Sepsis diagnosis and management: work in progress

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Definitions of sepsis

Sepsis vs infection

The words "sepsis" and "infection" are often used as synonyms, but they are distinct entities. Infection is a microbiological event, caused by bacteria, fungi, viruses etc., while sepsis is the host response to that infection, characterized by the release of many mediators and by a constellation of clinical and laboratory features (Table I), none of which are specific for sepsis. Whenever possible, infection should be defined by the organ primarily infected and the type(s) of microorganisms (e.g., a lung infection due to Pneumococcus or a urinary tract infection due to E. coli). While the presence of infection is essential for a diagnosis of sepsis, sometimes the source of infection cannot be identified, and sometimes the bacteriology remains negative. In some patients with sepsis, the causative infection may never be identified at all; this does not mean the patient does not have an infection, and hence cannot have sepsis, just that we are unable to locate or identify it. To help to rule out an infection, an objective measure such as the

Severe sepsis is a common disease process in the critically ill and is associated with substantial morbidity and mortality. Continuing research has provided considerable insight into the pathophysiology of sepsis over recent years, enabling various aspects of the sepsis response to be targeted. Discoveries related to the link between coagulation and inflammation have been particularly exciting, leading to the development of recombinant activated protein C. This review will discuss current definitions of sepsis, describe new approaches to classification and diagnosis of patients with sepsis, present recommendations for management, and briefly highlight areas of ongoing and future research.

Key words: Sepsis, diagnosis - Sepsis, therapy - Intensive care

Recent years have seen great advances in our understanding of the pathophysiology of sepsis and as a result new treatments have become available and more are being developed.

In addition, progress has been made in techniques to facilitate the diagnosis of sepsis.

In this article we will discuss the recent advances in the diagnosis and management of this important and common problem.
Infection probability score, which weights 6 variables (temperature, heart rate, respiratory rate, white blood cell count, C-reactive protein (CRP), sequential organ failure assessment score (SOFA)) to make a composite score, may be useful. In view of these conclusions, the participants introduced the PIRO (predisposing factors, infection, response, organ dysfunction) concept, a suggested means of staging sepsis, rather like many cancers are staged using the tumor, nodes, metastases (TNM) system. Using the emerging PIRO model could aid physicians in better characterizing heterogeneous groups of septic patients, providing insight into the continuum of sepsis, and improve the understanding and management of severe sepsis and septic shock.

**New concepts**

In the most recent International Sepsis Consensus Conference, the 29 experts charged with providing a conceptual and a practical framework to define the systemic inflammatory response to infection came to the following conclusions: first, that the concepts of sepsis (the host response to an infection), severe sepsis (sepsis associated with organ dysfunction) and septic shock (sepsis plus arterial hypotension despite adequate fluid resuscitation), as defined in the 1991 North American Consensus Conference, remain useful to clinicians and researchers, but that they do not allow for precise staging or prognostication of the host response to infection. Second, that while the concept of systemic inflammatory response syndrome (SIRS) remains useful as a concept, the diagnostic criteria for SIRS published in 1992 are too sensitive and non-specific, and an expanded list of signs and symptoms of sepsis may better reflect the clinical response to infection.

**PREDISPOSING FACTORS**

Predisposing factors include individual characteristics, such as age, chronic diseases, prolonged immunodepressant medications, etc., that may influence a patient's response to infection and/or indicate which therapies are likely to be most effective in that patient. Increasingly, the role an individual's genetic make-up may have on the development of sepsis and the severity of disease when it develops are being explored and various polymorphisms have been shown to influence the risk of infection and/or of mortality from sepsis. Single nucleotide polymorphisms, microsatellite, insertion and deletion polymorphisms are all forms of genetic variation that can characterize an individual's risk for sepsis, organ dysfunction, or death. A polymorphism of the tumor necrosis factor-α (TNF-α) gene, the TNF-2 allele, is associated with increased serum levels of TNF and a greater risk of mortality from septic shock. A polymorphism within the intron 2 of the interleukin-1 receptor antagonist (IL-1ra) gene (IL-1RN*2) has been associated with reduced IL-1ra production and increased mortality rates. Polymorphisms in the Toll-like receptor (TLR) and interferon-γ genes have also been identified influencing susceptibility to sepsis. Advances in genetics technology have now allowed investigators to design glass slides (chips) with minute quantities of short, gene-specific nucleotides. These gene-specific probe nucleotides, ideally one for each gene in the genome, are arrayed onto the chip surface to produce a DNA microar-

