# Biomarker-guided antibiotic cessation in sepsis: evidence and future challenges


## ABSTRACT

Sepsis is a medical emergency, which requires the initiation of broad-spectrum antimicrobial agents as early as possible. In the absence of positive microbiological cultures providing targeted antimicrobial advice, broad-spectrum antibiotics are commonly continued until there is clinical evidence of infection resolution. With an absence of robust evidence to inform when it is safe to stop antimicrobial agents in sepsis, the duration of antimicrobial courses may be longer than is required. Prolonged courses of potent broad-spectrum antimicrobials increase the risk of adverse drug events and contribute to the growing emergence of multidrug resistant pathogens, which is a global public health emergency. The protocolised use of protein biomarkers to guide clinical decision making can be used to help combat excessive durations of antimicrobials in patients with sepsis. This article reviews the current evidence for biomarker-guided antimicrobial discontinuation protocols in sepsis, identifies related evidence gaps and examines future innovation challenges in this field.


Sepsis results from a dysregulated inflammatory response to infection, culminating in multiple organ dysfunction and death. In England there are an estimated 123 000 cases of sepsis each year (UK Parliament, 2015), with a mortality rate of 30–50% (Daniels, 2011). On 26 May 2017, the World Health Organization designated sepsis a world health priority (Reinhart et al, 2017).

The Surviving Sepsis Campaign has updated international consensus guidance on the management of sepsis and septic shock (Rhodes et al, 2017). Recognizing the global health challenge of antimicrobial resistance, the guidance recommends (although based upon low quality evidence) that serial plasma procalcitonin measurements could guide clinical decision making and reduce prolonged, unnecessary exposure to potent broad-spectrum antimicrobials.


**Dr Andrew N Claxton,** Academic Clinical Fellow in Intensive Care Medicine, Nanomedicine Lab, Division of Pharmacy and Optometry, University of Manchester, Salford Royal NHS Foundation Trust, Salford M6 8HD

**Professor Paul M Dark,** Professor of Critical Care Medicine, Division of Infection, Immunity and Respiratory Medicine, Manchester University Foundation Trust, University of Manchester, Manchester; Honorary NHS Consultant in Critical Care Medicine, Salford Royal Foundation Trust; NIHR CRN National Specialty Lead (Critical Care), King's College London, London

Correspondence to: Dr AN Claxton (andrew.claxton@srft.nhs.uk)


This article examines the evidence for biomarker-guided antibiotic discontinuation in sepsis, identifies evidence gaps and highlights future innovation challenges.

## What is biomarker-guided antimicrobial discontinuation?

In sepsis, it has been established that the plasma concentration levels of C-reactive protein and procalcitonin rise as part of acute inflammatory cascades and fall as a result of appropriate treatments and illness resolution (Ugarte et al, 1999). Decreasing plasma concentrations of C-reactive protein and procalcitonin can be tracked daily in a patient treated for sepsis and may help determine when it is safe to stop antimicrobial treatment. Compared with C-reactive protein, procalcitonin is thought to have particular utility in the setting of bacterial sepsis (Meisner et al, 1999).

## What is the evidence for biomarker-guided antibiotic discontinuation protocols?

### C-reactive protein

C-reactive protein has been extensively examined in the setting of early sepsis diagnosis and prognostication (Vincent et al, 2011), but there is a paucity of data evaluating C-reactive protein in the context of antimicrobial discontinuation. The authors were only able to identify one open-label randomized controlled trial conducted in two Brazilian intensive care units with a small sample size of 94 patients with severe sepsis (Oliveira et al, 2013). In this study, C-reactive protein- and procalcitonin-based algorithms were compared to determine antibiotic duration – with both algorithms including antibiotic discontinuation rules based on relative declines and absolute biomarker values. Mean duration of antibiotic therapy was 8.1 days in the procalcitonin group *vs* 7.2 days in the C-reactive protein group ($P$=0.25), with no differences in all secondary outcomes, which included total antibiotic exposure, mortality and length of hospital stay. To the best of the authors' knowledge, no other randomized controlled trials have been published for C-reactive protein-based antibiotic guidance in adult patients with sepsis.

Within the paediatric setting, a number of trials have demonstrated that C-reactive protein can be used to guide antimicrobial therapy in neonatal sepsis (Ehl et al, 1997; Bomela et al, 2000), and can guide the cessation of antimicrobials 48 hours after admission in children with a non-infective systemic inflammatory response (Downes et al, 2017).

### Procalcitonin

Conversely procalcitonin has been studied widely for its utility in guiding antimicrobial administration. In 2015 the National Institute for Health and Care Excellence published its own guidance on the clinical and cost-effectiveness of using procalcitonin alongside standard clinical practice to guide antibiotic treatment in adults and children presenting for hospital care with confirmed or suspected sepsis.

