J R Coll Physicians Edinb 2016; 46: 263–9
http://dx.doi.org/10.4997/JRCPE.2016.413

Current clinical controversies in the management of sepsis

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ABSTRACT Sepsis remains a challenging clinical problem requiring prompt diagnosis and optimal clinical management if the continuing high mortality is to be contained. In this brief review I consider four specific questions that are the subject of ongoing controversy. First, whether the new 'Sepsis-3' definitions will be helpful, in particular in improving diagnosis, or whether the rapid move towards precision medicine will make the definition redundant. Second, should we routinely use combinations of antibiotics for the empiric treatment of sepsis. Third, whether there is any clinical benefit in continuous rather than bolus administration of β-lactam antibiotics. Finally, whether there is good evidence that biomarkers such as procalcitonin can help reduce the duration of antibiotic therapy.

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KEYWORDS antibiotics, definition, precision medicine, procalcitonin, sepsis

DECLARATION OF INTERESTS No conflict of interests declared

INTRODUCTION

Sepsis is a condition that impacts in particular on intensivists, general physicians, paediatricians, microbiologists and infectious diseases specialists, although it can present to almost any doctor, any time. This short review is based on a lecture given at the Royal College of Physicians of Edinburgh as part of their symposium on infectious diseases, and I make no apology for restricting my discussion to those topics which will be of particular relevance to practitioners with an interest in infection and its management. The selection of topics is, inevitably, a personal choice but I have identified four questions which I think are both topical and also reflect very real practical questions faced every day on the wards.

DOES THE NEW SEPSIS DEFINITION IMPROVE EARLY DIAGNOSIS AND MANAGEMENT?

The question of how best to define sepsis has exercised clinicians for at least 20 years. Previous efforts, in 1991[1] and 2001[2] had continued to cause much controversy; one of the most telling observations was that there was a remarkably low concordance between the stated definitions and what clinicians at the bedside actually thought.[3] Many believed that the enormous heterogeneity of the population that resulted from existing definitions was at least in part responsible for the difficulties that had been encountered by phase III trials, which had conspicuously failed to identify new drug treatments for sepsis. We[4] and others had pointed out that there was a pressing need to review those definitions, and earlier this year an international group of investigators published the so-called 'Sepsis-3' proposals.[5]

TABLE 1 Some of the strengths and weaknesses of the new Sepsis 3 definitions

STRENGTHS
- Well-founded proposals based on very large validation cohorts: go beyond 'expert opinion'
- Pragmatic and reduce complexity: remove redundant terms such as severe sepsis and septicaemia
- qSOFA* very easy to apply without needing any lab investigations
- Can be used both for early recognition in the emergency room and in clinical and epidemiological studies

WEAKNESSES
- Remains a syndromic diagnosis based on likelihood of hospital mortality
- No currently available clinical test will readily measure, or reflect the concept of a 'dysregulated immune response', which is not defined
- Criteria for recognising infection not defined; ignores the microbiology
- Paediatrics excluded
- Developed in first world practice and not suitable for use in low and middle-income countries
- Concern that they are over-sensitive (especially qSOFA); SIRS all over again?

*qSOFA, quick SOFA. See[5] and this paper for discussion

Almost immediately a torrent of comment and criticism was unleashed.[6–9] Table 1 summarises some of the advantages and potential problems with the new definitions. Some of these criticisms are unquestionably justified. Basing the definition on an injury severity score in effect states that you have sepsis if you have a severe enough infection. The derivation of the work in North

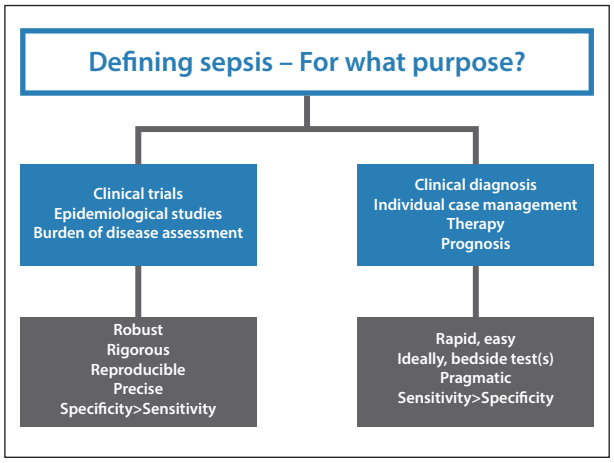

FIGURE 1 The tension between a definition used for clinical management compared to one used for clinical trials.

