Therapeutic Targets in Sepsis: Past, Present, and Future

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KEYWORDS

• Sepsis • Antibiotics • Treatment • Therapeutic targets

KEY POINTS

- Antibiotics and fluids have been the therapy of choice for sepsis since shortly after World War II.
- Although goal-directed targets and timing have changed since then, no additional targeted therapy is part of standard practice for sepsis.
- New approaches to translational investigation of targets are needed.
- Several new targets including the endothelium and late mediators of septic organ injury merit thorough investigation.
- Adaptive trial design might help to speed the large clinical trials of new sepsis therapies.

INTRODUCTION

Long before van Leeuwenhoek peered through his microscope to describe bacteria in 1676, microbial infections have been an enduring cause of human death. Although the evolution of modern germ theory identified and classified many of the pathogens that led to infectious death, it was not until the administration of intravenous fluids, first described during the English cholera epidemic of 1831,[1,2] and the discovery of penicillin, by Flemming in 1928,[3] that the first steps toward modern day management of sepsis were taken.

One striking characteristic of the systemic inflammatory response to infection is that, even after antibiotics kill invading microbes, the host inflammatory response endures and can contribute to organ injury and death.[4] Although many biologically well-informed attempts to limit the inflammatory response have been made in animal models of infection and human clinical trials, severe infection leading to septic organ injury remains a major cause of morbidity and mortality in intensive care units.[5] Furthermore, short of fluids and antibiotics, which have been widely used since the 1950s, no targeted biologic therapy has decreased sepsis mortality and none is currently considered part of standard clinical practice.[6] Significant steps forward in adrenergic pharmacology and organ support have improved mortality. However, mortality and long-term cognitive and physical disability from sepsis remain high and new treatments are needed.

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This article reviews the historical evolution of sepsis therapy (Table 1) and identifies possible causes for why rational therapies failed in human trials. In addition, this article examines potential future sepsis targets and considers which trial designs might optimize their success (Box 1, Table 2).

EVOLUTION OF SEPSIS THERAPY

Fluids

Although intravenous fluids did not become a mainstay of sepsis therapy until the early 20th century, the idea of delivering intravenous salt solutions to improve hemodynamics during infection can be traced to the cholera pandemic of 1831.[7] Dr William O'Shaughnessy, a 22 year-old recent medical graduate of Edinburgh University, with a keen interest in medical chemistry, traveled to Sunderland, England, the nidus of the cholera outbreak, to study and treat patients infected with cholera. His observations led him to question the use of bloodletting and emetics, which were the current state of the art therapies for cholera. He studied the blood of patients infected with cholera and found "a material diminution of water in the blood … and a notable decrease in the soluble salts," which he described in the Lancet in 1832.[1] Instead of bloodletting, O'Shaughnessy argued that trying to restore the original characteristics of healthy blood by delivering a salt solution, could improve the underlying diminution of the "water in blood."

Table 1
Major events in the treatment of sepsis

Year	Intervention
1832	Intravenous fluids for cholera
1905	Epinephrine for shock
1928	Penicillin discovered
1930	First use of penicillin for infection
1949	Norepinephrine used for shock
1970s	Steroids used for sepsis
1982	Polyclonal anti-LPS trial
1991	Monoclonal anti-LPS trials
1993	Anti-TNF trials
2001	Early goal-directed therapy
2014	ProCESS, ARISE, ProMISe

Abbreviations: ARISE, Australasian Resuscitation in Sepsis Evaluation; LPS, lipopolysaccharide; ProCess, Protocolized Care for Early Septic Shock; ProMISe, Protocolised Management in Sepsis; TNF, tumor necrosis factor.

Several months later, during the same cholera epidemic, Dr Thomas Latta drew on the observations of O'Shaughnessy and was the first recorded physician to deliver a warmed salt solution intravenously. He wrote "I have no doubt that it will be found … to be one of the most powerful, and one of the safest remedies yet used in this … hopeless state of collapse."[1] Although the intravenous delivery of saline would not become a standard treatment for sepsis until many years later, O'Shaughnessy's initial impressions of the central importance of fluid resuscitation for sepsis endures today.

Antibiotics

Alexander Flemming's sharp eye first noted that "mold juice" from the fungus *Penicillium chrysogenum* could kill *Staphylococcus* in culture on September 28, 1928.[3] His initial thought was that bacterial susceptibility to "mold juice" might help him to subclassify bacteria. However, eventually, he realized that "mold juice" or the key compounds within it, which he called "penicillin," might be used to treat bacterial infections in humans. Flemming worked hard to produce quantities of penicillin sufficient for in vivo study, but given the difficulty of purifying the compound from mold, he abandoned this pursuit 1940. Fortunately, in the same year, the team of Florey and Chain, working at Oxford, published a paper outlining a method of penicillin purification in quantities sufficient for clinical testing.[3] It then took many additional bright physicians, chemists, mycologists and defense-related funding from both England and the United States during World War II to advance Flemming's antibacterial "mold juice" to a reasonably priced clinical treatment for bacterial infections.[3]

Supporting Injured Organs

Today, timely administration of broad-spectrum antibiotics and restoration of intravascular fluid volume remain the cornerstones of treatment for sepsis. Even after the delivery of these 2 key therapies, patients frequently develop septic shock, requiring catecholamine vasopressors. Although the advances of fluids, antibiotics, and vasopressors have decreased mortality, a significant portion of patients still progress to develop organ injury. Although artificial organ support, including mechanical ventilation and continuous renal replacement therapy, can maintain organs after they have been injured, unraveling the early molecular events during sepsis held the promise of avoiding organ injury altogether.