Emerging drugs in sepsis

Marc Leone†, Julien Textoris, Fabrice Michel, Sandrine Wiramus & Claude Martin
†Service d’anesthésie et de réanimation, Hôpital Nord, Assistance Publique – Hôpitaux de Marseille, Université de la Méditerranée, Chemin des Bourrely, 13915 Marseille Cedex 20, France

Importance of the field: Sepsis remains a major cause of death in intensive care units. Despite an intense research, a new drug that is effective in reducing mortality in sepsis is still awaited.

Areas covered in this review: The literature was analyzed with Pubmed during the 2008 – 2009 period. If required, seminal articles published before 2008 were cited. Clinical trials focusing on ‘sepsis’ were first assessed. Next, relevant experimental data in this field were reported.

What the reader will gain: The goal of the review is to determine the role for new licensed antibiotics, to give an insight into the conflict on adjuvant therapies and to disclose new experimental concepts.

Take home message: New licensed antibiotics will offer the opportunity to refine the treatment choices. Direct hemoperfusion using polymyxin B-immobilized fiber column may be an option in sepsis due to Gram-negative bacilli. Among non-antibiotic drugs, new ongoing studies will clarify the role of drotrecogin alfa (activated) and low dose hydrocortisone. The modulation of monocytic human leukocyte antigen-DR seems the most prominent treatment. The use of cardiovascular drugs requires well-conducted clinical trials. The regulation of high mobility group box 1, adenosine blockade or correction of the impaired energy production is still at the experimental level.

Keywords: adenosine, HLA-DR, HMGB1, sepsis


1. Background

Sepsis is the major point of focus of drug discovery efforts in the critical care area. The management of septic patients is based on parallel strategies. First, the burden of infection should be promptly reduced by source control measures and early use of antimicrobial agents [1]. We review thereafter the possible place of new approved antimicrobial agents in this setting. Second, in addition to symptomatic treatments, the modulation of the host response remains a desired goal in sepsis. Only an anticoagulant with immunomodulatory and anti-inflammatory properties, that is, activated protein C, has shown to be efficient in severe sepsis [2]. Subsequent trials struggled to confirm the efficacy of recombinant human activated protein C [3]. Hence, to date, only antibiotics (and symptomatic measures of resuscitation) are at the disposal of intensivists in order to improve the outcome of patients with severe sepsis.

The literature was analyzed with Pubmed during the 2008 – 2009 period. If required, seminal articles published before 2008 are briefly cited. Randomized clinical trials responding to the key word ‘sepsis’ were first assessed. In the absence of randomized clinical trials, relevant results of other clinical trials were reported. Experimental data in the field of sepsis were next investigated. As > 2000 hits responded to the item ‘sepsis’ within the study period, we selected arbitrary examples of pathways that seem interesting. Regarding other pathways, we refer the reader to recent reviews.
2. Medical need

About 50% of the patients with septic shock do not survive. Intensivists have at their disposal several antibiotics. Although resistance is a critical issue, pan-resistant pathogens exceptionally remain reported in the literature. The judicious use of current antibiotics can help reduce the mortality. Among non-antibiotic drugs, activated protein C is the only drug available in the market.

To date, no immunomodulatory drugs have shown better efficacy than placebo in large randomized clinical trials. Nevertheless, adequate antimicrobial therapy is not enough to improve the survival of a large number of patients. Because the variability among patients with sepsis is very large, there is a need to have dedicated drugs according to the immune response of each individual.

3. Market review

The market size of sepsis is large because, in the US or the EU, severe sepsis affects about 750,000 hospitalized patients. In the intensive care unit, 15% of patients develop severe sepsis and septic shock. Several risk factors for the development of sepsis have been identified including male sex, race, age, comorbid medical conditions, alcohol abuse and a lower socioeconomic status.

The incidence of severe sepsis tends to increase year after year by 5%, probably due to the rising age of patients. The mortality of patients with severe sepsis remains around 40% and represents ~ 30% of overall hospital mortality rate [4].

4. Existing treatment

4.1 Antimicrobial therapy

4.1.1 Recent and emergent antibiotics

Intravenous antimicrobial therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures are obtained [1]. This recommendation is based on clinical studies showing an increase in mortality related to the delay to infuse antibiotics in severe sepsis patients [5,6]. Because this treatment is given before culture results are available, it is critical to provide an appropriate treatment. A relationship was demonstrated between the inappropriateness of empirical antimicrobial treatment and mortality [7,8].

Broad spectrum antibiotics should be systematically used in patients with risk factors for carriage of difficult-to-treat bacteria (i.e., Pseudomonas aeruginosa, Acinetobacter baumannii and oxacillin-resistant Staphylococcus aureus (ORSA)). In a population of patients with ventilator-associated pneumonia, the risk factors are shock state, prior antimicrobial therapy, prior stay in long-term facilities and late-onset infection [7]. The broad spectrum antibiotics should be de-escalated as soon as the culture results are obtained [9].