Two out of three of the following criteria:

- Respiratory rate ≥ 22/min
- Altered mental state (GCS ≤ 13)
- Systolic BP ≤ 100 mmHg

FIGURE 2 The criteria for measuring the qSOFA. GCS, Glasgow Coma Score.

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America and to a lesser extent Europe certainly means that, at a minimum, the conclusions need to be reviewed for doctors working in the third world. As others have argued,[9] there is perhaps confusion between having the condition 'sepsis' and what doctors recognise as a 'septic' patient. Sepsis-3 is really (and perfectly reasonably) focused on bacterial disease in intensive care units in Europe and North America, but does not say so; in other parts of the world, severe malaria might just as well fulfil the requirements.

Perhaps what has become slightly lost in these discussions is an understanding of what these definitions are designed to do. There is inevitably a tension between a construct whose primary function to accurately and unambiguously identify a homogeneous population suitable for inclusion in a clinical trial, and a pragmatic and easily applied definition that will allow for rapid diagnosis and inform immediate management (Figure 1). The Sepsis-3 investigators attempted to address this by developing the idea of the 'qSOFA' (quick SOFA), a slimmed-down version of the more detailed SOFA organ failure score.[10] The qSOFA has just three easily measured physiological variables (Figure 2); any two of these constitute a 'positive' result and an indication that the patient is at risk of sepsis. The authors point out that a positive qSOFA is *not* a surrogate definition of sepsis, rather just an indication that a patient might be at enhanced risk of sepsis. The difficulty here is the concern that such a low threshold (all that is needed is tachypnoea and a slightly low blood pressure) will simply result in an over-sensitive signal, similar to the problems that were found with systemic inflammatory response syndrome.[11–12] It is instructive to compare the great simplicity of the qSOFA with the recent guidance published by the National Institute for Health and Care Excellence, whose algorithms are considerably more complex.[13] 'Real life' clinical trials will be needed to determine if routine use of qSOFA does in fact result in better and earlier recognition of patients with sepsis without compromising the care of others by misdirecting resources and misleading clinical management.

Arguably more interesting is the application of the new Sepsis-3 definition of sepsis: 'life-threatening organ dysfunction caused by a dysregulated host response to infection'.[5] This has stimulated much debate: is all sepsis really life-threatening? What is meant by dysregulated? How do we measure (in a patient) a dysregulated host response? Does this new definition help with either of our two cardinal requirements; improved case definition or better case management? In the UK, NHS England has published an action plan to support hospitals in improving the outcome for patients with sepsis. The so-called 'Sepsis-6', based on early recognition with the NEWS early warning score, has been widely adopted and evidence suggests this approach has been effective.[14–15] It is not clear how the new Sepsis-3 definition, based on a two point change in the SOFA score, might improve these outcomes. But perhaps a more fundamental critique of the new definition is that it perpetuates the notion of sepsis as a single entity with a common pathophysiological basis, likely to be susceptible to a single therapeutic intervention (if only we could identify what that might be).

As we move closer to the world of personalised medicine, so the idea of 'splitting' patients with sepsis into subgroups becomes more attractive than leaving them 'lumped' into a single category.[16] These splits, or subtypes (some use the term endotypes), could be based on a whole range of phenotypic or biologic characteristics: we might identify adult patients with pneumococcal pneumonia, or patients with a particular combination of biomarkers, or an 'at-risk' genotype plus a specific clinical risk factor. This approach has significant challenges. The first is establishing plausible hypotheses, although this is becoming more tractable with the use of 'big data' and bioinformatics. The second is that these populations are by definition subgroups, and therefore

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smaller in number than we are used to working with, and there are both scientific and commercial pressures to try and avoid too narrow a focus. But the introduction of rapid diagnostic processes such as MALDI-TOF[17] means that real-time bacterial diagnosis is now almost a reality, and there are already examples of drugs being developed for the treatment of specific types of bacterial sepsis.[18] We only need to look to oncology to see how powerful this approach can be. It is entirely possible that in ten years' time the debate over the definition of sepsis will be redundant as it will no longer be a useful concept driving patient care.

