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Special Article

Management of Septic Shock: Current Concepts

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Abstract Despite the availability of potent antibiotics and a myriad of investigational agents directed against inflammatory mediators, septic shock has remained the most common cause of mortality in the intensive care unit. However, substantial progress has been made in our understanding of the pathophysiology, clinical staging, diagnosis and risk assessment of sepsis and septic shock. Currently, early goal-directed resuscitation and monitoring for haemodynamic support, prompt diagnosis, and effective control of the source of infection has remained the mainstay of management. In this article, the current concepts of the pathophysiology, clinical staging and empirical choice of antibiotics in sepsis and septic shock are briefly reviewed, and the rationale and indications for the use of activated protein C, replacement doses of corticosteroids, and other investigational immunotherapies in severe sepsis and septic shock are discussed.

Key words Sepsis; Shock

Introduction

Sepsis and septic shock continues to be a principal cause of death in Intensive Care Units (ICU) worldwide. In the United States alone, the Center for Disease Control estimated that >250,000 deaths annually were attributed to sepsis.[1] Despite great strides and technological advances in the supportive care of critically ill patients, the mortality rate from septic shock has remained unacceptably high at ~50%.[2] This review will focus on optimizing the management of severe sepsis and septic shock based on current concepts of pathophysiology, and evidence of improved survival from prospective, placebo-controlled, double-blind and randomized clinical trials.

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Defining and Staging Sepsis vs. Categorization of Infection

Early studies of sepsis suffered from imprecision in definition. The terms *sepsis, sepsis syndrome, septicemia, bacteremia,* and *septic shock* were almost used interchangeably. This led to difficulties in interpretation and comparison of epidemiologic and treatment studies. As it became apparent that the host response mediated by a wide gamut of endogenous inflammatory cytokines was as much a contributor to mortality as microbial virulence, the need to achieve a more uniform and meaningful definition of sepsis was apparent. This was achieved in 1992 by the publication of a consensus statement on definitions for the sepsis syndromes by the American College of Chest Physicians and the Society of Critical Care Medicine.[3] The main objective of these definitions was to help characterize the various stages of the associated inflammatory response and to differentiate infectious from non-infectious processes. The terms *septicemia* and *sepsis syndrome* were abandoned,

whereas a new entity, the *Systemic Inflammatory Response Syndrome* (SIRS), was created to highlight the host response to various insults, including infection. Sepsis, severe sepsis and septic shock were conceptualized to define a continuum of physiologic decline towards multiple organ dysfunction and increasing mortality (Table 1).

The Consensus Conference also emphasized the important contribution of the multiple organ dysfunction syndrome (MODS) to mortality in sepsis, but failed to arrive at a specific definition. Nevertheless, it recommended the development of scoring systems to assess the severity of illness and relative risks of patients. SIRS itself provided a crude stratification system, as mortality significantly increased in those with SIRS compared to those without,[3] and progressively rose in those who fulfilled more criteria.[4] More sophisticated systems for stratification of severity of illness have been developed, mainly for use in research settings. To-date, the Acute Physiology and Chronic Health Evaluation (APACHE II) score is the best validated system and remains widely adopted in clinical trials.[2]

Although adoption of a more uniform criteria for sepsis in the last decade has clearly facilitated enrolment of patients in recent therapeutic trials, there has been increasing controversy over the usefulness of these definitions for the septic syndromes. This is in part because of concerns that these broad definitions cannot provide accurate estimates of mortality which may range widely from 30% to 60% in this highly heterogeneous population of patients with sepsis.[5,6] For example, Brun-Buisson et al[7] noted that only three of four patients presenting with clinically suspected severe sepsis had documented infection. However, patients with clinically suspected sepsis but without microbiologic documentation and patients with documented infection share common risk factors and are at similarly high risk of death. Thus, it has been suggested that the broad and relatively non-specific definitions of septic syndromes could partly be responsible for the failure to demonstrate significant improvement in clinical trials of immunomodulatory therapies in severe sepsis and septic shock.[8-10] More restrictive criteria for the definition of sepsis have been sought, including the use of C-reactive protein and procalcitonin, that may allow more accurate diagnosis of sepsis and prediction of mortality.[11-13] Since the prognosis of septic syndromes is related to underlying diseases and co-morbidities as well as the severity of the inflammatory response and its sequelae, reflected in shock and organ dysfunction, the severity of illness score as well as acute organ failures and the characteristics of underlying diseases should be accounted for in any stratification of patients for therapeutic trials and outcome analysis.

