National Institute for Health and Care Excellence

Suspected sepsis: recognition, diagnosis and early management

[J] Evidence review for procalcitonin guided decision making

NICE guideline NG51

Evidence underpinning recommendations 1.8.2 and 1.8.16

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Draft for consultation

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1.1 Review question

This evidence review summarises the evidence for:

What is the clinical and cost effectiveness of serum procalcitonin measurement with standard care to support decision making regarding the early treatment of suspected sepsis compared to standard care alone?

Further technical detail can be found in the separate technical appendices for this review.

1.1.1 Summary of the protocol

Table 1: Summary of the protocol (PICOS)

Population	People with suspected sepsis • people aged 16 or over • people aged under 16 • people of any age who are pregnant or have recently been pregnant[1] [1] Someone is considered to have recently been pregnant in the 24 hours following a termination of pregnancy or miscarriage that occurred before 24 weeks gestation; for 4 weeks after a termination of pregnancy or miscarriage that occurred after 24 weeks gestation for 4 weeks after giving birth.
Interventions	Treatment decisions made using serum procalcitonin measurement available for use in the NHS plus standard care.
Comparator	Treatment decisions based on standard care at the time and setting the study was conducted in, without procalcitonin testing. This may be based on other microbiological tests, early warning scores, and/or clinical intuition.
Outcomes	Primary outcomes: People aged 16 or over: • Time to initiation of IV antibiotics • Duration of IV antibiotic treatment • Mortality within 30 days People aged under 16: • Time to initiation of IV antibiotics • Duration of IV antibiotic treatment • Mortality within 30 days People of any age who are pregnant or have recently been pregnant: • Time to initiation of IV antibiotics

	• Duration of IV antibiotic treatment • Mortality within 30 days (including maternal and neonatal/foetal mortality) • Neonatal adverse events: preterm birth, low birth weight, neonatal infection and neonatal sepsis Secondary outcomes: People aged 16 or over: • Length of hospital stay • Admission to ICU within hospital stay • Severity of disease (using scoring systems such as SOFA, SAPS II, APACHE II) • HRQoL People aged under 16: • Length of hospital stay • Admission to ICU within hospital stay • Severity of disease (using scoring systems such as pSOFA) • HRQoL People of any age who are pregnant or have recently been pregnant: • Length of hospital stay • Admission to ICU within hospital stay • Severity of disease (using scoring systems such as SOFA, SAPS II, APACHE II) • Neonatal admission to NICU or Special Care Baby Unit
Study type	• RCTs • If insufficient RCTs: Non-randomised controlled trials/Prospective cohort studies that have adjusted for relevant covariates in their analysis
Key confounders	• Age • Sex • Race • Renal function • Severity of illness • Comorbidities • Immune and inflammatory status • Vitamin D level

Abbreviations: SOFA= Sequential Organ Failure Assessment; SAPSII= Simplified Acute Physiology Score II; APACHE II= Acute Physiology And Chronic Health Evaluation II; pSOFA= paediatric Sequential Organ Failure Assessment; HRQoL= health related quality of life

For the full protocol see **appendix A** in the technical appendices document.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this

review question are described in the review protocol and in **appendix J** in the technical appendices document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Protocol deviation

A protocol deviation was made to exclude neonates (babies less than 28 days old) from the population of people under the age of 16. This was decided following discussion with clinical experts who advised that neonates would be given antibiotics without delay regardless of PCT results, therefore the research question is not applicable to this age group.

1.1.2.1 Search methods

The searches for the effectiveness evidence were run on 28 January 2026. The following databases were searched: MEDLINE ALL (Ovid); Embase (Ovid), Cochrane Database of Systematic Reviews, CDSR (Wiley), Cochrane Central Register of Controlled Trials, CENTRAL (Wiley), and Epistemonikos (Epistemonikos). Limits were applied to remove animal studies and irrelevant publication types such as letters and editorials. Filters were used to limit to systematic reviews, randomised controlled trials, observational studies, and evidence from Organisation for Economic Co-operation and Development (OECD) countries.