SHOULD COMBINATION ANTIBIOTIC THERAPY BE USED ROUTINELY IN THE EMPIRIC TREATMENT OF SEPTIC PATIENTS?

The general principles for the use of antibiotics in sepsis are uncontroversial:

- They should be started as soon as a clinical diagnosis of sepsis is made; speed is of the essence
- It is important to use a regimen with a sufficiently broad spectrum of activity that it will be active against all the most likely causative agents
- The dose should be optimised, using a loading dose if necessary and taking into account some of the variables (e.g. the use of haemoperfusion) that may alter the pharmacokinetics in septic patients
- Ideally, the regimen should be quickly de-escalated to narrow spectrum agents

There is a further consideration that is sometimes discussed, that the use of bactericidal drugs is preferable to bacteriostatic ones. Although this may seem intuitively correct there are few if any clinical data to support it.

The question that has exercised clinicians is whether in these very sick patients 'a sufficiently broad spectrum of activity' implies the routine use of combinations of antibiotics. The problem is that a 'bad guess' (that is, selecting an antibiotic regimen that turns out to be inactive against the organism subsequently isolated from blood cultures) is associated with a significantly higher mortality,[19] and this is a powerful incentive to take what would seem to be a prudent approach and prescribe multiple antibiotics. However there are advantages and disadvantages of using combination therapy (Table 2), although it is likely that if it were possible to show there was a measureable survival benefit from the routine use of two (or more) drugs then this would outweigh the potential disadvantages.

The current recommendations from the Surviving Sepsis Campaign[20] are that combination therapy is indicated for:

- Neutropenic patients with severe sepsis
- Patients who have, or are likely to have, infection with multidrug resistant organisms such as Acinetobacter or Pseudomonas
- Selected patients with severe infections associated with respiratory failure and/or septic shock, associated with Pseudomonas bacteraemia
- Shock from bacteraemic *Streptococcus pneumoniae* infection

TABLE 2 Advantages and disadvantages in the use of combinations of antibiotics for septic patients

ADVANTAGES

- Will usually provide a broader spectrum of activity than can be obtained with a single drug
- May produce an additive or even a synergistic effect
- May reduce the risk of the emergence of resistance during treatment*
- May produce beneficial non-antimicrobial pharmacological effects**

DISADVANTAGES

- Wider use of antibiotics generally likely to drive the problem of antimicrobial resistance
- Likely to risk increased toxicity
- May increase the risk of superinfection (e.g. with fungi)
- Increases the chance of unwanted or unexpected drug interactions
- Increased cost

*Most obviously in the case of anti-tuberculous therapy or treating HIV, for example. The evidence that this is an important consideration in short courses of antibiotics for septic patients is much less clear.

**The best example of this is the postulated immunological benefits of macrolides in treating severe pneumonia. See for example Emmet O'Brien et al.[43] Many other antibiotics have been shown to have immunological effects in vitro but the clinical significance of these findings is doubtful.

The authors acknowledge that the evidence to support these recommendations is of variable quality, but even setting aside these special cases, the question remains whether there is a benefit to using combination therapy in the routine management of the majority of septic patients. A widely cited paper[21] is often reported[22] as showing there is indeed a survival benefit from combination therapy. However, this was in fact a retrospective, propensity-matched analysis and not a prospective randomised controlled trial and even here the apparent benefit was limited to subsets of patients. Notably, the most potent β-lactams (e.g. carbapenems and anti-pseudomonal third and fourth generation cephalosporins) failed to demonstrate any benefit in combinations, probably because they are already acting at virtually 100% bactericidal activity against most common pathogens, so there is little room for any improvement. Separately, the same authors carried out a meta-regression analysis of some 50 studies and showed that there was no overall benefit from multiple

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agents, although there was a statistically significant effect in those who were most critically ill.[23] The most persuasive evidence comes from a large, well-conducted randomised controlled trial in typical ICU patients with sepsis of varying severity, which compared meropenem alone to a combination of meropenem plus moxifloxacin,[24] in which there was no evidence of benefit from the combination of antibiotics. Interpreting the information in this area is difficult because there is huge variability in the patient populations studied in the various trials, and indeed also in the antibiotic regimens used. Nevertheless, taken together the data indicate that there is no evidence to support the routine use of combined antibiotic therapy for most septic patients.