A recent international multicentre cohort study from Europe, Canada and Israel sought to further clarify the epidemiology and outcome of infection and sepsis occurring in adult ICU patients.[5] Approximately one-half of 8,353 consecutive patients in the ICU with length of stay >24 h had evidence of infection, either already infected at the time of admission (32%) or acquired following admission (19%). Thus, infection in ICU patients can be readily categorized into 3 groups: a) community-acquired infections; b) hospital-acquired infections before being transferred to the ICU; and c) ICU-acquired infections. Among these infected patients, 18% were without SIRS, 28% were associated with sepsis, 24% with severe sepsis, and 30% with septic shock. Although inflammatory

Table 1 Classification of sepsis, severe sepsis and septic shock

Clinical staging	Diagnostic criteria
Sepsis	Clinical evidence suggestive of infection plus:
	Signs of SIRS (≥2 of the following):
	Tachypnea: >20 breaths/min or $PaCO_2$ <32 mmHg (<4.3 kPa)
	Tachycardia: >90 beats/min
	Hyperthermia or hypothermia: >38°C or <36°C
	WBC >12,000 cells/mm^3, or <4,000 cells/mm^3, or >10% immature (band) forms
Severe sepsis	Sepsis with hypotension*, organ dysfunction and perfusion abnormalities such as:
	Oliguria: <0.5 mL/kg for at least 1 h in patients with urinary catheters
	↑ plasma lactate (>normal upper limit).
	Altered mental status
Septic shock	Severe sepsis as defined above despite adequate fluid resuscitation.
	Note. Patients who are on pressor agents may not be hypotensive

** <90 mm Hg or a 40 mm Hg decrease below baseline in the absence of other causes*

response to infection was present in almost 80% of infected patients, the hierarchy of primary sources of infection differed with both the origin (i.e. community- or hospital-acquired) and the time of infection (i.e. at admission or during ICU stay). Furthermore, crude mortality rates differed significantly among these groups, ranging from 12% in non-infected patients, to 22% in those with community-acquired infections, and 36-44% in those with hospital or ICU acquired infections. In contrast, when stratified according to the origin and timing of infection, mortality rates among patients with or without SIRS and with or without septic shock only differed among patients with community-acquired infection, but not in patients with ICU-acquired infection who were already infected at the time of admission. These data support the concept that identifying specific infections in the ICU setting is important, not just sepsis and sepsis-related conditions, a classification which eliminated about one-fifth of infections. However, until our knowledge of the precise pathophysiologic mechanisms of sepsis is more complete, not everyone agrees with the need for change in the definitions of septic syndromes at the present time.[14]

Sepsis as a Dynamic Model of Immune Hyperreactivity and Hypercoagulability

Intricate communication among all elements of the immune system is required for a timely, coordinated and appropriate response to microbial infection. Cytokines, characterized by redundancy (the same function shared by multiple cytokines) and pleiotropy (multiple functions carried by a cytokine), occupy a central role in this communication, allowing an almost infinitely adjustable milieu in accordance with the unique features of different organisms. However, this immune reactivity may overshoot and injure the host to an extent out of proportion to the actual damage by microbial invasion. SIRS followed by shock and multiple organ dysfunction may ensue.

Early studies focusing on endotoxins in gram-negative sepsis identified the prominent role of tumor necrosis factor (TNF) in the pathogenesis of septic shock. Secreted in the blood stream, TNF acts as an endocrine factor in synergy with other cytokines, notably IL-1, IL-6, and IL-8, to produce hypotension, lung injury and other organ dysfunction. Important secondary mediators in this chain of events include nitric oxide, platelet activating factor, complement, bradykinin, and products of arachidonic acid metabolism.[15] Based on these findings, numerous clinical trials have been undertaken in the past 15 years to evaluate various anticytokine and other anti-inflammatory treatment strategies in patients with severe sepsis or septic shock.[16] Unfortunately, none of these therapies have proven to be efficacious in reducing overall mortality. These trials have been predicated on the hypothesis that the systemic inflammatory response is similar for both gram-negative and gram-positive pathogens, and that blockade of the critical mediators of sepsis would provide a survival advantage for the patient regardless of the nature of the causative organism. However, it has become increasingly clear that a multitude of variables may interact to determine the responsiveness to anti-inflammatory agents in sepsis, and that the pathophysiologic mechanisms in gram-positive sepsis may be fundamentally different from those in gram-negative sepsis.[17] Furthermore, the immune response to sepsis is a dynamic process and may vary in the same patient over time.[18] Thus, it is the balance between the pro- and anti-inflammatory aspects of the immune response that may ultimately determine the outcome of an immunomodulatory treatment.[16]

