REVIEW

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Sepsis: Menu of new approaches replaces one therapy for all

ABSTRACT

Effective therapies for sepsis are being devised, after many failures. However, instead of a "one therapy for all" approach, management of sepsis will involve a menu of treatments, depending on the presence of inflammatory markers, the severity of disease, and other factors. This article looks at promising new therapies, including recombinant human activated protein C (rhAPC; drotrecogin alfa, Xigris), recently approved by the US Food and Drug Administration.

KEY POINTS

In a recent clinical trial, patients who received rhAPC had a 28-day mortality rate of 24.7%, compared with 30.8% in the placebo group, a relative risk reduction of nearly 20%. Of importance, at baseline, nearly all the patients in the study had biochemical evidence of coagulopathy and inflammation, 75% had two or more organ failures, and 70% were in septic shock.

Future therapies for sepsis could include corticosteroid replacement therapy, enteral feeds containing arginine and omega-3 fatty acids, intravenous infusions of Ringer's ethyl pyruvate solution, mechanical ventilation with low tidal volumes, hemoperfusion columns that bind bacterial toxins, and novel antiendotoxin and anti-inflammatory agents.

Sepsis is caused by cascades of inflammation and coagulation in which tumor necrosis factor alpha and interleukin-1 play a central role.

*The author has indicated that he owns stock in Eli Lilly and Company.

THE FIRST AGENT for treating sepsis, recombinant human activated protein C (rhAPC; drotrecogin alfa, Xigris) was recently approved by the US Food and Drug Administration. This paper reviews lessons learned from recent trials, including work with rhAPC, and the pathophysiology of sepsis.

We are finally making progress in treating sepsis, after a long string of disappointments.

Although improved understanding of the pathophysiology of sepsis had given rise to hopes that agents that block inflammation and coagulation could reduce mortality, until recently, clinical trials of these agents had disappointing results. More recent trials are better designed to determine an agent's effects in particular infections and populations.

Now, instead of a "one therapy for all" approach, we are finding that therapy directed against specific biochemical derangements must be targeted to patients who actually have these derangements. Management of sepsis may eventually involve a menu of treatments, depending on the presence of inflammatory markers, compensatory anti-inflammatory activity, the severity of disease, and other factors.

SEPSIS DEFINED

In 1992, a consensus panel of the American College of Chest Physicians and the Society of Critical Care Medicine convened to develop definitions of critical illness for the purposes of clinical trial design:

Systemic inflammatory response syndrome (SIRS) is the host response to critical illness of either infectious or noninfectious origin. (Noninfectious causes include burns, trauma, and pancreatitis.) SIRS can be readily

diagnosed at the bedside by the presence of at least two of the following four signs:

- Hyperthermia or hypothermia
- Tachycardia
- Tachypnea
- Leukocytosis or leukopenia.

Sepsis is SIRS due to a presumed or known infection.

Severe sepsis is sepsis with an acute associated organ failure.

Septic shock, a subset of severe sepsis, is defined as persistently low mean arterial blood pressure despite adequate fluid resuscitation.

Refractory septic shock is persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.[1]

THE LEADING CAUSE OF DEATH IN INTENSIVE CARE UNITS

Sepsis is the leading cause of death in noncoronary intensive care units and the 13th leading cause of death in the United States overall.[2] More than 700,000 cases of severe sepsis are estimated to occur each year in the United States.[3]

There are > 700,000 cases of severe sepsis each year in the US, and 1/3 of patients die

The incidence of sepsis is expected to increase over the next decade owing to the following factors: an aging population, an increasing immunosuppressed population, increased use of invasive catheters and prosthetic materials, and the growing problem of antimicrobial resistance.

The mortality rate in severe sepsis remains between 28% and 50%, depending on the country and institution.[4]

PATHOPHYSIOLOGY OF SEVERE SEPSIS

The inflammation cascade

Severe sepsis can start with an infection in any part of the body, including the lungs, abdomen, skin, soft tissue, urinary tract, or blood (eg, in meningococcemia). The pathogens are usually bacteria, although fungi, viruses, and parasites can also cause sepsis.

Trouble starts when components of the outer membrane of bacteria bind to the CD14 receptor on the surface of monocytes (FIGURE 1). These outer-membrane components include the lipid A moiety of lipopolysaccharide (endotoxin) in gram-negative organisms, and lipoteichoic acid and peptidoglycan in gram-positive organisms.

