Procalcitonin 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

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Scientific summary

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Background

This assessment is concerned with the value of procalcitonin (PCT) in managing antibiotic therapy in two distinct populations: adults and children with known or highly suspected sepsis who are being treated in intensive care units (ICUs) and adults and children who present to the emergency department (ED) with suspected bacterial infection. Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate therapy and to reduce unnecessary exposure to antibiotics. Reduction of antibiotic exposure is increasingly a priority for the UK NHS, in the context of efforts to conserve the effectiveness of existing drugs.

Procalcitonin is a 116-amino-acid precursor to calcitonin. Normal serum or plasma levels of PCT in healthy adults are ≤ 0.05 ng/ml. PCT can be produced by a variety of cell types in response to inflammatory stimuli, especially of bacterial origin. It does not usually rise significantly with viral or non-infectious inflammation and so has the potential to be used as a marker of bacterial infection. All methods for the quantification of PCT are based on immunoassay and there are currently a number of CE-marked automated assays available in the UK.

Objectives

The overall objectives of this project are to assess the clinical effectiveness and cost-effectiveness of adding PCT testing to the information used to guide antibiotic therapy in the following two populations:

1. adults and children with confirmed or highly suspected sepsis in intensive care settings
2. adults and children presenting to the ED with suspected bacterial infection.

For each of these populations we defined the following research questions:

- How does initiation of antibiotic therapy differ when PCT test results are added to the information available to treating clinicians?
- How does duration of antibiotic therapy and length of hospital/ICU stay differ when PCT test results are added to the information available to treating clinicians?
- How do clinical outcomes [e.g. septic shock, Sequential Organ Failure Assessment (SOFA) scores, in-hospital mortality] differ when PCT test results are added to the information available to treating clinicians?
- Does the addition of PCT testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy represent a cost-effective use of NHS resources?

Methods

Assessment of clinical effectiveness

Twelve databases, including MEDLINE and EMBASE, research registers and conference proceedings, were searched to June 2014. Search results were screened for relevance independently by two reviewers. Full text inclusion assessment, data extraction, and quality assessment were conducted by one reviewer, and checked by a second. Randomised controlled trials (RCTs) were assessed for quality using the Cochrane Risk of Bias tool. Analysis was stratified by objective. Summary relative risks (RRs) and weighted mean differences (WMDs) were estimated using random-effects models. Heterogeneity was investigated visually using forest plots and statistically using the I^2 and Q statistics. Observed heterogeneity was assessed using subgroup analysis.

Assessment of cost-effectiveness

In a de novo health-economic analysis the short-term cost-effectiveness of PCT testing in addition to current clinical practice compared with current clinical practice without PCT was assessed for (1) adults with confirmed or highly suspected sepsis in an ICU setting; (2) adults with suspected bacterial infection presenting to the ED; and (3) children with suspected bacterial infection presenting to the ED. Children with confirmed or highly suspected sepsis in an ICU setting were not considered as a result of the lack of data on clinical effectiveness in this population.

The structure of the decision tree starts with one decision node that denotes the use of PCT or current clinical practice without PCT. The key end points are (1) alive with antibiotic-related complications; (2) alive without antibiotic-related complications; and (3) death. The time horizon is 6 months (183 days), divided into an initial short-term (28 days) phase and a subsequent phase lasting 155 days. The mean expected costs, life-years (LYs), duration of antibiotic treatment and QALYs are calculated separately for both strategies.

Given the variation within the patient groups of interest, a 'lower clinical extreme' and a 'higher clinical extreme' is specified for each population and setting. For these 'clinical extremes' different baseline values are used for the mortality probability and resource-use parameters while applying the same RR or mean difference estimates for both clinical extremes.

One-way sensitivity analyses were performed for all stochastic input parameters between the 95% confidence intervals (CIs). Scenario analyses were performed to assess the impact of assumptions on the estimated outcomes.

Results

Clinical effectiveness

Eighteen parallel group RCTs (36 reports) were included in the clinical effectiveness review. Studies were generally of unclear quality due to limitation in reporting. Twelve of the included studies measured plasma/serum PCT levels using the BRAHMS PCT Sensitive Kryptor assay (Thermo Fisher Scientific, Waltham, MA, USA), two studies measured plasma/serum PCT levels using the VIDAS BRAHMS PCT (bioMérieux, Marcy l'Etoile, France), and four studies used quantitative PCT assays but did not specify the assay manufacturer.