The searches for the cost effectiveness evidence were run on 2 February 2026. The following databases were searched: MEDLINE ALL (Ovid); Embase (Ovid), EconLit (Ovid), and the International HTA Database (International Network of Agencies for Health Technology Assessment). Limits were applied to remove animal studies and irrelevant publication types such as letters and editorials. Filters were used to limit to evidence from Organisation for Economic Co-operation and Development (OECD) countries.

The validated NICE cost utility filter was used on MEDLINE and Embase and an economics evaluations filter, plus a quality-of-life filter was also used.

A NICE Senior Information Specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in Appendix B.

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in **appendix J** in the technical appendices document. See **appendix B** in the technical appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in **appendix C** in the technical appendices document.

One study was included for people aged 16 and over. For a summary of the included studies see Table 2 and for full references see the list of included studies (section 1.1.10)

The included study for people aged 16 and over did not report outcomes relating to severity of disease using scoring systems (such as SOFA, SAPS II, APACHE II) or health related quality of life.

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with the primary reason for exclusion, are given in **appendix I** in the technical appendices document.

1.1.4 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence for people aged 16 or over

Study details	Population	Intervention	Comparator	Outcomes
Todd (2026) PRONTO Study type: RCT Setting: Emergency departments Location: UK Funding source: NIHR	N= 5453 Adults (age 16 or over) presenting to the emergency department with suspected sepsis	Clinical management based on NEWS2 score and PCT-guided risk assessment.	Standard clinical management with risk assessment based on NEWS2 scoring.	Primary: • Time to initiation of IV antibiotics • Duration of IV antibiotic treatment • Mortality within 30 days (measured at 28 days) Secondary: • Length of hospital stay • Admission to ICU within hospital stay

Abbreviations: NIHR= National Institute for Health and Care Research; NEWS2= national early warning score 2; PCT= procalcitonin; HRQoL= health related quality of life; EQ-5D/5L= European quality of life 5 dimensions 5 level version.

See **appendix D** in the technical appendices document for full evidence tables.

1.1.5 Summary of effectiveness evidence

Informative statements

For people aged 16 and over:

- The evidence shows that treatment decisions based on procalcitonin testing + standard care may reduce mortality within 30 days compared to treatment decisions based on standard care.
- The evidence suggests that treatment decisions based on procalcitonin testing + standard care result in little to no difference in timing of antibiotics compared to treatment decisions based on standard care.
- The evidence suggests that treatment decisions based on procalcitonin testing + standard care result in little to no difference in the duration of IV antibiotic treatment compared to treatment decisions based on standard care.
- The evidence suggests that treatment decisions based on procalcitonin testing + standard care result in little to no difference in length of hospital stay compared to treatment decisions based on standard care.
- The evidence is very uncertain about the effect of treatment decisions based on procalcitonin testing + standard care on admission to ICU within hospital stay compared to treatment decisions based on standard care.

See **appendix F** in the technical appendices document for a GRADE summary table.

1.1.6 Economic evidence

1.1.6.1 Included studies

A search was performed to identify published economic evaluations of relevance to this review question. See the literature search strategy in **appendix B** and the economic review protocol in **appendix A** in the technical appendices document.

No economic studies were identified which were applicable to this review question. (see economic study selection flow chart in **appendix G** in the technical appendices document).

1.1.6.2 Excluded studies

See **appendix I** in the technical appendices document for a list of excluded economic studies, with reason for exclusion.

1.1.7 Economic model

A simple decision-analytic calculation was undertaken for a cohort of 1,000 adults with suspected sepsis. The unit cost of PCT testing was assumed to be £15 per test (Stevenson 2025), giving a total testing cost of £15,000 for the cohort.

Baseline 28-day mortality was set at 13%, corresponding to 130 deaths in the absence of PCT testing (Warhurst NICE HTA 2015). Applying a pooled relative risk for mortality of 0.82 (95% CI: 0.72 to 0.93) from the systematic review resulted in an estimated 106.6 deaths with PCT testing, equating to 23.4 deaths avoided per 1,000 patients.

An estimated lifetime gain of 12.68 discounted QALYs per survivor was applied (Stevenson 2025). This estimate assumes general UK population life expectancy and utility for patients who survive the sepsis episode. It is based on an average age at sepsis onset of 60 years, with 40% of patients being female.

