EVIDENCE APPRAISAL
REPORT

Technoleg Iechyd Cymru
Health Technology Wales

Procalcitonin point-of-care testing for initial assessment of suspected sepsis

EAR Number:
006 (June 2019)

FIELD: Infections

TYPE: Diagnostic

Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report[1]

Review of systematic reviews and additional primary studies

Procalcitonin point-of-care testing for initial assessment of suspected sepsis

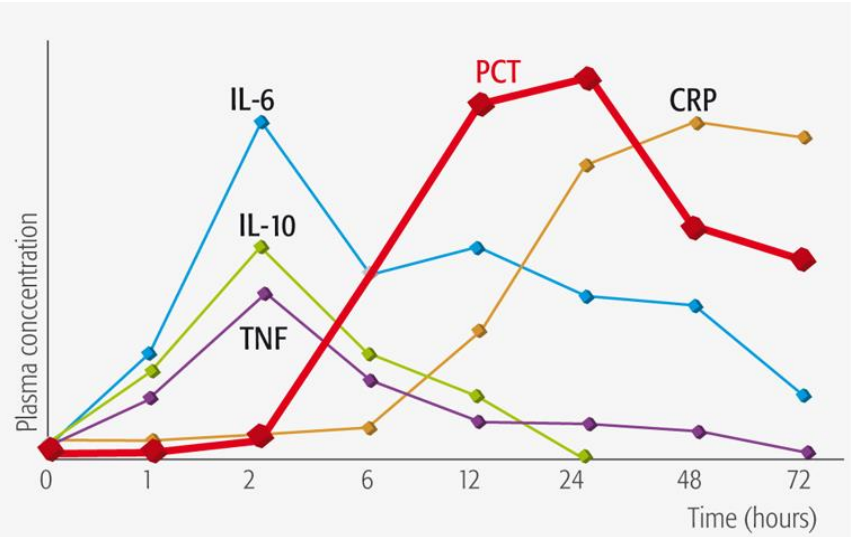

Figure 1. Kinetic profiles of different biomarkers of bacterial infection
CRP: C-Reactive Protein; IL-6: Interleukin-6; IL-10: Interleukin-10; PCT: Procalcitonin; TNF: Tumour Necrosis Factor. (Biomérieux) *adapted from* (Meisner 1999)

Topic referrer: Dr Martin Edwards, Paediatrician, Cardiff & Vale University Health Board

1. Health problem

Sepsis is a serious reaction to an infection whereby the immune system response becomes overactive and starts to cause damage to the body itself. It needs to be treated urgently because it can progress quickly and lead to serious consequences including organ failure, amputation and death (NICE 2017b). Sepsis can be difficult to diagnose, as many of its symptoms are non-specific. These symptoms may include fever or a very low body temperature, rapid breathing and altered mental status, such as reduced alertness or confusion. Young children in particular may initially

[1] Rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence. This is critically evaluated by researchers and the draft Evidence Appraisal Report is issued to experts for review and discussed by Health Technology Wales multidisciplinary advisory groups.

appear well in a standard clinical assessment, but a small proportion have serious bacterial infections which require immediate intervention.

In the UK, there are more than 250,000 episodes of sepsis annually and it is an important cause of death in people of all ages (The UK Sepsis Trust 2017). Sepsis is a leading cause of avoidable death and kills more people than breast, bowel and prostate cancer combined (NICE 2017b). In 2016, the World Health Organisation reported sepsis as a leading cause of mortality worldwide in children under the age of five (WHO 2016); and in 2017, sepsis was recognised as a global health priority (Reinhart et al. 2017).

Clinical teams must be able to rapidly distinguish between different agents of infection to guide appropriate treatment (NICE 2015). Often, antibiotic treatment is initiated in people with suspected sepsis before establishing whether there is a bacterial (rather than viral or fungal) infection; the Surviving Sepsis Campaign recommends initiation of IV antimicrobials within an hour (Rhodes et al. 2017). Antibiotics are associated with side effects including mild stomach upset and diarrhoea, and less commonly, allergic reactions and toxicity. 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 (NICE 2015). The ability to predict which patients with sepsis will deteriorate rapidly is also important. Sepsis that has progressed to septic shock is associated with mortality rates of 40% to 60%, increasing substantially for every hour of delay in starting appropriate antibiotic treatment (NICE 2015).

