonin assays, but did not specify the assay manufacturer.

5.5 There were 12 studies done in Europe (mainly Switzerland), 3 in China, and 1 in Brazil; no UK studies were identified. There were 2 studies (conference abstracts) that did not specify location.

5.6 The methodological quality of all included studies was appraised using the Cochrane risk of bias tool. Three studies were judged as having a high risk of bias and 1 as having a low risk of bias. All other studies were judged as having an unclear risk of bias because insufficient information was reported to make a judgement on 1 or more bias domains.

Clinical effectiveness in intensive care unit settings

Overview of studies

5.7 There were 8 randomised controlled trials that provided data on the effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in intensive care unit settings. All studies were done in adult populations. No studies done in paediatric intensive care unit settings met the inclusion criteria for the review.

5.8 There were 4 studies done in adults with confirmed or highly suspected sepsis, in whom antibiotic therapy was indicated. One study included adults being treated in an intensive care unit for suspected bacterial infection, or who developed sepsis during their stay. Two studies included adults being treated in intensive

care unit settings who were considered to be at increased risk of developing sepsis (1 study in adults with acute pancreatitis and 1 study in adults with ventilator-associated pneumonia). The final study included adults who were being treated for suspected bacterial infections in intensive care unit settings.

5.9 There was 1 study that assessed the effectiveness of using procalcitonin testing with standard clinical practice to guide the start of antibiotic treatment. All other studies assessed the effectiveness of using procalcitonin testing with standard clinical practice to decide when to stop antibiotic treatment.

Antibiotic duration

5.10 There were 4 studies that reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms. Two of these studies were done in patients with suspected or confirmed sepsis, 1 was done in patients with acute pancreatitis and 1 was done in patients with suspected bacterial infection and those who developed sepsis while in the intensive care unit. Three of these studies found that the addition of procalcitonin testing to standard clinical practice resulted in a statistically significant reduction in the mean duration of antibiotic therapy (Bouadma et al. 2010; Liu et al. 2013; Qu et al. 2012). The fourth study found that the addition of procalcitonin testing to standard clinical practice was associated with a trend towards reduction in the duration of antibiotic therapy, which was not statistically significant (Nobre et al. 2008). The summary effect estimate showed that the use of procalcitonin testing in addition to standard clinical practice was associated with a statistically significant reduction in the duration of antibiotic therapy (weighted mean difference -3.19 days; 95% confidence interval [CI] -5.44 to -0.95). However, between-study heterogeneity was high.

5.11 When the meta-analysis was restricted to the 2 studies done in populations with suspected or confirmed sepsis (Liu et al. 2013; Nobre et al. 2008), the summary effect estimate still showed that the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant reduction in the duration of antibiotic therapy (weighted mean difference -1.20 days; 95% CI -1.33 to -1.07).

5.12 There were 3 further studies that reported median duration of antibiotic therapy. Two of these studies were done in people with suspected or confirmed sepsis, and found that the addition of procalcitonin testing to standard clinical practice had no statistically significant effect on the duration of antibiotic treatment (Annane et al. 2013; Deliberato et al. 2013). The third study was done in adults with ventilator-associated pneumonia and found that the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant reduction in the median duration of antibiotic therapy from 15 days to 10 days (Stolz et al. 2009).

Duration of hospital stay

5.13 There were 7 studies that reported lengths of hospital stay ranging from 11 to 27 days in the intervention groups (procalcitonin testing plus standard clinical practice) and from 11 to 33 days in the control groups (standard clinical practice alone). Four of these studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms. Two of these studies found that the addition of procalcitonin testing to standard clinical practice resulted in a statistically significant reduction in the mean duration of hospital stay (Liu et al. 2013; Qu et al. 2012). One study found that the addition of procalcitonin testing to standard clinical practice was associated with a trend towards reduction in the duration of hospital stay, which was not statistically significant (Nobre et al. 2008). The fourth study found that the addition of procalcitonin testing to standard clinical practice did not reduce the duration of hospital stay (Bouadma et al. 2010). The summary effect estimate showed that the use of procalcitonin testing with standard clinical practice was associated with a statistically significant reduction in the duration of hospital stay (weighted mean difference -3.85 days; 95% CI -6.78 to -0.92). However, between-study heterogeneity was high.

5.14 Only 2 of the 4 studies were done in populations with suspected or confirmed sepsis (Liu et al. 2013; Nobre et al. 2008). When the meta-analysis was restricted to the 2 studies, the summary effect estimate showed that the addition of procalcitonin testing to standard clinical practice was associated with a greater reduction in duration of hospital stay (weighted mean difference -4.32 days; 95% CI -6.50 to -2.14).

5.15 There were 3 further studies that reported median duration of hospital stay. Of these, 2 were done in people with suspected or confirmed sepsis and 1 was done in people with ventilator-associated pneumonia. All found that the addition of a procalcitonin algorithm had no statistically significant effect on the duration of hospital stay (Annane et al. 2013; Deliberato et al. 2013; Stolz et al. 2009).

Duration of intensive care unit stay

5.16 There were 6 studies that reported lengths of intensive care unit stay ranging from 3.5 to 22 days in the intervention groups (procalcitonin testing plus standard clinical practice) and from 3 to 23 days in the control groups (standard clinical practice alone). Four of these studies reported data to allow the calculation of mean difference in the duration of intensive care unit stay between study arms. Two of these studies found that the addition of procalcitonin testing to standard clinical practice resulted in a statistically significant reduction in the mean duration of intensive care unit stay (Liu et al. 2013; Qu et al. 2012). One study found that the addition of procalcitonin testing to standard clinical practice was associated with a trend towards reduction in the duration of intensive care unit stay, which was not statistically significant (Nobre et al. 2008). The fourth study found that the addition of procalcitonin testing to standard clinical practice did not reduce the duration of intensive care unit stay (Bouadma et al. 2010). The summary effect estimate showed that the addition of procalcitonin testing to standard clinical practice was associated with a trend towards decreased duration of intensive care unit stay, which did not reach statistical significance (weighted mean difference -2.03 days; 95% CI -4.19 to 0.13). However, between-study heterogeneity was high.