This yields a total incremental gain of 296.7 QALYs. The corresponding incremental cost-effectiveness ratio (ICER) is approximately £50.55 per QALY gained. This is substantially below the lower NICE cost-effectiveness threshold of £20,000 per QALY gained. Using the upper bound of the 95% confidence interval for the relative risk of mortality (0.93) results in an ICER of £132 per QALY gained, which remains well below the lower NICE cost-effectiveness threshold.

There is recognised variation in baseline mortality risk. Using a higher hospital 30-day mortality estimate of 21% (Warhurst NICE HTA 2015) would increase the absolute number of deaths avoided and reduce the ICER to approximately £32 per QALY gained.

The QALY gain per survivor (12.68) is based on a cohort with a mean age of 60 years (Stevenson 2025). Assuming an older cohort (for example, mean age 80 years, consistent with the PRONTO RCT population; Todd 2026) would reduce lifetime QALY gains. A conservative scenario assuming a 50% reduction in QALY gains still results in an ICER of approximately £108 per QALY gained. Across all scenarios explored, PCT testing remains potentially cost effective.

1.1.8 Committee discussion and interpretation of the evidence

1.1.8.1 What are the key issues and priorities relating to this question?

The committee discussed if a procalcitonin (PCT) test should be undertaken to help healthcare providers identify sepsis, distinguish bacterial from viral infections, assess the risk of severe infection, and guide decisions about antibiotic use. The committee highlighted that PCT testing for suspected sepsis is not current practice in the UK but are aware of its use outside of the UK. The committee discussed whether there could be any benefit to the addition of a PCT test to existing blood tests such as C-reactive protein (CRP) for the assessment of risk of severe infection and to guide antibiotic decision making. This update follows on from previous NICE considerations of Procalcitonin testing for diagnosing and monitoring sepsis (DG18) in 2015 where there was insufficient evidence with which to recommend its routine adoption in the NHS with research recommendations developed. New research was identified for PCT testing prompting this update. The key issues are the possible use of PCT tests findings on time to initiation of IV antibiotics, duration of IV antibiotic treatment and mortality within 30 days compared to usual care, and secondarily length of hospital stay, admission to ICU within hospital stay, severity of disease (using scoring systems such as SOFA, SAPS II, APACHE II), and health related quality of life (HRQoL).

1.1.8.2 Certainty of evidence and the balance of effects

The committee discussed the findings of the 1 identified randomised control trial (RCT) PRONTO trial (Todd et al 2026) which was assessed as being at moderate risk of bias and directly applicable, and considered the superiority and non-inferiority respectively of procalcitonin-guided care with usual care compared with usual care alone for the outputs of intravenous antibiotic initiation at 3 hour (superiority) and 28-day mortality (non-inferiority) from triage assessment.

The PRONTO trial reported 5 outcomes of interest to the review, including all 3 of the primary outcomes. All findings were rated as either low certainty

(mortality within 30 days, time to initiation of IV antibiotics, duration of IV antibiotic treatment, and length of hospital stay) or very low quality (admission to ICU within hospital stay). Mortality within 30 days was the only outcome to show clear evidence of benefit when using PCT testing + standard care compared to standard care. All other outcomes found evidence of no effect.

The committee also considered additional analyses from the PRONTO trial to contextualise the findings. They examined Kaplan–Meier plots showing mortality rates over 28 days, sub-grouped by NEWS2 score, which showed that the mortality benefit was most pronounced in patients with medium or high NEWS2 scores. They also considered a subgroup analysis of mortality for patients who did or did not have an eventual diagnosis of infection, which showed no significant difference indicating the mortality benefit was not specific to those with infection. Finally, they discussed the Complier Average Causal Effect (CACE) analysis which presented adjusted odds ratios for different levels of adherence to the treatment algorithm. This showed that only 46% of clinicians fully treated patients according to the PCT + standard care algorithm, yet the mortality benefit was only slightly improved from the full sample in those that followed the PCT+ standard care algorithm. None of the additional analyses were assessed using GRADE.