<table>
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<th>TABLE I.—Common clinical and laboratory features of sepsis.</th>
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<tr>
<td>— Fever/hypothermia</td>
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<tr>
<td>— Increased cardiac output/low systemic vascular resistance</td>
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<tr>
<td>— Increased oxygen consumption</td>
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<tr>
<td>— Unexplained tachycardia</td>
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<tr>
<td>— Unexplained tachypnea/respiratory alkalosis</td>
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<tr>
<td>— Altered white blood cell count</td>
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<td>— Increased C-reactive protein levels</td>
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<td>— Increased procalcitonin levels</td>
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<td>— Unexplained hyperglycemia</td>
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<td>— Unexplained lactic acidosis</td>
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<tr>
<td>— Unexplained respiratory dysfunction (acute lung injury)</td>
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<tr>
<td>— Thrombocytopenia/disseminated intravascular coagulation</td>
</tr>
<tr>
<td>— Unexplained disorientation or confusion</td>
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<tr>
<td>— Unexplained alteration in liver function tests</td>
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<td>— Unexplained alteration in renal function</td>
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<td>— Capillary leak syndrome</td>
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ray. These can be used to generate an expression profile, the transcriptome, for the cell or tissue of interest. Genomics and the broader field of proteomics are likely to become increasingly routinely used in patient management.

INFECTION

Characteristics of the particular infection, such as site (e.g., lung versus urinary tract), responsible organism(s) (e.g., Gram-negative versus Gram positive, MRSA versus MSSA), severity, can have an effect on the host response and outcome, and may influence choice of treatment. However, while few would argue that an E. coli urinary tract infection is likely to be less life-threatening than a meningococcal meningitis, classifying the relative importance of infections on outcome is difficult. Using a systematic literature review and surveying 510 articles describing the outcome of infections, categorized by microorganism and site of infection, Cohen et al. recently generated specific risk codes for bacteremia, meningitis, pneumonia, skin and soft tissue infections, peritonitis, and urinary tract infections. For each infection site and organism, a two-digit code was generated according to the mortality rate associated with that infection (from 1: \( \leq 5\% \) to 4: \( >30\% \)), and the level of evidence available to support the mortality risk (level A representing evidence from more than 5 studies with more than 100 patients, through to level E insufficient evidence from case reports). They suggested this system be termed the grading system for site and severity of infection (GSSI) and although it needs to be validated, this could be a useful means of better characterizing the different risks associated with infections caused by different organisms in different sites. The timing of onset of infection may also influence outcomes. A recent study showed that patients who developed septic shock within 24 h of ICU admission were more severely ill, but had better outcomes than patients who developed septic shock later during their ICU stay.

RESPONSE

The degree of host response can be assessed according to the presence or absence of various clinical and laboratory features and to the degree of elevation of, for example, white cell count, CRP, procalcitonin (PCT) etc. The host response will vary between patients and over time in the same patient. Volk et al. described an early hyper-inflammatory phase followed by immunoparalysis based on the level of HLA-DR monocyte surface expression in septic patients. Improving our assessment of the host response could help direct therapies more appropriately.

ORGAN DYSFUNCTION

Organ dysfunction in severe sepsis is not a simple present or not variable, but a continuous spectrum involving many organs and varying with time and treatment. The degree of organ involvement can be assessed with various scoring systems, one of the most commonly used being the SOFA score.

Diagnosis of sepsis

Sepsis represents a major diagnostic problem for the intensivist and considerable effort is being concentrated on finding a sensitive and specific diagnostic marker; many have been suggested and a non-exhaustive list of proposed markers of sepsis is shown in Table II. Studies have shown that early therapy is critical in improving outcomes from sepsis, and the identification of a marker that would allow a clear diagnosis of sepsis would certainly help improve outcomes in these patients.

Procalcitonin (PCT) and CRP are 2 candidate markers of sepsis that have received a lot of attention. CRP is an acute phase protein that was first described in the early 1930s. CRP levels are widely used as a relatively non-specific marker of inflammation, and many studies have demonstrated increased CRP levels in patients with sepsis. Concentrations above 10 mg/dL on admission have been associated with particularly
TABLE II.—Some of the suggested markers of sepsis.