5.17 As with previous outcomes, only 2 of the 4 studies were done in populations with suspected or confirmed sepsis (Liu et al. 2013; Nobre et al. 2008). When the meta-analysis was restricted to the 2 studies, the summary effect estimate showed that the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant reduction in the duration of intensive care unit stay (weighted mean difference -2.31 days; 95% CI -3.97 to -0.65).

5.18 There were 2 further studies that reported median duration of intensive care unit stay. Both of these studies were done in people with suspected or confirmed

sepsis and both found that the addition of procalcitonin testing to standard clinical practice had no statistically significant effect on the duration of intensive care unit stay (Annane et al. 2013; Deliberato et al. 2013).

Adverse clinical outcomes

5.19 There were 5 studies that reported 28-day all-cause mortality (Bouadma et al. 2010; Liu et al. 2013; Nobre et al. 2008; Qu et al. 2012; Stolz et al. 2009). All found no statistically significant difference in mortality rates between patients in the intervention group (procalcitonin testing plus standard clinical practice) and those in the control group (standard clinical practice alone). The summary relative risk was 0.98 (95% CI 0.76 to 1.27). This finding was consistent when the meta-analysis was restricted to studies done in people with suspected or confirmed sepsis (relative risk 1.07; 95% CI 0.54 to 2.12).

5.20 There was 1 study that reported mortality at 60 days and found no statistically significant difference between the intervention and control groups (relative risk 1.15; 95% CI 0.89 to 1.48; Bouadma et al. 2010). One further study reported mortality at 5 days and found no statistically significant difference between the intervention and control groups (relative risk 1.0; 95% CI 0.25 to 4.04; Annane et al. 2013).

5.21 There were 3 studies that reported intensive care unit mortality. All found no statistically significant difference in the intensive care unit mortality rate between the intervention and control groups (Annane et al. 2013; Deliberato et al. 2013; Layios et al. 2012). The summary relative risk was 0.87 (95% CI 0.55 to 1.37). This finding was consistent when the meta-analysis was restricted to studies done in people with suspected or confirmed sepsis (relative risk 0.59; 95% CI 0.27 to 1.28).

5.22 There were 4 studies that reported rates of infection relapse or recurrence. All found no statistically significant difference in the infection relapse or recurrence rate between the intervention and control groups (Bouadma et al. 2010; Deliberato et al. 2013; Liu et al. 2013; Nobre et al. 2008). The summary relative risk was 1.37 (95% CI 0.77 to 2.44). This finding was consistent when the meta-analysis was restricted to the 3 studies done in people with suspected or

confirmed sepsis (relative risk 1.89; 95% CI 0.47 to 7.59).

5.23 A variety of other general and disease-specific adverse clinical outcomes were reported by 1 or more studies. These included multi-drug-resistant infection, sepsis-related mortality, multiple organ dysfunction syndrome, ventilator-associated pneumonia-related clinical deterioration, duration of mechanical ventilation, and Sequential Organ Failure Assessment score at various time points. No study reported a statistically significant difference between the intervention and control groups for any adverse clinical outcome assessed. None of the studies reported antibiotic-related adverse events.

Clinical effectiveness in emergency department settings

Overview of studies

5.24 There were 10 randomised controlled trials that provided data on the effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in emergency department settings. Two studies were done in children and the rest in adults. Most studies were done in people with respiratory presentations.

5.25 Of the adult studies, 2 were done in people with lower respiratory tract infection, 3 were done in people with community-acquired pneumonia, 1 included people with chronic obstructive pulmonary disease exacerbations, 1 included people with suspected asthma exacerbations, and 1 was done in people with urinary tract infection. Of studies done in children, 1 included children with lower respiratory tract infection and 1 included children with community-acquired pneumonia.

Antibiotic initiation

5.26 There were 7 studies, done in adults, which assessed the effectiveness of using procalcitonin testing with standard clinical practice to guide the start of antibiotic

treatment. All of these studies found that the addition of procalcitonin testing to standard clinical practice was associated with a reduction in antibiotic use (relative risk 0.77; 95% CI 0.68 to 0.87; Christ-Crain et al. 2004; Christ-Crain et al. 2006; Roh et al. 2010; Roh et al. 2013; Schuetz et al. 2009; Stolz et al. 2007; Tang et al. 2013).

5.27 There were 2 studies done in children that reported contradictory results for the proportion of patients in the intervention and control groups who had antibiotic treatment. The study done in children with community-acquired pneumonia found that the addition of procalcitonin testing to standard clinical practice to decide whether to start antibiotic treatment was associated with a statistically significant reduction in antibiotic use (relative risk 0.85; 95% CI 0.79 to 0.91; Esposito et al. 2011). Subgroup analyses showed that procalcitonin testing was associated with a greater reduction in antibiotic use for children with mild community-acquired pneumonia (relative risk 0.69; 95% CI 0.59 to 0.80) than for children with severe community-acquired pneumonia (relative risk 0.96; 95% CI 0.92 to 1.01).

5.28 The study done in children with lower respiratory tract infection (including community-acquired pneumonia and non-community-acquired pneumonia) reported a trend towards increased antibiotic use when procalcitonin test results were added to standard clinical practice (relative risk 1.12; 95% CI 0.94 to 1.35; Baer et al. 2013). Subgroup analyses showed that for children presenting with non-community-acquired pneumonia, the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant increase in antibiotic use (relative risk 2.71; 95% CI 1.46 to 5.01). But for children presenting with community-acquired pneumonia the addition of procalcitonin testing was associated with a trend towards reduction in antibiotic use (relative risk 0.92; 95% CI 0.79 to 1.08). When data from the 2 studies on children presenting with community-acquired pneumonia were combined the summary relative risk was 0.86 (95% CI 0.80 to 0.93).

Antibiotic duration

5.29 There were 2 studies done in adults that reported data to allow the calculation of mean difference in the duration of antibiotic therapy between study arms. Both of

these studies found that the addition of procalcitonin testing to standard clinical practice resulted in a statistically significant reduction in the mean duration of antibiotic therapy (Christ-Crain et al. 2004; Christ-Crain et al. 2006). The summary effect estimate showed that the addition of procalcitonin testing to standard clinical practice was associated with reduction in the duration of antibiotic therapy, which did not reach statistical significance (weighted mean difference -4.49 days; 95% CI -9.59 to 0.61). However, these studies included patients who did not have antibiotics in their estimates of mean duration. Therefore an additional meta-analysis was done, excluding patients who did not have antibiotic treatment. The summary effect estimate for patients who had antibiotic treatment (that is, weighted mean difference conditional on having antibiotics) was 1.48 days (95% CI -13.64 to 16.59).