There is an urgent clinical need for accurate tests of biomarkers (naturally occurring indicators) of serious bacterial infection to facilitate early diagnosis of sepsis. The tests need to be sensitive enough to pick up those with serious bacterial infections, whilst specific enough to be able to rule out those who do not have bacterial infections. This in turn will enable prompt selection of appropriate treatment, and avoid the use of antibiotics in those least likely to benefit. Biomarker-guided initiation (and termination) of antibiotic therapy might be an effective strategy to reduce unnecessary antibiotic use and help prevent further multidrug resistance (NICE 2017b).

The National Institute for Health and Care excellence (NICE) has reported that the inflammatory markers currently used in the NHS (white cell count and C-reactive protein, CRP) are non-specific and not sensitive enough for this purpose. The 2015 NICE diagnostic guidance on (laboratory) procalcitonin testing for diagnosing and monitoring sepsis showed that there was not enough evidence in this area to support its routine use in the NHS (NICE 2017b). The NICE clinical guideline CG160 on the assessment and initial management of fever in children under five years old replaced NICE clinical guideline CG47 from 2007, and was updated most recently in 2017 (NICE 2017a). The Guideline Development Group recommended that a UK study is carried out to assess the performance characteristics and cost-effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection in children with fever without apparent source. The evidence base contributing to this statement showed varying performance of both C-reactive protein and procalcitonin in detecting bacterial infection in a range of populations.

2. Health technology

Procalcitonin is an inflammatory biomarker which can be detected in the blood of people with bacterial infection. Levels of procalcitonin rapidly become elevated in people with severe systemic infection (sepsis), and decrease with effective antibiotic treatment.

Point-of-care testing (POCT) for procalcitonin has been developed to help with the rapid recognition and management of sepsis. It is not intended to be used in isolation, but as one of several tools to aid decision-making (as an adjunct to clinical judgement). Procalcitonin-guided treatment has potential to reduce:

- unnecessary antibiotic prescribing
- harm to patients as a consequence of delayed diagnosis, and
- associated healthcare costs.

Current standard of care for diagnosing sepsis varies throughout the UK; reference is often made to other inflammatory biomarkers (most commonly C-reactive protein, CRP). Unlike CRP, procalcitonin levels facilitate differentiation between infections of bacterial and viral origin. High levels of procalcitonin in the blood can be detected earlier than CRP, as illustrated in Figure 1.

This appraisal focuses particularly on the use of bedside procalcitonin *POCT* to facilitate early differential diagnosis of sepsis. EU Regulation 2017/746 has introduced more stringent regulatory requirements for POCT; when the regulation is fully implemented (2022) the need for detailed performance evaluation could impact on market availability (O'Brien et al. 2019).

3. Evidence search methods

The Population-Intervention-Comparator-Outcomes-Study design (PICOs) framework for the evidence appraisal was developed with input from the Health Technology Wales (HTW) Assessment Group, the topic proposer, and other UK experts (see Appendix 1).

A systematic literature search to study clinical effectiveness was undertaken on 21-22 August 2018. This aimed to identify the following types of evidence:

(i) health technology assessment reports, systematic reviews of randomised controlled trials (RCTs) and cost effectiveness studies,
(ii) individual studies published subsequent to any relevant systematic reviews, or individual studies from any date where no systematic reviews exist,
(iii) ongoing clinical trials.

Update searches were undertaken on 18-21 January 2019 & 22 April 2019. The update searches aimed to identify any studies pertaining to procalcitonin and quantitative POCT. No date restriction was applied to the update searches.

Databases searched included Medline, Embase and the Cochrane database of systematic reviews. In addition, guideline and technology appraisal databases and relevant websites were searched. The latter included those specifically relevant to healthcare and government in Wales. A copy of the search strategies used is available on request. Appendix 2 summarises the selection of articles for inclusion in the review.

Patient, safety and organisational issues were considered only if they were referred to by expert reviewers; no specific searches were undertaken. No resources relating to cost-effectiveness were identified.

4. Clinical effectiveness and safety

4.1. Reviews and studies

The literature searches carried out by HTW focused specifically on procalcitonin POCT, for use at initial presentation of patients with a history and symptoms consistent with sepsis. No high-level evidence (systematic review or health technology assessment) was identified which focused specifically on quantitative procalcitonin POCT. A horizon scan report from the University of Oxford (Gill et al. 2012) reported on the use of procalcitonin POCT to improve the early diagnosis of serious bacterial infection, but only identified a single test (Brahms PCT-Q), which was outside of scope due to its reliance on semi-quantitative methods.

