Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review found that using procalcitonin blood markers as guidance, antibiotic exposure may be reduced in critically-ill septic patients without affecting clinical outcomes, but further research was necessary. Although the authors' cautious conclusions reflected the evidence, they should be considered tentative given the potential for publication bias, substantial variation in the primary outcomes, and the small number of low quality included trials.

Authors' objectives
To assess the effectiveness and safety of procalcitonin-guided algorithms in the management of critically-ill septic patients in the intensive care unit.

Searching
MEDLINE (from inception), Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to April 2010 with no language restriction for relevant studies; minimal search terms were reported. Reference lists of retrieved studies were also scanned.

Study selection
Eligible studies were randomised controlled trials (RCTs) that reported on the outcomes of critically-ill patients with proven or suspected sepsis in the intensive care unit setting managed with a procalcitonin-guided algorithm compared with routine practice. Routine practice was defined as the institution and discontinuation of antibiotics guided by standard clinical and laboratory parameters without the knowledge of procalcitonin values.

Primary outcomes were measures of antibiotic exposure (duration of therapy and numbers of antibiotic-free days). Secondary outcomes included hospital and 28 day all-cause mortality, length of intensive care unit and hospital stay, days free from mechanical ventilation, rates of relapsed or persistent infection and superinfection, and cost.

In the included trials, participants were mostly critically-ill adults in medical, surgical or mixed intensive care units; participants in one trial were neonates with suspected early-onset sepsis in a neonatal/paediatric intensive care unit. Adult participants had either pneumonia (community, hospital-acquired or associated with the ventilator) or confirmed infection (mostly peritonitis) after surgery. The procalcitonin-guided algorithms mostly provided guidance on when to discontinue antibiotics; guidance was given on when to start antibiotics in one trial and for an overall management plan in another trial. Some physicians (range 16 to 53%) in some trials disregarded the algorithm stopping rules. Procalcitonin assays included either the time-resolved amplified cryptate emission (TRACE) technology assay, luminescence immunoassay or immunochromatographic method. Most trials were single-centre; two were multi-centre. Included trials were conducted in Europe and the USA. All trials were published after 2007.

Two reviewers independently selected studies for the review.

Assessment of study quality
Trials were assessed for risk of bias using the Cochrane risk of bias tool. Criteria included sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

The authors did not state how many reviewers assessed the studies for risk of bias.

Data extraction
Data were extracted on primary and secondary outcomes. Mean differences (MDs) for continuous data and odds ratios (ORs), with their 95% confidence intervals (CIs), were calculated. Authors of the included trials were contacted and provided information or clarifications on the data.

Two reviewers independently extracted data.
Methods of synthesis
Trials were pooled in meta-analyses. Summary effect measures (odds ratio and weighted mean differences, WMDs) with 95% confidence intervals were calculated, using the Mantel-Haenszel fixed-effect model and DerSimonian-Laird random-effects model. Data from the trial with neonate participants were not included in the meta-analyses but reported in narrative format. Heterogeneity was assessed with the $X^2$ test (with a value of $P<0.1$ indicating significance) and quantified using $I^2$.

Sensitivity analyses were undertaken to explore the effect of trial quality on duration of antibiotic treatment for first episode of infection, total duration of antibiotic treatment, and 28-day mortality.

Results of the review
Seven RCTs (1,131 patients, range 27 to 621) were included in the review. Six trials (1,010 patients) were of critically-ill adults; one trial (121 patients) was of neonates. Three trials were considered to be of high quality and four trials of low quality.

Procalcitonin-guided algorithms were associated with a reduction in the duration of antibiotic therapy for the first episode of infection compared with routine care in adults (WMD -2.36 days, 95% CI -3.11 to -1.61; five RCTs; $I^2=68%$; random-effects model) and reduction in the total duration of antibiotic treatment (WMD -4.38 days, 95% CI -6.08 to -2.68; three RCTs; $I^2=72%$; random-effects model). Substantial heterogeneity was identified for these analyses; fixed-effect and random-effects results were reported. Procalcitonin-guided algorithms were also associated with significantly more antibiotic-free days than routine care (WMD 2.94 days, 94% CI 1.92 to 3.96; three RCTs; $I^2=0%$). The finding of a reduction in the duration of antibiotic therapy in the first episode of infection was confirmed by results in the single trial with neonate participants.

There was no evidence of statistically significant differences in mortality or superinfection outcomes between groups in adults or neonates or in any of the other secondary outcomes in adults.

Sensitivity analyses did not markedly change the direction or significance of the results.

Cost information
One small trial (27 patients) reported that the cost of antibiotic treatment was significantly reduced by 17.8% in the procalcitonin-guided group compared with the control group.

Authors' conclusions
The implementation of a procalcitonin-based algorithm may reduce antibiotic exposure in critically-ill septic patients without compromising clinical outcomes, but further research is necessary.

CRD commentary
The review addressed a clear research question and inclusion criteria appeared appropriate. A number of relevant sources were searched with no language restrictions, but no specific attempts were made to identify unpublished studies, so publication bias could not be ruled out. Appropriate methods were used to select studies and extract data, but the authors did not specifically report their methods for the assessment of quality, so reviewer error and bias during this process could not be ruled out.

Less than half of the included trials were at low risk of bias, but sensitivity analyses were undertaken to explore the effect of trial quality on the results. The number of included trials was small and not all them provided data on all the outcomes. There was significant clinical heterogeneity among trials for the setting, case mix of participants, inclusion and exclusion criteria, type of infections under analysis, and specifics of the interventions (in particular, cut-offs used in the procalcitonin protocols). Substantial statistical heterogeneity was identified in the analyses of most of the primary outcomes. The authors noted that results may have been different if the control groups used locally applied practice protocols rather than routine practice. Most of the included trials were funded or sponsored by manufacturers of the procalcitonin assays, although the authors of the individual trials explicitly stated that these companies had no influence on the design of the trials or analyses of the data.

Although the authors' cautious conclusions reflected the evidence, they should be considered tentative given the
potential for publication bias, substantial heterogeneity in the primary outcomes, and the small number of low quality included trials.

Implications of the review for practice and research
Practice: The authors stated that the implementation of procalcitonin-guided algorithms should be viewed as an inadequately validated strategy for antibiotic control in critically-ill patients in intensive care units.

Research: The authors stated that further research was required to determine the effectiveness of infection and/or microorganism-specific cut-offs and the nature of endpoints in procalcitonin-guided algorithms. Further research should also compare these algorithms with protocols, include different types of intensive care unit patients, assess cost and standardise protocols and outcomes so that individual patient data may be used for analysis.

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