5.30 There were 4 studies, done in adults, which reported median duration of antibiotic therapy, or mean with no estimate of variance. The results of these studies were consistent with the 2 studies included in the meta-analysis, showing that the addition of procalcitonin testing to standard clinical practice was associated with a reduction in the duration of antibiotic therapy (Drozdov et al. 2014; Roh et al. 2010; Roh et al. 2013; Schuetz et al. 2009).

5.31 There was 1 study, done in children, which reported data on the duration of antibiotic therapy. This study found the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant reduction in the duration of antibiotic therapy (mean difference -1.8 days; 95% CI -3.1 to -0.5; Baer et al. 2013).

Duration of hospital stay

5.32 There were 6 included studies in adults that reported duration of hospital stay ranging from 8 to 12 days in the intervention groups (procalcitonin testing plus standard clinical practice) and from 8 to 16 days in the control groups (standard clinical practice alone). Two of these studies reported data to allow the calculation of mean difference in the duration of hospital stay between study arms. Neither study found a statistically significant difference between groups (Christ-Crain et al. 2004; Christ-Crain et al. 2006). The summary effect estimate showed that addition of procalcitonin testing to standard clinical practice was

associated with a non-significant trend towards reduction in the duration of hospital stay (weighted mean difference -0.80 days; 95% CI -2.37 to 0.78).

5.33 There were 4 studies done in adults that reported median duration of hospital stay, or mean with no estimate of variance. Two of these studies, both done in people with community-acquired pneumonia, reported results showing that addition of procalcitonin testing to standard clinical practice was associated with a reduction in the duration of hospital stay (mean duration 9.2 days and 14.6 days [Roh et al. 2010]; mean duration 14.6 days and 16.0 days [Roh et al. 2013]). The remaining 2 studies, (1 done in people with lower respiratory tract infection and 1 done in people with chronic obstructive pulmonary disease exacerbations) found that use of a procalcitonin algorithm did not affect the median duration of hospital stay (Schuetz et al. 2009; Stolz et al. 2007).

5.34 Both studies done in children reported data to allow the calculation of mean difference in the duration of hospital stay between study arms. These studies reported lengths of hospital stay ranging from 2.5 to 5.0 days in the intervention groups (procalcitonin testing plus standard clinical practice) and from 2.3 to 5.9 days in the control groups (standard clinical practice alone). When data on children presenting with community-acquired pneumonia were combined, the summary effect estimate showed that the addition of procalcitonin testing to standard clinical practice was associated with a small reduction in the duration of hospital stay (weighted mean difference -0.74 days; 95% CI -1.17 to -0.31; Baer et al. 2013; Esposito et al. 2011).

5.35 One study reported data on duration of intensive care unit stay. This study was done in adults with chronic obstructive pulmonary disease exacerbations. It reported no statistically significant difference in the mean duration of intensive care unit stay between the study groups (mean difference -0.40; 95% CI -1.06 to 0.26; Stolz et al. 2007).

Adverse clinical outcomes

5.36 There were 2 studies in adults that reported hospital re-admission rates. One study was in people with acute asthma exacerbations and the other was in people with urinary tract infection. Both studies found no statistically significant

difference in re-admission rates between patients in the intervention group (decision to stop antibiotics based on procalcitonin test result plus clinical judgement) and those in the control group (decision to stop antibiotics based on clinical judgement alone; Drozdov et al. 2014; Tang et al. 2013).

5.37 There were 2 studies (1 in adults with acute asthma exacerbations and 1 in adults with chronic obstructive pulmonary disease exacerbations) that reported the rate of second emergency department visits. Both found no statistically significant difference between the intervention and control groups (Stolz et al. 2007; Tang et al. 2013).

5.38 There were 6 studies done in adults that reported all-cause mortality at various time points, ranging from 14 days to 6 months (Christ-Crain et al. 2004; Christ-Crain et al. 2006; Drozdov et al. 2014; Roh et al. 2010; Roh et al. 2013; Schuetz et al. 2009; Stolz et al. 2007; Tang et al. 2013). All studies reported no statistically significant difference in mortality rates between the intervention and control groups. The summary relative risk was 0.95 (95% CI 0.71 to 1.27). This finding was consistent when the meta-analysis was restricted to the 2 studies reporting mortality at 6 months (relative risk 0.85; 95% CI 0.46 to 1.59). Neither of the 2 studies done in children reported mortality data.

5.39 There were 4 studies done in adults that reported data on rates of admission to the intensive care unit. All studies found no statistically significant difference in intensive care unit admissions between the intervention and control groups (summary relative risk 0.79; 95% CI 0.59 to 1.05; Stolz et al. 2007; Christ-Crain et al. 2004; Christ-Crain et al. 2006; Schuetz et al. 2009). Neither of the 2 studies done in children reported any information on intensive care unit admissions.

5.40 There were 2 studies, done in adults, which reported inconsistent results for rates of infection relapse or recurrence. One study, in adults with urinary tract infection, found no statistically significant difference in relapse or recurrence rates between the intervention and control groups (Drozdov et al. 2014). The second study, in adults with lower respiratory tract infection, found that the addition of procalcitonin testing to standard clinical practice was associated with a statistically significant reduction in infection relapse or recurrence rates (relative risk 0.57; 95% CI 0.36 to 0.92; Schuetz et al. 2009). One study, done in children with community-acquired pneumonia, reported very low rates of infection relapse

or recurrence and a non-significant trend towards lower rates in the intervention group (relative risk 0.23; 95% CI 0.04 to 1.34; Esposito et al. 2011).

5.41 There was 1 study, done in adults with lower respiratory tract infection, which reported numbers of patients having antibiotic-related adverse events. This study found that the addition of procalcitonin testing to standard clinical practice was associated with a reduction in antibiotic-related adverse events (relative risk 0.71; 95% CI 0.58 to 0.86).