1.1.8.3 Resources and cost-effectiveness

There was no existing economic evidence on PCT for people aged 16 or over. However, an exploratory analysis indicated that PCT testing is likely to be cost effective, with an incremental cost effectiveness ratio of £51 per QALY gained, which is well below NICE's lower cost-effectiveness threshold of £20,000 per QALY gained. This was driven by a large mortality benefit informed by the PRONTO trial (Todd et al 2026). The analysis indicated that, under various sensitivity analyses, including reduced lifetime QALYs gained per person, increased cost of the PCT test, and more conservative estimate of relative risk reduction in mortality, the results remained robust.

The committee discussed that the use of PCT would represent a change in practice, as it would be given in addition to other blood tests and could have a

resource impact on the NHS. There may also be an impact in processing the test, but the level of the impact of this will depend on current testing practice and the processes to undertake the test within laboratories. However, acknowledging the PRONTO trial's methodological limitations and that the greatest benefits seemed to be in people at moderate to high risk of sepsis, the committee recommended PCT only in these subgroups, which may help to offset some of the resource implications. The committee also noted that PCT requires new equipment; however, this is generally provided free of charge by PCT test manufacturers.

1.1.8.4 Equity

There was no clear evidence of inequity identified for PCT testing. However, the committee discussed that the use of procalcitonin testing represents a change in practice that is likely to have resource implications which may mean some variations in availability initially across settings and the decision to support procalcitonin testing would be down to individual trusts, ICSs and ICBs. The committee were reassured as procalcitonin testing is an additional test to those already recommended as part of carrying out a venous blood test which includes C-reactive protein and lactate. The recommendations currently outline its consideration for those identified as being at moderate risk or high risk of severe illness of death from sepsis as this is where the committee felt it would have greatest benefit in supporting decision making

1.1.8.5 Feasibility

The PCT tests used in the PRONTO trial (Todd et al 2026) are low-cost and provided information from a single test. The committee noted that the testing method was flexible as both venous blood draw and capillary sampling were used by different study sites. PCT testing is not yet routinely available in all hospitals.

1.1.8.6 Other considerations

The mechanism behind the apparent mortality benefit was the critical issue for discussion by the committee. There was no obvious explanation as to why the

PRONTO study (Todd et al 2026) found a decrease in mortality when using a PCT test if there were no differences in antibiotic initiation or other outcomes. The mortality benefit did not appear to be a product of more timely treatment for sepsis itself, so the committee discussed other possible drivers such as prompting clinicians to consider other diagnoses and provide more appropriate early treatment for patients with non-infectious illnesses. While there was no clear way to fully explain the findings of the PRONTO trial, the committee concluded that the decrease in mortality was sufficiently beneficial to justify the use of PCT testing.

1.1.8.7 Strength of the recommendations

The committee agreed that the evidence was too uncertain to make a strong recommendation but nonetheless felt that PCT testing should be recommended where a benefit is possible. For this reason, they decided upon a 'consider' recommendation with caveats for use in people evaluated as high or moderate risk of severe illness or death from sepsis.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.2 and 1.8.16. The review protocol that underpins the evidence searches for this review included people aged 16 and over, pregnant and recently pregnant people and children and young people under 16, the committee discussions and resulting recommendations are specific to people aged 16 and over.

1.1.10 References

1.1.10.1 Effectiveness evidence

Todd, S., Euden, J., Condie, J., Aston, S., Barlow, G., Brookes-Howell, L., et al.; PRONTO Trial Group. (2026). Procalcitonin testing combined with NEWS2 evaluation compared with usual care based on NEWS2 for identification of sepsis and antibiotic initiation in the emergency department in England and Wales (PRONTO): A multicentre, randomised, controlled, open-label, phase 3 trial. *The Lancet Respiratory Medicine*. Advance online publication. https://doi.org/10.1016/S2213-2600(25)00433-3

1.1.10.2 Economic evidence

Stevenson, M., Forsyth, J. E., Hossain, A., Lall, R., & Dark, P. (2025). Cost-effectiveness of procalcitonin-guided antibiotic duration for hospitalized patients with sepsis. Critical Care, 29(1), 508.

Warhurst, G., Dunn, G., Chadwick, P., Blackwood, B., McAuley, D., Perkins, G. D., et al. (2015). Rapid detection of health-care-associated bloodstream infection in critical care using multipathogen real-time polymerase chain reaction technology: a diagnostic accuracy study and systematic review. Health technology assessment (Winchester, England), 19(35), 1.