A new broad spectrum carbapenem, doripenem (Doribax®, Johnson & Johnson Pharmaceutical Research & Development, LLC, South Raritan, NJ, USA), is on the market. It is a parenteral 1-β-methyl carbapenem that has completed trials for nosocomial pneumonia, including ventilator-associated pneumonia, complicated intra-abdominal infection and complicated urinary tract infection [10]. In vitro, its activity is similar to that of imipenem against Gram-positive cocci and similar to that of meropenem against Gram-negative bacteria. Briefly, doripenem may keep an activity against extended spectrum β lactamase producing pathogens, and its minimal inhibitory concentrations are lower than that of imipenem against non-fermenting Gram-negative bacilli [11]. In a clinical study including patients with ventilator-associated pneumonia, only 18% (5/28) of P. aeruginosa isolates had minimum inhibitory concentration ≥ 8 µg/ml at baseline or following therapy in the doripenem arm compared with 64% (16/25) in the imipenem treatment group (p = 0.001) [12]. Its efficacy is improved when it is infused over a 4 hour period [12]. Doripenem, despite its excellent activity against P. aeruginosa, can lack activity against most of the strains that express resistance to the currently available carbapenems [13]. In addition, the emergence of resistance may parallel its use.

Ertapenem (Invanz®, Merck, WestPoint, PA, USA) is another carbapenem with broad spectrum activity. However, it has a limited activity against non-fermenting Gram-negative bacilli [14]. This antibiotic was first proposed for the management of complicated skin infections and intra-abdominal infections. Currently, ertapenem is used in selected patients with documented infection by a fermenting Gram-negative bacilli producing extended spectrum β lactamase. It represents a possible agent for de-escalation.

In patients with ventilator-associated pneumonia, non-coverage of ORSA is one of the most frequent causes of failure of the empirical antimicrobial therapy [15]. Vancomycin remains the standard of care for the treatment of ORSA infections. Its administration may worsen a pre-existing renal failure in patients with severe sepsis. Linezolid (Zyvoxid®, Pfizer, New York, NY, USA) is an alternative for the treatment of ORSA infections, especially in patients with renal impairment. It inhibits bacterial protein synthesis by binding to the 23S ribosomal subunit, thereby, hindering binding of mRNA to the ribosome. Linezolid has an acceptable safety profile. Except for gastrointestinal adverse events, other more serious adverse events, for example, thrombocytopenia and myelosuppression, were rarely reported. In terms of efficacy, linezolid showed efficacy equivalent to vancomycin in various patients [16,17]. Although several authors support the fact that linezolid may be a cost-effective alternative to vancomycin [18-20], its direct cost remains higher, and the evidence demonstrating its direct superiority are still lacking. The results of the Zephyr study (NCT00084266), which is an ongoing study comparing linezolid and vancomycin in patients with ventilator-associated pneumonia, should clarify this issue. Currently, linezolid should be probably preferred to vancomycin in patients with suspected or proven ORSA infection and renal impairment.
Other drugs were recently approved to treat infection due to ORSA. Ceftobiprole (Zeftera, Johnson & Johnson Pharmaceutical Research & Development, LLC) is the first of a new generation of extended spectrum cephalosporins with activity against Gram-positive cocci including ORSA, penicillin-resistant Streptococcus pneumoniae and Enterococcus faecalis. No activity was found against Enterococcus faecium. Ceftobiprole rapidly binds and forms a stable inhibitory acyl-enzyme complex with the penicillin-binding protein 2a, which provide activity against β-lactam resistant Gram-positive cocci [21]. It has also activity against Gram-negative bacilli including Citrobacter sp., Escherichia coli, Enterobacter sp., Klebsiella sp., and Serratia marcescens. Ceftobiprole is active against 69 and 45% of isolates of P. aeruginosa and A. baumannii, respectively [22]. It has no activity against Proteus vulgaris, extended spectrum β-lactamase producing pathogens and most anerobes [21]. Ceftaroline (Forest Laboratories, Inc., New York, NY, USA) is another broad spectrum cephalosporin with potent in vitro activity against MRSA [23]. In a Phase II study, this drug was as effective as standard therapy in treating skin and skin structure infections [24]. Its activity against S. pneurniae strains resistant to existing parenteral cephalosporins deserves further development [25,26].

Glycylcyclines are a novel class of antibiotics related to the tetracyclines. Tygcyclline (Tygacil®, Pfizer), which is the first commercially available agent of this class, has a bacteriostatic activity against a wide range of bacteria, including ORSA, vancomycin resistant enterococci, multi-drug resistant S. pneumoniae, extended spectrum β-lactamase producing pathogens and A. baumannii. Tigecycline is not active against Proteus, Providencia and Pseudomonas spp. [27].