The National Institute for Health and Care Excellence guidance was informed by a commissioned independent systematic clinical and cost-effectiveness review funded by the National Institute of Health Research Health Technology Assessment programme (Westwood et al, 2015). This review included eight randomized controlled trials that were performed in adult critical care environments. Within this setting, four studies (Nobre et al, 2008; Bouadma et al, 2010; Qu et al, 2012; Liu et al, 2013) provided data that allowed the calculation of mean antibiotic duration, with three of these (Bouadma et al, 2010; Qu et al, 2012; Liu et al, 2013) showing that the addition of procalcitonin to standard practice produced a statistically significant reduction in mean antibiotic duration (between 1.2 and 5.2 days). The other study (Nobre et al, 2008) showed a non-significant trend towards a decrease in duration of antibiotic treatment. Once these four studies were combined in a meta-analysis, the summary effect estimate indicated that the addition of procalcitonin to standard practice produced a significant reduction in antibiotic treatment duration (weighted mean difference -3.19 days, 95% confidence interval -5.44 to - 0.95). The specific details of the procalcitonin algorithm varied between studies, but all discontinuation protocols included a component that advised antimicrobial cessation when procalcitonin levels were below 0.5 ng/ml, and strongly encouraged antimicrobial cessation when procalcitonin levels were below 0.25 ng/ml.

Data from these four trials also allowed the calculation of the mean duration of hospital stay overall. With the studies combined, the summary effect estimate showed that addition of procalcitonin to standard practice produced a statistically significant reduction in length of hospital stay (weighted mean difference -3.85 days, 95% confidence interval -6.78 to -0.92). In addition the independent review team assessed the methodological quality of these four studies by using the Cochrane risk of bias tool, and found that while three of the studies had an unclear risk of bias because of unclear blinding (Bouadma et al, 2010; Qu et al, 2012; Liu et al, 2013), unclear allocation concealment (Qu et al, 2012; Liu et al, 2013) and unclear randomization (Qu et al, 2012), one study (Nobre et al, 2008) was at high risk of bias as a result of incomplete reporting of outcome data. Consequently the independent review concluded that there was a lack of high quality evidence to support procalcitonin-guided antimicrobial cessation.

The four trials detailed above were published between 2008 and 2013, from centres outside the UK, and with few details about standard care. It is therefore difficult to compare the antimicrobial stewardship practices in a 'standard-of-care' arm with those in the UK. Furthermore the management of sepsis in the UK is continually improved via updated clinical guidance from the National Institute for Health and Care Excellence (2017), thus it is uncertain if the benefit shown in these trials of adding procalcitonin to standard sepsis management would be realized in a contemporary UK health-care setting.

In terms of safety, the independent review found five studies (Nobre et al, 2008; Stolz et al, 2009; Bouadma et al, 2010; Qu et al, 2012; Liu et al, 2013) that reported 28-day all-cause mortality and showed no difference in mortality between groups (summary relative risk 0.98, 95% confidence interval 0.76–1.27). One study (Bouadma et al, 2010) included mortality at 60 days, and again showed no significant difference in outcome (relative risk 1.15, 95% confidence interval 0.89–1.48). The review also identified no difference in the incidence of adverse events between groups; however, as none of the studies were adequately powered for safety, one can only conclude that there is no evidence of a lack of safety.

The Stop Antibiotics on Procalcitonin guidance Study (SAPS) (de Jong et al, 2016) from the Netherlands – a health-care system with comparatively low consumption of antimicrobials internationally (Van De Sande-Bruinsma et al, 2008) – was identified by the National Institute for Health and Care Excellence (2015) but reported after production of their diagnostic guidance. The study was an open label randomized controlled trial comparing duration of antimicrobial treatment guided by procalcitonin *vs* standard care. A cut-off point of 0.5 ng/ml was used, consistent with previous studies (Bouadma et al, 2010; Qu et al, 2012). The trial demonstrated a significant reduction in the duration of antimicrobial treatment (median duration 5 days (interquartile range 3–9 days) in the procalcitonin group *vs* 7 days (interquartile range 4–11 days) in the standard-of-care group; between-group absolute difference 1·22, 95% confidence interval 0·65–1·78, $P<0·0001$), as well as a surprising improvement in 28-day and 1-year mortality for patients randomized to the procalcitonin arm which could not be readily explained by the authors. The median cumulative costs of antimicrobial treatment per patient were €18 cheaper in the procalcitonin arm compared to the standard care arm (€107 *vs* €125 respectively, $P=0.0006$), indicating a potentially substantial health-care saving across a population.

