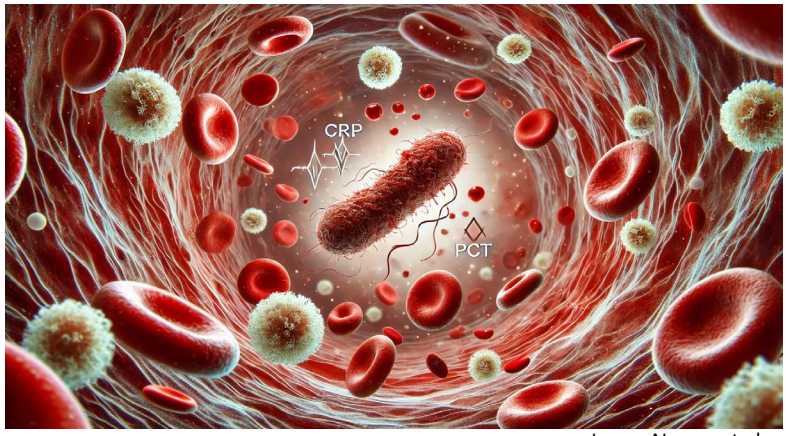
Biomarker-Guided Antibiotic Duration for Hospitalized Patients
The ADAPT-Sepsis Randomized Trial

Paul Dark, JAMA, 12/2024

BACKGROUND

Optimizing the duration of antibiotic treatment reduces
- Overtreatment
- Adverse effects
- Antibiotic resistance

Biomarker-guided discontinuation has shown safe reduction in antibiotic duration, but the body of evidence remains low.



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RESEARCH AIM

To determine weather treatment protocols monitoring C-reactive protein (CRP) or procalcitonin (PCT) reduce duration of antibiotic treatment while maintaining treatment safety.

RESULTS

Enrollment January 2018 to June 2024:

	PCT-guided (n=918)	CRP-guided (n=924)	Standard Care (SC) (n=918)	SC vs. PCT	SC vs. CRP
Days of antibiotic treatment, mean (SD)	9.8 (7.2)	10.6 (7.7)	10.7 (7.6)	***P = 0.01***	P = 0.79
28-d mortality, N°/totals	184/879 (20.9%)	184/874 (21.2%)	170/878 (19.4%)	Difference 1.57 (-2.18 to 5.32)	Difference 1.69 (-2.07 to 5.45)

No significant differences were observed for secondary endpoints such as infection relapse, superinfection, adverse antibiotic reactions, and ICU/hospital length of stay.

METHODS

Design: Multi-centre randomized trial (UK).

Population:
- ICU patients ≥18 years of age
- Antibiotic treatment initiated for sepsis

Intervention:
- PCT-guided vs. CRP-guided vs. standard care (SC)

	Strong stop	Supports stop
PCT	< 0.25 µg/L	0.25-0.49 µg/L or fall by > 80%
CRP	< 25 mg/l	Fall by > 50%

Primary outcome:
- Effectiveness outcome: Days of antibiotic treatment up to 28 days
- Safety outcome: 28-days all cause mortality

Statistical Analysis:
- Intention-to-treat analysis with linear mixed-effect models for the effectiveness outcome.
- Noninferiority analysis with mixed-effect logistic regression using margin of 5.4% for the safety outcome.

CONCLUSION

The use of daily PCT-guided protocols reduces the duration of antibiotic treatment without compromising survival in critically ill patients with sepsis.

SIS COMMENTS

The increased expression of inflammatory mediators during bacterial infections was recognized long before sepsis was identified as a multi-organ failure resulting from a dysregulated inflammatory response to infection. Even though they were never fully integrated into clinical guidelines, inflammatory proteins have been widely used as biomarkers for both diagnosing (severe) infections and monitoring treatment success.

CRP, discovered in 1930 by William S. Tillett and Thomas Francis Jr., was one of the first biomarkers introduced into clinical practice for tracking the inflammatory response in disorders such as sepsis [1]. However, the low specificity and slow kinetics, with a response delay of up to 48 hours, raise concerns about its suitability for sepsis diagnosis and longitudinal monitoring of infections. Despite these limitations, CRP is widely used in monitoring treatment success with antimicrobial therapy.

PCT, a more recent discovery from the 1970s, only gained recognition as an inflammatory biomarker in the 1990s [2, 3]. It offers advantages over CRP due to its higher specificity for bacterial infections and faster kinetics, with inflammatory peaks occurring approximately 24 hours after infection onset. Theoretically, PCT thereby provides more dynamic information on treatment effects.

In 2004, Christ-Crain and colleagues conducted the first RCT demonstrating that PCT-guided treatment in patients with lower respiratory tract infections significantly reduces antibiotic exposure [4]. Following this, Nobre and co-workers applied this concept to septic patients, showing a reduction in antibiotic treatment duration when guided by PCT-based algorithms [5].
Since then, multiple clinical trials have investigated the efficacy and safety of PCT-guided protocols, confirming not only a reduction in antibiotic treatment duration but also demonstrating a beneficial impact on 28-day mortality, as evidenced by a meta-analysis conducted by Wirz et al. in 2018 [6].

The work of Dark and colleagues, published in December 2024, represents the largest study to date, reinforcing the evidence from previous trials. In addition to demonstrating a significant reduction in antibiotic treatment duration, it confirms the absence of adverse effects on a large scale, addressing various concerns such as recurrent infections and all-cause mortality at 90 days. Hence, this study not only validates the reduction in antibiotic consumption but also provides strong evidence supporting the safety of PCT-guided protocols, advocating for their broader implementation in critical care practice [7].
On the other hand, it might be a matter of discussion if a reduction of antibiotic exposure is indeed clinically relevant.

1. Tillett and Francis, J Exp Med, 1930
2. Le Moullec et al, FEBS Lett, 1984
3. Asciot et al, Lancet, 1993
4. Christ-Crain, Lancet, 2004
5. Nobre, AM J Respir Cirt Care Med, 2008
6. Wirz, Crit Care, 2018.
7. Dark, JAMA, 2024

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