One should note a new role for old antibiotics. Due to the emergence of infections due to multi-drug resistant Gram-negative bacilli, the systemic use of colistin was assessed in several recent studies. Clinically, colistin (3 millions IU (240 mg) every 8 h) and high dose ampicillin/sulbactam were comparably safe and effective treatments for critically ill patients with multi-drug resistant A. baumannii ventilator-associated pneumonia [28]. A clinical study assessed the steady-state serum concentrations of colistin after intravenous administration of 225 mg of colistin methanesulfonate every 8 or 12 h in critically ill patients. This dosage resulted in a suboptimal C\text{max}/MIC ratios for many strains of Gram-negative bacilli currently reported as sensitive [29]. An additive question is whether the administration of a loading dose may benefit critically ill patients [30]. Colistin was also used as nebulized drug in critically ill patients with pneumonia. In a series of five patients, nebulization of 1 million IU seemed efficient in four patients [31]. In these studies, no significant adverse events were reported, making its use in patients without renal dysfunction relatively safe.

In our opinion, the empiric use of new cephalosporin or tigecycline should not be recommended in patients at high risk of multi-drug resistant pathogen carriage. Their lack of efficacy against key pathogens makes their use unsafe in severe sepsis. Combination of antibiotics may represent an alternative way, but further research is needed in this area. Recent advances in the management of antimicrobial agents may probably result in a reduction of mortality in the septic patients. Table 1 briefly summarizes the characteristics of recent antibiotics.

4.1.2 Direct hemoperfusion using polymyxin B-immobilized fiber column

Direct hemoperfusion using a polymyxin B-immobilized fiber column was first developed in 1994. The rationale underlying extracorporeal therapy with direct hemoperfusion with polymyxin B-immobilized fiber column would be to remove circulating endotoxin by adsorption, thus, preventing progression of the biological cascade of sepsis. In Japan, >60,000 patients have received this treatment. In a critical review of the literature, this device seems to have favorable effects on the outcome of patients with severe sepsis [32]. These findings generate the need for a randomized clinical trial that was designed to determine whether polymyxin B hemoperfusion added to conventional medical therapy improves clinical outcomes and mortality compared with conventional therapy alone. Sixty-four patients with severe sepsis or septic shock from intra-abdominal Gram-negative infections were randomized to conventional therapy or conventional therapy plus two sessions of polymyxin B hemoperfusion. Early use of polymyxin B hemoperfusion was associated with improved hemodynamics and reduced 28-day mortality [33]. Although highly promising, these results need to be validated in other studies. This treatment should be preferentially effective against Gram-negative bacteria, as reported in intra-abdominal infections. Several adverse events are possible, especially the cartridge clotting. However, somewhere, the large use of polymyxin B hemoperfusion in Japan guarantees the feasibility and safety of this device.

4.1.3 Phospholipid emulsion

With the exception to antibiotics, most clinical trials assessing drugs directed against bacteria aimed to reduce mortality in patients with severe sepsis failed to demonstrate any benefit. The rationale for using most of these drugs relied on animal experiments showing an excessive pro-inflammation after administration of endotoxin. This model probably poorly reflected the condition of our critically ill patients [34]. The last Phase II multi-center, randomized, placebo-controlled clinical trial tested the efficacy of a phospholipids emulsion (GR270773) in Gram-negative severe sepsis. The treatment did not reduce 28-day all-cause mortality or reduce the onset of new organ failure [35]. Neutralizing endotoxin failed to improve the survival of patients with severe sepsis.

4.2 Non-antimicrobial therapy

Although critical, the present review does not consider issues related to pathogen or host variability, timing of treatments and sources of infection. However, one should note that most
recent advances have been done in these areas [36,37]. Many treatments are shown to be effective prior to the onset of sepsis, whereas very few are effective after the onset of sepsis [38]. Moreover, sepsis variability relating to infectious sources (urinary, lung, line sepsis), different pathogens (Gram-positive, Gram-negative, fungal) and host characteristics (e.g., genetic variability, nutrition) are likely to promote distinct sepsis phenotypes [39].