Binding of the CD14 receptor sends a signal to the interior of the monocyte via the recently described Toll-like receptors, telling it to produce the inflammatory cytokines tumor necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1).[5,6]

These cytokines have a direct toxic effect on tissues. They also activate phospholipase A_2, leading to increased concentrations of platelet-activating factor. In addition, they promote nitric oxide synthase activity, tissue infiltration by neutrophils, and neutrophil activity.[7,8]

Link between inflammation and coagulation

Interleukin-1 and TNF-alpha also promote coagulation in several ways. They directly stimulate the endothelium and monocytes to express tissue factor, the first step in the extrinsic pathway of coagulation. Tissue factor leads to production of thrombin, which itself is inflammatory. Thrombin leads to fibrin clots in the microvasculature, a sequelae most easily recognized in meningococcal septic shock with purpura fulminans.

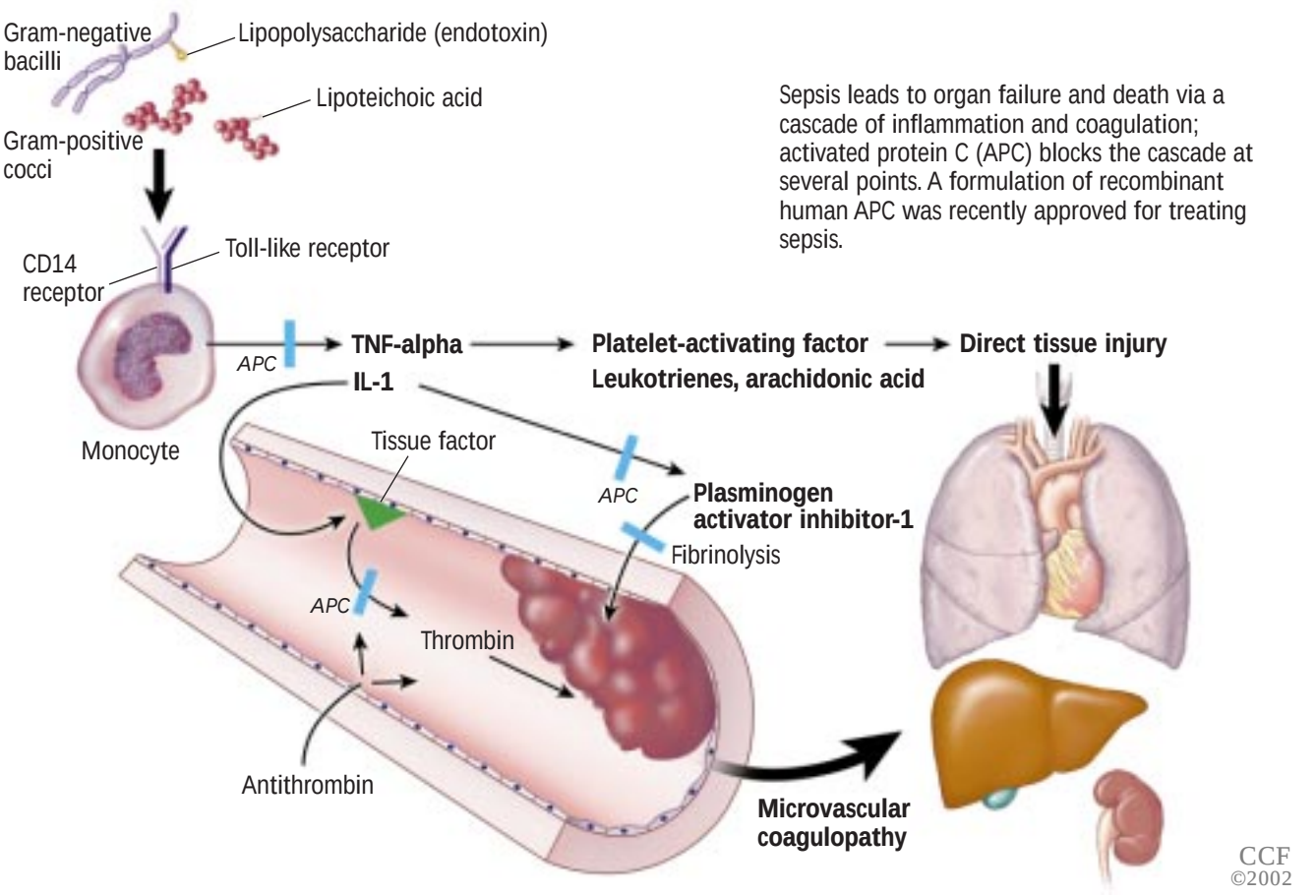
Further, these cytokines impair fibrinolysis by promoting production of plasminogen activator inhibitor-1, a potent inhibitor of fibrinolysis.[9]

Inflammatory cytokines also disrupt the body's natural modulators of coagulation and inflammation, activated protein C and antithrombin.