Although disseminated intravascular coagulation (DIC) is common in septic shock, it was only realized recently that activation of the coagulation cascade is also important in the pathogenesis and progression of sepsis. In fact, the inflammatory and coagulant pathways reinforce each other in septic shock.[19] Endotoxins and certain cytokines activate the extrinsic coagulation pathway through the expression of tissue factors by monocytes and endothelial cells. Thrombin is generated, which in turn stimulates multiple inflammatory pathways as well as plasminogen-activator inhibitor 1 (PAI-1) and thrombin-activable fibrinolysis inhibitor (TAFI).[20] This results in suppression of the endogenous fibrinolytic system. Three other homeostatic mechanisms which normally regulate the coagulation system are also rapidly down-regulated or depleted during sepsis, including antithrombin, tissue factor pathway inhibitor, and the protein C pathway.[19] One product of widespread coagulation is d-dimers. In patients with sepsis, it can be demonstrated that d-dimers correlate with levels of several pro-inflammatory cytokines including TNF, IL-6, and IL-8, and that both the accumulation of d-dimers and depletion of protein C predict mortality.[21,22] Thus, the pro-coagulant and pro-inflammatory states are intertwined, and there are several synergistic pathways by which these mechanisms can initiate and perpetuate organ injury in patients with sepsis.

As these mechanisms of sepsis become better elucidated, there is increasing hope that additional options may become

available for the treatment of sepsis. Indeed, Bernard et al[23] recently reported the results of a large clinical trial in which recombinant human activated protein C significantly reduced mortality in patients with severe sepsis. Protein C inhibits Factors Va and VIIIa of the coagulation pathway, augments fibrinolysis by neutralizing PAI-1, and reduces the production of inflammatory cytokines by monocytes. Other trials with agents designed to inhibit coagulation and inflammation, such as recombinant tissue factor pathway inhibitor, are currently under way.[24] Notwithstanding these exciting new developments, the institution of early goal-directed resuscitation and monitoring for haemodynamic support, rapid diagnosis, appropriate choice of empirical antibiotics, and effective control of the source of infection have remained the gold standard of management for septic shock. Activated protein C and corticosteroids should also be considered in certain subsets of patients in light of the promising results from several recent randomized, double-blind, placebo-controlled clinical trials. A practical algorithm for the management of severe sepsis and septic shock based on these current concepts is presented below.

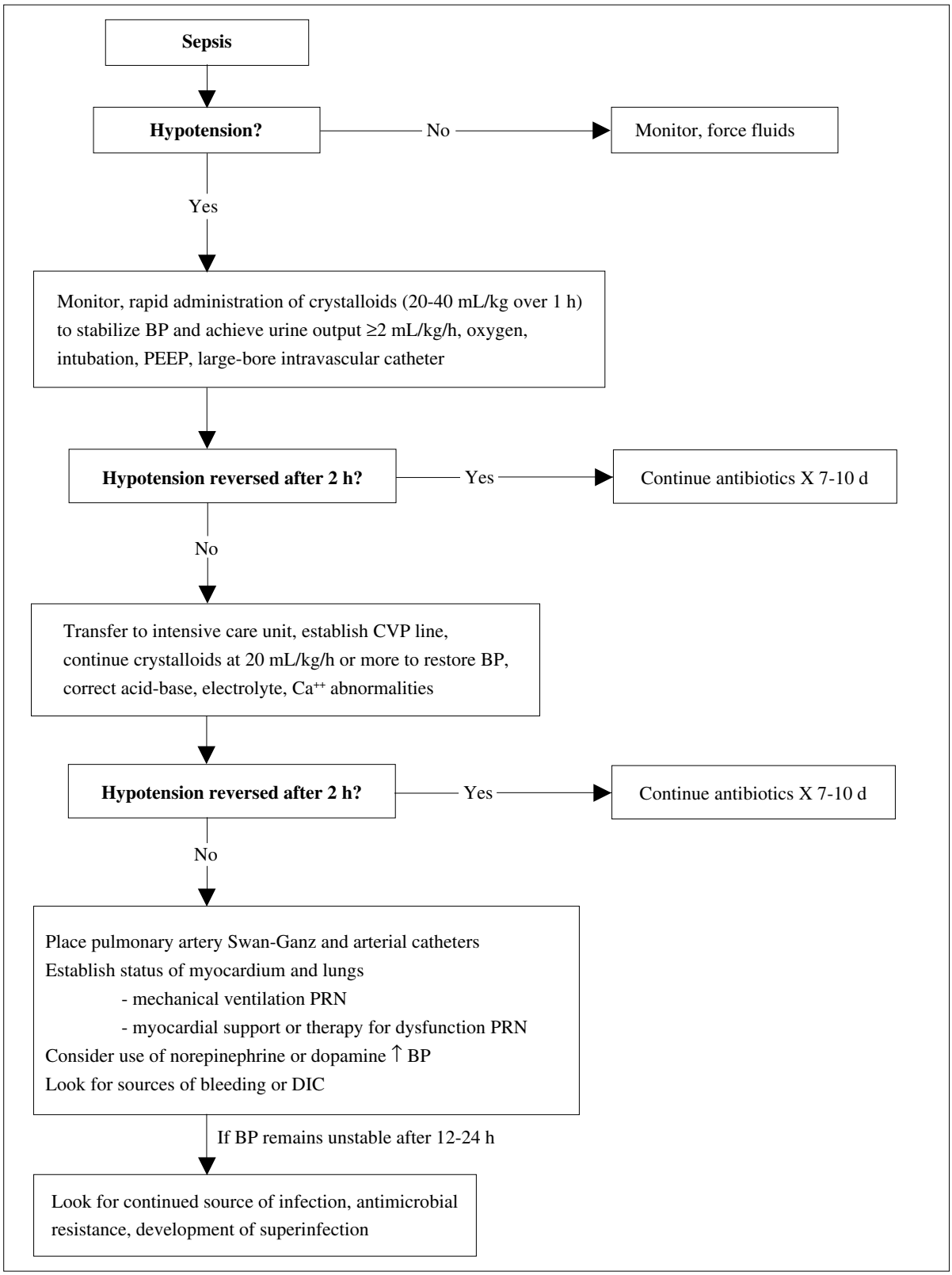
Early Goal-Directed Resuscitation and Monitoring