No substantial safety concerns were identified.

4.2. Primary evidence

One trial met the inclusion criteria for this review, and reported diagnostic accuracy (Waterfield et al. 2018b). The design and results of the trial is summarised in Table 1.

No evidence was identified on clinical outcomes resulting from the use of procalcitonin POCT, such as antibiotic use, length of hospital stay, mortality, or complications/consequences of sepsis.

4.3. Ongoing trials

The literature search identified a number of ongoing trials of *laboratory* procalcitonin testing. Two studies of procalcitonin POCT were identified which might inform a future review.

A multicentre Dutch study of POCT (TeSD-IT) aims to recruit 1000 acutely ill adults with fever, confusion or general deterioration (or otherwise suspected of a serious infection) who receive an out-of-hours visit from a general practitioner (Netherlands Trial Tegister 2018). The primary outcome is diagnosis of sepsis within 72 hours of inclusion, with a number of secondary outcomes being evaluated up to 30 days of follow-up. This study is observational in design and therefore would not be considered high quality. Rather than comparing procalcitonin POCT against standard care, the aim is to develop a single POCT decision tool using composite measures of clinical signs, CRP, lactate *and* procalcitonin levels. The anticipated completion date is listed as December 2019, but it is not clear whether or not the study started as planned in June 2018.

Similarly, anecdotal evidence suggests that a duplex procalcitonin and proADM (another sepsis marker) assay is being trialled for POCT.[2]

The Petechiae in Children (PiC) study (Waterfield et al. 2018a) is a multicentre prospective diagnostic accuracy study in children presenting to UK emergency departments with suspected meningococcal disease. Some of the children have been assessed using procalcitonin POCT. Results are expected to be reported in late 2019 or early 2020.

[2] Expert comment 2019

Table 1. Study details: (Waterfield et al. 2018b)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, United Kingdom. n = 126 Median age 42 days (interquartile range 14 to 70 days) Recruitment period: September 2017 to January 2018	**Population:** Any child under 90 days of age presenting with signs or symptoms suggestive of possible bacterial infection. **Index test:** POCT for procalcitonin using the BRAHMS procalcitonin assay on the Samsung LABGEO IB10® analyser. **Reference standard/comparator:** Invasive bacterial infection (IBI) defined as isolation of a bacterial pathogen in blood or cerebrospinal fluid culture. **Outcomes measured:** diagnostic accuracy.	**Study design:** prospective. Infants were included at the discretion of the attending clinician thereby introducing potential selection bias. The reference standard test was conducted after the index test and without knowledge of the index test results.	• This study aimed to assess the use of PCT to diagnose invasive bacterial infections in infants with signs of infection. Furthermore, sensitivity and specificity are reported for detection of all (invasive and non-invasive) bacterial infections. It is not clear how many of these cases would be at risk of sepsis. • Some neonates (<4 weeks of age) were included in the study; it was not possible to separate out the results for this subgroup. The median age was 42 days (IQR 14-70).

Results

In total 4 children out of the sample of 126 were confirmed to have invasive bacterial infection and 10 had non-invasive bacterial infection.

Diagnostic accuracy was measured at three different procalcitonin cut-off levels:

	PCT Cut-off 0.25 ng/ml		PCT Cut-off 0.5 ng/ml		PCT Cut-off 1.0 ng/ml	
	Invasive Bacterial Infection	All Bacterial Infection	Invasive Bacterial Infection	All Bacterial Infection	Invasive Bacterial Infection	All Bacterial Infection
Sensitivity, % (95% CI %)	1.00 (0.40 to 1.00)	0.86 (0.56 to 0.97)	1.00 (0.40 to 1.00)	0.86 (0.56 to 0.97)	1.00 (0.40 to 1.00)	0.86 (0.56 to 0.97)
Specificity: % (95% CI %)	0.72 (0.63 to 0.80)	0.77 (0.68 to 0.84)	0.91 (0.84 to 0.95)	0.97 (0.92 to 0.99)	0.92 (0.85 to 0.96)	0.98 (0.93 to 0.99)
Positive Predictive Value, % (95% CI %)	0.11 (0.03 to 0.26)	0.32 (0.18 to 0.49)	0.27 (0.09 to 0.55)	0.80 (0.51 to 0.95)	0.29 (0.10 to 0.58)	0.86 (0.56 to 0.97)
Negative Predictive Value, % (95% CI %)	1.00 (0.95 to 1.00)	0.98 (0.93 to 1.00)	1.00 (0.96 to 1.00)	0.98 (0.93 to 1.00)	1.00 (0.96 to 1.00)	0.98 (0.93 to 1.00)

CI: confidence interval; IQR: Interquartile range; PCT: procalcitonin; PICO: population, intervention, comparator and outcome; POCT: point-of-care.