Three of the eighteen studies were judged at high risk of bias, one as low risk of bias, and all other studies were judged at unclear risk of bias, as insufficient information was reported to make a judgement on one or more bias domains.

Adults and children with confirmed or highly suspected sepsis in intensive care settings

Eight studies (12 reports), all conducted in adults, evaluated patients with sepsis in the ICU setting. Populations in ICU studies included adults with confirmed or highly suspected sepsis (four studies), adults being treated for suspected bacterial infection and those who developed sepsis during their ICU stay (one study), adults with acute pancreatitis (one study), adults with ventilator-acquired pneumonia (one study), and adults being treated for suspected bacterial infections (one study).

Procalcitonin algorithms were associated with a reduction in antibiotic duration (WMD –3.19 days, 95% CI –5.44 to –0.95 days, $I^2 = 95.2\%$; four studies). Uncertainty around this effect was reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (WMD –1.20 days, 95% CI –1.33 to –1.07 days; two studies). Data on resource use indicated that PCT algorithms were associated with a reduction in the duration of hospital stay (WMD –3.85 days, 95% CI –6.78 to –0.92 days, $I^2 = 75.2\%$; four studies) and a trend towards a reduction in the duration of ICU stay (WMD –2.03 days, 95% CI –4.19 to 0.13 days, $I^2 = 81.0\%$; four studies). Uncertainty around these effect

estimates was also reduced when the analysis was restricted to studies conducted in populations with suspected or confirmed sepsis (duration of hospital stay WMD –4.32 days, 95% CI –6.50 to –2.14 days, two studies; duration of ICU stay WMD –2.31 days, 95% CI –3.97 to –0.65 days, two studies). There were no differences between intervention groups for any adverse clinical outcomes assessed including mortality at various time points, infection relapse/recurrence, mechanical ventilation, multiple organ dysfunction syndrome and SOFA score. No study reported data on antibiotic-related adverse events.

Adults and children presenting to the emergency department with suspected bacterial infection

Ten studies (16 publications), eight in adults and two in children, evaluated patients presenting to the ED with suspected bacterial infections. One study was conducted in adults with urinary tract infection; all others included adults or children with respiratory presentations.

Procalcitonin algorithms were associated with a reduction in the proportion of adults receiving antibiotics (RR 0.77, 95% CI 0.68 to 0.87; seven studies), the proportion of children with community-acquired pneumonia (CAP) receiving antibiotics (RR 0.86, 95% CI 0.80 to 0.93), and in the duration of antibiotic therapy in adults (two studies) and children (one study). However, the observed reduction in duration of antibiotic therapy appeared to be driven by the inclusion in the analysis of participants who did not receive any antibiotic therapy. Four further studies reported data in a form that could not be included in the meta-analysis; all found that PCT algorithms were associated with a reduction in the duration of antibiotic therapy in adults and children. PCT algorithms were associated with a trend towards reduction in the duration of hospital stay (WMD –0.80 days, 95% CI –2.37 to 0.78 days; two studies); the effect of PCT on duration of hospital stay was inconsistent across the six adult studies reporting this outcome. PCT algorithms were associated with a small reduction in the duration of hospital stay in children (WMD –0.74 days, 95% CI –1.17 to –0.31 days; two studies). There was no difference between intervention groups for duration of ICU stay, hospital re-admission or secondary ED visits. Adverse clinical outcomes including mortality at various time points, infection relapse/recurrence, composite measures of adverse outcomes, mechanical ventilation, need for steroids, and complications of pneumonia generally showed no differences between intervention groups. Data from one study in adults and two in children indicated that PCT algorithms were associated with a reduction in antibiotic-related adverse events.

Assessment of cost-effectiveness

Base-case analysis

The base-case analyses indicated that PCT dominates current clinical practice for all populations in that it was both cost-saving and more effective. The cost-saving ranged from £368 for children with suspected bacterial infection presenting to the ED (lower clinical extreme) to £3268 adults with confirmed or highly suspected sepsis in an ICU setting (lower clinical extreme). PCT testing resulted in only a small quality-adjusted life-year (QALY) gain. For adults with suspected bacterial infection presenting to the ED this was 0.005 for the lower and higher clinical extremes, and for adults with confirmed or highly suspected sepsis in the ICU setting it was 0.001, respectively, for both clinical extremes. For children with suspected bacterial infection presenting to the ED, the QALY gains were < 0.001 for both clinical extremes. The differences between the lower and higher clinical extremes were small for all settings and populations.