- White blood cell count
- C-reactive protein
- Procalcitonin
- Endotoxin
- Cytokines – IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, TNF, IFN-γ, PAF
- TNF-receptors
- IL-1 receptor antagonist, IL-1 receptors
- Complement factors
- Endothelin-1
- ICAM-1, VCAM-1
- Phospholipase A2
- PGE2
- Nitrates/nitrites
- Lactoferrin
- Elastase
- Neopterin

High mortality rates, and increasing or persistently high levels indicated a poor prognosis, while declining values were associated with a more favorable prognosis. PCT was described more recently as a potential marker of infection and is not yet routinely measured in many hospital laboratories. PCT may be superior to CRP in discriminating infectious from other inflammatory diseases. In addition, PCT has more rapid kinetics, being produced and cleared more rapidly than CRP, so may be better able to identify infection early and to follow disease progress. Indeed several studies have shown that PCT levels are correlated with the severity of sepsis as measured by the APACHE II or sequential organ failure assessment scores.

Importantly, none of the markers currently available is specific to sepsis, and a diagnosis of sepsis cannot be conclusively made on the basis of the presence of any one item; however, the presence of several features can help increase the diagnostic likelihood in a patient with a suggestive clinical picture. The results of ongoing studies into markers of sepsis, such as the The Genetic and Inflammatory Markers of Sepsis (GenIMS) study, are eagerly awaited. The rapid and accurate identification of the nature of the infection is also of critical importance. As an example, identifying fungal or resistant organism more rapidly would notably improve the appropriateness of antimicrobial treatment strategies.

**Management**

The management of sepsis can be considered in 3 sections: treatment of infection, hemodynamic resuscitation and organ support, and modulation of the host response.

**Treatment of infection**

The source of infection must be identified wherever possible and eliminated by surgical removal of an infected focus when applicable, and appropriate antimicrobial therapy must be started without delay. If the causative microorganism is unknown, empiric antibiotics should be started based on the likely culprit and local antibiotic patterns of prevalence and resistance. Patients who receive appropriate antibiotics have a better outcome than those who are initially treated with an ineffective antibiotic, yet a recent study of septic ICU patients found that in as many as 1/3 of patients the first line choice of antibiotic was inappropriate. Infectious disease specialists who are familiar with local hospital and community pathogens and resistance patterns should be involved in antimicrobial selection decisions in all patients with severe sepsis.

**Hemodynamic resuscitation**

Another basic aspect of the management of the patient with severe sepsis or septic shock is optimal resuscitation, essentially involving administration of sufficient fluids, and vasoactive agents when required. Usually the criteria for starting resuscitation include: mean arterial pressure <65 mmHg, mixed venous oxygen saturation (SvO₂) <70%, urine output <0.5 mL/kg/h, blood lactate concentration >1.5 mEq/L, or a worsening of the peripheral capillary circulation. The choice of one fluid type over another and the ideal endpoint of fluid resuscitation have generated considerable debate and a discussion of these aspects is beyond the remit of this paper.
Fluid resuscitation should be commenced as early as possible in the course of septic shock (even before ICU admission). Requirements for fluid infusion may be difficult to determine, and such decisions can be facilitated by repeated fluid challenges. A fluid challenge comprises 4 components: the type of fluid to be administered (e.g., natural or artificial colloids, crystalloids); the rate of fluid infusion (e.g., 500 to 1 000 mL over 30 min); the endpoints (e.g., mean arterial pressure >70 mmHg, heart rate <110 beats/min); the safety limits (e.g., central venous pressure not higher than 15 mmHg).

The choice of vasoactive agent has also been the subject of considerable debate with conflicting opinions in particular regarding the supremacy of dopamine or norepinephrine. Current guidelines recommend either drug as a first-line agent, and a randomized, controlled, double-blinded clinical trial comparing the 2 drugs is currently underway in Europe.

Modulation of the host response

DROTRECOCIN ALFA (ACTIVATED)