4.2.1 Monocytic HLA-DR role in sepsis

The exploration of monocytic human leukocyte antigen-DR (mHLA-DR) brings interesting evidence. Low levels of mHLA-DR surface expression are associated with immune cell dysfunctions in patients with sepsis [40]. In parallel, prolonged downregulation of mHLA-DR has been associated with reduced survival. GM-CSF can increase mHLA-DR expression and endotoxin-induced pro-inflammatory cytokine production in ex vivo whole blood cultures of patients with severe sepsis. A prospective, randomized, double-blind, placebo-controlled, multi-center trial was conducted in order to test the efficacy of GM-CSF to reverse sepsis-associated immunosuppression as assessed by restoration of mHLA-DR expression [41]. GM-CSF was injected subcutaneously at a dose of 4 g/kg/day for five consecutive days. GM-CSF or placebo was then continued for three additional days at either 8 or 4 g/kg/day depending on mHLA-DR quantification results. A rapid increase in mHLA-DR was observed in all patients in the GM-CSF group. Production of pro-inflammatory cytokines was more sustained in the patients treated with GM-CSF than in those treated with placebo, whereas IL-10 production tends to be reduced in this group. Time of mechanical ventilation, length of intensive care unit stay and length of hospital stay were all shorter in patients receiving GM-CSF. After the intervention, a significant decline of a specific severity score was observed in the GM-CSF group, but not in the placebo group compared with baseline. The mortality was similar in both groups but the study was not designed to explore this outcome (Table 2). However, a note of caution should be brought because, in a randomized clinical trial, G-CSF administered to non-neutropenic patients with septic shock did not improve outcomes [42]. A large randomized clinical trial is needed in order to explore the effect of GM-CSF administrated according to this study scheme on mortality of patients with sepsis.

4.2.2 Steroids

High dose steroids failed to show a benefit in severe sepsis. Annane et al. demonstrated that relative adrenal insufficiency was frequent in patients with septic shock. Then, a low hydrocortisone (50 mg every 6 h) or placebo were administered to patients with septic shock. This randomized, multi-center clinical trial showed that hydrocortisone administration was associated with a reduced mortality [43]. In a large randomized clinical trial, the CORTICUS study group failed to confirm these results (Table 3) [44]. Detractors stressed on several limitations of this trial: high rate of inappropriate antimicrobial therapy, failure to reach the enrolment target of 800 patients, low mortality rate in the control group, use of etomidate and late use of hydrocortisone administration. However, a large observational study using an adequate propensity score did not find a positive impact of low dose steroids for persistent hypotension despite fluid resuscitation and/or lactate > 36 mg/dl [5]. Ongoing studies will confirm whether or not low dose hydrocortisone should be used in severe sepsis.

4.2.3 Coagulation pathway

The coagulation pathway is based on the rational that patients with severe sepsis develop disseminated intravascular coagulation resulting in microvascular dysfunction and misuse of oxygen. In line with this concept, drotrecogin alfa (activated) (Xigris®, Lilly, Indianapolis, IN, USA) was tested in patients with severe sepsis. Drotrecogin alfa (activated) is an anticoagulant inhibiting factor V and VIII. It has also anti-inflammatory and anti-apoptotic properties and may thereby prevent organ tissue damage. The PROWESS (recombinant

---

Table 1. Recent antibiotics in sepsis.

<table>
<thead>
<tr>
<th>Class</th>
<th>International denomination</th>
<th>Market name</th>
<th>Target pathogens</th>
<th>Resistant pathogens</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem</td>
<td>Doripenem</td>
<td>Doribax®</td>
<td>GPC, GN, ESBL, PA</td>
<td>ORSA</td>
<td>[10-13]</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Invanz®</td>
<td></td>
<td>Fermenting GNB with ESBL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezold</td>
<td>Zyvoxid®</td>
<td>GPC, ORSA</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Extended spectrum</td>
<td>Ceftobiprole</td>
<td>Zeftera®</td>
<td>GPC, GNB, ORSA, PRSP</td>
<td></td>
<td>[16-20]</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Ceftaroline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>Tigecycline</td>
<td>Tygacryl®</td>
<td>GPC, GNB</td>
<td></td>
<td>[21-26]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESBL: Extended spectrum β-lactamases; GN: Gram-negative; GNB: Gram-negative bacilli; GPC: Gram-positive cocci; ORSA: Oxacillin-resistant Staphylococcus aureus; PA: Pseudomonas aeruginosa; PRSP: Penicillin-resistant Streptococcus pneumoniae.

---

44 Expert Opin. Emerging Drugs (2010) 15(1)
human activated protein C worldwide evaluation in severe sepsis trial demonstrated a 6.1 absolute decrease in mortality in patients with severe sepsis [45]. The drug was licensed by both the FDA and the European Medicines Evaluation Agency. However, use of drotrecogin alfa (activated) in patients with severe sepsis remains a hot topic, probably because the PROWESS trial was never confirmed in another trial. In contrast, several other trials testing drotrecogin alfa (activated) in patients with severe sepsis remains a hot topic, probably because the PROWESS trial was never confirmed in another trial. In parallel, animal models demonstrate that drotrecogin alfa (activated) increases survival in septic animals [48,49]. Cohort studies also showed that drotrecogin alfa (activated) improves hemodynamics [50,51] and increases survival (Table 3) [5]. However, as these studies have several limitations, new clinical trials are mandatory in order to confirm whether or not this drug should be used in patients with septic shock.

