Current management of Gram-negative septic shock

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Purpose of review
Sepsis is a common condition in critically ill patients and associated with high morbidity and mortality. Sepsis is the result of infection by many potential pathogens, including Gram-negative bacteria. There are no specific antisepsis therapies and management relies largely on infection control and organ support, including hemodynamic stabilization. We discuss these key aspects and briefly mention potential immunomodulatory strategies.

Recent findings
New aspects of sepsis management include the realization that early treatment is important and that fluids and vasopressor agents should be administered simultaneously to insure rapid restoration of an adequate perfusion pressure to limit development and worsening of organ dysfunction. New immunomodulatory therapies, both suppressive and stimulatory, are being tested.

Summary
Early diagnosis enabling rapid treatment can optimize outcomes. The multiple components of adequate sepsis management necessitate a team approach.

Keywords
fluid administration, immunomodulation, infection, organ dysfunction

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Patients with persisting hypotension requiring vasopressors to maintain mean arterial pressure more than 65 mmHg and a serum lactate level more than 2 mmol/l (18 mg/dl) despite adequate volume resuscitation are said to have septic shock [1]. Sepsis is largely caused by bacteria, but can also be the result of infection with other microorganisms including fungi, viruses, and parasites. Among the bacterial causes, Gram-negative and Gram-positive bacteria occur with similar frequency overall [2]. The most frequently isolated Gram-negative organisms in patients with sepsis are *Escherichia coli*, *Klebsiella* spp., *Enterobacter*, and *Pseudomonas* spp. [2].

The treatment of septic shock occurring as a result of Gram-negative organisms is currently not very different from the treatment of septic shock because of other organisms. There are some differences in initial microorganism recognition and signaling by pathogen-recognition receptors according to bacterial species and the precise patterns of mediator release and activation may vary depending on the invading pathogen [3]. However, there is considerable crosstalk and receptor collaboration [4,5] and these pathways ultimately converge leading to the same effects on cellular and organ function [6,7]. In the past, attempts were made to separate the hemodynamic presentation of sepsis ('warm' or 'cold' shock states) according to the type of microorganism [8], but with improved understanding of the similar pathophysiological events regardless of causative microorganism, this approach has now been abandoned. Several studies have shown no differences in mortality rates according to bacterial class [9]. Indeed, outcomes are influenced by multiple other factors including appropriateness of initial antibiotics, antimicrobial sensitivity and virulence,

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KEY POINTS

- In terms of management, there is no clear distinction between Gram negative and other causes of sepsis.
- Early and appropriate antibiotics are key, as well as effective source control.
- All patients need fluid, and evaluation of the presence or degree of edema provides no useful information regarding fluid requirements.
- In terms of vasoactive agents, norepinephrine is the vasopressor of choice. Routine use of vasopressin may be dangerous and the place of angiotensin II is not yet clear. Dobutamine possibly has a place to increase cardiac output.
- Moderate doses of hydrocortisone should be considered in severe forms.

source of infection, severity of illness, and patient age and comorbidities [10–12].

The management of septic shock includes three major components, as shown in Fig. 1. Importantly, infection control and hemodynamic support need to be performed promptly and together. In a classical experimental study in a model of peritonitis, Natanson *et al*. [13] showed that no animals survived with no treatment, 13% survived when treated with antibiotics or with cardiovascular stabilization, and when antibiotics and cardiovascular stabilization were combined, survival reached 43%.

INFECTION CONTROL

Antibiotic therapy must be both appropriate, in terms of effectiveness against the causative microorganism(s), and adequate, in terms of dose and duration. Results from microbiological cultures, which should be taken prior to starting antibiotics whenever possible, without delaying antibiotic administration, still take several days to become available. Broad-spectrum empiric therapy is thus indicated in the majority of patients to insure that all likely microorganisms are covered. When deciding which empiric antibiotic(s) to use, various factors should be taken into account, including the most likely focus of infection, knowledge of local microbiological flora and resistance patterns, any recent or ongoing antimicrobial therapy, the immune status and the origin of the patient (nursing home, other hospital, home), and disease severity. Specific antimicrobial choices, dosing, and duration of treatment for Gram-negative sepsis have been covered in other manuscripts in this issue.

The need for early antibiotic administration is particularly important in septic shock. This logical statement is supported by epidemiological data. For example, in a large series of 18 000 patients included in the Surviving Sepsis Campaign database [14], mortality increased from about 25% when antibiotics were administered within 1 h to about 33% when they were administered more than 6 h after recognition of the sepsis syndrome. Admittedly, this may not seem to be a large difference and other factors, including difficulty recognizing sepsis in some patients with atypical presentation and/or comorbidities, may complicate the picture, but the effect is clinically relevant and appropriate antibiotics should be administered as soon as possible after diagnosis.

