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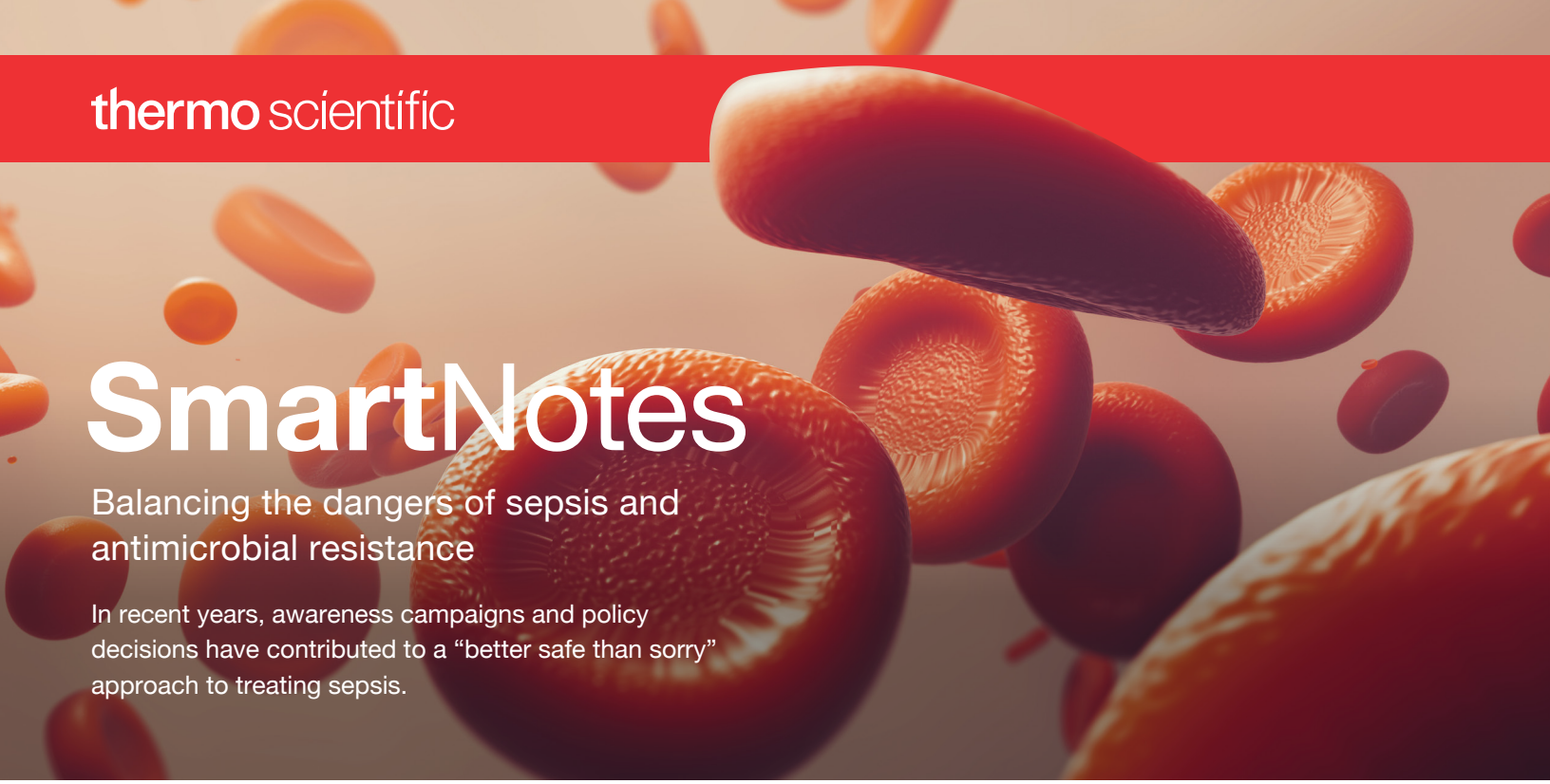

SmartNotes

Balancing the dangers of sepsis and antimicrobial resistance

In recent years, awareness campaigns and policy decisions have contributed to a "better safe than sorry" approach to treating sepsis.

However, such models mean patients may receive unnecessary antibiotics – a trend that can act as a contributing factor to the development of antimicrobial resistance (AMR).

Part of the problem is the difficulty associated with confirming the condition. Sepsis aetiology is complicated. Differential diagnoses vary from patient group to patient group, and are influenced by a wide range of factors including geographic location, presence and type of infection, comorbidities, and host genome, to name but a few.

In addition, there is an ambiguity around the interpretation and application of the mortality codes for infections that often result in sepsis. Inconsistencies in terminology compromise accurate epidemiology. This may be contributing to underestimation of the scale of the problem, and, therefore, a lack of impetus to monitor the impact of treatment strategies and evaluate novel therapeutics and diagnostics.[1]

Crucially, the diagnostic tools healthcare professionals have at their disposal are imperfect. But if we are to balance the twin dangers of sepsis and AMR, we need to utilize every weapon in our arsenal.