5. Organisational issues

There has been variable adoption of procalcitonin testing in the UK, availability being subject to suitability of local analyser platforms. Uptake of procalcitonin testing is believed to be significantly higher in the rest of Europe. The NHS Wales Shared Services Partnership reports that there are no known contracts in place for procalcitonin POCT in Wales. An AQT90 Flex Analyser has been temporarily loaned to WEQAS (a local provider of quality assessment services) by the manufacturer (Radiometer), to compare its performance with that of a laboratory test. CRP POCT is currently used in Swansea Bay University Health Board and Betsi Cadwaladr University Health Board. NHS Wales spends approximately £20,000 per annum on CRP POCT (also a recent change the preferred POCT device may influence this in future).[3]

POCT are most likely to be used in situations when fast decision-making is crucial. They can be used in a variety of locations, including primary care/community settings and emergency units in hospitals, and accessible at all times of the day or night. Tests are processed individually and immediately, rather than blood samples being transported to a laboratory for processing in larger batches. Results can be available within 20 minutes (Radiometer, ThermoFisher Scientific). These factors may be relevant when considering equity due to potential geographical variation in access to laboratory testing facilities, particularly as procalcitonin testing is not currently available in all Health Boards.

There are resource implications when using POCT. For example, a user of the Samsung LABGEO IB10® analyser reports[4]:

- Although running a test takes only 20 minutes, daily quality control checks are recommended (an additional 40 minutes per day).
- It may be challenging to identify who will take responsibility for the maintenance, governance, validation and quality checking of this equipment.

Decisions about the implementation of POCT are made by the All Wales POCT Coordinators Group.

6. Conclusions

This literature review did not identify any published evidence about the clinical effectiveness of procalcitonin POCT to facilitate the initial assessment and diagnosis of sepsis (in either adult or paediatric populations). A single study was identified that studied the accuracy of procalcitonin POCT to diagnose bacterial infections. This study has limited value in addressing the current review question due to its population definition of invasive bacterial infections (which may not directly represent those with suspected sepsis), and inclusion of an unknown proportion of neonates. No evidence was found on the use of quantitative procalcitonin POCT in adult or paediatric populations aged over 90 days.

Evidence from one study (126 patients) indicates that procalcitonin POCT has sensitivity of 1.0 (95% CI 0.40 to 1.00) and specificity of 0.92 (95% CI 0.85 to 0.96) for the diagnosis of invasive bacterial infections in infants at a procalcitonin cut-off of 1.0 ng/ml; lower cut-offs had the same sensitivity but poorer specificity. CRP at a cut-off of 20mg/l performed similarly to a procalcitonin cut-off of 1.0ng/ml.

Procalcitonin was tested using the BRAHMS procalcitonin assay performed on a Samsung LABGEO IB10® portable immunoassay analyser. No evidence supporting the use of other procalcitonin POCT

[3] Personal communication 2018
[4] Expert comment 2019

assays or analysers in this population, and the generalisability of this evidence to other devices is not known. We did not identify any evidence on how procalcitonin POCT affects antibiotic use, length of hospital stay, mortality, or complications/consequences from sepsis in people with suspected sepsis.

Although there is a larger body of evidence relating to laboratory testing of procalcitonin, the current status in the UK is that its use is not supported (NICE 2015). High quality health technology assessments of laboratory procalcitonin testing in the UK are due to report within the next few years, after which NICE may review its guidance (ISRCTN11369832, ISRCTN47473244). As the diagnostic accuracy of POCT procalcitonin is reported to be equivalent to that of laboratory testing (Kutz et al. 2016, Pisarev et al. 2019), positive outcomes might prompt an update to the POCT guidance for Wales.

In conclusion, evidence to inform the use of procalcitonin POCT in the assessment and diagnosis of sepsis is currently very limited. One trial was identified which satisfied the review criteria. Whilst this study reported high diagnostic accuracy for the test, there is uncertainty about the relevance of the very young population included. No evidence was identified that demonstrated whether procalcitonin POCT alters treatment decisions or clinical outcomes in people with suspected sepsis, when compared with standard diagnostic tests alone.