It is essential to meticulously monitor the patient's circulating volume and ventilatory status, with immediate resuscitation if required. If simple measures do not quickly restore hemodynamic stability, intensive care should be instituted early with invasive hemodynamic monitoring and aggressive cardiovascular support (Figure 1).[25,26] Early institution of mechanical ventilation and sedation and the judicious use of muscle relaxants or neuromuscular blockade may also help to reduce oxygen demand and improve oxygen delivery and extraction at the tissue level.[27] Unlike other varieties of shock, septic shock is characterized by a normal or increased cardiac output. Systemic vascular resistance is reduced while the mixed venous oxygen saturation (SvO_2) may be increased, indicative of maldistribution of blood flow. Initial resuscitation with fluid colloid or crystalloid may be sufficient in severe sepsis by increasing cardiac preload. In septic shock, inotropic or vasopressor support is invariably required. Dopamine (5-20 μg/kg/min) is the traditional first-line agent. Mainly at the expense of increased heart rate, it increases the cardiac index. The dose is usually titrated to maintain a systolic blood pressure at ≥90 mm Hg. Contrary to earlier opinion, the so-called 'low-dose' dopamine regimen does not preserve renal function despite apparent benefit shown in animals and healthy volunteers. This might be due to the marked variability and reduced clearance of dopamine in critically ill patients, and the unpredictability of plasma dopamine levels based on the infusion rate.[28] In a randomized, placebo-controlled trial of 328 patients in the ICU, dopamine at 2 μg/kg/min neither reduced the serum creatinine nor the likelihood of renal replacement therapy.[29] Duration of ICU and hospital stay, and overall mortality were not different between the dopamine- and placebo-treated groups either. Norepinephrine (0.03-1.5 μg/kg/min) has peripheral vasoconstricting activity and may be superior to dopamine in septic shock by increasing peripheral resistance and improving splanchnic perfusion.[30,31] Phenylephrine (2-10 μg/kg/min) also has potent vasoconstricting properties and increases the mean arterial pressure. Its relative lack of chronotropy makes it useful in patients with tachy-arrhythmias. Dobutamine (2-25 μg/kg/min) is inotropic but does not effectively increase blood pressure. It should be reserved for patients with a persistently low cardiac index or underlying left ventricular dysfunction. When added to norepinephrine, it may improve splanchnic blood flow.[32] The value of targeting the cardiac index by maximizing oxygen delivery to supranormal levels remains controversial as studies to-date have yielded conflicting results.[33,34]

Recently, Rivers et al[35] demonstrated convincingly in a randomized controlled trial that early goal-directed therapy in providing haemodynamic support before admission to the ICU can significantly reduce in-hospital mortality compared to patients assigned to standard therapy (30.5% vs. 46.5%; $p<0.01$). This survival benefit from early goal-directed therapy appears to be primarily due to prevention of sudden cardiovascular collapse which was significantly higher in the standard therapy group than in the early therapy group ($p=0.02$). Apart from a reduction of mortality, early goal-directed therapy was also associated with a shorter duration of hospital stay (mean±SD, 14.6±14.5 vs. 18.4± 15.0 days; $p=0.04$) and less consumption of health care resources. The haemodynamic end-points targeted for early therapy in this study were relatively straight forward, and are summarized in Table 2.