A randomized multi-center clinical trial entitled PROWESSshock (NCT00112164) should test the efficacy of drotrecogin alfa (activated) in patients with septic shock. In parallel, Annane et al. promote a study entitled APPROCHS (NCT00625209) which compares septic shock patients treated with hydrocortisone, drotrecogin alfa (activated), both of them, or double placebo. These two studies should allow concluding on the role of drotrecogin alfa (activated) in patients with severe sepsis. In parallel, research on anticoagulant use in sepsis is still fertile. The benefit of drotrecogin alfa (activated) was frequently assimilated to the positive effect of a low cost anticoagulant agent, that is, unfractioned heparin. Three hundred and nineteen patients were randomized to receive unfractioned heparin or placebo. The study was not able to show a beneficial effect of this treatment [52]. In animals, a novel inhibitor of activated thrombin-activatable fibrinolysis inhibitor (EF6265) has been tested with success [53]. Uses of enoxaparin and unfractioned heparin were compared in endotoxemic rats. Enoxaparin (Lovenox®, Aventis, Bridgewater, NJ, USA) seems to attenuate endothelial damage with less bleeding [54].

### 4.2.4 Non-antibiotic, non-immune drugs: the metabolic and cardiovascular systems

Several non-antibiotic drugs are under evaluation in sepsis. Most of these drugs are already on the market for cardiovascular indications. Statins, ACE inhibitors, angiotensin II receptor blockers (ARBs) and β-blockers have been suggested as effective drugs to improve the outcome of septic patients.

#### 4.2.4.1 Statins

Statins are a class of lipid-lowering drugs which inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase [55]. They have powerful anti-inflammatory effects that are independent of their lipid-lowering effect, through the blockade of mevalonate synthesis. The mevalonate pathway is an important cellular metabolic pathway present in all eukaryotes and several bacteria. It is critical for the production of dimethylallyl pyrophosphate and isopentenyl pyrophosphate, which serve as the basis for the biosynthesis of molecules used in processes as diverse as terpenoid synthesis, protein prenylation, cell membrane maintenance, hormones, protein anchoring and N-glycosylation. It is also part of steroid biosynthesis. Recent literature tends to show a beneficial effect of statins in sepsis [56]. Observational studies show that the patients who are admitted to hospital with infection and received statin therapy have a lower in-hospital mortality compared with patients who do not receive a statin [57-59]. The only randomized clinical trial was designed to determine the effect

---

**Table 2. Non-antibiotics drugs derived from cardiovascular therapeutic.**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Possible effects in sepsis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Blockade of mevalonate synthesis</td>
<td>Anti-inflammatory effect by reduction of pro-inflammatory cytokine production</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Inhibition of angiotensin synthesis</td>
<td>Block the endotoxin-induced inflammatory response</td>
</tr>
<tr>
<td>Sartan</td>
<td>Antagonism or inhibition of angiotensin II receptors</td>
<td>Mitogenic, apoptosis regulation, regulation of tissue neutrophil accumulation</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Blockade of β1-receptors, β2-receptors or both</td>
<td>Divergent according to receptors and studies Modulation of inflammatory cytokines</td>
</tr>
</tbody>
</table>

**Table 3. Existing non-antibiotic drugs in sepsis.**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Possible effects in sepsis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Treatment of relative adrenal insufficiency</td>
<td>Vascular reactivity improvement</td>
</tr>
<tr>
<td>Drotrecogin alfa (activated)</td>
<td>Inhibition of factor V and VIII</td>
<td>Anticoagulant, anti-inflammatory effect and anti-apoptotic effect</td>
</tr>
</tbody>
</table>
Emerging drugs in sepsis

of statin administration on cytokine production. Statins were associated with a reduction in the levels of inflammatory cytokines in patients with acute bacterial infections [60]. In brief, statins have an anti-inflammatory effect and the patients who take statins as drugs for cardiovascular reasons seem to have less severe outcome when they develop a sepsis than those who do not take this medication.

4.2.4.2 ACE inhibitors
ACE inhibitors are used to treat arterial hypertension, prevent albuminuria and treat left-ventricular dysfunction. They have the ability to inhibit degradation of specific neurotransmitters of the cough reflex. Because of this side effect, one may suggest that they can lower the risk of pneumonia in specific groups of patients, such as the elderly and patients with cerebrovascular injuries [61,62]. Their preventive effect was apparent in elderly users (0.24; 95% CI, 0.07 – 0.88) [62]. In a rat model of sepsis, an ACE inhibitor (enalapril) blocks the endotoxin-induced inflammatory response and protects against the acute lung injury associated with endotoxemia [63]. In a descriptive review, Rafailidis et al. concluded that ACE inhibitors may contribute to risk reduction of community-acquired pneumonia in debilitated patients with stroke [64]. However, as ACE gene polymorphism may impact on the susceptibility to sepsis [65], additional investigations are needed to determine the relevance of this medication (Table 2).