The development and licensing of drotrecogin α (activated), recombinant activated protein C, marked a turn-up on the rather downward sloping history of anti-sepsis therapeutics, in which multiple immunomodulatory agents have fallen to the wayside as one after another clinical trial failed to show that they had any beneficial effect on outcome. With indications that the coagulation system was keenly involved in the pathogenesis of sepsis, the spotlight fell on mediators of the coagulation pathway and their potential ability to influence sepsis outcomes. The Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study was a multicenter, randomized, controlled trial involving 1 690 patients from 164 centers in 11 countries. Given at a dose of 24 µg/kg of body weight/h for 96 h, drotrecogin α (activated) reduced mortality rates from 30.8% in the placebo group to 24.7% in the treatment group, which equated to one additional life saved for every 16 patients treated. Drotrecogin α (activated)-treated patients also showed significantly faster resolution of cardiovascular and respiratory dysfunction and significantly slower onset of hematological organ dysfunction than patients who received placebo. Apart from an increased risk of bleeding, mostly associated with invasive procedures, there were no other safety concerns with drotrecogin α (activated) in the PROWESS study. A further prospective study was conducted in 361 centers to confirm these findings and provide additional safety data. This study, ENHANCE, enrolled 2375 adult patients and treated them with the same dose of drotrecogin α (activated) as in the PROWESS study. The results confirmed the efficacy and safety of drotrecogin α (activated). A further analysis of the safety profile of drotrecogin α (activated) in more than 6 500 patients who received the drug in clinical trials or commercially reported that 43% of bleeding events that occurred in patients who received drotrecogin α (activated) were procedure-related, and that severe thrombocytopenia and meningitis may be risk factors for serious bleeding events in patients receiving the drug. As a result of the inherent risk of bleeding, drotrecogin α (activated) use is contraindicated in patients with active internal bleeding, recent hemorrhagic stroke, intracranial or intraspinal surgery, or severe head trauma, trauma with an increased risk of life-threatening bleeding, presence of an epidural catheter, and intracranial neoplasm or mass lesion or evidence of cerebral herniation. If a surgical procedure is necessary during treatment, the infusion should be stopped 2 h prior to the intervention and restarted 12 h after adequate hemostasis has been obtained. Drotrecogin α (activated) is expensive, but in cost-effectiveness analyses, it has been shown to be comparable to other accepted ICU interventions. Children were not included in the PROWESS study, suggested that results from open label studies and although drotrecogin α (activated) has the same pharmacokinetics, pharmacodynamic effects, and safety profile in the pediatric population, a phase III randomized controlled trial in children with
Vincent Severe sepsis has recently been discontinued for lack of efficacy. Drotrecogin α (activated) is currently licensed for use in adult patients with severe sepsis and a high risk of mortality (e.g., as assessed by the APACHE II score). This decision is supported by the recent Administration of Drotrecogin alfa [activated] in Early Severe Sepsis (ADDRESS) study that failed to show effectiveness of drotrecogin α (activated) in patients with less severe disease.

Steroids

In a randomized controlled trial conducted in 19 ICUs across France and including 300 patients with septic shock, patients with relative adrenal insufficiency (as assessed by non-response to a corticotrophin test) were treated with hydrocortisone (50 mg i.v. every 6 h) and fludrocortisone (50 µg per os daily) or placebo for 7 days. Treated patients had a reduced mortality compared to non-responders treated with placebo (53% vs 63%, hazard ratio 0.67, 95% CI 0.47-0.95, P=0.02).48 In a recent meta-analysis of randomized studies in patients with severe sepsis or septic shock treated with corticosteroids, overall use of corticosteroids did not significantly affect mortality.49 However, with longer courses (>5 days) of lower dose corticosteroids (≤300 mg hydrocortisone or equivalent), mortality at 28 days and hospital mortality were reduced.49 Another meta-analysis reached similar conclusions.50 Nevertheless, some questions remain unanswered, including the optimal test for adrenal insufficiency and whether the results can be extrapolated to patients with severe sepsis not in shock. It is not entirely clear whether steroids treat sepsis per se, or enhance hemodynamic support. Indeed, studies have indicated that steroids can increase the response to adrenergic agents. At present, steroid use in sepsis should be administered only in the presence of shock.

The future

As our understanding of the pathophysiology of sepsis improves, in particular the mechanisms of cell-to-cell signaling and the importance of apoptosis, more potential therapeutic targets become apparent. Here we will briefly mention just some of the many agents under research, focusing on those that are, or are almost, at the clinical trial stage.

New anti-endotoxin agents

Endotoxin (lipopolysaccharide, LPS) is a component of the Gram-negative bacterial cell wall and is a key initiator of sepsis. Once in the circulation, endotoxin binds to LPS binding protein (LBP), and the LPS-LBP complex interacts with CD14 on the surface of monocytes and macrophages resulting in cellular activation. The LPS-LBP complex can also interact with soluble CD14 and this can then interact with another receptor on the endothelial cell, which itself lacks surface CD14. LPS can also form complexes with serum lipoproteins, including low density lipoproteins (LDL), high density lipoproteins (HDL), and apolipoprotein A, which provide a means of eliminating LPS from the circulation.43 In acute illness, lipoprotein levels are reduced,52, 53 this reducing LPS clearance. Recent studies have indicated that intensive insulin therapy to maintain blood glucose levels less than 6.1 mmol/L improved outcomes predominantly by reducing deaths from sepsis-induced multiple organ failure.54 The incidence of nosocomial infections was also reduced. A further study from Van den Berghe et al. noted that intensive insulin therapy also increases HDL and LDL levels and multivariate analysis suggested that it was this change in lipid levels, rather than an effect on glucose levels, that contributed to the beneficial effects of this approach on mortality and morbidity.55 Replacing lipoproteins may therefore represent a novel method of treating sepsis. Experimental studies in human volunteers and animal models did indeed show that HDL reduced flu-like symptoms during endotoxemia, and blocked the endotoxin-induced release of TNF, IL-6 and IL-8. Interestingly, HDL administration also reduced CD14 expression on monocytes.56 In a porcine model of sepsis, an emulsion...
of phospholipid, the predominant lipid in HDL, lowered serum endotoxin and TNF-α levels significantly, preserved cardiac output and ejection fraction, and attenuated increases in systemic and pulmonary vascular resistances. A clinical trial with this phospholipid emulsion is ongoing.