Aggressive Diagnosis and Control of the Source of Infection

Early diagnosis of infection is the key to appropriate choice of antibiotics and effective control of the source of sepsis, thus favoring an improved outcome. Although the



Abbreviations: PEEP = positive end-expiratory pressure; CVP = central venous pressure; DIC = disseminated intravascular coagulation.

Figure 1 Early management of septic shock (First 4 hours).

Table 2 Haemodynamic targets and resuscitation measures for early goal-directed therapy*

Parameter	Threshold	Targeted goal	Resuscitation measure
CVP	<8 mm Hg	8-12 mm Hg	Crystalloid or colloid infusion
Map	<65 mm Hg	≥65 mm Hg	Vasopressors
	>90 mm Hg	≤90 mm Hg	Vasodilators
$ScvO_2$	<70%	≥70%	Transfusion of red cells until Hct ≥30%
	<70%	≥70%	Inotropic agents

*Therapy to be initiated for at least 6 h upon arrival in the Emergency Room and prior to admission to the ICU or a hospital bed. Sedation and mechanical ventilation were administered to decrease oxygen consumption in those patients in whom haemodynamic optimization could not be achieved. Adapted from Rivers et al.[35]

CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation

presence of characteristic hemodynamic abnormalities makes the diagnosis of an infection readily apparent in the advanced stage of septic shock, this is not necessarily the case during the early stages of sepsis. Furthermore, there are various non-infectious causes of SIRS (Table 3).[36,37] This knowledge is essential so that infection can be diagnosed with confidence and concurrent conditions are not overlooked. A systematic approach to early and accurate diagnosis is required. A meticulous physical examination should be performed to localize the site and extent of infection, and to rule out cryptic sources such as nosocomial sinusitis or acalculous cholecystitis. Microbiologic studies including blood cultures and radiologic investigations will usually yield a specific diagnosis or at least narrow down the differential diagnosis. There has been some confusion as to what constitutes proper blood collection for culture. Current recommendations are that two to three sets of blood cultures are adequate for maximal sensitivity.[38] They should be taken from different sites but not necessarily at separate times unless continuous bacteremia is suspected as in infective endocarditis. One set of blood culture is generally inadequate as interpretation will be difficult for atypical organisms or to differentiate true pathogens from skin contaminants. Studies have yielded conflicting results regarding the need of needle change in inoculation of blood culture bottles.[39,40]

The pattern of microbial etiology in sepsis has changed. In the 1960s and 1970s, gram-negative sepsis by *Enterobacteriaceae* and *Pseudomonas aeruginosa* predominated. In recent years, gram-positive infections with *Staphylococcus aureus, Staphylococcus epidermidis* and enterococci have increased dramatically. Candidal infections are also rapidly increasing, but viral and protozoan causes of septic shock continue to be rare. Reasons for the increase in gram-positive and candidal infections are probably multifactorial. The widespread use of antibiotics effective against gram-negative bacteria, development of resistance in gram-positive pathogens, invasive medical procedures and intensive immuno-

Table 3 Non-infective causes of SIRS

Tissue injury
- Surgery/trauma
- Hematoma/venous thrombosis
- Myocardial/pulmonary infarction
- Transplant rejection
- Pancreatitis
- Erythroderma

Metabolic
- Thyroid storm
- Acute adrenal insufficiency

Therapy-related
- Blood products
- Cytokines, especially granulocyte-macrophage colony stimulating factor
- Anesthetic-related malignant hyperpyrexia, especially halothane
- Neuroleptic malignant syndrome, for example, caused by haloperidol
- Opiates/benzodiazepines

Malignancy
- Hypernephroma/lymphoma
- Tumor lysis syndrome

Neurological
- Subarachnoid hemorrhage

suppressive treatments are among the possible contributory factors. The sites of infection in patients with severe sepsis have also changed. Abdominal and urinary tract infections used to be the most common but are now overtaken by lung and primary blood infections.[36,5]