Also published after the National Institute for Health and Care Excellence review was the ProGUARD study (Shehabi et al, 2014) from the ANZICS trials group, which was a single centre randomized controlled trial that was designed to investigate the effectiveness of a low cut-off point for procalcitonin in reducing antimicrobial prescribing. The trial used a much lower cut-off value of 0.1 ng/ml compared to other trials, and there was no significant difference in the duration of antimicrobial treatment, ventilator-free days, intensive care unit length

**Table 1. Responses to Intensive Care Society/Association of Surgeons of Great Britain and Ireland survey (*n*=380 responses)**

| | | C-reactive protein | Procalcitonin |
|---|---|---|---|
| As part of your routine practice for sepsis, do you measure C-reactive protein or procalcitonin? (% of responders) | Yes, daily for all patients | 53.1 | 1.9 |
| | Yes, occasionally for all patients | 9.2 | 1.1 |
| | Yes, daily for selected patients | 17.8 | 5.8 |
| | Yes, occasionally for selected patients | 10.8 | 17.4 |
| | Rarely or never | 9.2 | 73.8 |
| If yes, do you use an agreed protocol? (%) | Yes | 2.5 | 17.6 |
| | No | 97.5 | 82.4 |

of stay or hospital length of stay. There was also no significant difference in hospital mortality or in 90-day all-cause mortality. However, the authors recognized that a different choice of algorithm for procalcitonin, aligned to other studies internationally, could have impacted on antimicrobial free days (Shehabi et al, 2014).

Given the concerns around the potential impact of a risk of bias in the research performed internationally, and the lack of evidence of translation of findings to the NHS, the National Institute for Health and Care Excellence recommended that future research into procalcitonin should include identifying when antibiotic treatment can be stopped safely for adults and children with confirmed or highly suspected sepsis in the intensive care unit. There have been no studies conducted into the use of procalcitonin to guide antimicrobial discontinuation in children. Clinical experts advised the National Institute for Health and Care Excellence committee that the majority of septic children in paediatric intensive care units are under the age of 1 year, and thus will have different care and resource needs to adults. Consequently the committee concluded that results from adult trials should not be extrapolated to children (National Institute for Health and Care Excellence, 2015). While there is evidence to support the use of C-reactive protein monitoring in the paediatric setting, results from trials performed two decades ago (Ehl et al, 1997; Bomela et al, 2000) may not be realized in a modern setting. In the adult literature, there appears only one previous trial of C-reactive protein-guided antimicrobial discontinuation, thus there is a clear evidence gap for C-reactive protein monitoring to guide antibiotic duration in this setting.

## Challenges to progressing the evidence base for biomarker-guided antimicrobial duration in sepsis in the UK

### Is there equipoise in the UK for a trial?

To start to establish if there is equipoise and interest in performing a new trial in the UK, between November and December 2015 the authors surveyed health-care professionals who regularly care for patients with sepsis, with support from the Intensive Care Society and the Association of Surgeons of Great Britain and Ireland. The results are summarized in *Table 1*. As expected measurement of C-reactive protein levels is widely used in NHS trusts as part of routine care in sepsis, but there is little evidence that this is used systematically. Procalcitonin measurement is less widely used, but procalcitonin measurement is more likely to be used within a locally agreed protocol.

Simultaneously and independently a survey of NHS laboratories was also conducted in order to understand the current availability of procalcitonin analysis, results of which are included in *Table 2*. C-reactive protein testing is widely available, but far fewer trusts offer routine analysis for procalcitonin.

The survey results show that within the UK there is no evidence of the widespread use of biomarker-guided discontinuation protocols using either C-reactive protein or procalcitonin, and therefore there is sufficient equipoise to conduct a trial in this area. Additionally, there is enthusiasm within the community as 76.5% of those who responded to the Intensive Care Society and the Association of Surgeons of Great Britain and Ireland survey expressed an interest in being involved in a future trial evaluating the effectiveness of C-reactive protein and procalcitonin to guide antibiotic discontinuation in adult patients with sepsis.