Complex aetiology

According to the World Health Organization, sepsis accounted for almost 20% of all global deaths in 2017.[2]

It is a broad term that refers to life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] In most cases sepsis is a serious complication of an infection, and, unless it is recognised and treated quickly, it can lead to septic shock, multiple organ failure and, ultimately, death.

In the UK in the 2015 Parliamentary and Health Service Ombudsman report, *Time to Act*, outlined the cases of ten people, including an eight-year-old girl, who died after not receiving the treatment they urgently needed.[4]

It resulted in a push to detect and treat suspected sepsis more rapidly, but providing early treatment is complicated, mainly as there is no single diagnostic test to determine the infective agent, progress, and severity. Rather, healthcare teams employ a jigsaw approach, using clinical features, inflammatory biomarkers, and microbiology.

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In a bid to overcome these complexities, anyone entering an NHS hospital with clinical features equating to a National Early Warning Score-2 (NEWS-2) of five is flagged as a sepsis risk, and should be prescribed broad-spectrum antibiotics within an hour.[5]

But this "better safe than sorry" approach can have unintended consequences on AMR, a global threat that could lead to an estimated 10million deaths a year by 2050.[6]

The possible differential diagnoses of such a NEWS-2 score of five in an elderly patient, for instance, could be influenza or a cold, which would render the antibiotics unnecessary.

Such policies can also result in arbitrary course lengths, usually seven or 14 days, meaning people often stay on antibiotics longer than needed. It is worth noting that in around 40% of patients, the pathogen is not identified, and treatment is not deescalated.[7]

Stewardship, biomarkers, and advanced diagnostics

Overtreating people with antibiotics can put them at risk of unnecessary side effects. Furthermore, it is at odds with the medical community's efforts to limit AMR by preserving antibiotics for those who really need them.

Confirming the presence, identity, and resistance profile of a causative agent in sepsis is essential to good antimicrobial stewardship – or making sure the right patient gets the right treatment at the right time.

Of course, the complexity of the condition feeds into the complexity of its diagnostics. But according to a 2017 paper in *The Lancet*, "we should not be looking for perfection".

Rather, when dealing with antibiotic overuse, we need strategies that can mitigate the global bacterial resistance problem, it said.[8]

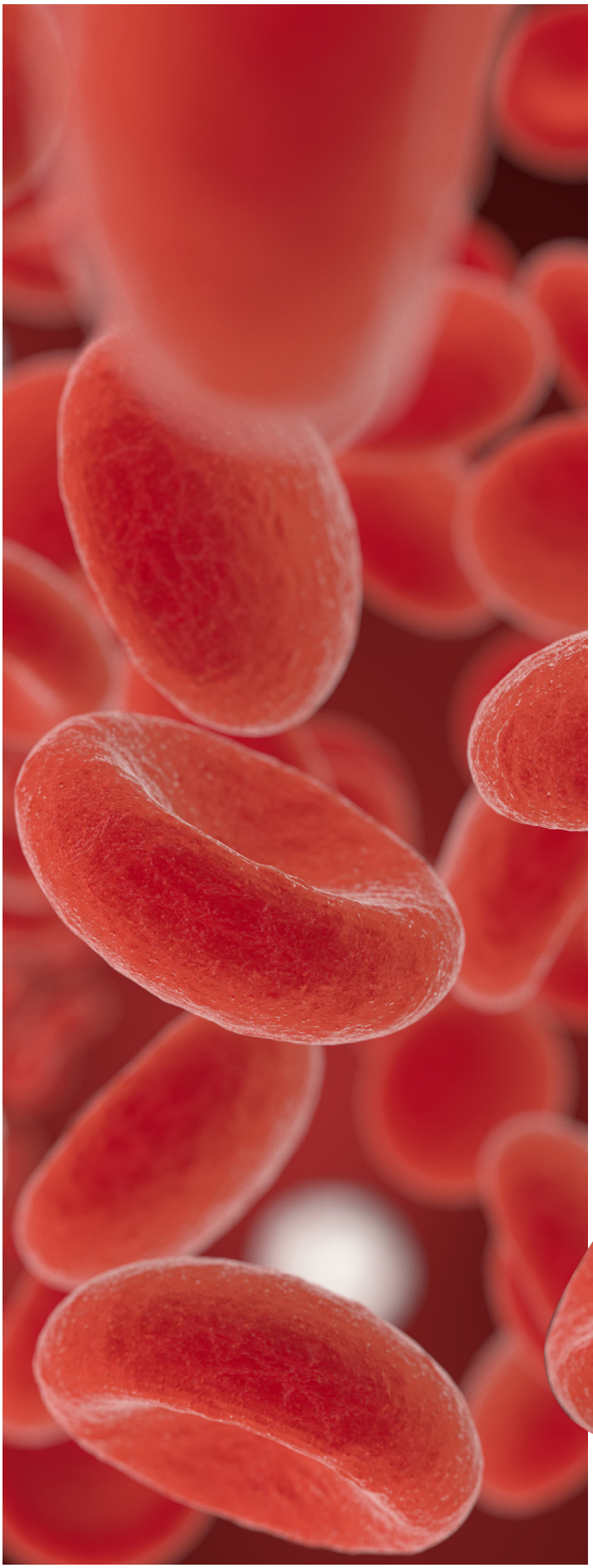
Various randomized controlled trials have demonstrated the value of the biomarker procalcitonin (PCT) in helping to differentiate between viral and bacterial infections, and informing treatment de-escalation strategies.