5.42 Both studies, done in children, reported the numbers having antibiotic-related adverse events (Baer et al. 2013; Esposito et al. 2011). When data on children with community-acquired pneumonia were combined, results showed that the addition of procalcitonin testing to standard clinical practice was associated with a non-significant reduction in antibiotic-related adverse events (relative risk 0.37; 95% CI 0.04 to 3.49). This finding was consistent when data for all children in both studies were included in the meta-analysis (summary relative risk 0.40; 95% CI 0.06 to 2.78).

5.43 A variety of other general and disease-specific adverse clinical outcomes were reported by 1 or more studies. These included composite adverse outcome measures, need for steroids, need for mechanical ventilation and complications from pneumonia. No study reported a statistically significant difference between the intervention and control groups for any adverse clinical outcome.

Costs and cost effectiveness

Systematic review of cost-effectiveness evidence

5.44 The External Assessment Group did a search to identify existing economic evaluations of people with sepsis or bacterial infection having care in emergency departments or intensive care units. Two studies were considered eligible for inclusion in the systematic review.

5.45 There was 1 study (Michaelidis et al. 2013) that considered procalcitonin testing in 2 scenarios. The first analysis was based on adults with an acute respiratory

tract infection presenting to an outpatient clinic and judged by their physicians to need an antibiotic prescription. The second analysis was based on adults with an acute respiratory tract infection presenting to an outpatient clinic before any decision to start antibiotic therapy. Procalcitonin-guided antibiotic therapy was both more costly and more effective than standard care alone. The incremental cost-effectiveness ratios (ICERs) were $118,828 and $575,249 per quality-adjusted life year (QALY) gained for the first and second analyses respectively.

5.46 The second study (Smith et al. 2013) considered the cost effectiveness of procalcitonin-guided antibiotic therapy in adults with community-acquired pneumonia in a hospital setting. Procalcitonin-guided antibiotic therapy was both more costly and more effective compared with standard care alone. For patients with low-risk community-acquired pneumonia, procalcitonin-guided antibiotic initiation is likely to be cost effective if the maximum acceptable ICER was $90,000 per QALY gained. For the same patients, procalcitonin-guided antibiotic initiation and monitoring is likely to be cost effective if the maximum acceptable ICER was $40,000 per QALY gained. For patients with high-risk community-acquired pneumonia, procalcitonin-guided antibiotic initiation and monitoring is likely to be cost effective if the maximum acceptable ICER was $170,000 per QALY gained.

Economic analysis

5.47 The External Assessment Group developed a de novo economic model designed to assess the cost effectiveness of the addition of procalcitonin testing to standard clinical practice compared with standard clinical practice alone for:

- adults with confirmed or highly-suspected sepsis in an intensive care unit setting
- adults with suspected bacterial infection presenting to the emergency department
- children with suspected bacterial infection presenting to the emergency department.

5.48 Children with confirmed or highly-suspected sepsis in an intensive care unit setting were not considered because there was insufficient clinical evidence.

Model structure

5.49 There were 2 decision tree models constructed:

- 1 in the intensive care unit setting that incorporated discontinuation of antibiotics only
- 1 in the emergency department setting that incorporated both starting and stopping antibiotics.

5.50 The structures of both models started with a decision node that denotes the use of procalcitonin testing in addition to standard clinical practice or standard clinical practice alone. The key endpoints were:

- alive with antibiotic-related complications
- alive without antibiotic-related complications
- death.

5.51 The time horizon was 6 months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase of 155 days. This time horizon was adopted to be consistent with the outcomes reported in the studies included in the clinical-effectiveness systematic review.

5.52 A 'lower clinical extreme' and a 'higher clinical extreme' were specified for each population and setting. For these 'clinical extremes', different baseline values were used for: mortality; duration of antibiotic therapy; probability of starting antibiotic treatment (emergency department setting only); length of hospital stay; and length of stay in an intensive care unit. The same relative risks and mean difference estimates were applied for both clinical extremes.

Model inputs – all-cause mortality and adverse events

5.53 The baseline probabilities and relative risks for all-cause mortality were taken from the systematic review of clinical effectiveness. Results from meta-analysis were used where possible. When a meta-analysis result was not available, data from the most plausible single source were chosen. Mortality rates for children presenting to the emergency department with suspected bacterial infection were not available from the systematic review. Therefore national background mortality rates were assumed, based on the expert opinion that mortality rates for children presenting to the emergency department are close to 0.

5.54 Antibiotic-related adverse events were incorporated in the economic model through the time on antibiotic treatment, using a disutility for having antibiotic treatment. Disease-specific complications were not included in the economic model and therefore were assumed to be equal for the intervention and control groups.

Health state utilities

5.55 Searches were undertaken to find relevant utility value studies on adults and children with sepsis or bacterial infection presenting to, or being treated at, emergency departments and intensive care units.

5.56 For adults being treated in the intensive care unit, a utility of 0.53 was used for the initial short-term phase, and a utility of 0.68 was used for the subsequent phase (Drabinski et al. 2001).

5.57 No utility values were found for adults presenting to the emergency department with suspected infection. Therefore, utility values for adults presenting to primary care with lower respiratory tract infection were used; 0.70 for the initial short-term phase and 0.86 for the subsequent phase (Oppong et al. 2013).

5.58 For children presenting to the emergency department, a constant base utility of 0.99 was assumed (utility for local infection; Bennett et al. 2000).

5.59 To incorporate antibiotic-related adverse events in adults being treated in the intensive care unit, a disutility of 0.046 for being on antibiotic treatment was used

(Oppong et al. 2013).

Costs and resource use

5.60 Resource use consisted of duration of hospital stay (days), intensive care unit stay (days) and antibiotic treatment duration (days). The estimates were retrieved from studies identified in the systematic review of clinical effectiveness. Results from meta-analysis were used where possible. When a meta-analysis result was not available, data from the most plausible single source were chosen. Where necessary, data were identified through consultation with experts for unpublished data.

5.61 Cost data were drawn from routine NHS sources (for example, NHS reference costs and British national formulary) and information provided by manufacturers of the procalcitonin tests.