Protein C circulates as an inactive zymogen, a form of proenzyme. In the presence of thrombin and the endothelial surface-bound protein thrombomodulin it is converted to activated protein C. Recent studies showed that inflammatory cytokines can shear thrombomodulin from the endothelial surface and even lead to down-regulation of this molecule, thus preventing activation of protein C.[10]

Activated protein C, with its cofactor protein S, turns off thrombin production by cleaving factors Va and VIIIa.[11] Activated protein C also restores fibrinolytic potential by inhibiting plasminogen activator inhibitor-

Pathophysiology of severe sepsis



Sepsis leads to organ failure and death via a cascade of inflammation and coagulation; activated protein C (APC) blocks the cascade at several points. A formulation of recombinant human APC was recently approved for treating sepsis.

FIGURE 1

1.[12] In vitro studies reveal that activated protein C has direct anti-inflammatory properties, including inhibiting the production of inflammatory cytokines by lipopolysaccharide-stimulated monocytes, inhibiting leukocyte adhesion and rolling, and inhibiting neutrophil accumulation.[13–15]

Antithrombin, the second natural endothelial regulator affected during sepsis, inhibits thrombin production at multiple steps in the coagulation cascade; it also binds to and inhibits thrombin directly.[16] When bound to the endothelial cell surface, antithrombin leads to production of the anti-inflammatory molecule prostacyclin.[17] Evidence exists that neutrophil elastase cleaves glycosaminoglycans off the surface of the endothelial lining, thus limiting the anti-inflammatory properties of antithrombin.[18]

Severe sepsis: The final common pathway

The vicious cycle of inflammation and coagulation leads to cardiovascular insufficiency, multiple organ failure, and, in 28% to 50% of patients, death.[4] Cardiovascular insufficiency can occur both at the level of the myocardium as a result of the myocardial depressant effects of TNF-alpha, or at the level of the vessel due to vasodilatation and capillary leak.[19]

DISAPPOINTING RESULTS FROM CLINICAL TRIALS

Armed with this knowledge of the cascade of events in sepsis, researchers conducted at least 30 phase III clinical trials of various agents expected to interrupt the process, mostly anti-inflammatory molecules (TABLE 1).[20–35] Approximately 20,000 patients were

entered, most of whom had a clinical diagnosis of severe sepsis.

The results were disappointing. At best, these agents reduced the 28-day all-cause mortality rate only modestly, and the Food and Drug Administration has approved none of them for treating sepsis.

LESSONS LEARNED

Why were these agents not as effective as hoped? Some possible reasons involve the agents tested, while others involve the populations in which they were tested.

Molecule-specific issues

Lack of biologic activity. Some of the agents tested were simply not biologically active. E5 and HA-1A, two endotoxin binders, were found to bind and inhibit endotoxin in vitro, but only weakly.[36] In a study of a monoclonal antibody to TNF, circulating bioactive TNF-alpha levels did not decrease in patients receiving the monoclonal antibody.[27]

Pathogen-specific efficacy. Another reason is that many of the anti-inflammatory agents vary in efficacy in different types of infections. Most of them had modest benefit in patients with gram-negative infections but little or no benefit in gram-positive infections.[37] In one trial,[30] patients with gram-positive infections who received the p75 TNF:IgG fusion protein actually had a *higher* mortality rate than did patients who received placebo.[30]

Early in sepsis, inflammatory mediators predominate

Drug-drug and drug-disease interactions may also explain the failure of these agents in sepsis trials. In a recent trial of antithrombin in sepsis,[38] no treatment effect was demonstrated in the overall group, but a trend towards efficacy was seen in patients who did not receive heparin concomitantly.