Source control, when necessary, must also be accomplished rapidly. Source control is a heterogeneous problem because it can range from relatively simple catheter removal to more complex percutaneous drainage for an intra-abdominal abscess. It is, therefore, difficult to specify a time limit that could

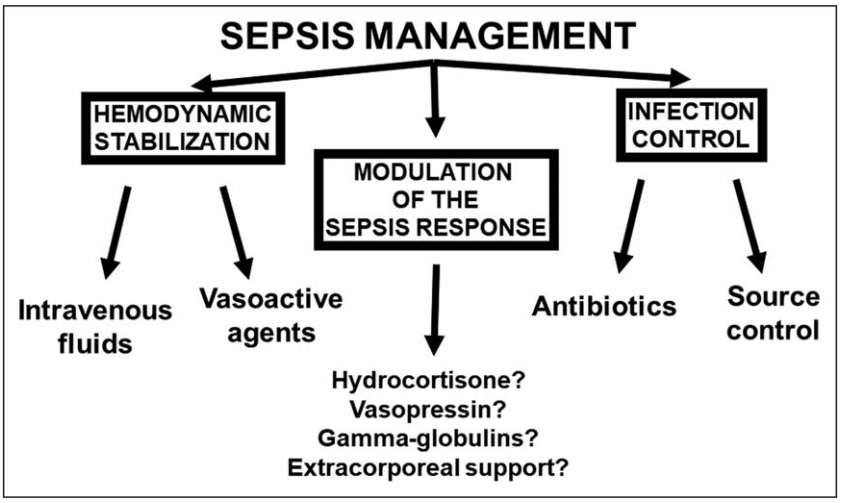

FIGURE 1. The three components of sepsis management.

apply to every patient and situation, but care needs to be taken to insure that time is not lost waiting for source control interventions; for example, if surgery is needed for an acute abdomen, the procedure should be performed without delay. Importantly, although trying to find a source of infection is of paramount importance because it can influence management, one should recognize that in roughly 20–25% of cases, no source will be identified.

HEMODYNAMIC SUPPORT

Resuscitation for patients with septic shock requires both fluid and vasopressor agents. The overall resuscitation period will follow four phases that can be summarized by the letters SOSD [15]:

(1) Salvage – this is a short phase during which fluids and vasopressor agents are administered with little monitoring, the aim being to keep the patient alive and minimize deterioration in organ function. It is difficult to give fluids by formula, because individual requirements vary substantially from one patient to the other. Therefore, monitoring equipment should be placed as soon as possible.
(2) Optimization – during this phase, fluid administration rates are adjusted according to the results obtained from various monitoring techniques and clinical evaluation.
(3) Stabilization – fluid administration rates are maintained to insure patient stability, but fluid boluses are no longer necessary and doses of vasoactive agents kept constant.
(4) De-escalation – fluid administration is limited to allow for elimination of edema fluid and vasopressor agents are decreased.

The duration of each of the four phases can vary substantially from one case to another, but recognizing these phases can help to identify the priorities in patient management.

Fluids

Fluids are always required, not only to correct true hypovolemia because of poor intake and increased internal (edema) and external losses, but also to compensate for the vasodilation associated with the sepsis process and help to achieve the hyperkinetic (high cardiac output) state required in sepsis. Hence, the fundamental reason for fluid administration is to improve tissue perfusion by increasing cardiac output, and the risk is that excess fluids will increase cardiac filling pressures, with increased edema formation.

Physicians must consider these two aspects when prescribing fluids and arrange for the two components, that is, cardiac output or an index of tissue perfusion and a cardiac filling pressure, usually the central venous pressure, to be monitored. When the benefit/risk ratio becomes too low, that is, when cardiac output increases proportionately less than filling pressures, fluid administration should be stopped. The fluid challenge technique should include only small amounts of fluids given over a 10-min period, to avoid the risks of fluid overload [16]. Similarly, fluid administration should be stopped when the immediate risk of poor tissue perfusion seems to be substantially attenuated. This strategy is also applied in children and neonates [17]. One should avoid giving large amounts of fluids over a relatively long period of time because if the patient does not respond, too much fluid will have been given with the associated risks of fluid overload and no benefit.

During the optimization phase, attempts to assess likely fluid responsiveness can be tried before any fluid administration is given. One option is the assessment of pulse pressure variation or stroke volume variation in patients who do not stimulate the respirator, but this is a relatively rare condition, limiting the usefulness of this approach. A passive leg raising maneuver can also be considered, but this technique is more complex than it appears, as it requires careful and continuous assessment of stroke volume during the test. Hence, the fluid challenge is still the preferred method to assess ongoing fluid needs and enable the benefits of fluid infusion to be maximized (increase cardiac output) while minimizing the risks (edema formation). Unfortunately, just assessing the degree of edema does not help evaluate fluid requirements and the term 'fluid overload' can be misleading [18].

Crystalloids are considered as the initial fluid of choice, although albumin can have a place early in patients who are already edematous in a context of hypoalbuminemia (patients with decompensated cirrhosis represent a typical example), and later if the patient has already received large amounts of crystalloids. Saline solution can be selected initially in the absence of severe acidosis, but chloride levels must be monitored [19] because hyperchloremia can have deleterious effects, most notably on the kidneys. Otherwise, balanced solutions (Ringer's lactate or Plasmalyte R) represent the best option.

Vasoactive agents

Norepinephrine is the vasopressor of choice; dopamine should no longer be used in this setting [20]. Epinephrine is also best avoided because it is more

likely to induce arrhythmias, can reduce splanchnic blood flow, and may increase blood lactate levels as a result of increased cellular metabolism. The place of angiotensin II is not yet well defined, but it may be of value in patients with renal failure [21▪] or in acute respiratory distress syndrome (in which angiotensin II levels may decrease and become inadequate) [22].

In patients who poorly tolerate fluids, administration of dobutamine may be considered to increase cardiac output; small doses are usually sufficient. A low central venous oxygen saturation value can be a useful trigger for administration of dobutamine or for a blood transfusion if the hemoglobin concentration is decreased.

MODULATION OF THE HOST RESPONSE

As experimental studies first began to elucidate the mechanisms underlying the inflammatory response to infection, multiple molecules involved in initiating or propagating the response have become potential targets for therapeutic intervention. Yet, although many agents have reached clinical trials, none has so far been persistently shown to have beneficial effects on patient outcomes.

Glucocorticoids

Recent results have shed new light on the ongoing debate regarding corticosteroid use in sepsis. In the presence of severe septic shock, administration of moderate doses of hydrocortisone (200 mg/day) should be considered [23▪▪] until shock is resolved, because relative adrenal insufficiency may develop.

Vasopressin

Vasopressin should not be considered as just another vasopressor agent, but as a form of hormonal support, because vasopressin stores may be decreased in septic shock. However, the exact place for vasopressin administration in patients with sepsis is hard to define. Vasopressin derivatives may perhaps decrease edema formation [24] but carry the risk of inducing severe vasoconstriction and decreasing blood flow to the cutaneous, splanchnic, and coronary regions. If vasopressin is used, it should be administered in small doses of about 0.03 U/min without titration, and only in hyperkinetic states demonstrated by the presence of high cardiac output.

Gamma globulins

Although there is no place for routine administration of gamma globulins in patients with sepsis, a recent clinical trial suggested a benefit of an IgM-enriched mixture in patients with severe community-acquired pneumonia who had low IgM levels and significant inflammatory response [25▪].

Extracorporeal removal of toxins

One cannot discard the role of endotoxin in the pathophysiology of Gram-negative sepsis, but anti-endotoxin strategies have not been particularly effective. Moreover, endotoxin is not released only in Gram-negative infections; indeed, measuring endotoxin levels is not very helpful to distinguish Gram-negative from Gram-positive infections [26]. Nevertheless, given the role of endotoxin and other mediators in sepsis pathophysiology, there is a sound rationale behind a potential beneficial effect of extracorporeal techniques to remove these compounds, including hemofiltration, hemoadsorption, and coupled plasma filtration adsorption. However, although appealing, the effectiveness of this approach is difficult to demonstrate. Many studies have reported some hemodynamic improvement, but questions remain regarding the optimal device, timing, duration, and frequency of treatment [27], as well as how to insure that only excess harmful compounds are removed. The use of polymyxin-based hemoperfusion to remove endotoxin has not been shown to be successful and is not currently recommended [28▪].

Immunostimulation

Although attempts to modulate the immune response in sepsis have largely focused on immunosuppressive therapies, more recently the potential importance of immunostimulatory approaches has been increasingly raised, with the recognition that patients with sepsis also develop immunosuppression. Importantly, the immune status of patients with sepsis varies among patients and in the same patient during the course of their disease. Some promising immunostimulatory strategies include interferon-gamma, granulocyte–macrophage colony stimulating factor, interleukin-7, and anti-programmed cell death protein 1 antibodies [29].

Pharmaconutrition

The use of pharmaconutrition – the supplementation of feeds with various macronutrients (e.g., glutamine, arginine, and fish oil) and micronutrients (e.g., selenium, vitamin C, vitamin E) – to improve outcomes has generated considerable interest in patients with sepsis. However, clinical trials have failed to consistently demonstrate any positive

effects of the different supplements on outcomes and there is no evidence to support the routine use of macronutrient supplements in patients with sepsis [30,31]. Supplementation with vitamins or selenium should not be provided except in certain cases of malnutrition resulting in deficient levels. In patients with septic shock, nutrition can be withheld completely [32].

CONCLUSION

The management of septic shock is challenging, but good and appropriate treatment can make a clear difference in complication rates and survival. The likely outcome can be influenced by many factors including the pathogenicity of the infecting bacteria, the speed of diagnosis, and various host factors, including immune status and comorbidities. Hence, treatment should be individualized and guided by repeated clinical and laboratory review. Importantly, septic shock is always associated with increased blood lactate levels, and blood lactate levels should be measured serially (typically every hour) to be sure they are decreasing with time, which indicates that the resuscitation process is effective. If lactate levels do not decrease then the diagnosis and/or ongoing treatment should be reexamined. As the treatment of septic shock involves multiple diverse interventions all of which need to be performed rapidly without delay, a team approach should be used, not only during working hours but 24 h a day.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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