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Precision Medicine in Sepsis



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Multiple failed clinical trials testing immunomodulatory therapies for sepsis argue for a new approach. While precision medicine has been successfully implemented in other fields, testing it in sepsis poses challenges, which this review will discuss, along with potential implementation strategies.

Sepsis has an estimated annual incidence of 1.3 million cases and 230,000 deaths (Stoller et al. 2016). Short-term mortality has declined in the adult population from approximately 40% to 20% from 2001 to 2010 (Gaieski et al. 2013). Short-term mortality of neonatal and paediatric patients with sepsis has had a similar decline, from 20% to 10% (Balamuth et al. 2014) in the corresponding time period. Despite a decline in early mortality, survivors of sepsis hospitalisation continue to incur multiple long-term effects, including increased risk of mortality and morbidity (Yende and Iwashyna 2012; Prescott et al. 2014; Mayr et al. 2014).

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Significant advancement has been made in understanding the pathogenesis of sepsis and septic shock at the molecular and cellular level in the past 20 years using preclinical and in vitro models. Many potential therapies have shown promise in preclinical models and hundreds of therapies have been tested in randomised clinical trials (RCTs) in humans. However, none, with the possible exception of glucocorticoids, have consistently shown improvement in mortality. Subsequently, there are no immunomodulatory therapies currently approved by the U.S. Food and Drug Administration for sepsis. This review focuses on the role of precision medicine to develop strategies to modulate the immune response to improve outcomes in sepsis.

Why Test a Precision Medicine Approach for Sepsis?

There are several potential reasons for the failure of immunomodulatory therapies in human trials. These include difficulty in extrapolating findings in animal models to patients with multiple co-morbidities, and the need to consider patient heterogeneity. It is likely that many of the immunomodulatory therapies tested to date may be beneficial for some patients, but they have not been targeted to the right patient at the right time.

Precision medicine, as currently understood, attempts to integrate clinical phenotype with patient genetic and molecular data to define a subgroup of patients that may benefit from a particular therapy. This subclassification integrates clinical, genetic and pathobiological data with treatment response to classify distinct disease endotypes (Anderson 2008). Within pulmonology, recent efforts have focused on defining endotypes within asthma, with some success in defining distinct treatment response patterns (Lötvall et al. 2011; Fajt and Wenzel 2014). Precision medicine has also been successfully implemented in oncology. Clinical trials and treatment protocols in oncology often use advanced molecular, genetic, and biomarker data (Kaufman 2014), with significant improvement in outcomes of melanoma and breast cancer. Within

critical care, investigators have also classified acute respiratory distress syndrome into two distinct endotypes with different clinical and inflammatory biomarker profiles. These endotypes have differential responsiveness to positive end-expiratory pressure (PEEP) (Calfee et al. 2014) and different fluid management strategies (Famous et al. 2016) in retrospective analyses of clinical trials.

Early Efforts to Test Precision Medicine in Sepsis

Prior trials of targeted therapy in sepsis have defined an altered molecular pathway and evaluated the efficacy of a molecule that is known to resolve that alteration in preclinical models. The majority of RCTs that have been performed for sepsis therapies to date have enrolled a broad group of patients with sepsis, or narrowed enrollment to a subgroup of patients based on the degree of organ failure or presence of septic shock. However, only a few trials have attempted to test immunomodulatory therapies based on biomarker profiles. The Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial, a multicentre trial (n=2,634) of an anti-tumour necrosis factor (TNF) F(ab')₂ monoclonal antibody, randomised all patients to treatment or placebo, but pre-specified that patients with a presumed hyperinflammatory phenotype, defined by elevated circulating interleukin (IL)-6 levels, would benefit from anti-TNF therapy. The trial did find a mortality benefit in the overall analysis, but the benefit was not statistically significantly different in patients with elevated IL-6 levels (Panacek et al. 2004). Meisel et al. conducted a multicentre RCT (n=38) and tested GM-CSF in patients who were immunosuppressed, as evidenced by low HLA-DR expression on monocytes (Meisel et al. 2009), and showed an improvement in HLA-DR expression, ex vivo TLR response, intensive care unit length of stay and mechanical ventilation duration. The Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES) trial (Klein et al. 2014) is ongoing and is testing the anti-endotoxin strategy, polymyxin haemoperfusion, in 360 patients who had endotoxaemia at enrollment.

There have been several post hoc analyses of failed sepsis trials that have identified potential sepsis endotypes. For example, a post hoc analysis of a phase III trial of anakinra, an IL-1 receptor antagonist, stratified patients with clinical features of macrophage activation syndrome (MAS), including hepatobiliary dysfunction and disseminated intravascular coagulation, and found a significant survival benefit in this subgroup of patients (Shakoory et al. 2016; Opal et al. 1997). Another approach is to identify endotypes in observational studies. For instance, in paediatric patients with septic shock, Wong and colleagues defined endotypes of patients based on multiplex gene analysis. They found that patients who expressed one of the endotypes had improved outcomes with glucocorticoid treatment (Wong et al. 2016). Proof-of-concept clinical trials showing that a precision medicine approach would be successful in sepsis are lacking.

