



Review Article

Prospects for the Management of Sepsis in an Era of Personalised Medicine

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ARTICLE INFO

Article History

Received 08 March 2019
Accepted 08 March 2019

Keywords

Genomics
omics
personalised medicine
precision medicine
sepsis

ABSTRACT

Sepsis remains an unmet medical need, and sustained attempts by intensivists have indeed yielded an incremental improvement in outcomes. However, despite many attempts to introduce novel therapeutic molecules, there has been no step change in survival rates. Precision (or personalised) medicine (PM) has emerged in recent years as an approach that seeks to make use of person-specific, real-time data to choose a therapeutic regimen designed specifically for the individual patient. PM has been used most successfully in oncology where chemotherapy regimens can be tailored to specific cancer genotypes. This review considers the options for using PM to improve the outcome in sepsis. There are several challenges. The nature of omics technology is that it involves multiple analytes, each of which usually has a very modest effect; hence large numbers of patients need to be studied. Sophisticated bioinformatic analysis is required that is not suitable for routine clinical use. Sepsis is a fast-moving situation and it is likely that PM profiles would change quickly. This is a huge challenge, since it requires the physician to accurately place the patient in the appropriate cohort that is relevant to the test being used. Many septic patients have comorbidities that complicate data interpretation. Finally, the nature of PM is that it is designed for the individual patient, or at least for a homogeneous group of patients who share specific characteristics. As we have seen, that is difficult to achieve in sepsis, which is a heterogeneous condition. PM is likely to be harder to use in sepsis than in some other clinical settings.

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1. INTRODUCTION

Improving the outcome for patients with sepsis has been an enduring challenge in clinical medicine for at least the past 30 years. It would be wrong, of course, to say that nothing has changed and that there has been little improvement in survival rates. On the contrary, there have been extraordinary developments in our understanding of the basic science, and marked improvement in the clinical management of sick patients in the care of intensivists and infectious diseases physicians. Nevertheless, it is right to acknowledge that those improvements have largely been incremental changes in supportive care, better ventilator and fluid management, infection prevention and control, and microbiological diagnosis [1]. We have not seen the successful introduction of a specific therapeutic agent that targets the pathological processes in sepsis *per se*, and which can reverse, or at least ameliorate the tissue injury and consequent organ damage that are the clinical hallmarks of sepsis. It is no accident that in 2017 the World Health Organization (WHO) identified sepsis as the final common pathway for most deaths due to infectious disease worldwide, and urged member states to improve the detection, prevention, and treatment of sepsis as a priority [2]. As the statement from the WHO pointed out, much could be achieved by the better use

of techniques already well known and widely available, even in less-developed economies, by improving hand hygiene and other infection prevention methods and by better antibiotic stewardship.

There has been considerable debate and speculation on the reasons for the repeated failure of trials of novel therapeutic agents [3,4]. Some of the explanations are straightforward: small sample size, poor trial design, and inadequate dosage have all played a part. However, an enduring theme is the challenge provided by the heterogeneity of sepsis. Put simply, sepsis is a syndromic diagnosis; it is not a disease in the sense that diabetes mellitus or rheumatoid arthritis are cognate pathophysiological processes. This heterogeneity creates considerable challenges for investigators, and it is in this context that the concept of personalised (or precision) medicine (PM) has emerged as an attractive new approach¹. How might the principles of PM be applied to sepsis and how likely is it to be successful?

2. WHAT IS PM AND WHY MIGHT IT BE HELPFUL FOR SEPSIS?

In one sense there is nothing new about the principle of tailoring the treatment to the specific requirements of an individual patient;

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Peer review under responsibility of the Dr. Sulaiman Al Habib Medical Services Group Company

¹Some people distinguish between precision medicine, the process of optimising the treatment for a group of patients, for example, based on a genomic signature, and PM, in which treatment is designed for an individual patient based on their specific needs or preferences. In my opinion this is not a helpful distinction and I use the two terms interchangeably here.

we use different insulin regimens for different diabetic patients, and some rheumatoid patients respond better to anti-Tumour Necrosis Factor (TNF) and others to anti-interleukin-6. The concept of PM has really only emerged in response to the recent advances in genomics and latterly, metabolomics and other omics technologies, which have allowed more precise definition of individual patient signatures – often described as endotypes [5]. In its most familiar form PM has been extensively and effectively deployed in the treatment of cancer, where treatment regimens can now be selected based on the particular molecular signature of the malignancy. Although PM largely arose from this idea of designing specific chemotherapeutic regimens, its scope has now widened.