A precursor of the hormone calcitonin, PCT is detected at very low levels in healthy individuals, but is upregulated by the cytokines released in response to bacterial infections.[7] It has been shown to lead to more adequate diagnosis and appropriate treatment – the cornerstone of antibiotic stewardship.[9]

A review of the literature published in 2017 concluded that PCT-based algorithms could safely reduce antibiotic use. While treatment should not be delayed in critically ill people with suspected sepsis, said the paper, PCT levels of <0.5 µg/L ,or levels that decrease by ≥80% from peak, can guide discontinuation once they stabilize.[7]

Rapid antibiotic susceptibility testing (AST) also has a role to play. Traditional methods of AST, which can define pathogens and guide right first-time treatment plans, can take up to 72 hours due to the requirement for overnight cultures. But new ways of doing things are emerging.

Microscopic techniques have been shown to be able to determine the antimicrobial susceptibility of bacteria from a positive blood culture bottle in just six hours.[10] Advances in flow cytometry and isothermal calorimetric methods, though still under investigation, are also shifting the dial.



Expanding the benefits

Utilizing diagnostics and biomarkers to reduce the overuse of antibiotics in sepsis is key to tackling AMR and the resulting spread of antibiotic-resistant infections.

But unnecessary antibiotic use also exposes people to risk of unnecessary side effects, which can range from gastrointestinal and dermatological issues, to renal, and hematologic abnormalities.[11]

It also drives up unnecessary healthcare costs. A health economics analysis performed in the US in 2019 compared the cost effectiveness of PCT-guided antibiotic stewardship to that of standard care. They found an average per patient saving of $11,311, driven primarily by a shorter length of hospital stay, and a reduced need for ventilation.[12]

In addition, studies have shown that returning an AST result 24 hours earlier than standard time frames could deliver per patient cost savings of between $2,500 and $20,000 through reducing disease severity and hospital stay duration,[13] and cut mortality rates by around 40%.[14]

In short, right first-time clinical decisions not only help to protect the global population, but they also protect at an individual and healthcare system level. Tackling the very real danger of sepsis takes a targeted, rather than a blanket approach.

And by adding biomarkers, such as PCT, and advanced methods like rapid AST to the diagnostic jigsaw, we can start to balance the twin threats of sepsis and AMR.

[1] Tidswell R, Inada-Kim M, *et al.* (2021). Sepsis: the importance of an accurate final diagnosis.
https://pubmed.ncbi.nlm.nih.gov/33152272/

[2] World Health Organization. (2020). Sepsis.
https://pubmed.ncbi.nlm.nih.gov/33152272/

[3] Singer M, Deutschman C, *et al.* (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3).
https://jamanetwork.com/journals/jama/fullarticle/2492881

[4] Parliamentary and Health Service Ombudsman. (2015). Time to Act.
https://www.ombudsman.org.uk/publications/time-act-severe-sepsis-rapid-diagnosis-and-treatment-saves-lives-0

[5] NICE. (2020). National Early Warning Score systems that alert to deteriorating adult patients in hospital.
https://www.nice.org.uk/advice/mib205/chapter/The-technology

[6] IACG. (2019). No time to wait: Securing the future from drug-resistant infections.
https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_summary_EN.pdf?ua=1

[7] Rhee C. (2017). Using procalcitonin to guide antibiotic therapy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5414114/

[8] Fontela P, Papenburg J. (2018). Procalcitonin and antibiotic use: Imperfect, yet effective.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30593-5/fulltext

[9] Jong E, van Oers JA, *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.
https://www.thelancet.com/article/S1473-3099(16)00053-0/fulltext

[10] Choi J, Jeong HY, et al. Direct, rapid antimicrobial susceptibility test from positive blood cultures based on microscopic imaging analysis. Scientific reports. (2017) https://doi.org/10.1038/s41598-017-01278-2

[11] Tamma P, Avdic E, *et al.* (2017). Association of adverse events with antibiotic use in hospitalized patients.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2630756

[12] Mewes J, Pulia M, *et al.* (2019). The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalised patients with suspected sepsis or lower respiratory tract infections in the US: A health economic model analysis.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0214222#sec017

[13] Perez KK, Olsen RJ, et al. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Archives of Pathology and Laboratory Medicine. (2013) https://doi.org/10.5858/arpa.2012-0651-oa

[14] Patel TS, Kaakeh R, et al. Cost analysis of implementing matrix-assisted laser desorption ionization–time of flight mass spectrometry plus real-time antimicrobial stewardship intervention for bloodstream infections. Journal of clinical microbiology. (2017) https://doi.org/10.1128/JCM.01452-16

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