This finding is explainable: heparin negates the anti-inflammatory properties of antithrombin by diverting the antithrombin away from endothelial surface glycosaminoglycans, thus preventing production of prostacyclin.[16] In addition, during sepsis, neutrophils release elastase, a molecule that cleaves antithrombin, especially when heparin is given exogenously.[18]

Population-specific issues

Severe sepsis is not homogeneous. The enrollment criterion used in nearly all of the sepsis trials to date was the clinical diagnosis of severe sepsis. However, one therapy may not benefit all patients with this diagnosis. It is important that the intended target for therapy be present in the population being studied.[27]

For example, in trials of antiendotoxin agents and anticytokine therapy, the inflammatory cytokine targeted was absent in a large percentage of patients enrolled.[39] This is explainable, as the net state of inflammation during a septic episode is a dynamic process. Early in sepsis, inflammatory mediators predominate. Later, anti-inflammatory mediators may predominate, or monocytes may lose their responsiveness and lymphoid tissue may undergo apoptosis. These later events may result in "immunoparalysis." In fact, during this so-called compensatory anti-inflammatory response stage of the disease, an anti-inflammatory therapy might be harmful.[40]

Non-sepsis-related deaths. The studies used the end point of death from any cause at 28 days. If a trial using this end point is to determine whether an agent is effective in sepsis, sepsis must be the primary cause of death in the study population. In many trials, however, a substantial percentage of deaths were due to severe underlying diseases and not to sepsis.[41] The statistical power of these studies to detect an agent's efficacy was thus diminished.

Therapy may be less beneficial in less-severe disease. Many of the agents tested in humans were first tested and found effective in animals. Of interest, the animals who received placebo in these trials had mortality rates of 80% to 100%—considerably higher than in humans. In tests of the same agents in which the animals that received placebo had mortality rates comparable with those in humans with severe sepsis (30%–35%), these agents showed little benefit or actually showed harm.[42] Human clinical trials of anti-TNF molecules and IL-1 receptor antagonists have demonstrated this phenomenon as well.[29,31]

It would make sense that patients with less-severe disease and less inflammation would be closer to homeostasis and could be potentially harmed by an intervention.

TABLE 1

'Negative' trials of therapy in sepsis

AGENTS	NO. OF TRIALS	RESULTS AND COMMENTS
High-dose corticosteroids[20]	9	Trend towards worse outcome in treated group
Antiendotoxin antibody		
J5 antiserum[21]	1	Benefit did not correspond with presence of J5 antibodies
HA-1A[22,23]	2	Benefit in gram-negative infections with shock in first trial, but not confirmed in second trial
E5[4,24–26]	3	Benefit in patients without shock in early trials, but not confirmed
Anti-TNF monoclonal antibodies (murine and human)[27]	10*	Consistent 3.5%–4.0% decrease in mortality (NS)
TNF receptor:IgG constructs		
P55[28,29]	2	Benefit in patients with early shock in first trial, but not confirmed in second trial
P75[30]	1	No benefit overall; harm in gram-positive infections
IL-1ra antagonists[31,32]	2†	Consistent 4% decease in mortality (NS)
Platelet-activating factor antagonists[33,34]	2	Benefit in patients with gram-negative infections in first trial, but not confirmed in second trial
Ibuprofen[35]	1	3% reduction in mortality (NS) Improvement in metabolic parameters

*Phase II and III
†Phase III

ADVANCES IN SEPSIS TRIALS

Three recent trials, the MONARCS,[43] PROWESS,[44] and Ger-inf-05 trials,[45] demonstrate advances in sepsis trial design and, potentially, in the treatment of severe sepsis.

The MONARCS trial

The Monoclonal Anti-TNF: a Randomized Controlled Sepsis (MONARCS) trial,[43] conducted in 157 sites in North America, examined the safety and efficacy of afelimomab, an anti-TNF monoclonal antibody, in severe sepsis.

What is novel about this trial is the use of a marker to target the therapy and select for a population with a greater disease severity. It used a rapid test to identify patients with IL-6 levels greater than 1,000 pg/mL. IL-6 is a cytokine that is a marker of the net state of inflammation and of disease severity.

At 28 days, the overall mortality rate in the afelimomab group was 35.9%, compared with 32.9% in the placebo group (P = .049), a difference consistent with the treatment effect observed in other anti-TNF trials.

The PROWESS trial

The Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial[44] was a phase III trial of recombinant human activated protein C (rhAPC). The trial was stopped when the second interim analysis found overwhelming evidence of efficacy: the 28-day mortality rate in the rhAPC group was 24.7%, compared with 30.8% in the placebo group, a relative risk reduction of 19.4% and an absolute risk reduction of 6.1% (P = .005).