In the case of sepsis, we need to consider what we want from a PM approach. What question are we asking? For instance, one could imagine that it might be possible to identify subsets of patients with differing prognoses (risk stratification) because we want to know how to triage patients to the most appropriate place for their care. Alternatively, we might be interested to identify those whose sepsis is driven by bacterial versus fungal infection (diagnosis) in order to optimise antimicrobial therapy, or for infection control purposes. Finally, we may want to use PM to identify those who are likely to respond to a particular drug or combination of drugs (therapy) in particular where there is an opportunity to identify a specific therapeutic target (e.g., measuring TNF levels in order to select patients who might respond to anti-TNF therapy). Importantly then, PM should not just be thought of as genomics; the principles of PM can be applied in several different domains [Table 1](#).

Clinical data are extraordinarily rich, particularly in an intensive care unit setting where it is common for multiple parameters to be continually, or repeatedly, monitored. Machine learning techniques can be used to explore these data sets and link the findings to clinical outcome. For instance, studies have suggested that sepsis patients can be subdivided into four phenotypic endotypes with differing clinical patterns [6].

Several large investigations have examined genomic signatures based on genome-wide expression profiles; certain patterns were associated with a more severe outcome and those patients could be identified by designing biomarkers based on the genomic signature [7]. Transcriptomics and epigenomics are variations on this theme that can provide additional, or more specific information.

Metabolomics measures and studies endogenous small molecules (and proteomics protein molecules) that are present in a single biological sample and then uses methods of systems biology to analyse the large datasets that are generated [8]. While genomics sometimes detects small differences that may have direct clinical implications, so-called omics studies measure molecular changes in clinical samples (blood, urine, etc.) that reflect actual clinical changes as a result of the disease process. In that sense they may be more informative,

but the disadvantage is the huge amount of data that is generated and the need for sophisticated analytical techniques in order to make sense of the results.

Pharmacogenomics is a well-recognised principle in therapeutics although it has not had particular application in sepsis. Antibiotic selection perhaps urgently needs a more personalised approach. At present the consensus is that high-dose, broad-spectrum antibiotics should be used—the antithesis of a personalised approach. It is clear why clinicians are reluctant to be more selective—the problems with antimicrobial resistance, and the need to “get it right first time” are persuasive. Yet, there is evidence that this might be too simplistic, and that dose regimens might need to be titrated to individual patient requirements [9,10].

Literally hundreds of biomarkers have been proposed as being of value, for diagnosis, prognosis, or for therapeutic monitoring in sepsis. A few of these are now in clinical use; procalcitonin, for example, has found wide application either as a means of identifying bacterial infection or for determining the duration of antibiotic therapy [11]. Biomarkers have obvious potential attraction as a means of delivering PM. The challenges, though, are considerable. Biomarkers must have easy applicability—that is, they should be quickly and easily used, ideally at the bedside, and secondly, they must have high utility—that is, have high positive (and/or negative) predictive value. They also need to identify a therapeutic target for which an intervention exists. An early example of this idea was the suggestion that patients with markedly elevated interleukin-6 levels would respond to anti-TNF therapy [12]; unfortunately, the trial was not successful. Ideally, a biomarker identifies a particular subset of patients who are uniquely susceptible to a particular therapeutic intervention that significantly improves the outcome. Thus far, this simple idea has proved elusive. A more complex idea is to combine a series of biomarkers into an index or score [13,14]. Although this seems attractive it compounds the difficulties and seems unlikely to be useful.

Finally, the concept of microbiological diagnosis as the basis for a PM approach is instructive. At one end of the spectrum is the belief that knowing the microbial cause of the sepsis is largely irrelevant, other than for epidemiological purposes. In this view, sepsis is the final common pathway of tissue injury and is essentially similar, irrespective of whether the infection was caused by *Escherichia coli* or *Staphylococcus aureus* [15]. Broad-spectrum antibiotics can eventually be tailored once the organism has been isolated, but given the need for early intervention and the risks of antimicrobial resistance, many doubt the need to be too concerned about the diagnosis. In contrast, others have argued that there are indeed significant differences in the pathological processes initiated by different organisms [16,17]. It is obvious, for example, that the pathology in meningococcal sepsis is different to that caused by a strain of *S. aureus* positive for toxic shock syndrome toxin [18]. It is true that at present we do not know enough to be able to take advantage of these differences (other than to use the correct antibiotic) but that does not mean we should not see this as a potentially important means of deploying a PM approach. There are already some examples of how this might be done. For example, genomic analyses have revealed that certain strains of *S. aureus* are more likely to cause persistent bacteraemia [19], and strains of *Streptococcus pyogenes* that produce virulent bacterial superantigenic toxins can be targeted by novel immunological molecules [20]. Treating Multidrug-Resistant (MDR) infections is dependent on knowing the precise resistance spectrum of the causative strain;

Table 1 | Principle of personalised medicine has applications in various aspects of sepsis management

| |
|-----------------------------|
| Clinical data |
| Genomics |
| Metabolomics and proteomics |
| Pharmacogenomics |
| Biomarkers |
| Microbiological diagnosis |
| Antibiotic selection |

there is considerable interest now in developing strain-specific phage therapy, for example, to treat MDR *Acinetobacter* or staphylococcal infections [21–23].