5.62 An average unit price for the procalcitonin test was calculated to be £13.79, based on the list prices of the tests (excluding VAT) and with no discounts assumed. Overhead costs including capital, service and maintenance, and calibration costs were included. These were calculated from the initial capital costs, the lifetime of the assay (assumed to be 5 years) and the average number of tests per day (assumed to be 272). A similar estimation was done for the maintenance and calibration costs.

Base-case analysis

5.63 The following assumptions were applied in the base-case analysis:

- The duration of hospital stay retrieved from the systematic review of clinical effectiveness included days in hospital after infection relapse or recurrence.
- Relative risks for all-cause mortality for children presenting to the emergency department were assumed to be equal to those for adults presenting to the emergency department.
- There was no disutility for the hospital stay.

- The baseline utility for children presenting to the emergency department was constant over time.
- The disutility for being on antibiotic treatment was equal for all settings and populations.
- Procalcitonin testing used for starting antibiotics in the emergency department and stopping antibiotics in the intensive care unit was used to calculate the average number of tests per day.
- There were no costs associated with antibiotic-related adverse events.
- There were no differences in disease-specific complications between the group with procalcitonin testing and the group without procalcitonin testing.
- There were no differences in long-term costs and effects between the group with procalcitonin testing and the group without procalcitonin testing.

5.64 Base-case analyses indicate that procalcitonin testing with standard clinical practice dominates standard clinical practice alone for all populations, that is, it was both cost saving and more effective.

5.65 The cost savings ranged from £368 for children with suspected bacterial infection presenting to the emergency department (lower clinical extreme) to £3268 for adults with confirmed or highly-suspected sepsis in an intensive care unit setting (lower clinical extreme).

5.66 The use of procalcitonin testing with standard clinical practice resulted in only a small QALY gain compared with standard clinical practice alone. For adults with suspected bacterial infection presenting to the emergency department this was 0.005 for the lower and higher clinical extremes, and for adults with confirmed or highly-suspected sepsis in the intensive care unit setting it was 0.001 for both clinical extremes. For children with suspected bacterial infection presenting to the emergency department, the QALY gains were less than 0.001 for both clinical extremes.

5.67 Procalcitonin testing with standard clinical practice always has a higher probability of being cost effective than standard clinical practice alone if the maximum acceptable ICER is between £0 to £60,000 per QALY gained. If the

maximum acceptable ICER is £20,000 per QALY gained the probability of procalcitonin testing with standard clinical practice being cost effective compared with standard clinical practice alone is:

- 85% and 98% respectively for the lower and higher clinical extremes for children with suspected bacterial infection presenting to the emergency department.
- 88% for adults with suspected bacterial infection presenting to the emergency department (both clinical extremes).
- 97% and 95% respectively for the lower and higher clinical extremes for adults with confirmed or highly-suspected sepsis in an intensive care unit setting.

Analysis of alternative scenarios

5.68 The following scenario analyses were performed to assess the impact of assumptions on the estimated outcomes:

- assume no difference in mortality
- assume an increased cost of £50 per test
- assume no overhead costs for the tests
- alternative utility value for adults in the intensive care unit
- assume no disutility for being on antibiotic treatment
- assume no difference in duration of antibiotic treatment
- assume no difference in hospital stay (including intensive care unit stay)
- assume lower prices for hospital and intensive care unit stay
- assume that procalcitonin testing in the emergency department was solely used to start antibiotic treatment (not to stop antibiotic treatment).

5.69 The scenario analyses that assumed no difference in hospital stay had a

substantial impact on all populations and settings. Treatment based on procalcitonin testing with standard clinical practice became more costly (incremental costs varied between £7 for adults in the intensive care unit and £25 for children in the emergency department) and remained more effective (QALY gain varied between less than 0.001 for children in the emergency department and 0.007 for adults in the intensive care unit) compared with standard clinical practice alone. For children presenting to the emergency department with suspected bacterial infection, this resulted in ICERs of £287,076 per QALY gained for the lower clinical extreme and £35,219 per QALY gained for the higher clinical extreme. For adults in both settings (and both clinical extremes), ICERs varied between £3390 and £3948 per QALY gained.

5.70 None of the other scenario analyses resulted in substantial changes to the base-case ICERs, and use of procalcitonin testing with standard clinical practice remained cost effective compared with standard clinical practice alone.

One-way sensitivity analyses

5.71 One-way sensitivity analyses were performed for all stochastic input parameters between the 95% confidence intervals.

5.72 The one-way sensitivity analysis on relative mortality risk for adults with suspected bacterial infection presenting to the emergency department resulted in substantial changes to the base-case ICERs. Analyses showed that when using the upper bound of the 95% confidence interval (1.590; base-case value 0.850) procalcitonin testing with standard clinical practice guided treatment was less costly (£772) and less effective (QALY loss 0.025) compared with standard clinical practice alone. This resulted in ICERs of £30,469 per QALY lost (lower clinical extreme) and £30,446 per QALY lost (higher clinical extreme).

5.73 None of the other one-way sensitivity analyses resulted in substantial changes to the base-case ICERs, and use of procalcitonin testing with standard clinical practice remained cost effective compared with standard clinical practice alone.

6 Considerations

6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of using procalcitonin testing with standard clinical practice to guide antibiotic therapy in the following populations: adults and children with confirmed or highly-suspected sepsis in intensive care settings; and adults and children with suspected bacterial infection presenting to the emergency department.

6.2 The Committee considered the role of procalcitonin and noted that it is a more specific biomarker for bacterial infection than other biomarkers that are currently widely used for diagnosing and monitoring bacterial infection and sepsis. Other biomarkers, such as C-reactive protein and white blood cell count are inflammatory markers that have low specificity for the diagnosis of bacterial infection.

6.3 The Committee considered the equivalence of the 5 assays for procalcitonin testing that were included in the scope. It noted that most of the studies measured procalcitonin levels using the BRAHMS PCT Sensitive Kryptor assay and 2 studies measured procalcitonin levels using the VIDAS BRAHMS PCT assay. No relevant studies were identified that used the ADVIA Centaur BRAHMS PCT assay, the Elecsys BRAHMS PCT assay or the LIAISON BRAHMS PCT assay. The Committee heard from the manufacturers that they consider all assays to be comparable because they all use the same capture and detection antibodies in an immunoassay format. It also heard from the External Assessment Group that all assays have been standardised using the BRAHMS PCT LIA assay. The Committee noted that the Kryptor analyser is not widely available in NHS laboratories and therefore there may be a cost impact for laboratories in buying the Kryptor analyser. The Committee concluded that the procalcitonin assays could be considered technically comparable and noted that this meant NHS laboratories would have flexibility in the choice of analyser.