The success of this agent in this trial appears to be due not only to the biologic effect of rhAPC but also the population in

TABLE 2

Cleveland Clinic guidelines for using rhAPC (drotrecogin alfa, Xigris)

INDICATIONS

To be considered for rhAPC therapy the patient should meet all three of the following criteria

1 A known or suspected site of infection indicated by one or more of the following:

- Purulent sputum or respiratory sample
- A chest radiograph with new infiltrates not explained by a noninfectious process
- Spillage of bowel contents noted during an operation
- Radiographic or physical examination evidence of an infected collection
- White blood cells in a normally sterile body fluid
- Positive blood culture
- Evidence of infected mechanical hardware by physical or radiologic examination

2 Evidence of systemic inflammatory syndrome as indicated by at least three of the following:

- Hypothermia or fever: core body temperature ≤ 36°C (96.8°F) or ≥ 38°C (100.4°F)
- Tachypnea: ≥ 20 breaths/minute or on mechanical ventilation for an acute process
- Tachycardia: ≥ 90 beats per minute (unless the patient has a pacemaker or is on pharmacologic therapy for preexisting tachycardia)
- White blood cell count ≥ 12,000 or ≤ 4,000 cells/mm^3 or > 10% bands on differential count

3 Sepsis-induced organ failure criteria

(Note: Organ failure may not be explained by another non-sepsis illness, and cannot be greater than 48 hours in duration.)

- Severe sepsis (criteria 1 and 2) with an APACHE II score ≥ 25

AND

- Cardiovascular system dysfunction: patient must either have:

Evidence of septic shock, defined as mean arterial pressure < 60 mm Hg or systolic arterial pressure < 90 mm Hg or the need for vasopressors to maintain these blood pressures in the face of adequate intravascular volume (central venous pressure > 8 mm Hg or pulmonary artery occlusion pressure > 12 mm Hg), or after an adequate fluid challenge (12 mL/kg) has been given

OR

Two or more of the following organ failures:

Respiratory system dysfunction: Pao_2/Fio_2 ratio < 200

Renal dysfunction: urine output < 0.5 mL/kg/hour for 1 hour in the face of adequate intravascular volume (central venous pressure > 8 mm Hg or pulmonary artery occlusion pressure > 12 mm Hg, or after an adequate fluid challenge (12 mL/kg) has been given

Hematologic dysfunction: thrombocytopenia (< 80,000 platelets/mm^3 or a 50% drop in the last 3 days), or an international normalized ratio (INR) > 1.2 not explained by liver disease or concomitant warfarin usage

Unexplained metabolic acidosis: pH < 7.30 with an elevated plasma lactate level that is > 1.5 times the upper limit of normal

which it was studied. All the patients in this study had a clinical diagnosis of severe sepsis, and nearly 100% had biochemical evidence of coagulopathy and inflammation, the target that rhAPC was intended to treat. The population studied was also of appropriate disease severity, with nearly 75% having two or more organ failures at baseline, and 70% in septic shock. In fact, the majority of the benefit seen in the trial occurred in patients with greater disease severity (with Acute Physiology and Chronic Health Evaluation [APACHE] II scores ≥ 25).

rhAPC seemed to have potent biologic activity. D-Dimer levels were measured to assess rhAPC's effect on thrombin generation, and IL-6 levels were measured to assess its effect on inflammation. The agent reduced both of these markers significantly.

Of interest, the pathogen type did not affect the efficacy of rhAPC: treated patients had a lower mortality rate regardless of whether they had pure gram-positive infections or pure gram-negative infections.[44]

CONTRAINDICATIONS

Active internal bleeding
Surgery in the previous 12 hours
Thrombocytopenia (≤ 20,000 platelets/mm^3)
Evidence of postoperative bleeding
Evidence of gastrointestinal bleeding
History of central nervous system mass lesion or evidence of cerebral herniation
History of stroke, arteriovenous malformation, cerebral aneurysm, intracranial or intraspinal surgery, or severe head trauma requiring hospitalization, within last 3 months
Cirrhosis (history of esophageal varices, portal hypertension)
Evidence of a bleeding complication following a percutaneous procedure, eg, decreasing hemoglobin, flank hematoma after femoral line placement
Nephrostomy tubes in place
Unexplained mental status changes or neurologic examination changes
Therapeutic doses of heparin (≥ 15,000 U/day) within the previous 8 hours, low-molecular-weight heparin at a dose higher than prophylaxis within the previous 12 hours
Systemic thrombolytic therapy within the past 3 days, aspirin > 650 mg/day within the past 3 days, glycoprotein IIb/IIIa antagonists within the past 7 days, warfarin within the past 4 days, or clopidogrel or ticlopidine within the past 4 days
End-stage disease processes in which there is not a commitment to aggressive management or in which the patient has an advanced directive to withhold life-sustaining treatment
Enrollment in a clinical trial involving a molecule that targets the coagulation cascade
Pulmonary, splenic, or liver contusions following trauma
Presence of an epidural catheter
Pediatric patients (< 18 years) unless treating purpura fulminans