Other anti-endotoxin strategies currently undergoing clinical testing include anti-CD14 antibodies, extracorporeal endotoxin absorption, and lipid A analogs.

**Macrophage migration inhibitory factor (MIF)**

By modulating the expression of TLR4, the signal-transducing molecule in the LPS receptor complex, macrophage migration inhibitory factor (MIF) induces the production of various pro-inflammatory mediators. MIF levels are raised in patients with sepsis and correlate with outcome, and animal studies have demonstrated improved survival with MIF neutralization.

**High-mobility group B-1 protein**

High-mobility group B-1 protein (HMGB1) acts as a late mediator of systemic inflammation, and is released from endotoxin-stimulated macrophages some 8-12 h after the release of the early cytokines. HMGB1 induces the activation of transcription factors and the release of pro-inflammatory mediators by monocytes and endothelial cells. In animal models of sepsis, anti-HMGB1 antibodies, even when given late after sepsis induction, improved survival and reduced sepsis-induced organ injury. Ethyl pyruvate, which inhibits HMGB1 production *in vivo*, also improved survival in a mouse model of sepsis. Unlike many animal models when the onset of sepsis is determined artificially, in patients the onset is often difficult to define and many patients will be diagnosed relatively late, making the longer time frame of HMGB1 of particular interest as it may be effective even when targeted later in the sepsis process.

**Hemoperfusion strategies**

Blood purification systems have been proposed for the treatment of sepsis based on the rationale that by removing inflammatory mediators, this strategy could improve outcomes. However, hemoperfusion *per se* removes all mediators, both good and bad and may not be beneficial in all patients at all times. Some studies have suggested that coupled plasma filtration adsorption (CPFA) improves blood pressure and restores immune function in patients with septic shock. However, further study is needed to determine which technique may be most beneficial, and at present hemofiltration is not recommended unless there is co-existing renal failure.

**Conclusions**

Severe sepsis and septic shock are still associated with high mortality rates, but progress is being made. Early diagnosis is vital in improving outcomes and development of more effective markers of sepsis will help in allowing treatments to be instituted as early as possible in the disease process. Appropriate infection control strategies and adequate haemodynamic stabilization remain essential, but must now be combined with drotrecogin alfa (activated) if there is no contraindication, and other immunomodulatory strategies as they become available. It is unlikely that one agent will ever be discovered to cure all patients with sepsis, just as one antibiotic cannot treat all infections, and one chemotherapy drug is not active against all cancers. Sepsis treatment must be seen as a package, with different patients requiring different packages, and the package contents varying with time in the same patient. Attempts to characterize patients, such as the PIRO system, will help in identifying which therapies are best given to which patients and when, and as new interventions undergo clinical testing, treatment protocols must be adapted accordingly. This is a rapidly moving field, very much a work in progress, and the success of drotrecogin alfa (activated) has given new impetus to the search for effective diagnostic and therapeutic strategies in patients with sepsis.
RIASSUNTO

Diagnosi di sepsi e sua gestione: attuali progressi

La sepsi grave è un processo patologico comune nel paziente criticamente ammalato ed è associato ad una sostanziale morbilità e mortalità. In questi ultimi anni la continua ricerca ha fornito notevoli dati sulla fisiopatologia della sepsi, evidenziando vari aspetti della risposta alla sepsi che devono essere colpiti. Le scoperte relative alla correlazione tra coagulazione e infiammazione sono state particolarmente eccitanti, consentendo lo sviluppo della proteina C attivata ricombinante. Questa revisione discuterà delle attuali definizioni di sepsi, descriverà i nuovi approcci alla classificazione e alla diagnosi dei pazienti con sepsi e presenterà le raccomandazioni per la gestione della sepsi, evidenziando vari aspetti della risposta alla sepsi che devono essere colpiti.

Parole chiave: Sepsi, diagnosi - Sepsi, terapia - Terapia intensiva.

References