See Also: [ARDS and Precision Medicine](#)

Barriers to Implementing Precision Medicine in Sepsis

There are several important differences between chronic diseases, such as cancer and asthma, and acute conditions, such as sepsis. Endotypes have to be identified within hours in sepsis, in contrast to chronic diseases, where endotypes could be identified over days or weeks. This rapidly evolving time course of critical illness renders use of potentially advanced diagnostic strategies, such as gene-expression microarray, of limited utility. While this remains a significant barrier, progress has been made in more rapidly testing and defining endotypes with Nanostring technology, which has been implemented successfully in retrospective analyses (Wong et al. 2015; Cuenca et al. 2013), but remains challenging to implement in a prospective fashion.

In conjunction with the need to measure biomarkers rapidly, sepsis frequently causes differential endotypes in the same patient over time, exemplified by the well-recognised immunosuppression following the initial exaggerated inflammatory state. This interpatient endotypic variation has been postulated as one underlying mechanism for the failure of clinical trials in sepsis (Marshall 2014; Iskander et al. 2013; Cohen et al. 2015).

Pathogenic mutations in oncologic processes are often specifically maladaptive, and complete inhibition is feasible and may not be harmful. In contrast the pathologic host response in sepsis is multifaceted and multidirectional, and modulation of a molecule or a pathway may have deleterious effects. For example, restoration of immunosuppression in septic patients may increase the risk of acute respiratory distress syndrome. Similarly, prolonged inhibition of a pathway may worsen immunosuppression and increase the risk of secondary infections.

Potential Approaches to Implementing Precision Medicine

Precision medicine cannot work unless drug response or treatment-response phenotypes are properly identified. Many investigators have used biomarkers to identify patient groups who are more or less likely to have bad outcomes (prognostic markers), but not those more or less likely to respond to a therapy (predictive markers). This distinction is critical. For example, the high IL-6 group in MONARCS had a higher mortality rate, but no difference in drug response (Panacek et al. 2004). Outcome phenotypes are far easier to discover, and can potentially be identified in any observational cohort. In contrast, drug-response phenotypes are most readily determined through interrogation of an observational cohort or secondary analyses of a RCT by examining an interaction between the treatment and the phenotype. Identifying drug-response phenotypes is important. If these phenotypes are not correctly identified, investigators may narrow enrollment in a clinical trial to the wrong group.

These endotypes can be identified by measuring genomic, proteomic and microbiome markers in large observational cohorts. The electronic health record can be leveraged to efficiently identify such endotypes (e.g., BioVu victor.vanderbilt.edu/pub/biovu). Using big data will require harmonisation of data across multiple sites and replication of these endotypes in multiple data sets. Novel statistical methods, including latent class analysis, machine learning and principal components analysis will be necessary. However, a key limitation of relying only on observational studies is that results could be confounded. Replicating results in secondary analyses of clinical trials would be important to validate these endotypes, though such data sets are not routinely available.

The results of observational studies described above should be used to optimise the design of clinical trials. If endotypes are not readily available or multiple endotypes are identified, adaptive trials could be used. These trials could enrol and randomise patients across multiple endotypes. As different groups of patients progress through the trial, their response to interventions in different biomarker-defined groups triggers, via pre-specified Bayesian models, adaptations in the randomisation scheme (response-adaptive randomisation). These rules allow the trial to reduce exposure of patient subgroups that may be harmed by the treatment and improve trial efficiency. For example, the I-SPY2 trial for breast cancer used a remarkably small sample size to test 7 regimens in 8 biomarker-defined groups (Barker et al. 2009; Park et al. 2016).

Conclusion

While the implementation of precision medicine in sepsis will be difficult, it is apparent that the current paradigm for novel therapeutic sepsis trials has been insufficient to address the heterogeneity of this disease. It is not clear that precision medicine will lead to better outcomes, but success in other fields, such as oncology, argues for abandoning the one-size-fits-all approach and testing a more targeted approach. Critically ill patients with sepsis represent a unique challenge for precision medicine. Rapidly evolving pathophysiology, multisystem organ failure and high mortality risk combine to make successful precision medicine difficult to operationalise. However, the lack of progress and significant persistent burden of disease highlight the importance of improving clinical trial design and care of this persistent and deadly disease.

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Conflict of Interest

Andrew Prout declares that he has no conflict of interest. Sachin Yende declares that he has no conflict of interest

Abbreviations

RCT randomised controlled trial

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