The diagnosis of *nosocomial*, especially *ventilator-associated pneumonia* presents special challenges.[41] Conditions other than infection can commonly cause new radiologic infiltrates in critically ill patients. Furthermore, microbial colonization down to the lower tracheobronchial tree is the rule in the intubated patient, making interpretation of endotracheal aspirates difficult. For the same reason, bronchoscopy specimens with either bronchoalveolar lavage or protected brushings are rarely diagnostic. Although a pathologic diagnosis may be made with transbronchial or open lung biopsy, most intubated patients with sepsis will not tolerate the procedure. In the face of uncertainty, broad-spectrum antibiotics are often prescribed at the risk of suprainfection with resistant organisms.[42]

On the other hand, modern imaging techniques have greatly facilitated the diagnosis of otherwise occult infections. Intra-abdominal abscesses are now readily diagnosed by a combination of ultrasonography and contrast-enhanced CT scan, so much so that blind laparotomy to diagnose occult infection is no longer justified. Nevertheless, a high index of suspicion is still required in order that appropriate investigations are initiated.

Aggressive surgical measures are often indicated for more effective control of the source of infection. This applies in particular to intra-abdominal sepsis, as antimicrobials alone rarely succeed in the treatment of sepsis from a ruptured viscus, infected foreign body, or a subphrenic abscess. There are three broad categories of surgical intervention: i) drainage of abscess; ii) debridement of devitalized tissue or removal of infected foreign body; and iii) diversion, repair, or excision of an ongoing focus of contamination from a hollow viscus.[43] Except in selected life-threatening situations such as necrotizing fasciitis or a ruptured mycotic aneurysm, source control should be delayed after resuscitation and stabilization of the patient, as premature surgical intervention entails risks of its own. In severe necrotizing pancreatitis, delayed surgery (>12 days after diagnosis) may actually improve the outcome, as necrotic tissue is not well demarcated early in the course of disease, rendering early surgery hazardous.[44] On the other hand, the availability of CT- or US-guided percutaneous drainage will allow earlier intervention in many patients with intra-abdominal abscesses, as the risks of more invasive surgery are avoided. The timing of surgical intervention is therefore a compromise of risks and requires careful assessment on a case-by-case basis.

Empirical Choice of Antibiotics

In septic shock, appropriate choice of antibiotics is one of the few specific treatment modalities that have been shown to consistently reduce mortality.[45] However, the quality of evidence is suboptimal, primarily derived from retrospective, observational studies. In addition, studies in the last decade have mainly focused on neutropenic patients whose pathophysiology may differ from non-neutropenic patients. As new antibiotics with a wider spectrum of activity or enhanced potency are developed, many older studies have also lost clinical relevance. In practice, broad-spectrum and rapidly bactericidal antibiotics are generally preferred for the empirical treatment of infection in the early stages of severe sepsis or septic shock when the source and nature of infection is unclear. The rationale is that polymicrobial infections are relatively common in patients with severe sepsis, particularly if acquired in the ICU.[5] Appropriate choice of antibiotics requires knowledge of the suspected site of infection, the most likely pathogens, local patterns of antimicrobial susceptibility, history of drug hyper-sensitivity and prior use of antibiotics. Combinations of antibiotics may be required for additive or synergistic effects, and to reduce the likelihood of the emergence of resistance. As more clinical and microbiologic information becomes available, the antibiotic regimen can be further tailored and guided by *in vitro* susceptibility data. A list of empirical antibiotic regimens according to the suspected sites of infection is summarized in Table 4. More detailed guidelines for the antibiotic management of septic patients with neutropenia have been developed by the Infectious Disease Society of America.[46] It is hoped that similar evidence-based treatment guidelines will also be available for the management of other subsets of septic patients in the future.

Activated Protein C and Other Anti-coagulation Strategies

As discussed earlier, activated protein C has both anti-inflammatory and anticoagulant activity, and has been shown to significantly reduce mortality both in pediatric patients with meningococcal sepsis,[47] and in adults with severe sepsis or septic shock.[23,48] In the latter (known as the