4.2.4.3 Renin-angiotensin-aldosterone system modulation
ARBs, also known as sartans, are a group of drugs that modulate the renin-angiotensin-aldosterone system. Their main use is in arterial hypertension, diabetic nephropathy and congestive heart failure. Blockade of angiotensin II receptors directly causes vasodilation, reduces secretion of vasopressin and reduces production of aldosterone [66]. Angiotensin II is mitogenic for lung cells and plays an important role in the fibroproliferative response to lung injury [67]. It is also known as regulators of apoptosis of alveolar epithelial cells and tissue neutrophil accumulation. Thus, ARBs have been shown to protect from lung injury induced by acid aspiration, sepsis or N-formylmethionyl leucyl-phenylalanine via a number of potential mechanisms [68]. In animal models, the ARBs can also protect against ventilator-induced lung injury [67]. Mice treated with ARBs after cecal ligation and puncture produced less pro-inflammatory cytokines, less severe lung injury and had better survival [69]. Of note, all these studies were conducted in animal models. The translation of these findings in humans deserves a note of caution, although ARB use was associated with decreased mortality in patients with severe sepsis (Table 2) [70].

4.2.4.4 β-Blocker
β-Blocker is a class of drugs used in a wide variety of diseases. Cardiac arrhythmias, cardioprotection after acute coronary syndrome and hypertension are common well-known indications. Most immune cells express β2-receptors on their surface. Catecholamines control expression of cytokines, neutrophil function and immune cell migration [71]. Peripheral β1-receptor blockade commenced 6 h after lethal endotoxia or fecal peritonitis did not improve survival of rats with severe sepsis. In contrast, if commenced before a septic insult, peripheral β1-receptor blockade offers anti-inflammatory effects with mortality reduction [72]. In parallel, non-selective inhibition of the β-adrenergic effects of catecholamines exacerbates the sepsis-induced increase of selected inflammatory cytokines [73]. At the renal level, blockade of the β2-receptor before lipopolysaccharide injection is associated with an exaggerated pro-inflammatory response. This can not only clear invading pathogens but also inflict damage to host tissues and result in acute renal failure [74]. In contrast, a surgical model shows that β2-receptor blockade reduces macrophage cytokine production and improves survival [75]. Of note, the β2-receptor was blocked before the septic insult. There are a lot of contradictions among all these results. This underlines the challenge to translate animal research results to clinical practice. In humans, only two retrospective studies explored the effects of β-blockers on sepsis outcome. The conclusions driven from these studies are very limited (Table 2) [76,77]. Because β-blockers are vasodilating agents and may have negative inotrope effects, their use in patients with severe sepsis should not be indicated before their positive effects be confirmed in relevant experimental studies.

5. Current research goals
Among the current research goals, two pathways seem attractive. HMGB1 is a ubiquitous nuclear protein released by activated macrophages and monocytes. It functions as a late mediator of lethal endotoxemia and sepsis. Several properties make this mediator a potential therapeutic target. As recombinant HMGB1 isolated from bacterial cultures is commonly contaminated by bacterial lipids, this explains early reports showing the induction of systemic inflammation following HMGB1 treatments [78]. Early studies showing that anti-HMGB1 administration improves sepsis outcomes have not been confirmed [79]. However, HMGB1 seems to enhance immune responses when administered in combination with other pro-inflammatory agents and is shown to be a chemotaxin for various immune cells. Reducing the secretion of HMGB1 is one of the therapeutic effects of ghrelin [80,81], which has also a potent antibacterial activity in septic mice [81]. Such treatment may have a place in septic patients in future years.

Adenosine, a pure nucleoside, may participate in the hemodynamic disturbances of critical illness. Adenosine is a strong vasodilating agent whose concentrations are high in patients with septic shock [82]. Adenosine can activate four subtypes of receptors: A1, A2A, A2B and A3. Inactivation of A1 and A3...
receptors increases mortality in murine models of sepsis induced by cecal ligation and puncture [83,84]. The modulation of adenosine receptors can affect the survival of septic animals. Several ways are possible because of the multiplicity of receptors.

Oxygen delivery may not be the unique mechanism of organ failure during sepsis. Impaired energy production appears to be a core mechanism underlying the development of organ dysfunction [85]. This led to the concept of ‘cytopathic injury’ [86], describing a fundamental change in the function of parenchymal and inflammatory cells during sepsis [87]. In this regard, there are several promising therapies that are developed elsewhere (MitoQ [88], Poly(ADP-ribose) polymerase inhibitors [89], anti-oxidants [90], selenium [91]).

6. Scientific rationale

In the last decades, severe sepsis was regarded as a model of pro-inflammation. Thus, immune treatment was aimed at reducing the inflammatory response by acting on specific mediators. This approach remained unsuccessful despite several clinical trials which were strongly supported by industrials [92]. In parallel, the concept of immunosuppression progressively emerged [93]. As highlighted elsewhere [93], immune system of septic patients is unable to respond to a second challenge of endotoxin. This state of non-responsiveness is designed by the term ‘anergy’ [94]. As reported by Hotchkiss and Karl, autopsy studies in people who died of sepsis disclosed a profound, progressive, apoptosis-induced loss of cells of the adaptive immune system [93]. Recent clinical findings tend to confirm the rationale of this approach [95,96]. This implies that restoring the immune response should be a priority in sepsis.