6.4 The Committee considered the quality of the studies included in the systematic review of clinical effectiveness. It noted that the External Assessment Group generally considered the studies to be at unclear risk of bias because insufficient information was reported in the publications. The Committee also noted that the

studies were heterogeneous, and most reported low event numbers. In addition, several studies reported median results that could not be incorporated into the summary estimates and the economic model. The Committee concluded that these factors contributed to the uncertainty in clinical effectiveness.

6.5 The Committee considered the implications of adding procalcitonin testing to standard clinical practice in intensive care unit settings and in the emergency department. It noted that clinical outcome results, such as mortality, infection relapse or recurrence and re-admission rates, were not statistically significantly different between patients in the intervention groups (procalcitonin testing plus standard clinical practice) and those in the control groups (standard clinical practice alone). The Committee concluded that using procalcitonin testing with standard clinical practice is unlikely to result in worse clinical outcomes compared with standard clinical practice alone.

6.6 The Committee discussed whether antibiotic stewardship practices differ between hospitals. The Committee noted the Public Health England report on the English surveillance programme for antimicrobial utilisation and resistance (2014) showed that combined GP and hospital antibiotic prescribing had increased by 6% between 2010 and 2013, despite the publication of the 'Start smart – then focus' toolkit for antimicrobial stewardship (2011). The Committee also considered whether the lack of suitable laboratory tests to inform antibiotic prescribing decisions was a possible reason for the lack of improvement in antibiotic stewardship. The Committee concluded that improved antimicrobial stewardship and consequent reduction in antibiotic use was not currently being achieved in the NHS, and that this could reflect that guidance on antimicrobial stewardship was not being fully adhered to in all NHS hospitals.

Intensive care unit settings

6.7 The Committee considered the impact on resource use of adding procalcitonin testing to standard clinical practice in intensive care unit settings. The Committee noted that most studies found reductions in resource use when procalcitonin was added to standard clinical care. However, the Committee noted that studies included in the review were done in Switzerland, France, Belgium, Brazil and China; no UK studies were included. It further noted that many of the studies

were done and published several years ago, and that clinical practice for antibiotic stewardship has changed considerably in the last few years. The Committee therefore considered whether the results of these studies were generalisable to the NHS. The Committee heard from the External Assessment Group that many of the studies did not clearly report how treatment decisions were made in the control arms. The Committee heard from clinical experts that when details of the control arm were reported, they did not reflect current standard clinical practice in the UK. The Committee also heard from clinical experts that in NHS intensive care units, antibiotic stewardship is considered daily during ward rounds that include microbiologists and intensivists (doctors who specialise in the care and treatment of patients in intensive care). The Committee therefore concluded that in the intensive care unit setting, the reductions in resource use reported in the included studies when procalcitonin was added to standard clinical practice were unlikely to be realised in the NHS.

6.8 The Committee considered the potential reasons for the reduction in resource use in intensive care unit settings reported in included studies. The Committee discussed whether the reductions were directly due to the use of procalcitonin, or whether the reductions may be due to the introduction of a clinical protocol that included use of a biomarker. It heard from clinical experts that in intensive care unit settings in the UK, protocols are used to guide care. The Committee noted that it was unclear if protocols were used to guide care in the control arms in the studies included in the systematic review, whereas the intervention arms included a procalcitonin algorithm with defined thresholds. The Committee concluded that in intensive care unit settings they could not be certain whether the reductions in resource use in the included studies were caused by use of procalcitonin or by use of a clinical protocol. Therefore, because clinical protocols are standard clinical practice in the NHS, the Committee also concluded that it is uncertain whether the potential reduction in resource use in intensive care settings would be realised from introducing procalcitonin testing into protocol-guided care.

6.9 The Committee considered the results of a survey that had been done by a company. The principal investigators of all the included studies in the assessment were contacted and asked to provide clarification on the exact methods used within the control arm referred to in section 6.8, and how this compares with the current UK approach to antibiotic stewardship. The Committee noted that

although the survey provided some reassurance, the questionnaire contained a generic description of the UK standard of care and a leading question was used to obtain details of the control arms in the studies, so the survey findings were considered at risk of bias. The Committee also reviewed a list of studies done in the UK that was provided by the companies. The Committee heard from the External Assessment Group that these studies were not comparative studies and therefore cannot be used to assess the benefits of adding procalcitonin to standard clinical practice. The Committee concluded that although it was useful that more evidence had been submitted at consultation, there was still uncertainty about the generalisability of the studies and the additional benefit that procalcitonin testing would provide in the NHS.

6.10 The Committee noted that no studies were found that were done in children with confirmed or highly-suspected sepsis in intensive care unit settings. It considered whether the data identified in an adult population could apply to children. It heard from clinical experts that a large proportion of children in paediatric intensive care units are younger than 1 year and are likely to have different care and resource needs. The Committee therefore concluded that data on adults in an intensive care unit should not be extrapolated to children.

6.11 The Committee considered trials in progress. It noted that the 'Stop Antibiotics on guidance of Procalcitonin Study (SAPS) had recently been completed and results were expected to be available after publication of this guidance. The Committee noted that this study is much larger than any of the studies included in the systematic review of clinical effectiveness (estimated 1800 patients). The Committee also considered an Australian study, published after the completion of the External Assessment Group's systematic review of clinical effectiveness (Shehabi et al. 2014), which found that using procalcitonin testing with standard clinical care in adults in an intensive care unit did not significantly reduce the duration of antibiotics. The Committee noted that the control arm of this study included antimicrobial stewardship implemented by twice-weekly infectious diseases rounds, which is similar to standard clinical care in the UK. However, the Committee also heard from the External Assessment Group that this study used a lower threshold of procalcitonin test values to determine discontinuation of antibiotics compared with the studies included in the systematic review (0.1 nanograms per millilitre and 0.25 nanograms per millilitre), which would likely result in longer durations on antibiotics.