DOSAGE AND GUIDELINES FOR MONITORING rhAPC USE

Give rhAPC 24 μg/kg/hour as a continuous infusion for a total of 96 hours
If a surgery or percutaneous procedure needs to be performed, stop rhAPC 2 hours before the procedure
rhAPC can be restarted 1 hour after a percutaneous procedure and 12 hours after a surgical procedure if adequate hemostasis has been achieved
If evidence of gastrointestinal bleeding occurs, stop rhAPC immediately; an endoscopy should be performed
Patients should receive stress ulcer prophylaxis, such as sucralfate, a histamine-2 antagonist, or a proton-pump inhibitor
If a patient requires full-dose therapeutic heparin for the treatment of a thrombotic event, the rhAPC infusion should be stopped
If a patient requires renal replacement therapy, attempts should be made to run the dialysis with rhAPC alone; if clotting occurs, the lowest dose of heparin necessary to maintain the patency of the dialysis filter should be used

TABLE 2 contains guidelines for the use of rhAPC.

The Ger-inf-05 study

The Ger-inf-05 study[45] evaluated the effect of replacement doses of corticosteroids (hydrocortisone 50 mg intravenously every 6 hours plus fludrocortisone 50 μg by mouth daily for 7 days) in patients with septic shock that was refractory to fluids and vasopressors. The specific population of interest in this study was patients who did not respond to the adrenocorticotropin (ACTH) stimulation test, a group in which it would be scientifically reasonable to consider adrenal replacement.

In this small study (N = 299), adrenal replacement therapy was associated with a statistically significant reduction in mortality in the 76% of patients who were adrenal hyporesponders (relative risk = 0.670, P = .023).

This study is another example of a therapy being given in an appropriate target population.

FUTURE DIRECTIONS

The success of rhAPC in severe sepsis and steroid replacement therapy in refractory septic shock with adrenal hyporesponsiveness represents not the end of severe sepsis research and therapy but the beginning. On the basis of ongoing research, one can envision multi-targeted treatment for severe sepsis akin to what is done in the treatment of cancer and HIV. Such treatment might include, depending on the clinical setting, many of the agents currently being studied.

Lessons from past sepsis trials should allow the design of clinical trials that demonstrate the true efficacy of new agents.

Potential future treatments for severe sepsis

Immunonutrition. Enteral feeds containing arginine and omega-3 fatty acids have been shown to decrease hospital days, ventilator days, and infectious complications in critically ill patients.[46]

Prescription intravenous fluids. Ringer's ethyl pyruvate solution has been shown to be a scavenger of reactive oxygen species that can lead to oxidant-mediated cellular and organ injury in a rat model of mucosal injury.[47]

Ventilator strategies. In a landmark study,[48] patients with acute respiratory distress syndrome who received mechanical ventilation with lower tidal volumes (6 mL/kg) had a lower mortality rate and more ventilator-free days than patients who received traditional tidal volumes (12 mL/kg).

Anti-endotoxin agents. Novel agents include more potent inhibitors of endotoxin, including highly conserved antibodies to gram-negative outer membrane proteins, as well as lipid A partial structure antagonists that compete with endotoxin for the CD14 receptor and Toll-like receptor on the surface of monocytes.

Endothelial modulators. rhAPC and tissue factor pathway inhibitor could potentially be used to decrease thrombin generation in sepsis and its resulting inflammation.

Anti-inflammatory agents. Novel anti-inflammatory agents include inhibitors of toxic neutrophilic enzymes such as elastase, and enzymes and proteins involved in cytokine signaling.

Binding columns. Several hemoperfusion columns are being developed to bind bacterial products involved in sepsis. One of these columns binds the toxin responsible for hemolytic uremic syndrome, another binds the superantigens responsible for streptococcal and staphylococcal toxic shock, and a polymyxin column binds the endotoxin moiety of gram-negative organisms.

Corticosteroid replacement therapy. Patients with septic shock and adrenal hyporesponsiveness could receive physiologic replacement of a glucocorticoid and mineralocorticoid.

The success of rhAPC is not the end of sepsis research, but the beginning

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The future treatment for sepsis may resemble multi-drug treatment for HIV or cancer