7. Further research

Diagnosis of sepsis is complex, and each of the available diagnostic tools has limitations. A number of ongoing UK studies are expected to report on the effectiveness and cost-effectiveness of laboratory procalcitonin testing within the next few years. Further studies are needed that assess the effectiveness of procalcitonin POCT, particularly with respect to whether its use can alter treatment choices in cases of suspected sepsis when compared to standard diagnostic pathways.

8. Contributors

The HTW staff and contract researchers involved in writing this report were:

- D Jarrom and R Poole – Lead authors
- C Davis – Co-author
- B Coles – Literature searching
- J Washington – Literature searching, methods and reference management
- S Myles – Project oversight

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK commented on drafts of this report, reporting any declarations of interest in advance. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. Reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Experts who contributed to this appraisal:

- Dr Martin Edwards, Consultant Paediatrician, Cardiff and Vale UHB
- Dr Thomas Waterfield, Paediatric Emergency Medicine Doctor, Belfast Health & Social Care Trust
- Professor Enitan Carrol, Professor of Paediatric Infection, University of Liverpool
- Dr Kordo Saeed, Consultant Clinical Microbiologist/ Clinical Lead for Microbiology, Hampshire Hospitals NHS Foundation Trust
- Professor Timothy Rainer, Professor of Emergency Medicine, Cardiff University
- Annette Thomas, All-Wales POCT Co-ordinators Group
- Mike Pattrick, Product Manager AQT90 FLEX immunoassay analyser, Radiometer Ltd
- Ross Stevenson, Business Development Manager, Thermo Fisher Scientific

Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

9. References

Biomérieux. Kinetic profiles of different biomarkers of bacterial infection (graph). Available at: https://www.biomerieux-diagnostics.com/vidas-brahms-pct [Accessed 29 Apr 2019].

ISRCTN11369832. Using procalcitonin to guide duration of antibiotics. Intention to publish date: 01/09/2021. ISRCTN Registry. Available at: https://doi.org/10.1186/ISRCTN11369832 [Accessed 14 May 2019].

ISRCTN47473244. Biomarker-guided duration of antibiotic treatment for sepsis. Intention to publish date: 01/09/2021. ISRCTN Registry. Available at: https://doi.org/10.1186/ISRCTN47473244 [Accessed 14 May 2019].

Kutz A, Hausfater P, Oppert M, et al. (2016). Comparison between B.R.A.H.M.S PCT direct, a new sensitive point-of-care testing device for rapid quantification of procalcitonin in emergency department patients and established reference methods - a prospective multinational trial. Clinical Chemistry & Laboratory Medicine. 54(4): 577-84. doi: https://dx.doi.org/10.1515/cclm-2015-0437

Meisner M. (1999). Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. [German]. LaboratoriumsMedizin. 23(5): 263-72. doi: http://dx.doi.org/10.1515/labm.1999.23.5.263

Netherlands Trial Tegister. (2018). TeSD-IT: Testing for sepsis in primary care: diagnostic and prognostic study investigating the potential benefits of point-of-care testing. Available at: https://www.trialregister.nl/trial/6848 [Accessed 29 Apr 2019].

NICE. (2015). 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). Diagnostics guidance DG18. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/dg18 [Accessed 29 Apr 2019].

NICE. (2017a). Fever in under 5s: assessment and initial management. Clinical guideline CG160. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/cg160 [Accessed 29 Apr 2019].

NICE. (2017b). Sepsis: recognition, diagnosis and early management. NICE guideline NG51. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng51 [Accessed 29 Apr 2019].

O'Brien K, Gloeckner L, Jordan K, et al. (2019). C-reactive protein point-of-care testing (CRP POCT) to guide antibiotic prescribing in primary care settings for acute respiratory tract infections (RTIs). Rapid assessment on other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. EUnetHTA Project ID: OTCA012. Available at: https://www.eunethta.eu/wp-content/uploads/2019/02/EUnetHTA_OTCA012_CRP-POCT_31012019.pdf [Accessed 22 May 2019].

