Abstract:
The past several decades have seen the proposal of many novel therapies for sepsis, but none have been successfully introduced into current standard practice. Anti-inflammatory therapies seek to quell the overwhelming inflammation and coagulation dysregulation most often present during sepsis onset. More recently, immunostimulatory therapies have been investigated, seeking to rescue the paralyzed immune system that often develops later in the course of sepsis leading to secondary nosocomial infections and death. Other approaches include renal replacement therapies and plasma exchange, which attempt to remove sepsis proinflammatory and anti-inflammatory mediators nonspecifically. While we await an effective drug or therapy, current investigations with novel approaches are presented here.

Keywords:
sepsis; pediatric; treatment; therapies; adjuvant; adjunctive; review

*Division of Pediatric Critical Care Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; †Division of Pediatric Critical Care Medicine, Lucile Packard Children's Hospital, Palo Alto, CA.
Reprint requests and correspondence: Jay Rilinger, MD, Department of Pediatrics, Division of Pediatric Critical Care, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Ave, Box #205, Chicago, IL 60611.
jrilinger@luriechildrens.org

1522-8401

Adjunctive Therapies in Sepsis

Jay F. Rilinger, MD*, Elora Hussain, MD†, Mary E. McBride, MD*

The cornerstone of sepsis therapy remains early broad-spectrum antibiotics, aggressive fluid resuscitation, source control, and cardiovascular support with vasopressors and/or inotropic medications.[1] Although the past decades of research have improved our understanding of the complex pro-inflammatory and anti-inflammatory pathways and the disturbances in the complement and coagulation systems present in sepsis, this knowledge has thus far failed to translate into effective therapies. Previous research produced a number of pharmaceutical agents targeting these pathways, although none have consistently reduced mortality in sepsis. Subsequent work has revealed the contribution of the anti-inflammatory phase to sepsis mortality. Therapies targeting this process seek to provide immunostimulation. Unlike these targeted approaches, extracorporeal therapies have taken a broader, nonspecific approach to removing both proinflammatory and anti-inflammatory mediators. Although no single therapy has yet been introduced into common practice, several therapies have shown promise and, yet, require further study and confirmation in larger clinical trials. Any effective novel sepsis therapy will likely first be explored in adult studies. Given the differences between adult and pediatric sepsis, application to a pediatric population will require additional trials.

ANTI-INFLAMMATORY THERAPIES

Many of the previously developed therapies for sepsis have attempted to suppress the inflammatory cascade that manifests in the acute phase with capillary leak, hypotension, and shock (Table 1). Unfortunately, no medication targeting the anti-inflammatory pathway has proven to decrease mortality in sepsis.[2] Many therapies proven in animal models have failed to replicate that success in human trials. Alternatively, Xigris, Eli Lilly,

TABLE 1. Anti-inflammatory therapies in sepsis.

Anti-Inflammatory Therapies	Clinical Studies	Recommendations for Use
Corticosteroids	Pediatric RCTs of broad use in sepsis without adrenal insufficiency are few, retrospective, or lacking in demonstrated mortality benefit.[27,28]	Use in suspected/documented adrenal insufficiency recommended. No evidence for use outside the above situation.
IVIG	No consistent mortality benefit in adults or neonates[17,18]; improved mortality in small moderate-quality studies.[15,16]	Not recommended for routine use in sepsis; consider in toxic shock syndrome.
Antithrombin III	No change in mortality, increased bleeding in adults[12]; no pediatric RCTs.	Use not recommended in pediatric or adult sepsis.
Statin therapy	Adult data mostly retrospective or observational[22-24]; no data in children.	Further research required.
rAPC	No mortality benefit in adults[10] or pediatrics[6] demonstrated.	No longer commercially available; not recommended.[1]

Abbreviations: RTC, randomized controlled trials; IVIG, intravenous immunoglobulin; Anti-AT3, antithrombin III; rAPC, recombinant activated protein C.

Indianapolis, IN (activated protein C [APC]) found success in human clinical trials,[3] was approved by the Food and Drug Administration, and was even included in the Surviving Sepsis Guidelines.[4] However, subsequent research trials found it inefficacious, and it has since been withdrawn from the market.[5,6] The causes of these failures are likely several-fold. Animal models are often healthy and lack the comorbidities found in most patients. Animal models also have a different genomic response in inflammatory disease states.[7] Furthermore, the heterogeneity of the human response to infection makes a single-drug therapy unlikely to be successful for all individuals. Although anti-inflammatory therapies have not found success in clinical trials, they may find a role when tailored to the specific patient and in a specific time point or phase of illness. Use of epigenetics and individualized patient therapy may direct the future use of specific targeted therapies.[8]

Activated Protein C

Protein C is a plasma serine protease that when activated plays an important role in anticoagulation by inactivating factors V_a and $VIII_a$. Given the observed deficiencies of APC in sepsis[9] and its anti-inflammatory and antithrombotic effects, recombinant APC (rAPC) was developed as a sepsis therapy. In phase 3 trials, rAPC demonstrated improved mortality.[5] However, despite gaining regulatory approval for adults in 2001, in subsequent adult trials, no mortality benefit of rAPC was identified, leading to withdrawal of the drug from the market in 2011.[10] Neither did rAPC show improved mortality or time to resolution of organ failure in the large pediatric RESOLVE study.[6] Thus, use of rAPC is not recommended in sepsis.

Antithrombin III

Antithrombin III (AT3) is a plasma glycoprotein that inhibits the activation of multiple coagulation factors in the intrinsic pathway. Although the safety and efficacy of AT3 in pediatrics have not been formally studied, its off-label use in pediatric units has increased recently in presumed or documented AT3-deficient states associated with extracorporeal membrane oxygenation (ECMO), cardiopulmonary bypass, disseminated intravascular coagulation (DIC) with sepsis, and liver failure.[11] Antithrombin III levels are reduced in sepsis, and it was postulated that administration could improve outcomes. Although no pediatric randomized controlled trials (RCTs) of AT3 exist, a phase III adult trial did not demonstrate mortality benefit in severe sepsis and septic shock and had increased risk of bleeding.[12] Because risks appear to outweigh any benefit, current Surviving Sepsis Guidelines recommend against its use in sepsis in adults or children.[1]

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) consists of pooled immunoglobulins extracted from more than 1000 donors. It is used in multiple and heterogeneous disease states, although its role in sepsis is still to be determined. Intravenous immunoglobulin has multiple anti-inflammatory actions including the binding of endotoxin, antibacterial activity, and reduction of cytokine production, complement activation, and