In summary, there appears to be good reason to think that applying the principles of PM to sepsis would offer many opportunities. How realistic is it that these can be translated into clinical benefit?

3. OPPORTUNITIES AND CHALLENGES TO CLINICAL APPLICATION

Personalised (or precision) medicine has already made its way into routine clinical practice in sepsis. An obvious example is the choice of antibiotics; a unit with a high prevalence of MDR *Acinetobacter*, for instance, will need to choose its empirical regimen appropriately. A more specific example is the choice of benzylpenicillin plus clindamycin for the treatment of patients with shock due to *Streptococcus pyogenes*, so-called streptococcal toxic shock syndrome. Procalcitonin is an example of a classical biomarker that is widely used; in the main to help judge when it would be safe to stop a course of antibiotics [11]. Finally, SeptiCyt Lab is a four-gene classifier approved by the US Food and Drug Administration that can be used to distinguish between patients with sepsis or systemic inflammation not related to infection [24].

So, there is nothing in principle that prevents us from extending these approaches to some of the other applications of PM. However, there are significant practical problems. For example, there is already a large body of data describing multiple examples of genetic associations with susceptibility (and sometimes resistance to) sepsis [25]. Yet none of these are proven to be of clinical utility. Why should that be?

There are (at least) five reasons for the problem. (1) The nature of omics technology is that it involves multiple analytes, each of which usually has a modest independent effect; hence, large numbers of patients need to be studied in order to avoid both type I and II statistical errors. (2) These kinds of studies require sophisticated bioinformatic analysis; this may be available for research settings but would not be suitable for routine clinical use. (3) Sepsis is a fast-moving situation that is different from cancer for which PM has been so successful. It is likely that any given PM profile would be completely different in the early stages of meningococcal sepsis compared to a patient who had been in an intensive care unit for a week with unresolved pneumonia. Indeed, the profile of the same patient 24 h apart could be different. This is a huge challenge to the PM approach, since it requires the physician to accurately place the patient in the appropriate cohort that is relevant to the test being used; a challenge not made any easier by the fact that the diagnosis of sepsis itself remains controversial. (4) Many septic patients have comorbidities that complicate interpretation of the data. For instance, a patient may have acute renal failure as a complication of a bowel perforation; the renal failure generates an omics profile in its own right that interacts dynamically with that generated by the sepsis. This is a different scenario from a patient with breast cancer, for instance. (5) The nature of PM is that it is designed for the individual patient, or at least for a homogeneous group of patients who share specific characteristics. As we have seen, that is difficult to achieve in sepsis, which is a hugely heterogeneous condition. The *reductio ad absurdum* is that PM trials in sepsis have to be carried out on single patients. Nevertheless, it does illuminate a real problem with the field.

Table 2 | Requirements that need to be considered when developing tests to be used in personalised medicine

| | |
|-----------------|----------------|
| Consistency | Simplicity |
| Reproducibility | Predictability |
| Specificity | Utility |
| Ease of use | Safety |

Finally, there are the challenges that apply to any diagnostic test; some of which are particularly relevant when thinking about PM Table 2. Most of these are self-explanatory. Tests must actually be useful, that is, make a real difference to management or outcome; they must be consistent and reliable; and they should have a high positive and/or negative predictive value. They need to be safe in the sense that even if they fail the risk for the patient does not increase. Finally, they should be quick, easy, and ideally inexpensive to use, preferably as bedside tests. When one applies this simple schema to the genetic tests for susceptibility, mentioned above, it is immediately easy to see why they have not made any impact on sepsis care.

4. CONCLUSIONS—A PRAGMATIC AND OPTIMISTIC APPROACH

It would be wrong to conclude from this short review that the prospects for the use of PM in sepsis are bleak. There are certainly challenges, and it seems improbable that even in the medium term, PM will have the same impact in sepsis as it undoubtedly has had in some types of cancer. However, as noted above, we are already using some types of PM and we will increasingly be able to identify some subsets of patients for whom we can tailor their care. So-called “big data” analyses, or the use of bioscores may help to unravel the complexity. A stepwise and pragmatic approach is likely to bring incremental improvements in outcome [26].

CONFLICTS OF INTEREST

There is no conflict of interest.

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