7. Competitive environment

Using Pharmaprojects search, five Phase III and II current clinical trials were identified in the field of sepsis (Table 4). A brief description of each drug is reported thereafter. Pyridoxylated hemoglobin polyoxymethylene (VTR-PHP), named stabilized hemoglobin, Ajin, is a human stroma-free hemoglobin modified with pyridoxal-5'-phosphate and polyoxymethylene. It is an NO scavenger. An ongoing Phase III clinical trial should include 450 patients with catecholamine-resistant distributive shock for up to 150 h. The primary end point is 28-day all-cause mortality. Eritoran tetrasodium, a structural analogue of the lipid A portion of endotoxin, is aimed at antagonizing the toll-like receptor 4. In a Phase II clinical trial, this treatment appeared well tolerated. There was an observed trend toward a lower mortality rate at the 105 mg dose in subjects with severe sepsis and high predicted risk of mortality [97]. This should be confirmed in a pivotal randomized, double-blind, placebo-controlled Phase III trial which expects to enroll 2000 adult patients with severe sepsis, with end points of survival at day 28.

Talactoferrin alfa is a recombinant human protein with immunostimulatory and anti-inflammatory properties. A randomized double-blind placebo-controlled Phase II trial in 190 patients with at least one organ dysfunction due to sepsis should assess the effect of drotrecogin alfa and talactoferrin alfa on 28-day all-cause mortality. CytoFab is a polyclonal anti-TNF antibody fragment [98]. AstraZeneca is planning to initiate a Phase IIb trial in 300 patients with severe sepsis in early 2010. A second Phase II trial with CytoFab should be conducted in 480 severe sepsis patients. WCK-771A is a broad spectrum intravenous fluoroquinolone antibacterial with activity against both Gram-positive and-negative pathogens, including ORSA and vancomycin/glycopeptide intermediate S. aureus, under development by Wockhardt as a treatment for sepsis. A Phase II clinical trial is ongoing.

8. Potential development issues

A note of caution should be brought to findings based on clinical observations. In order to improve the understanding of this finding, we recommend the reading of the review recently published by Leibovici [99]. Briefly, positive results have more chance to be sent for publication and published than negative results. No large randomized clinical trials are available to confirm the findings of several small non-interventional studies. In addition, observational studies may be biased for unknown reasons, despite an apparent adequate method. A few common problems in performing and interpreting a logistic regression analysis are the sample size, the candidate-independent variables and the analysis of interactions. A simple example may highlight this limitation. In septic shock, from 2006, the timing of antibiotic administration appears one of the major determinants of survival. In the past years, this variable was not systematically introduced in the analysis of retrospective database. Then, the patient with a good medical follow-up will take adequately his or her cardiovascular treatment, including statin, ACE, ARB or β-blocker. If this patient develops a septic episode, he or she will be probably treated with antibiotics earlier than the non-compliant patient who has no regular medical follow-up.

On the other hand, animal models have also several limitations. As developed elsewhere, they poorly reflect human diseases [34]. The genetic background is similar among laboratory animals, which is not the case for humans. In addition, methodological issues may explain some discrepancies. For example, anti-mediators are frequently administered between the infection occurs [34]. That was probably why modulation of these mediators was effective in animal models and failed in humans.

Hence, animal models should be improved in order to mimic clinical conditions. After completion of animal experimentation, only repeated randomized clinical trials may confirm the validity of a treatment before translating research into clinical practice.
Table 4. Drugs in Phase II and III clinical trial for sepsis.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxylated hemoglobin</td>
<td>Ajinomoto (originator)</td>
<td>Human stroma-free hemoglobin modified with pyridoxal-5'-phosphate and polyoxyethylene</td>
<td>Shock, distributive</td>
<td>Phase III clinical trial</td>
<td>NO scavenger</td>
</tr>
<tr>
<td>polyoxyethylene</td>
<td>Curacey (licensor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stabilized hemoglobin, Ajin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eritoran tetrasodium</td>
<td>Eisai (originator)</td>
<td>Structural analogue of the lipid A portion of endotoxin</td>
<td>Septic shock</td>
<td>Phase III clinical trial</td>
<td>Toll-like receptor 4 antagonist</td>
</tr>
<tr>
<td>Talactoferrin alfa</td>
<td>Agenrix (originator)</td>
<td>Recombinant human protein</td>
<td>Severe septic shock</td>
<td>Phase II development in sepsis</td>
<td>Upregulates IL-18 production, shifts immune response from TH2 to TH1</td>
</tr>
<tr>
<td></td>
<td>Santen (licensor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CytoFab, anti-TNF Ab, Protherics</td>
<td>BTG (originator)</td>
<td>Polyclonal anti-TNF antibody fragment</td>
<td>Severe sepsis</td>
<td>Phase II clinical trial</td>
<td>Blockade of TNF action</td>
</tr>
<tr>
<td></td>
<td>AstraZeneca (licensor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCK-771A</td>
<td>Wockhardt (originator)</td>
<td>Broad spectrum intravenous fluoroquinolone</td>
<td>Septic shock</td>
<td>Phase II clinical trial</td>
<td>DNA topoisomerase ATP hydrolyzing inhibitor</td>
</tr>
<tr>
<td>Alkaline phosphatase, AM-Pharma</td>
<td>AM-Pharma (originator)</td>
<td>Highly purified, therapeutic-grade bovine alkaline phosphatase</td>
<td>Sepsis</td>
<td>Phase II clinical trial</td>
<td>Alkaline phosphatase stimulant</td>
</tr>
</tbody>
</table>