Table 4 Empirical antibiotic regimens according to suspected sites of infection

Source of infection	Common pathogens	Initial antibiotic regimen
Oral cavity, lower respiratory tract	*Streptococcus viridans, Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Peptostreptococcus* spp., *Prevotella* spp., *Fusobacterium* spp., *Legionella pneumophila*.	Third-generation cephalosporin *or* Extended spectrum penicillin
Gastrointestinal tract, female pelvis	Enteric gram-negative bacilli, *Bacteroides fragilis, Peptostreptococcus* spp., *Clostridium* spp., *Enterococcus* spp.	Extended spectrum penicillin +/- aminoglycoside *or* Ciprofloxacin + metronidazole
Urinary tract	*Escherichia coli, Pseudomonas aeruginosa*, other enteric gram-negative bacilli, *Staphylococcus saprophyticus, Enterococcus* spp.	Ciprofloxacin *or* aminoglycoside
Cardiac valves	*Staphylococcus aureus, Streptococcus viridans, Enterococcus* spp., *Corynebacterium* spp., *Coxiella burnetii*, HACEK group (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella* spp.)	Penicillin +/- vancomycin
Central nervous system	*Neiserria meningitidis, H. influenzae, S. pneumoniae, S. aureus*, enteric gram-negative bacilli, *Bacteroides* spp., *Nocardia asteroides, Peptostreptococcus* spp.	Extended spectrum penicillin
Necrotizing skin and soft tissues	*S. aureus*, enteric gram-negative bacilli, *B. fragilis, Clostridia* spp., *Peptostreptococcus* spp., *Enterococcus* spp.	Extended spectrum penicillin +/- aminoglycoside
Intravascular devices-associated	*S. aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus*, enteric gram-negative bacilli, *Candida* spp.	Vancomycin

PROWESS trial), 1690 adult patients with severe sepsis or septic shock and ≥1 organ dysfunction were randomized to receive either placebo or recombinant human activated protein C (Xigris®) within 24 h at a dose regimen of 24 μg/kg/h by continuous infusion for 96 h. Activated protein C significantly reduced the 28-day all-cause mortality rate from 30.8% to 24.7%, a relative risk reduction of 19.4% (p=0.005). After lengthy deliberation, the US FDA approved this expensive drug for use in adult patients with severe sepsis and an APACHE II score of ≥25. In practical terms, dysfunction of more than one organ system may also be a valid indication. However, the cost of this treatment is prohibitive (~US$ 6,000 per course) and clearly not cost-effective for patients with less severe sepsis.[49] In addition, there is an increased risk of serious hemorrhage during the infusion period. Hence, it should be avoided in patients with prolonged PT and APTT, thrombocytopenia (<30,000/mm^3), and predisposing conditions such as gastrointestinal ulceration. Activated protein C represents a major breakthrough in a long line of research searching for clinically proven therapy based on known pathophysiologic mechanisms of sepsis. Additional studies are required to determine the efficacy and cost-effectiveness of this treatment for children and patients with less severe sepsis, and these are currently underway.

In addition to protein C, other therapeutic agents directed at inhibition of the extrinsic coagulation pathway are also under active clinical investigation. For example, recombinant tissue factor pathway inhibitor (TFPI) was found to improve survival in an animal model of gram-negative sepsis[50] and was found to be safe in patients with severe sepsis in a phase II, placebo-controlled, single-blind, dose escalation study.[24] A large phase III study is underway.

Another investigational anticoagulant, Antithrombin III (AT-III), reduced mortality as well as length of ICU stay in small clinical trials.[51] However, a subsequent phase III trial involving more than 2,000 adult patients with severe sepsis or septic shock failed to demonstrate a beneficial effect on 28-day all-cause mortality.[52] Furthermore, high-dose AT-III treatment was associated with an increased risk of hemorrhage when co-administered with heparin. In those who did not receive heparin, a significant reduction in 90-day mortality was achieved. It is possible that the increased risk of bleeding in those who also received heparin may have confounded the early outcome. Alternatively, it is possible that the relative lack of anti-inflammatory activity

by AT-III may have limited its usefulness in patients with severe sepsis, and that its beneficial effect is no more than anticoagulation with heparin. At present, use of AT-III in severe sepsis and septic shock cannot be routinely recommended despite its commercial availability. Of note, administration of low-dose heparin is commonly practiced in ICU patients to prevent thrombo-embolism and may by itself improve survival in patients with sepsis.[53]