### Performance bias in trials of protocolised biomarkers

One issue raised in the independent review of procalcitonin (Westwood et al, 2015), and as a direct consequence of individual patient randomization within the same centre, was the inherent risk of performance bias in the trials analysed, which were all open label. The patients in the intervention arms would have been obvious to the treating teams, and were at particular risk of increased interventions

**Table 2. Responses to NHS laboratory survey (*n*=55 responses)**

| | | C-reactive protein | Procalcitonin |
|---|---|---|---|
| Do you routinely offer C-reactive protein or procalcitonin analysis in your laboratory? (% of responses) | Yes | 98.2 | 18.2 |
| | No | 1.8 | 81.8 |

## KEY POINTS

- There is an absence of robust evidence to inform when it is safe to stop antimicrobials in sepsis. This leads to prolonged courses which can contribute to the growing emergence of multidrug resistant pathogens.
- C-reactive protein and procalcitonin have the potential to guide antimicrobial regimens, but there are limitations to the current evidence base.
- The ADAPT-Sepsis trial in adults, and the BATCH trial in children aim to evaluate the clinical and cost-effectiveness of biomarker-guided antimicrobial discontinuation protocols in sepsis.

and clinical surveillance (Stolz et al, 2007; Nobre et al, 2008; Deliberato et al, 2013). This could have contributed to more optimal antimicrobial use and improved patient outcomes compared with standard care.

Given the risk that the positive results seen in some of the trials could in part have been the result of performance bias, it is important that a future trial addresses this challenge. In the setting of individual patient randomization, this could be achieved by developing a blinding strategy by providing standardized protocolised advice to clinicians rather than assay results. Furthermore, careful documentation of care received by all patients in a trial through process evaluations would also contribute to monitoring the risk of performance bias and its potential impact.

### Study interventions

An appropriate trial design could be to compare C-reactive protein- and procalcitonin-guided treatment protocols with standard care in a three-arm randomized controlled trial. It would be important to include a protocolised C-reactive protein intervention arm, as there is a paucity of evidence of its effectiveness in guiding antimicrobial discontinuation, and it is already available in all UK hospitals.

The design of the biomarker-guided protocols will need to be based upon appropriate evidence of thresholds to stop antimicrobial treatment. The only previous randomized controlled trial in adults that involved the protocolised use of C-reactive protein to guide antimicrobial cessation (Oliveira et al, 2013) used an absolute discontinuation threshold of ≤25 mg/litre and a relative discontinuation threshold if C-reactive protein levels fell by 50% or more from baseline: the best available international evidence for C-reactive protein.

There is greater evidence for procalcitonin-guided antibiotic discontinuation protocols in sepsis (Westwood et al, 2015). From all studies reviewed, there was a consistent strong recommendation to stop antimicrobials for procalcitonin levels <0.25 ng/litre, and/or an advisory recommendation if procalcitonin levels were <0.5 ng/litre. In some studies (Bouadma et al, 2010; Shehabi et al, 2014) a fall in procalcitonin levels by ≥80% was used to advise antimicrobial cessation.

In a pragmatic study, a control group should reflect current standard clinical care. Within the NHS, standard clinical care is based upon guidelines from Public Health England, which recommends antimicrobial courses to not exceed 7 days unless specified by local policy or microbiological advice (Public Health England, 2015). While there is no available high quality published evidence of the UK mean duration of antimicrobials in sepsis and its variation, participants in the control groups of the studies included in the independent review had a pooled mean duration of 12.3 days (5–16.06 days) (Westwood et al, 2015), whereas participants in the control group in the SAPS trial had a median antimicrobial duration of 7 days (4–11 days) (de Jong et al, 2016).

## Conclusions

The increasing prevalence of antimicrobial-resistant organisms is a significant public health challenge. Biomarker-guided antimicrobial discontinuation protocols are a potential method of providing clinicians with evidence of when to stop treatment and thus limit the duration of powerful broad-spectrum antimicrobial agents, reducing the opportunity for resistant organisms to develop.

To progress the evidence base within the UK, two new trials have been awarded funding through the National Institute of Health Research Health Technology Assessment programme; the 'Biomarker-guided duration of antibiotic treatment in hospitalised patients with moderate to severe sepsis (ADAPT-Sepsis) trial (trial registry number: ISRCTN 47473244) and the 'Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection' (BATCH) trial (trial registry number: ISRCTN 11369832)

By recognizing the strengths and limitations of previous trials within this sphere, these new studies are ideally positioned to provide evidence of the clinical and cost-effectiveness of biomarker-guided antimicrobial discontinuation protocols in sepsis. **BJHM**

*Conflict of interest: Dr AN Claxton: none; Professor P Dark was a member of the National Institute for Health and Care Excellence Diagnostic Advisory Committee that produced the diagnostic guidance (DG 18) discussed in this article – the views expressed are those of the authors and not the National Institute for Health and Care Excellence.*


Bomela HN, Ballot DE, Cory BJ, Cooper PA (2000) Use of C-reactive protein to guide duration of empiric antibiotic therapy in suspected early neonatal sepsis. *Pediatr Infect Dis J* **19**: 531–535. https://doi.org/10.1097/00006454-200006000-00008.