Despite this, there remains a legitimate concern that in some clinical situations, and indeed in some countries, the risk of multi-drug resistant Gram-negative sepsis is so high that combination therapy is essential. In particular it has been suggested, somewhat counter-intuitively, that infections with carbapenemase-producing organisms such as some strains of *Klebsiella pneumoniae, Pseudomonas aeruginosa* and Acinetobacter might benefit from treatment with combined carbapenem antibiotics.[25–26] The logic is that together the two drugs can overcome the so-called target attainment minimum inhibitory concentration (MIC) threshold, despite in vitro resistance. However, a more recent paper[27] presented data contradicting this, suggesting that combination therapy was only effective if the drugs were effective in vitro, and relied on combinations of non-carbapenems such as colistin or tigecycline. None of these papers is free from methodological problems and this remains an unresolved issue.

SHOULD BETA-LACTAM ANTIBIOTICS BE GIVEN AS A CONTINUOUS INFUSION IN SEPTIC PATIENTS?

The broad antimicrobial spectrum of β-lactams, as well as their good safety profile, makes them a common choice as empirical agents for septic patients. Different antibiotics have different modes of action, and in the case of β-lactams the time above the MIC (T > MIC) (that is, the duration of time that the antibiotic concentration in the relevant tissue space exceeds the minimal inhibitory concentration required to kill the bacteria) is the critical pharmacokinetic characteristic that determines efficacy. For this reason, many have argued that it makes more sense to administer β-lactams as a continuous infusion since that will optimise the T>MIC. The situation is further complicated because the profound fluid shifts that may occur in septic patients, as well as interventions such as haemofiltration, can markedly affect the pharmacokinetics of many drugs, including antibiotics.[28] Indeed, studies in sepsis have demonstrated marked variability in the serum levels of β-lactams during treatment,[29] and have also shown that administering these drugs by continuous infusion does indeed improve the pharmacokinetic parameters.[30]

Against this background there have been several attempts to determine if continuous infusion of β-lactams has any impact on the clinical outcome. The answer is far from clear.[31] In a preliminary study in 2013, Dulhunty and colleagues showed that although continuous infusion improved the pharmacokinetics there was no overall effect on ICU survival, albeit there was a statistically significant improvement in clinical cure.[30] More recently, the BLISS trial reached almost identical conclusions.[32] In the meantime, Dulhunty had published a further large randomised controlled trial that failed to show any advantage from continuous infusion.[33] Finally, a meta-analysis of 632 patients studied in the three large controlled trials concluded that there was a statistically significant benefit of continuous infusion in both clinical cure *and* survival, but when this was analysed by multivariate analysis the independent effect of continuous infusion was lost.[34] A murky picture indeed.

Advocates of this approach might argue that it is unreasonable to require ICU survival or hospital outcome to be the primary endpoint of these trials since the purpose of the intervention is to improve the treatment of the infection, and there are many other reasons why patients may not survive their ICU or hospital admission even if their infection were treated effectively. Other suggestions include the possibility that it is only subsets of septic patients (usually, those who are sickest) who will benefit, or that it is necessary to undertake therapeutic drug monitoring to ensure that even with continuous infusion, optimal drug levels are achieved.[35] Increasing the doses of β-lactams to bring them into the optimal zone does carry some risks: very high doses have been associated with neurotoxicity, although generally this seems to be unusual. Finally, we have suggested that rather than the serum level of the antibiotic, the critical measure of efficacy is the actual bactericidal effect in vivo, in the appropriate tissue space, against the specific infecting organism. We described a method for measuring this based on the time required for a culture to become positive in the presence of the antibiotic (time-to-positivity, T_{POS}) and showed that there was a correlation between T_{POS} and ICU length of stay.[36] It is a more laborious method than just measuring serum levels and it remains to be seen if it will be of clinical utility.

In summary, continuous infusion of β-lactams is a logical proposition with no significant risks, but if one takes ICU survival as the ultimate test of a new intervention then the data currently do not support this strategy.