Pisarev V, Chumachenko A, Tyurin I, et al. (2019). Prognostic value of a genetic polymorphism of AQP5 in sepsis depends on a source of infection. Critical Care. Conference: 39th International Symposium on Intensive Care and Emergency Medicine. Belgium. 23(Supplement 2). doi: http://dx.doi.org/10.1186/s13054-019-2358-0

Radiometer. AQT90 FLEX rapid procalcitonin (PCT) test. Available at: https://www.radiometer.com/en/products/immunoassay-testing/aqt90-flex-immunoassay-analyzer/pct-on-the-aqt90-flex-immunoassay-analyzer [Accessed 29 Apr 2019].

Reinhart K, Daniels R, Kissoon N, et al. (2017). Recognizing sepsis as a global health priority: a WHO resolution. New England Journal of Medicine. 377(5): 414-7. doi: https://dx.doi.org/10.1056/NEJMp1707170

Rhodes A, Evans LE, Alhazzani W, et al. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2016. Critical Care Medicine. 45(3): 486-552. doi: https://dx.doi.org/10.1097/ccm.0000000000002255

The UK Sepsis Trust. (2017). The sepsis manual: responsible management of sepsis, severe infection and antimicrobial stewardship. Available at: https://www.e-lfh.org.uk/wp-content/uploads/2018/02/Sepsis_Manual_2017_final_v7.pdf [Accessed 29 Apr 2019].

ThermoFisher Scientific. B·R·A·H·M·S direct Reader. Available at: https://www.brahms-instruments.com/brahms-instruments/brahms-direct-reader.html [Accessed 29 Apr 2019].

Waterfield T, Lyttle MD, Fairley D, et al. (2018a). The "Petechiae in children" (PiC) study: evaluating potential clinical decision rules for the management of feverish children with non-blanching rashes, including the role of point of care testing for Procalcitonin & Neisseria meningitidis DNA - a study protocol. BMC Pediatrics. 18(1): 246. doi: https://dx.doi.org/10.1186/s12887-018-1220-x

Waterfield T, Maney JA, Hanna M, et al. (2018b). Point-of-care testing for procalcitonin in identifying bacterial infections in young infants: a diagnostic accuracy study. BMC Pediatrics. 18(1): 387. doi: https://dx.doi.org/10.1186/s12887-018-1349-7

WHO. (2016). Disease burden and mortality estimates: child causes of death, 2000–2017. World Health Organization. Available at: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html [Accessed 29 Apr 2019].

Appendix 1 - PICOs inclusion and exclusion criteria to inform selection of evidence appropriate to the appraisal topic

	Inclusion criteria	Exclusion criteria
Population	People presenting to hospital with suspected serious community-acquired systemic infection or suspected sepsis (including fever without apparent source) Settings: • Emergency departments • Medical assessment units • Children's assessment units Subgroups (if reported in the literature): • Adults (16+ years) • Children (< 16 years)	Excluded indications: • Neutropenic sepsis • Sepsis secondary to trauma/burns Excluded settings: • Critical/intensive care, PICU or high dependency units • Primary care/community
Intervention	Quantitative procalcitonin POCT at initial triage for diagnostic or prognostic purposes	• Laboratory procalcitonin testing • Procalcitonin POCT for ongoing monitoring of treatment effectiveness or antibiotic stopping decisions
Comparators	• C-reactive protein (CRP) POCT for diagnostic or prognostic purposes • Laboratory testing of other inflammatory markers for diagnostic or prognostic purposes	Tests for ongoing management/monitoring of treatment effectiveness or antibiotic stopping decisions
Outcome measures Follow-up length = until hospital discharge	Technical outcomes: • Measurements of patient flow through department (such as time between presentation to hospital and initiation of antibiotics) • Diagnostic and prognostic accuracy Clinical effectiveness: • Proportion of patients admitted to critical care/HDU/PICU • Length of hospital stay • Duration of antibiotic treatment • Mortality • Complications or consequences of sepsis (e.g. organ failure, amputation) • Adverse reactions or effects of antibiotic use Costs, cost-effectiveness, or resource use/budget impact data	
Study design	Studies will be prioritised for inclusion according to the evidence hierarchy (see below). Lower level evidence will not be included unless higher level evidence is insufficient in quality or quantity. We will search a variety of databases and grey literature, and will consider ongoing trials. 1) Secondary evidence syntheses such as systematic reviews, meta-analyses, health technology assessment reports 2) Randomised controlled trials 3) Observational studies (e.g. case series)	

HDU: high dependency unit; PICO: population, intervention, comparator and outcome; PICU: paediatric intensive care unit; POCT: point-of-care testing

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness