Sepsis: Clinical Approach, Evidence-Based at the Bedside 25

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Introduction

Sepsis is a common disease in intensive care medicine representing almost one third of patient admissions. Its incidence has substantially increased over the past decades and overall mortality has declined during this period of time. It was reported that sepsis incidence increased from 82.7 to 240.4 per 100,000 population between 1979–2000. At the same time, sepsis global mortality decreased from 27.8 to 17.9% [1–3]. However, the absolute number of deaths significantly increased from 21.9 to 43.9 per 100,000 population. Male gender, some chronic diseases like diabetes, immunosuppressive states, human immunodeficiency virus infections, and malignancies are factors that increase the risk for sepsis. Some particular conditions like progressive number of organ dysfunctions, in-hospital-acquired infections and increasing age are associated with higher risk of death [1,4]. On the other hand, septic shock mortality only diminished from 61.6 to 53.1% [5]. This slight decline in mortality observed during recent decades could be attributable to improvements in supportive care and/or avoidance of iatrogenic complications. For example, the instrumentation of early goal resuscitation protocols not aiming at supranormal targets for cardiac output and oxygen delivery, and the use of lung protective strategies could explain at least in part this favorable change. Other strategies directed to treat the pathophysiological mechanisms involved in the septic process like recombinant human-activated protein-C (rhAPC), have also contributed to improve survival. However, mortality remains unacceptably high and further improvement in sepsis management is needed. Novel therapeutic approaches are under investigation and will probably be incorporated in the clinical practice in the near future.

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Since 2002 the Surviving Sepsis Campaign was introduced with the initial goal of increasing clinicians' awareness about severe sepsis mortality and to improve outcome in this patient population. It was pursued to generate a change in the standard of care that could finally result in a significant mortality reduction. A consensus committee from several international organizations was created and evidence-based guidelines were elaborated [6]. Despite the fact that most of these recommendations were not supported by high levels of evidence, they represented the international consensus on the best available standards of care for the management of sepsis. These guidelines were recently updated and continue to be the core of the Surviving Sepsis Campaign [7]. The clinical practice needs clear and concise recommendations based on the best available level of evidence.

Definitions

Sepsis is defined as the host response to infection. In other terms, it is the clinical syndrome that results from the inflammatory response to infection. In the clinical setting, sepsis is diagnosed when an evident or suspected infection courses with a systemic response called the systemic inflammatory response syndrome (SIRS). According to the 1991 North American Consensus Conference, SIRS was defined by the presence of at least two of the following signs: body temperature >38ºC or <36ºC, heart rate >90 beats/min, respiratory rate >20 breaths/min (or $PaCO_2$ <30 torr), and/or white blood cells count >12,000 or <3,000/mm^3 [8]. However, these signs are too sensitive and nonspecific for sepsis and could occur in many other different situations not related to infection. In an attempt to better reflect the systemic response to infection, the clinical manifestations described by Bone et al. were expanded by the 2001 Consensus Conference [9]. Other possible signs, symptoms, and laboratory findings were summarized (Table 25.1). Again, most of them are also nonspecific for sepsis. It is well known that infection and sepsis are sometimes difficult to confirm.

In an attempt to improve diagnostic capabilities, some biological markers were developed. Procalcitonin (PCT) and C-reactive protein (C-RP) have been proposed but it is considered that there is still no ideal biological marker for sepsis diagnosis [10,11]. None of the mentioned biomarkers are absolutely specific, meaning that diagnosis or prognosis cannot be made solely on this basis.

An infection probability score (IPS) was also proposed to be calculated from several variables: body temperature, heart rate, respiratory rate, white blood cells count, C-reactive protein, and sequential organ failure assessment score (SOFA). The potential role of such an index was recently evaluated [12].

Some concepts and definitions remained unchanged after the last consensus conferences and should be emphasized. The following terms are widely accepted.

Infection is the pathologic process caused by the invasion of normally sterile tissues, fluids, or cavities by pathogenic microorganisms.

Sepsis is the clinical syndrome defined by the presence of infection and a systemic inflammatory response syndrome.

Table 25.1 Clinical manifestations of sepsis

General signs and symptoms
    Fever or hypothermia
    Tachypnea/respiratory alkalosis
    Tissue edema (positive fluid balance)

Generalized hematological/inflammatory reactions
    White blood cells increased (sometimes leukopenia)
    Increased inflammatory biological markers:
        Plasma C-reactive protein greater than 2 SD above normal.
        Plasma procalcitonin greater than 2 SD above normal

Hemodynamic and metabolic alterations
    Arterial hypotension
    Tachycardia
    Increased cardiac output
    Low systemic vascular resistances
    High S_vO_2 >70%
    Cardiac index >3.5 L/min/m^2
    Decreased skin perfusion
    Decreased urine output
    Increased lactatemia >2 mmol/L
    Decreased capillary refill
    Decreased base deficit

Multiple organ dysfunction
    Acute lung injury
    Altered mental status
    Acute renal Injury.
    Hyperglycemia in the absence of diabetes
    Thrombocytopenia (<100,000/μL)/disseminated intravascular coagulation
    Liver dysfunction. Hyperbilirubinemia >4 mg/dL
    Ileus. Intolerance to feeding

Severe sepsis relates to the presence of sepsis and one or more related organ dysfunctions.

Septic shock should be diagnosed when severe sepsis courses with acute circulatory failure. Cardiovascular compromise becomes evident when arterial hypotension remains after adequate fluid infusion or there is need for vasopressor therapy. Systemic hypotension is defined when arterial systolic pressure remains <90 mm Hg, mean arterial pressure <60 mm Hg, or there is a decrease in blood pressure >40 mm Hg from previous values.

Pathophysiology of Sepsis

Different processes could occur during severe sepsis and septic shock at the same time. Hypovolemia, maldistribution of blood flow within or between organs, vasoreg-

ulatory-perfusion abnormalities, peripheral microcirculatory failure, and myocardial dysfunction are major hemodynamic disturbances observed during sepsis. Hemodynamic parameters could course with normal or decreased mean arterial pressure while cardiac output may vary from low to higher than normal. The hemodynamic values change in response to volume replacement and the severity of myocardial dysfunction. Systemic tissue hypoxia occurs when cardiovascular failure and low cardiac output dominates the clinical presentation. The presence of low mean arterial and central venous pressures, and decreased central venous oxygen saturation when confirmed, should cause immediate therapeutic interventions. Efforts should be made to correct systemic hemodynamic abnormalities in order to avoid the development of global tissue hypoxia.

However, cytokine release from the inflammatory reaction or prolonged tissue hypoxia is followed by severe microcirculatory abnormalities that become a central protagonist of organ dysfunction/failure [13]. The main significance of microvascular dysfunction has been studied during sepsis and major changes like decrease of both capillary density and microvascular blood flow were documented in vivo by video microscopy [14]. Thus, peripheral gas exchange becomes impaired and tissue dysoxia ensues. These abnormalities also occur despite normal or even supranormal hemodynamic variables. In terms of peripheral oxygen metabolism, severe heterogeneity of oxygen distribution within the tissues is characteristic during septic shock. Under- and overperfuse areas coexist within the same tissue resulting in an inhomogeneous tissue oxygen partial pressure distribution (P_tO_2). In these conditions, metabolic demands are not met by microvascular oxygen delivery, making peripheral shunting and tissue dysoxia the cause of organ failure.

However, metabolic abnormalities also occur at the cellular level. Mitochondria dysfunction is secondary to oxidative and nitrative stress initiated by the inflammatory reaction. Energetic failure develops and less high energy compounds are available for cellular function. This situation was referred to as cytopathic hypoxia and leads to multiple organ failure and death. Mitochondria dysfunction and decreased ATP production was documented during the course of sepsis in experimental and clinical situations. Efforts should be made to preserve mitochondrial functioning and improve the cellular energetic state [15–17].

Diagnosis and Clinical Evaluation

Early and accurate recognition of the signs and symptoms of sepsis is mandatory after patient admission. Risk factors like age, gender, race, immunocompromised states, presence of invasive instrumentation maneuvers, or any other condition that could represent a via for bacterial colonization. Clinical presentation and laboratory findings are essential. Fever is the hallmark of infection, but hypothermia is also possible in some patients. Other nonspecific signs like tachycardia, tachypnea, and hypotension should also be documented. When looking for the source of infection a careful physical examination should be complemented with x-rays images, CT scans,

ultrasound, etc. Finally, it is necessary to investigate the presence and severity of organ dysfunction. In the vast majority of the cases this information is easily collected and diagnosis becomes straightforward. However, this is not always the case. It is important to realize that the septic patient is always at risk of death and some clinical signs may be indicative of disease severity. Clinical demonstration of acute respiratory and/or circulatory failure, or any other organ dysfunction are indicative of the aggressive host response to the septic insult [8,9].

Since organ failure is an integral part of severe sepsis, a brief summary of major organ dysfunctions will follow.

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

Pulmonary or extrapulmonary ALI is present in about 60–70% of severe sepsis. It is defined by pulmonary infiltrates in the chest x-ray and the absence of left ventricular failure (pulmonary wedge pressure <18 mm Hg). Pulmonary gas exchange is impaired showing a PaO_2/FIO_2 ratio under 300 for ALI or below 200 for ARDS. Most of the time, the severity of ALI/ARDS determines mechanical ventilation. While mechanical ventilation will restore pulmonary gas exchange and decrease systemic metabolic demands, detrimental effects should be avoided by a rational application of protective ventilatory strategies.

Central Nervous System Dysfunction, Septic Encephalopathy

When the focus of infection is located outside the central nervous system (CNS), the neurologic compromise could be attributable to septic encephalopathy. Some other conditions may add secondary effects such as hypoxemia, metabolic and electrolytical disorders, and cerebral hypoperfusion during shock states. Symptoms may vary from agitation, confusion, delirium, and coma. No focal neurologic deficits are present but myoclonias and seizures are possible [18]. Severe CNS derangement requires airway protection and ventilatory support.

Liver Dysfunction

Liver dysfunction is characterized by some degree of hepatomegalia and total bilirubin plasma levels >2 mg/dL. Higher conjugate bilirubin concentration is characteristic and increased gamma glutamil transferase is frequently observed. Moderate levels of aminotransferases generally <200 UI can also be found.

Coagulation and Hematologic Disorders

Decreased red blood cells without bleeding evidence and platelets <100,000/mm^3 are frequent findings. Coagulation cascade has been widely studied. Sepsis enhances

coagulation and impairs fibrinolysis. Endogenous-activated protein C that prevents microvascular thrombosis is decreased during sepsis. When small and medium microvessels become occluded, the disrupted microcirculation generates tissue dysoxia. Given the context of severe sepsis, rhAPC could contribute to ameliorate coagulation disorders [19].

Acute Renal Injury

Renal dysfunction could course with normal or decreased urine output. Increase in creatinine level >0.3 mg/dL from previous values or a percentage increase >50%, or a reduction in urine output (oliguria <0.5 ml/kg/h for more than 6 h) defines acute renal injury and is associated with poor outcome.

Hemodynamic Failure, Septic Shock

Arterial hypotension unresponsive to volume expansion defines septic shock. Variable degrees of hemodynamic dysfunction may vary from hypodynamic to hyperdynamic shock. Mortality increases according to the presence of shock, and metabolic markers like arterial lactate are useful to characterize disease severity and the response to treatment [8]. Despite the fact that lactate concentration depends on the balance between tissue production and metabolism, a plasma level >4 mmol/L should be considered as indicative of circulatory failure.

Gastrointestinal Tract

Some other organ compromise could also be part of the multiple organ dysfunction syndrome. Splanchnic ischemia and intramucosal acidosis ensue early during the course of sepsis. Clinical expression includes changes in smooth muscle function like ileum or diarrhea. Gastrointestinal bleeding because of stress ulcer or acute gastritis may also be a manifestation of sepsis. Gastric intramucosal pH monitoring was used to identify and guide resuscitation therapy. Increased levels of intraluminal pCO_2 are associated with tissue ischemia and mucosal acidosis.

Neuromuscular Dysfunction

Skeletal muscles are also affected by inflammatory mediators and reactive oxygen species. There is simultaneous decrease in protein synthesis and proteolysis. In conjunction, these factors explain decreased muscular force. Respiratory muscles are involved and respiratory pump failure may aggravate or precipitate an acute respiratory failure.

Multiple organ dysfunction is part of the severe sepsis syndrome. Poor prognosis

is related to increased number of organ failures. Technical resources for the management of organ dysfunction have improved in recent years and consume a substantial part of the therapeutic effort. Most of the described dysfunctions are reversible as long as the infectious disease becomes controlled. However, the additive effects of the different failures may initiate a series of independent processes that may aggravate the patient status and be the cause of death. Prognostic scores are helpful to predict mortality and some organ failure scores were proposed to evaluate severity and to follow the evolution of septic patients. The Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA) are frequently used for this purpose [20,21].

To identify the source of infection and the microbial agent is crucial during sepsis. Microbiological investigation is mandatory and adequate antibiotic therapy must be initiated as early as possible [7]. Most of the time the diagnosis results from a correct anamnesis and clinical examination. Suspicion of sepsis must be followed by complete bacteriological cultures, taking samples from blood and other possible foci of infection. Some other special exams should not be deferred and may add complementary information. Positive blood cultures are only confirmed in about 50% of the cases [22]. No bacterial etiology is identified in 20–30% of septic patients. Almost 45% of the initial antibiotic selection should be changed or adjusted after blood cultures are informed. Decreased mortality is related to prompt bacteriological identification [23]. Despite the fact that infection is generally caused by bacterial agents, virus and fungal agents are possible, especially in immunocompromised patients. Epidemiological data coming from each ICU or hospital could be helpful when hospital-acquired infections are under study. Infection is a frequent complication in polytrauma and in the critically ill patient who was subject to invasive procedures. Increased life expectancy and special situations like organ transplant create further opportunities for microbial invasion and sepsis development.

As mentioned before, biochemical markers of infection could be helpful in particular situations where diagnosis is not straightforward. Procalcitonin (PCT), C-Reactive Protein (CRP), and some interleukins like Interleukin-6 (Il-6) have been proposed to contribute to diagnosis. However, further evidence is needed before these biomarkers are incorporated in the clinical practice. Actually, some authors have considered PCT as a good indicator for severe sepsis and septic shock [24,25]. Research on new biomarkers continues with the aim of early detection of patients at risk of severe sepsis [26].

Evidence-Based Clinical Management of Severe Sepsis

The current management of severe sepsis and septic shock aims to control infection, achieve hemodynamic stabilization, modulate the immune response, and provide metabolic and organ support. Evidence-based medicine has become the cornerstone of medical practice but it is difficult to apply in patients with sepsis. The SSC is a global initiative that involves several international organizations with the common

objective of elaborating evidence-based guidelines and recommendations for the management of severe sepsis and septic shock. Lack of high-level evidence coming from large RCT is a severe limitation in sepsis. To accomplish these goals, experts determined that improving patient care was a possible task and could lead to a significant decrease in mortality. Despite the fact that only a few of the Guidelines were supported by high levels of evidence, it was agreed that they represent the best available evidence for the management of the septic patient. During the last consensus conference a grade system was agreed upon by the participants. Guidelines were classified from A to D based on the levels of evidence; however, at the same time a strong or weak recommendation was introduced by the panel of experts [7]. The International Guidelines of the Surviving Sepsis Campaign will be briefly discussed below.

Initial Resuscitation

This group of measurements should be accomplished within the first 6 h of patient admission. This could probably happen in the emergency department before ICU admission. Early identification and comprehensive resuscitation of septic patients will have a significant impact on outcome. The first 6 "golden hours" constitute a critical opportunity for the patient [27,28]. Resuscitation should be started immediately when hypotension or elevated serum lactate (>4 mmol/L) are detected and treatment should not be delayed until ICU admission. Initial resuscitation not only includes hemodynamic stabilization but also simultaneous administration of empiric antimicrobial drugs and actions directed toward the control of infection [7].

Hemodynamic Resuscitation

Early resuscitation is initially based on aggressive volume expansion. It could be administered via a peripheral vascular access while a central venous line and central venous pressure (CVP) measurement are instrumented somewhat later within the initial hours. When fluid therapy does not restore arterial blood pressure or lactate remains elevated, administration of vasopressors becomes mandatory. The resuscitation goals are based on easily obtainable physiologic variables. Treatment targets CVP pressures between 8 and 12 mm Hg, mean arterial pressure ≥65 mm Hg, urine output ≥0.5 mL/kg/h, and superior cava vein oxygen saturation ≥70% or mixed venous oxygen saturation ≥65% [7,29].

Fluid Therapy

No difference between crystalloids and colloids fluid was demonstrated [30]. However, it is mentioned that resuscitation with crystalloids is less expensive but

requires more fluid to achieve the same end points and may result in more edema formation. Fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 min are recommended, but larger volumes or infusion rates could be required [7].

Vasopressors

When resuscitation goals are not rapidly achieved vasopressor therapy must be started. There is no high-quality primary evidence to recommend norepinephrine over dopamine. However, norepinephrine could be more effective in reversing hypotension in patients with septic shock. The selected vasopressor, either norepinephrine or dopamine, should be titrated until MAP ≥65 mm Hg. Epinephrine is another alternative vasoactive agent when blood pressure is poorly responsive to norepinephrine or dopamine. Low-dose dopamine should not be used for renal protection [31]. In patients requiring vasopressors, an arterial catheter and continuous arterial pressure monitoring must be instrumented.

Inotropic Therapy and Packed Red Blood Cells

If central venous oxygen saturation remains <70% further fluid infusion and/or packed red blood cells transfusion should be considered. Hematocrit ≥30% is desirable to assure systemic oxygen delivery. Increase in cardiac index by the effect of dobutamine infusion to a maximum 20 μg/kg/min is recommended. Dobutamine is the first line inotrope for patients with measured or suspected low cardiac output and adequate or high left ventricular filling pressures. A combination of inotropes/vasopressors, such as norepinephrine and dobutamine, is recommended if cardiac output is not directly measured [7].

Antibiotic Therapy

Antibiotics should be administered during the first hour of the initial resuscitation. The time taken to initiate effective antimicrobial therapy is one of the strongest predictors of outcome in septic shock [32]. Initial antimicrobial selection should be wide enough to cover likely pathogens. There is evidence that failure to initiate appropriate antimicrobial therapy within this period of time correlates with increased mortality [33].

Source Identification and Control

Source control includes an appropriate diagnosis of the specific site of infection within the first 6 h. Surgical procedures aimed at abscess draining, debridement of

infected necrotic tissue, or removal of potentially infected devices should be instrumented without delay [7]. These practices are believed to be important for infection control but no randomized trials support them [34].

Maintenance Therapy

Most of the measurements initiated in the previous stage will continue during the following hours. At the same time, some other therapeutic interventions could be started earlier, during the initial resuscitation phase.

Steroids

Two big trials of patients with vasopressor-unresponsive septic shock showed a significant and faster resolution of shock when steroid therapy was associated [35,36]. Thus, low-dose intravenous hydrocortisone (≤300 mg/day) should be considered for adult septic patients when hypotension is poorly responsive to fluid resuscitation and vasopressors. On the other hand, an adrenocorticotrophic hormone (ACTH) stimulation test is not recommended. Steroid therapy must be weaned once vasopressors are no longer required [7].

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

The importance of lung-protective strategies for patients with ALI/ARDS is supported by clinical trials and has been widely accepted [37]. Low tidal volume (6 mL/kg) and upper limit plateau pressure ≤30 cm H_2O are desirable in patients with ALI/ARDS. This respiratory pattern may result in $PaCO_2$ increase above normal or permissive hypercapnia. A prone position should be considered when potentially injurious levels of FIO_2 or plateau pressure cannot be controlled. Titration of positive end expiratory pressure (PEEP) should be made according to bedside measurements in an attempt to reach optimal levels of respiratory system compliance [7].

Glucose Control

Several randomized, observational clinical trials showed reductions in ICU mortality when intensive insulin therapy was utilized [38,39]. A large randomized trial recently showed that intense glucose control increased mortality. These authors found that a blood glucose target <180 mg/dL resulted in lower mortality than a target between 81 to 108 mg/dL. Higher episodes of hypoglycemia were reported in the tight glucose control group [40]. Based on this report, intense insulin therapy is questionable. However, the SSC recommendation is to maintain blood glucose levels below 150 mg/dL [7].

Recombinant Human-Activated Protein C (rhAPC)

Recent studies reported nonsignificant mortality reduction after rhAPC administration in patients with a low risk of death or in the pediatric population. Furthermore, rhAPC administration is associated with increased risk of bleeding. The evidence concerning rhAPC use in adults is primarily based on two RCTs: the PROWESS and the ADDRESS (stopped early for futility) [41,42]. Additional information comes from an open-label observational study, the ENHANCE that suggested that early administration of rhAPC was associated with better outcomes [43]. As a result, the latest recommendation of the SSC is to consider rhAPC only for adult patients at high risk of death (APACHE II ≥25 or multiple organ failure). During patient selection, possible contraindications for rhAPC administration should be discharged.

Blood Product Administration

Red blood cell transfusion should be administered when haemoglobin decreases below 7.0 g/dL. A hemoglobin target between 7.0 to 9.0 g/dL in adult septic patients is recommended. Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding evidence or planned invasive procedures. Administer platelet concentrates when platelet counts are $<5,000/mm^3$ regardless of bleeding. Platelet counts between 5,000 to $30,000/mm^3$ do not call for platelet administration unless there is a significant risk of bleeding [7].

Other Measures

- Sedation and analgesia in sepsis. It is recommended to use sedation protocols with daily interruption/lightening to produce awakening [7].
- Renal replacement therapy. Current evidence is insufficient to draw strong conclusions regarding the best replacement therapy method for ARI in septic patients [44,45]. It is not clear whether high doses of renal replacement may influence patient outcome [46]. Intermittent hemodialysis and continuous veno-venous hemodiafiltration (CVVH) are considered equivalent for septic patients. However, CVVH and sustained low-efficiency dialysis will probably offer a safer and easier management in hemodynamically unstable patients.
- Bicarbonate therapy. Sodium bicarbonate infusion must not be used for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with a pH ≥7.15 [7].
- Deep vein thrombosis prophylaxis. Use either low-dose unfractioned heparin (UFH) or low-molecular weight heparin (LMWH), unless contraindicated. Use a mechanical prophylactic device when heparin is contraindicated [7].
- Stress ulcer prophylaxis. Stress ulcer prophylaxis based on H2 blockers or proton pump inhibitors could be used for septic patients [7].
- Nutritional support. It is very important to initiate early nutritional support in

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critically ill patients. Enteral nutrition is generally safer and more effective than total parenteral nutrition. Immunonutrition needs to be further studied before clear recommendations can be made.

As mentioned before, these guidelines were based on the best available evidence. Ongoing and future studies will provide further valuable information and changes in these recommendations will become necessary. The use of these guidelines is not easy in clinical practice. It was an objective of the SSC to facilitate the instrumentation of these recommendations [47]. In the last phase of the SSC the concept of sepsis bundles was introduced. This idea aimed to create a series of simple recommendations easily applicable as packages of measurements for the clinical setting [48]. Conceptually, a bundle is a group of interventions that when implemented together will result in better outcomes. The bundles were developed in conjunction with the Institutes for Health Care Improvement (IHCI). Different tools were created to assist clinicians at the bedside. These clinical tools and databases are available on the SSC web page. Treatment of severe sepsis can be organized into two groups of interventions known as the initial resuscitation bundle (initial 6 h) and the management bundle (24 h bundle) [49]. Table 25.2 summarizes this particular approach. Some recent works have studied bundles compliance and new favorable results on outcomes are coming. It has been shown that bundles compliance is associated with a reduction in ICU mortality and length of stay [50,51].

Table 25.2 Sepsis bundles

Sepsis resuscitation bundle (initial 6 h)
　　1. Serum lactate measured
　　2. Blood cultures obtained before antibiotic administration
　　3. Broad spectrum antibiotics administered within 3 h for ED or 1 h for ICU admission
　　4. If hypotension and/or lactate >4 mmol/L
　　　　Deliver minimum of 20 mL/kg crystalloid or colloid equivalent
　　　　Apply vasopressors for hypotension not responding to fluid resuscitation
　　5. If persistent hypotension and/or lactate >4 mmol/L
　　　　Achieve central venous pressure >8 mm Hg
　　　　Achieve central venous oxygen saturation >70%

Sepsis management bundle (24 h bundle)
　　1. Low dose steroids in septic shock
　　2. Drotrecogin alfa activated administered in accordance with ICU policy
　　3. Glucose control <150 mg/dL
　　4. Inspiratory plateau pressures <30 cm H_2O in mechanically ventilated patients

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