Replacement Doses of Corticosteroids

The use of corticosteroid therapy in patients with sepsis and septic shock has been controversial for some time.[54] Earlier studies employed high (pharmacologic) doses of steroids for short duration, typically methylprednisolone at 30 mg/kg at varying intervals for one to two days. A meta-analysis of 10 randomized and placebo-controlled trials of such therapy failed to showed significant benefit in reducing mortality, although there was no evidence for an increased risk in adverse events such as bleeding, hyperglycemia or secondary infection either.[55] These earlier results, however, did not rule out the possibility that stress (replacement) doses of corticosteroids (~300 mg of hydrocortisone per day) may be beneficial, particularly for those patients with documented acquired adrenal deficiency or lack of adrenal reserve. Such a condition (defined by an inadequate response to corticotrophin administration with <10 mg/dL increase in serum cortisol levels) is relatively common in patients with severe sepsis or septic shock and appears to be associated with increased mortality.[56] Favorable hemodynamic responses following stress doses of hydrocortisone were reported in several small clinical trials in terms of shock reversal or duration of vasopressor use, and in one study a significant reduction of mortality was achieved.[57,58] The strongest evidence came from a large randomized, placebo-controlled trial of hydrocortisone (50 mg every 6 hours) and fludrocortisone (50 µg orally once daily) for seven days in 300 adult patients.[59] All subjects had catecholamine-dependent septic shock and required mechanical ventilation. Most (229/299) were non-responders to the corticotrophin test, defined as an increase in serum cortisol of ≤9 µg/dL. In this subgroup, the 28-day mortality was reduced with corticosteroid treatment (53% vs 63%, p=0.02). The duration for vasopressor therapy was also significantly reduced. In contrast, there was no effect on mortality or duration of vasopressor therapy among the corticotrophin responders. The rate of adverse effects was similar in the placebo and treatment groups. Further studies are clearly needed to address the need for steroid supplementation in patients with adequate adrenal reserve or less severe sepsis. Nevertheless, based on these promising results, consensus is forming that stress doses of steroids such as described in this trial should be seriously considered in patients with severe sepsis, particularly those with refractory shock and an inadequate response to the corticotrophin test.[54,60]

Other Investigational Immunotherapies

Antiendotoxin therapy with human monoclonal antibody (HA-1A) initially yielded encouraging results.[61] However, subsequent multicenter trials failed to demonstrate a survival benefit when administered to patients within six hours of the onset of septic shock,[62] or among children with meningococcal septic shock.[63]

Polyclonal intravenous immune globulins (IVIG) (0.4 g/kg/day for 5 to 7 days) have also been used as empiric adjunctive therapy for fulminant infections by organisms such as *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae*, and *Pseudomonas aeruginosa*, and in toxic shock syndrome associated with staphylococcal and streptococcal superantigens. Their efficacy is proven in hereditary or acquired immunodeficiency,[64,65] but to-date there is no consistent evidence that IVIG reduces mortality in patients with septic shock.[66,67] In streptococcal toxic shock syndrome, the use of IVIG (2g/kg for one to two doses) has been associated with reduced mortality compared to historical controls.[68] *In vitro* evidence also suggests that IVIG can neutralize superantigen activity.[69] Pending further confirmation of these beneficial effects, the use of IVIG has become common practice in this rapidly fatal infection. N-acetylcysteine, ibuprofen, prostaglandin E1, and pentoxifylline have been or are being investigated as adjunctive therapies in septic shock, but definitive studies showing sustained improvements in hemodynamic parameters or overall survival are lacking.[60] Similarly, nitric oxide inhibition, and anticytokine therapy such as antibodies to tumor necrosis factor, soluble tumor necrosis factor receptor and interleukin-1 receptor antagonist have yet to show convincing benefit in well-designed clinical trials.[70]

Conclusions

As the underlying mechanisms of sepsis and septic shock are better understood, research is undertaken to develop

more targeted goals of therapy. The recent findings regarding the beneficial effects of replacement corticosteroids and activated protein C are examples of such efforts. The possible interaction of different immune therapies and their cost-effective use in the clinical setting should be next on the research agenda. In addition, the current debate on the diagnostic criteria and definitions for sepsis may result in a better system for staging and categorization of patients, and provide more homogeneous groups of patients who can be identified at earlier stages of their clinical course and may benefit from new therapies for septic shock. However, a priority that should not be overlooked is the need to optimize hemodynamic support and antimicrobial therapy by improving the diagnosis and control of the source of infection. An important objective is to prevent rather than treat the late consequences of septic shock and reduce its attendant high mortality. To this end, the Surviving Sepsis Campaign has been launched by the ESICM (European Society of Intensive Care Medicine), ISF (International Sepsis Forum) and SCCM (Society of Critical Care Medicine). Its objectives include, among others, an increased awareness and knowledge of physicians, and redefinition of standards of care for critically ill patients.[71] Although estimates of the prevalence of sepsis or septic shock often vary among different populations, sepsis as a cause of mortality is consistently prominent in developed and developing countries alike. The best outcome will derive only from optimal care in all aspects of its management.

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