According to Pharmaprojects (http://www.pjbpubs.com/pharmaprojects/).
9. Conclusion

Within the recent period, the most relevant advances in the field of sepsis are related to global strategy elaboration. Small advances have been made in the field of drugs. New licensed antibiotics will probably offer the opportunity to clinicians to refine their treatment choice. However, the last progresses are due to the definitions of new strategies based upon an early use of broad spectrum antibiotics followed by a rapid de-escalation. Among non-antibiotic drugs, the modulation of HLA-DR seems promising but deserves in-depth investigations. Regarding the role for cardiovascular drugs, randomized clinical trials are needed in order to eliminate confounding factors and to determine whether these drugs are active when administered after the septic insult. Alternative ways, such as the regulation of HMGB1 or adenosine, should not be discarded.

10. Expert opinion

Sepsis generates a lot of research. Several therapeutic approaches have been suggested in the literature within the last period. First, behavior in front of a septic patient probably changed with strong guidelines for starting without delay aggressive treatments including antibiotics. New antibiotics may find a place in this strategy, but only therapeutic niches are available. No real advances have been done regarding adjuvant therapies in sepsis. Both hydrocortisone and drotrecogin alfa (activated) remain a matter of debate with confirmatory ongoing studies. However, the beneficial impact of anticoagulants in sepsis seems to be widely accepted. Extracorporeal epuration of endotoxin may represent a promising treatment. Several ongoing studies should conclude in a short period whether or not cardiovascular drugs such as statins, ACE, ARBs and β-blockers are useful in sepsis.

The anti-inflammatory treatments, neutralizing pro-inflammatory cytokines, failed to improve the outcome of patients with sepsis. This leads to the emergence of the concept of immunosuppression in sepsis. To date, this way to apprehend the septic patient was not clearly translated in clinical practice, but promising results can be awaited. The use of GM-CSF already provided good results in a small cohort of patients. The adjuvant treatment, in the future, should aim at stimulating the immune response. Acting on late, ubiquitous or global mediators (such as HMGB1 and adenosine) may be an efficient practice.

The best treatment may depend on the patient immune status. This status should be monitored by transcriptional approach in order to provide an individual based therapy. Such an approach will make possible providing a selected drug to each individual. Models should be based on the current use of antibiotics with rapid diagnosis techniques.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography


Emerging drugs in sepsis

randomized, double-blind study of febrile neutropenic patients with cancer.
Clin Infect Dis 2006;42:597-607


73. Lang CH, Nystrom G, Frost RA. Beta-adrenergic blockade exacerbates sepsis-induced changes in tumor necrosis factor alpha and interleukin-6 in skeletal muscle and is associated with impaired translation initiation. J Trauma 2008;64:477-86


Emerging drugs in sepsis


88. Supinski GS, Murphy MP, Callahan LA. MitoQ administration prevents endotoxin-induced cardiac dysfunction. Am J Physiol Regul Integr Comp Physiol 2009;297:R1095-102


Affiliation
Marc Leone1 MD PhD, Julien Textoris2 MD, Fabrice Michel3 MD, Sandrine Wiramus2 MD & Claude Martin3 MD

1Author for correspondence
2Assistant Professor in Anaesthesiology and Critical care medicine, Service d’anesthésie et de réanimation, Hôpital Nord, Assistance Publique – Hôpitaux de Marseille, Université de la Méditerranée, Chemin des Bourrely, 13915 Marseille Cedex 20, France Tel: +33491968650; Fax: +33491962818; E-mail: marc.leone@ap-hm.fr
3Fellow in Anaesthesiology and Critical care medicine, Service d’anesthésie et de réanimation, Hôpital Nord, Assistance Publique – Hôpitaux de Marseille, Université de la Méditerranée, Marseille, France

3Professor of Anaesthesiology and Critical care medicine, Service d’anesthésie et de réanimation, Hôpital Nord, Assistance Publique – Hôpitaux de Marseille, Université de la Méditerranée, Marseille, France

For personal use only.