Bouadma L, Luyt CE, Tubach F et al (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* **375**: 463–474. https://doi.org/10.1016/S0140-6736(09)61879-1

Daniels R (2011) Surviving the first hours in sepsis: Getting the basics right (an intensivist's perspective). *J Antimicrob Chemother* **66**: 11–23. https://doi.org/10.1093/jac/dkq515

de Jong E, van Oers JA, Beishuizen A et al (2016) Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis* **16**: 819–827. https://doi.org/10.1016/S1473-3099(16)00053-0

Deliberato RO, Marra AR, Sanches PR et al (2013) Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. *Diagn Microbiol Infect Dis* **76**: 266–271. https://doi.org/10.1016/j.diagmicrobio.2013.03.027

Downes KJ, Weiss SL, Gerber JS et al (2017) A pragmatic biomarker-driven algorithm to guide antibiotic use in the pediatric intensive care unit: The optimizing antibiotic strategies in sepsis (OASIS) study. *J Pediatric Infect Dis Soc* **6**: 134–141. https://doi.org/10.1093/jpids/piw023

Ehl S, Gering B, Bartmann P, Högel J, Pohlandt F (1997) C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. *Pediatrics* **99**: 216–221. https://doi.org/10.1542/peds.99.2.216

Liu B, Li H, Lei Y, Zhao S, Sun M (2013) Clinical significance of dynamic monitoring of procalcitonin in guiding the use of antibiotics in patients with sepsis in ICU. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* **25**: 690–693

Meisner M, Tschaikowsky K, Palmaers T, Schmidt J (1999) Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. *Crit Care* **3**: 45–50. https://doi.org/10.1097/00000542-199709001-00243

National Institute of Health and Care Excellence (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). https://www.nice.org.uk/guidance/dg18 (accessed 9 December 2017)

National Institute of Health and Care Excellence (2017) Sepsis: Quality standard QS161. https://www.nice.org.uk/guidance/qs161 (accessed 9 December 2017)

Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J (2008) Use of procalcitonin to shorten antibiotic treatment duration in septic patients: A randomized trial. *Am J Respir Crit Care Med* **177**: 498–505. https://doi.org/10.1164/rccm.200708-1238OC

Oliveira CF, Botoni FA, Oliveira CRA, Silva CB, Pereira HA, Serufo JC, Nobre V (2013) Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis. *Crit Care Med* **41**: 2336–2343. https://doi.org/10.1097/CCM.0b013e31828e969f

Public Health England (2015) Start Smart - Then Focus Antimicrobial Stewardship Toolkit for English Hospitals. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF (accessed 13 December 2017)

Qu R, Ji Y, Ling Y et al (2012) Procalcitonin is a good tool to guide duration of antibiotic therapy in patients with severe acute pancreatitis. A randomized prospective single-center controlled trial. *Saudi Med J* **33**: 382–387.

Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S (2017) Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med* **377**: 414–417. https://doi.org/10.1056/NEJMp1704633

Rhodes A, Evans LE, Alhazzani W et al (2017) *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.* Springer, Berlin Heidelberg

Shehabi Y, Sterba M, Garrett PM et al (2014) Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis: A randomized controlled trial. *Am J Respir Crit Care Med* **190**: 1102–1110. https://doi.org/10.1164/rccm.201408-1483OC

Stolz D, Christ-Crain M, Bingisser R et al (2007) Antibiotic Treatment of Exacerbations of COPD. *Chest* **131**: 9–19. https://doi.org/10.1378/chest.06-1500

Stolz D, Smyrnios N, Eggimann P et al (2009) Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: A randomised study. *Eur Respir J* **34**: 1364–1375. https://doi.org/10.1183/09031936.00053209

Ugarte H, Silva E, Mercan D, De Mendonça A, Vincent J-L (1999) Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med* **27**: 498–504.

UK Government (2015) Hospital Episode Statistics, Health and Social Care Information Centre 2015. http://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2015-09-16/10526/ (accessed 8 December 2017)

Van De Sande-Bruinsma N, Grundmann H, Verloo D et al (2008) Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis.* **14**: 1722–1730. https://doi.org/10.3201/eid1411.070467

Vincent J-L, Donadello K, Schmit X (2011) Biomarkers in the Critically Ill Patient: C-reactive Protein. *Crit Care Clin* **27**: 241–251. https://doi.org/https://doi.org/10.1016/j.ccc.2010.12.010

Westwood M, Ramaekers B, Whiting P et al (2015) 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. *Health Technol Assess (Rockv)* **19**: 3–236. https://doi.org/10.3310/hta19960