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TABLE 3 Considerations in selecting short courses of antibiotics for septic patients

Perceived benefits
- Reduced exposure to antibiotics
- Limiting the emergence of resistance
- Reducing drug induced toxicity
- Reducing the potential for adverse drug interactions
- Reducing the cost

Potential risks
- Inadequate treatment/failure to eradicate the infection
- Increased rate of relapse
- Risks related to late secondary/distant complications (e.g. metastatic abscess formation in *Staphylococcus aureus* infections)

As an endnote to this topic, advocates of more precise use of antibiotic in sepsis have recently described a new regimen for the use of continuous infusion of vancomycin in septic patients.[37] One senses the beginning of another bumpy road to demonstrate clinical benefit.

SHOULD WE ROUTINELY USE BIOMARKERS TO LIMIT THE DURATION OF ANTIBIOTIC TREATMENT?

Most clinicians would agree that as a general principle, it is right that the duration of a course of an antibiotic should be the shortest possible commensurate with obtaining a satisfactory clinical outcome. This applies, of course, to all clinical settings and not just sepsis, but it is interesting that the question of *duration* of therapy is relatively poorly studied. There are a few well known examples – urinary tract infections or tuberculosis for instance – but by and large antibiotic prescription is based on custom and practice rather than hard data gleaned from comparative clinical trials. Still, the potential advantages of shorter courses of antibiotics are relatively uncontroversial (Table 3), and since the ICU is an area of high antibiotic use there is considerable pressure to see how antibiotic use could be constrained.

Biomarkers represent a potentially attractive way of controlling antibiotic use. There is a vast literature on the use of biomarkers in sepsis (a September 2016 PubMed search yielded 7,563 papers) but in terms of their role in antibiotic control most recent work has focused on procalcitonin. There are broadly two approaches one could take to the use of biomarkers (they are not mutually exclusive): the first asks, can I use a biomarker to tell me that the patient does not have an infection and I do not need to start antibiotics, or else that having started I am now sufficiently confident that this is not an infection and I can stop the antibiotic treatment? Interestingly, the Surviving Sepsis Campaign takes this approach, recommending, albeit with only moderate confidence, that procalcitonin or other similar biomarkers can be used to 'assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection'.[20] The alternative strategy seeks to use a biomarker to answer the question, 'is the infection cured and can I safely stop the antibiotic?'

These two contrasting approaches represent a very different appetite for risk. In the first, the clinician must be so confident in the test (i.e. that both the sensitivity and specificity must be well in excess of 95%) that they would feel comfortable in either not starting antibiotics, or else stopping the antibiotics, in an unstable, toxic patient who might appear clinically 'septic' but in whom the test is saying that infection is not involved. Unsurprisingly, clinicians have been reluctant to invest such faith, either in a single test or in a combination of tests. A more cautious approach is to allow the biomarker to guide the duration of treatment, with the assumption that this will mean shorter courses of treatment. (Of course that is not necessarily the case. It is possible that a biomarker would indicate that despite clinical evidence to the contrary, antibiotic treatment should continue. In practice this seems to be a very uncommon situation.)

There is now a reasonably strong body of evidence that suggests that the use of procalcitonin will provide safe and reliable information about when antibiotics may be stopped in septic patients on the ICU.[37] Studies showed that sequential (usually daily) measurements could identify patients with or without positive cultures and also those who were destined to survive or to die,[38] and several trials have demonstrated that antibiotic use is reduced in patients managed with an active protocol based on procalcitonin measurements.[39,40] More surprisingly, a recent large trial also showed a survival benefit.[41] As the authors acknowledge, it is not immediately apparent why that should be: they speculate that it may be down to earlier recognition and management of non-infective conditions. A recent Health Technology Assessment[42] concluded that, despite limited data, '[procalcitonin] testing may be effective and cost-effective when used to guide discontinuation of antibiotics in adults being treated for suspected or confirmed sepsis in ICU settings'.

CONCLUSION

Sepsis is still a common and difficult problem. There is no 'silver bullet' on the horizon, and in the meantime we need to optimise those aspects of the treatment that we can control using the best quality data we have. In the face of the looming problem of antimicrobial resistance, we must use the antibiotics we still have as wisely and sparingly as possible.

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