

## Key areas of current research in sepsis therapeutics



Advances in sepsis therapeutics continue to be made on a regular basis and important avenues of current research include improving endothelial cell function to protect the endothelium and limit oedema formation, blood purification techniques to help restore immune homeostasis, and immunostimulatory therapies for patients with immune exhaustion, according to a review paper in the journal *Critical Care Clinics*.

Disturbed endothelial function plays a key role in the development of sepsis and associated organ dysfunction, partly as a result of altered endothelial permeability leading to oedema formation. The article cites several potential therapies that have been developed offering endothelial cell protective functions, including vasopressin, interferon (IFN)-beta, and thrombomodulin.

In addition, sepsis is known to be associated with coagulopathy, and this is linked to endothelial damage. "These observations formed part of the rationale behind investigating natural anticoagulants, such as activated protein C, in the treatment of sepsis," the article says. "Clinicians are aware of the so-called rise and demise of activated protein C (APC) for the treatment of sepsis. APC may be effective in some patients, but it is too difficult to define which patients will benefit."

As more is learned about the importance of the endothelial barrier in the pathogenesis of sepsis, other potential targets include FX06 (peptide Bb15-42), angiopoietin, sphingosine-1 phosphate receptors, and the Slit-ROBO pathway. In a mouse model of polymicrobial sepsis, for instance, FX06 administration was associated with reduced inflammation, which the investigators attributed to sustained vascular integrity.

### Important challenges for researchers

However, the article notes that despite several decades of sepsis research, no specific therapies for sepsis have emerged and current management still relies on source control, antibiotics, and organ support. For clinicians and researchers, the key challenge is how best to identify those patients who are most likely to respond to any particular therapy so that inclusion criteria can be selected accordingly.

"One of the reasons for the many failed trials of potential new interventions has been the lack of clear patient inclusion criteria, resulting in heterogeneous populations unlikely to all respond positively to the intervention in question," Jean-Louis Vincent MD, PhD, and David Grimaldi MD, PhD, both with the Department of Intensive Care, Erasme Hospital in Brussels, Belgium, write in the journal article.

Still, the years of research and unsuccessful trials have not been in vain. Much has been learned about sepsis pathogenesis, providing multiple new potential targets for antisepsis interventions. Also, clinicians have increasingly realised that not all patients with sepsis are the same and no single intervention will work in all patients with sepsis. "Therapies need to be adapted to individual patients, depending on their immune status and associated organ dysfunction at the time of intervention," Drs. Vincent and Grimaldi point out.

The authors emphasise the need for studies to be conducted in groups of patients who are most likely to benefit from the intervention in question. They are happy to note that new studies are increasingly including this approach in their design. Several studies have used sophisticated techniques to better characterise patients with sepsis, which could be used to more appropriately target interventions. For example, Davenport and colleagues identified two subphenotypes of patients with community-acquired pneumonia: patients with a type 1 sepsis response signature (SRS) profile had an immunosuppressed phenotype and higher 14-day mortality than patients with the type 2 SRS profile.

"Clinicians are some way from being able to incorporate these high-technology approaches into clinical trial inclusion criteria, but biomarkers can already help identify patients who are more likely to respond to specific therapies and follow their response," the authors write. As another example, studies assessing the effects of recombinant gelsolin in patients with community-acquired pneumonia will only enrol patients with low gelsolin levels; this is a known biomarker associated with higher mortalities in patients with sepsis.

Source: [Critical Care Clinics](#)

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Published on : Tue, 21 Nov 2017