Cost-effectiveness acceptability curves showed that PCT-guided treatment has a probability of $\geq 84\%$ of being cost-effective for all settings and populations considered (at willingness-to-pay thresholds of £20,000 and £30,000 per QALY).

Sensitivity and scenario analyses

The one-way sensitivity and scenario analyses indicated that the base-case outcomes were robust. Only one sensitivity analysis showed a relevant change in the incremental outcomes. This was the one-way sensitivity analysis for the relative mortality risk for adults with suspected bacterial infection presenting to the ED. This analysis showed that, when using the upper bound of the 95% CI, PCT-guided treatment was

less costly and less effective than current clinical practice, leading to savings of £30,469 (lower clinical extreme) and £30,446 (higher clinical extreme) per QALY lost. This indicates that PCT-guided treatment is cost-effective, based on a threshold of £30,000, i.e. that a QALY lost is accepted given the obtained savings for PCT-guided treatment. The scenario analyses that assumed no difference in hospital stay had a substantial impact on all analyses. For all analyses, PCT-guided treatment became more costly and remained more effective (instead of dominating current clinical practice). For the children presenting to the ED, this resulted in an incremental cost-effectiveness ratio (ICER) of £287,076 for the lower clinical extreme and £35,219 for the higher clinical extreme. For adults in both settings and both clinical extremes the ICER varied between £3390 and £3948.

Conclusions

Implications for service provision

The addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults being treated for suspected or confirmed sepsis in ICU settings and in adults presenting to the ED with respiratory symptoms and suspected bacterial infection, without any adverse consequences for clinical outcome. In ICU settings, the PCT algorithm was primarily used to inform decisions on when to discontinue antibiotic treatment, whereas in ED settings the primary application was decisions on whether or not to initiate antibiotic treatment. The use of a PCT algorithm may also be associated with reductions in hospital and ICU stay. Very limited data suggest that similar effects may apply for children presenting to the ED with respiratory symptoms and suspected bacterial infection, in particular the subgroup with CAP. No evidence was identified on the effectiveness using a PCT algorithm to guide antibiotic treatment for children with suspected or confirmed sepsis in the ICU. However, it is important to note that evidence was limited and none of the identified studies was conducted in the UK. It is not clear whether or not the control arms of these studies were representative of standard practice in the UK, for example if a more protocolised approach is used in the UK than in the countries where studies were conducted; if the control arms were not comparable with standard practice in the UK then any apparent effects of PCT testing may not be reproducible in the NHS.

Available evidence suggests that the addition of PCT testing to current clinical practice leads to cost-savings and a very small QALY gain and thus dominates current practice. Hence PCT testing potentially represents a cost-effective use of NHS resources for adults with confirmed or highly suspected sepsis in an ICU setting, adults with suspected bacterial infection presenting to the ED, and children with suspected bacterial infection presenting to the ED. However, although the economic analysis indicates that there is little decision uncertainty, not all uncertainties can be captured in the parameters and thus be reflected in the outcomes of the economic assessment. This ‘scenario uncertainty’ includes the generalisability of the results to the UK setting. Therefore, it is important to note that the results of the economic assessment should be interpreted with caution. This applies in particular to the ED setting as another generalisability issue arises: the applicability of the presented outcomes to patients other than those with respiratory symptoms. The paucity of evidence on long-term outcomes might further add to uncertainty.

Suggested research priorities

Further studies are needed to assess the effectiveness of adding PCT algorithms to the information used to guide antibiotic treatment in children with suspected or confirmed sepsis in ICU settings. Additional research is needed to examine whether the outcomes presented in this report are fully generalisable to the UK setting and whether the outcomes found for the ED setting are also applicable for patients other than those with respiratory symptoms. Finally, although it is likely to add to the gain in effectiveness and/or cost-savings only for PCT-guided treatment, it would be of relevance to examine long-term costs and effects of PCT-guided treatment, including its potential impact on antibiotic resistance.

Study registration

This study is registered as PROSPERO CRD42014010822.

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