Emergency department settings

6.12 The Committee considered the impact on resource use of adding procalcitonin testing to standard clinical practice in the emergency department. As with the intensive care unit setting (section 6.7), the Committee noted that most studies found reductions in resource use when procalcitonin testing was added to standard clinical practice. It noted further that studies were done in Switzerland, China and Italy, and that more than half of included studies were published before 2012. The Committee heard from clinical experts that in the emergency department there is much more variation in clinical assessment and in the decision to give antibiotics, compared with the intensive care unit. The Committee heard further from clinical experts that for patients with suspected bacterial infection at low risk of sepsis, clinical assessment can be variable, and therefore the clinical benefits of adding procalcitonin to standard clinical practice are uncertain. The Committee also heard from clinical experts that severely ill patients at high risk of sepsis would have care according to a clinical protocol and in line with the Surviving Sepsis Campaign's guidelines (2012). The Committee considered the results of the survey and UK-based studies provided by the companies and concluded that uncertainty remains around the generalisability of the studies to NHS practice (see section 6.9). The Committee therefore concluded that it was uncertain whether the reductions in resource use shown in studies done in other countries would be applicable to the NHS.

6.13 The Committee noted that most of the studies included in the systematic review of clinical effectiveness in an emergency department setting were done in people with suspected bacterial infection in the lungs. The Committee considered whether the data identified would be applicable for suspected bacterial infections in other sites. The Committee heard from clinical experts that for bacterial infections such as urinary tract infections, other tests are available that can be used to make a diagnosis. It also heard that lower respiratory tract infections are more difficult to diagnose compared with bacterial infections in other sites. The Committee concluded that the results from the systematic review could not be applied to people presenting to the emergency department with suspected bacterial infection outside the lungs.

6.14 The Committee noted that the studies done in emergency department settings included many patients who were sent home without antibiotics. This reduced

the number of patients from whom resource use data could be gathered and therefore increased the uncertainty in the results, leading to fewer statistically significant reductions in resource use compared with studies done in intensive care units. The Committee was also concerned that there was limited longer term follow-up of people who were sent home without antibiotics; therefore the risk of these people having the incorrect treatment and then re-attending medical services is unknown.

6.15 The Committee considered the heterogeneity of the populations in the emergency department studies and noted that they included a wide range of conditions (lower respiratory tract infections including community-acquired pneumonia, chronic obstructive pulmonary disease exacerbations, severe asthma exacerbations, urinary tract infection). The Committee noted that some studies reported conflicting results when analysing different subgroups of patients. For example, the study by Esposito et al. (2011) found that using procalcitonin testing with standard clinical practice was associated with a greater reduction in antibiotic use for children with mild community-acquired pneumonia than for children with severe community-acquired pneumonia. The Committee also heard from an expert on the Committee that people presenting to the emergency department with chronic obstructive pulmonary disease exacerbations are highly likely to be admitted and given antibiotics, but that most of these patients do not have proven bacterial infection. The Committee discussed whether the benefits of procalcitonin testing in severely ill patients at high risk of sepsis might be different from the benefits in less severely ill patients. The Committee concluded that the heterogeneity in the populations resulted in a high-level uncertainty about the benefits of procalcitonin testing that would be realised in clinical practice. It considered that focused studies in explicitly-defined patient groups were needed to address this uncertainty.

6.16 The Committee noted that there were limited data on children presenting to the emergency department with suspected bacterial infection. It heard from clinical experts that over the last decade, the number of children admitted to hospital with suspected bacterial infection after presenting to an emergency department has increased by 28% because of increased uncertainty and lack of confidence in clinical assessment. The Committee noted the study by Baer et al. (2013) that reported a trend towards increased antibiotic use when procalcitonin test results were added to standard clinical practice. The Committee also noted that there

was no agreed threshold for procalcitonin that should be used to encourage or discourage antibiotic use in children with suspected bacterial infection. The Committee considered whether the results of a laboratory test could cause clinical judgement to be overruled; potentially leading to people with test results just above the threshold having antibiotics, whereas clinical judgement alone would have led to antibiotics being withheld or stopped. The Committee was concerned that without robust evidence, the introduction of procalcitonin testing into standard clinical practice may not reduce the use of antibiotic therapy, but could potentially increase antibiotic exposure and hospital admissions. The Committee concluded that more robust evidence is needed on the use of procalcitonin testing with standard clinical practice in children presenting to the emergency department with suspected bacterial infection.

6.17 The Committee heard from experts on the Committee that hospital laboratories perform a large volume of C-reactive protein tests, many of which may be requested unnecessarily. The Committee was concerned that without the correct clinical risk assessment protocols in place, procalcitonin testing could be done in all people presenting to the emergency department with a respiratory tract infection. It noted that some test results will be false positives and may influence clinical judgement resulting in people having antibiotics unnecessarily. The Committee further noted that procalcitonin testing is unlikely to replace C-reactive protein testing for clinical decision-making. It also noted that the costs of unnecessary tests were not included in the cost-effectiveness analysis. The Committee concluded that if procalcitonin testing were to be recommended for routine use in the emergency departments, it is possible that many unnecessary tests would be performed and clear guidance on their use would be needed to minimise this risk.

Other considerations

6.18 The Committee discussed the use of length of stay as a key outcome measure in studies on procalcitonin testing, both in intensive care unit settings and after admission through the emergency department. It noted that length of stay may be influenced by factors other than procalcitonin testing, such as differences in local protocols and preferences of treating clinicians. The Committee concluded that measuring length of stay may not reliably capture the potential benefits of

procalcitonin testing. It encouraged further research using clinically meaningful outcomes.

6.19 The Committee considered the long-term outcomes that may occur after sepsis and noted that no evidence was identified on these long-term outcomes. It heard from a patient expert on the Committee that post-sepsis syndrome affects up to 50% of survivors, and constitutes: insomnia; nightmares, vivid hallucinations and panic attacks; disabling muscle and joint pains; extreme fatigue, poor concentration and decreased cognitive functioning; and loss of self-esteem. In some cases, post-sepsis syndrome can lead to post-traumatic stress disorder, which, without the correct support, can last for years. Additionally, survivors of sepsis may be more vulnerable to developing respiratory viral infections than the general population. The Committee concluded that future research should consider including long-term outcomes to more fully capture the impact of sepsis on patients.

6.20 The Committee noted that outcomes relating to antibiotic stewardship were not included in the model. The Committee discussed the potential contribution that procalcitonin testing could make to improving antimicrobial stewardship by reducing the incidence of antibiotic-resistant infections. The Committee noted its earlier conclusions about the uncertainty of whether the reductions in resource use reported in the studies would be realised in clinical practice in the NHS (sections 6.7 to 6.8 and section 6.12). It concluded that procalcitonin testing may contribute to improving antibiotic stewardship in the NHS if it leads to a reduction in antibiotic use. The Committee also heard from clinical experts that procalcitonin testing would only be 1 component of an antimicrobial stewardship approach and other factors may also contribute substantially to improving antimicrobial stewardship. The Committee concluded that the benefit procalcitonin would provide in addition to other measures to improve antibiotic stewardship was not clear.

6.21 The Committee considered the assumptions used in the economic model. Firstly, the Committee discussed the assumption that there were no differences in disease-specific complications between the intervention and control groups. It heard from the External Assessment Group that studies generally reported these complications as a compound outcome that could not be separated out, and that no statistically significant difference was found between the groups. The

Committee concluded that the assumption was valid. Secondly, the Committee considered the assumption that a laboratory would perform 272 procalcitonin tests per day. The Committee considered that this might be an overestimate, especially for smaller hospital laboratories. The Committee heard from the External Assessment Group that this value was used to calculate the overhead costs per test, and that in sensitivity analyses varying the total test cost by 10 fold did not affect the cost-effectiveness results. An alternative estimate of 30 to 40 tests per day was suggested by a company based on sales data. The Committee heard from the External Assessment Group that using a value of 30 tests per laboratory per day increased the cost of procalcitonin testing by £4 in the emergency department setting and £7 in the intensive care unit setting, but this did not affect the model results.

6.22 The Committee considered the time horizon used in the model. It noted that the time horizon used in the model is 6 months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase lasting 155 days. It noted that this time horizon reflected the outcomes reported in the studies included in the systematic review of clinical effectiveness, which did not report data on long-term outcomes. The Committee concluded that the time horizon used was appropriate given the clinical data available.

6.23 The Committee considered the cost effectiveness of adding procalcitonin testing to standard clinical practice in intensive care unit settings and in the emergency department. It noted that in all scenarios assessed, procalcitonin testing with standard clinical practice dominated standard clinical practice alone, that is, it was more effective and less costly. However, the Committee acknowledged that the change in quality-adjusted life years (QALYs) was extremely small. The Committee noted its earlier conclusion that the use of procalcitonin testing with standard clinical practice is unlikely to result in worse clinical outcomes compared with standard clinical practice alone (section 6.5). It therefore concluded that the QALYs for each group could be considered broadly equal, that is, adding procalcitonin testing to standard care does not result in a meaningful change in QALYs.

6.24 The Committee considered whether the cost savings generated through reductions in resource use were large enough to offset the additional cost of procalcitonin testing. It noted its earlier conclusion about the uncertainty of

whether the reductions in resource use reported in the studies included in the systematic review would be realised in clinical practice in the NHS (sections 6.7 to 6.8 and section 6.12). The Committee therefore concluded that it was uncertain whether savings would be large enough in a UK setting to offset the cost of procalcitonin testing.

6.25 The Committee noted that procalcitonin testing is currently used with standard clinical care in a few centres in the UK to guide decisions on antibiotic treatment in emergency departments and intensive care units. The Committee acknowledged that the evidence suggested that the addition of procalcitonin testing to standard clinical care was unlikely to result in worse clinical outcomes (section 6.5). The Committee encouraged centres currently using procalcitonin testing to guide decisions on antibiotic treatment in emergency departments and intensive care units to take part in relevant data collection and research.

7 What research is needed

7.1 The Committee recommended that robust evidence is generated to show the impact of adding procalcitonin testing to standard clinical practice in the NHS, to guide the use of antibiotic treatment in people with confirmed or highly-suspected sepsis in intensive care units and in people with suspected bacterial infections presenting to the emergency department. The impact on resource use when procalcitonin testing is used in combination with protocol-driven clinical care in the NHS is of particular relevance. The Committee encouraged the collection of data for longer-term clinical outcomes of sepsis that contribute to post-sepsis syndromes.

7.2 Focused studies in explicitly-defined patient groups are recommended, including:

- Children having antibiotics for a suspected or proven infection in an intensive care unit.
- Children and adults presenting to the emergency department with respiratory tract infection.
- Adults presenting to the emergency department with exacerbations of chronic inflammatory respiratory conditions such as chronic obstructive pulmonary disease.

8 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 7 into its guidance research recommendations database and highlight these recommendations to public research bodies.

9 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee

Dr Mark Kroese
Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research, University of Sheffield

Dr Phil Chambers
Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Professor Paul Collinson
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NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Frances Nixon
Topic Lead

Sarah Byron
Technical Adviser

Robert Fernley
Project Manager

10 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University.

- Westwood ME, Ramaekers BLT, Whiting P, et al. Procalcitonin (PCT) testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: A systematic review and cost-effectiveness analysis. January 2015.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

Manufacturers/sponsors:

- bioMerieux UK Ltd
- Roche Diagnostics Ltd
- Siemens Healthcare Diagnostics
- Thermo Fisher Scientific

Professional/specialist and patient/carer groups:

- British Infection Association
- Children's Cancer and Leukaemia Group
- Dudley Group NHS Foundation Trust
- Group B Strep Support

- Intensive Care Society
- Meningitis Research Foundation
- MRSA Action UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Sepsis Trust

Others

- British In Vitro Diagnostics Association (BIVDA)
- Department of Health
- Department of Microbiology, North West London Hospitals NHS Trust and Ealing Hospital NHS Trust
- Healthcare Improvement Scotland
- Imperial College NHS Trust
- Imutest Limited
- Integrated Medicines Ltd
- Manchester Centre for Health Economics, The University of Manchester
- NHS England
- Spectral Platforms
- Welsh Government

Update information

Minor updates since publication

December 2025: Diagnostics guidance 18 has been migrated to HealthTech guidance 386. The recommendations and accompanying content remain unchanged.

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