CHAPTER 1

Introduction

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The burden of sepsis on health care is significant. Worldwide, 13 million people become septic each year and 4 million die. In the United States alone, this accounts for approximately 750,000 cases per year, 215,000 resultant deaths, and annual costs of 16.7 billion dollars. Not only is the incidence of severe sepsis higher than that of the major cancers (Figure 1.1) but it has also estimated that in the United Kingdom just under 37,000 deaths are caused annually by the condition—a figure higher than that for lung cancer, or for breast and bowel cancer combined (Figure 1.2). Mortality rates for severe sepsis are 30 to 50%; for septic shock, even higher than 50%. Furthermore, the incidence of sepsis is increasing and will continue to do so as the population ages. Clinicians are challenged to manage this disease in an aging population with multiple co-morbidities, relative immunosuppression and a changing pattern of causative microorganisms.

Defining sepsis

The increasing incidence of sepsis and the high mortality rates associated with the disease have led to global efforts to understand pathophysiology, improve early diagnosis and standardize management. Understanding the spectrum of the disease is important for gauging severity, determining prognosis and developing methods for standardization of care in sepsis. At an international consensus conference in 1991, sepsis was defined as the systemic inflammatory response syndrome (SIRS) with a suspected source of infection. Organ dysfunction and hypoperfusion abnormalities characterize severe sepsis, while septic shock includes sepsis-induced hypotension despite adequate fluid resuscitation. SIRS and suggested criteria for identifying organ dysfunction and hypoperfusion are discussed further in the next chapter. Although imprecise, these definitions allow for a more uniform approach to clinical trials and the care of the patient with sepsis.

The use of SIRS criteria for the identification of sepsis has been felt by many to be arbitrary and non-specific. In 2001, the terminology was revisited in another consensus conference. At that time, the primary categories of sepsis, severe sepsis and septic shock were confirmed as the best descriptors for the disease process.

The primary change introduced was a more comprehensive list of signs and symptoms that may accompany the disease. This list is described in Chapter 2. In addition, a staging system was proposed for the purpose of incorporating both host factors and response to a particular infectious insult. This concept, termed PIRO (Predisposition, Infection, Response, Organ dysfunction) addresses the need to define, diagnose and treat patients with sepsis more precisely, as a variety of evidence-based interventions now exist to improve outcomes in severe sepsis and septic shock. The PIRO model remains hypothetical and is currently being evaluated in several studies.

Pathophysiology – an overview

The pathophysiology of sepsis is dealt with in detail in Chapter 5. Integral to the development of diagnostic and management strategies is an understanding of the interplay between the host’s immune, inflammatory and pro-coagulant responses in sepsis. When a given infectious agent invades the host, a non-specific or innate response is triggered via toll-like receptors (TLRs) on immune cells. TLRs are transmembrane proteins with the ability to promote signaling pathways downstream, triggering cytokine release, neutrophil activation and stimulating endothelial cells. This occurs in response to their recognizing a specific pathogen-associated molecule such as lipopolysaccharide. Activation of humoral and cell-mediated – ‘adaptive’ – immunity follows, with specific B- and T-cell responses and release of both pro- and anti-inflammatory cytokines (some examples of which are listed in Table 1.1) mediated through nuclear factor kappa B. Production of both groups of mediators is significantly increased in patients with severe sepsis.

As adaptive immunity is triggered and the inflammatory cascade of sepsis unfolds, the balance is shifted towards cell death and a state of relative immunosuppression. At this late stage, accelerated lymphocyte apoptosis (programmed cell death) occurs and production of pro-inflammatory mediators may reduce. End-organ dysfunction ensues. Various mediators, including tumour necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), induce nitric oxide production. Not only does this reduce systemic vascular resistance but it also causes myocardial depression and left ventricular dilatation with decreased ejection fraction. The end result of these hemodynamic changes is an elevated cardiac output and generalized vasodilatation. This is often described as ‘high-output’ shock.

As the inflammatory response progresses, myocardial depression becomes more pronounced and may result in a falling cardiac output. Capillary leakage occurs with peripheral and pulmonary oedema that may progress to acute lung injury and acute respiratory distress syndrome (ARDS). A surge in catecholamines, angiotensin II and endothelin causes renal vasoconstriction and increases the risk of renal failure developing. Some of these processes and changes are illustrated in Figure 1.3.

The above changes are accompanied by alterations in the coagulation cascade towards a prothrombotic and antifibrinolytic state mediated by decreased antithrombin III, protein C, protein S and tissue factor pathway inhibitor levels (Figure 1.4). Increased thrombin leads to endothelial and platelet activation. As a result, there is fibrin deposition and microvascular thrombosis which may threaten end organs. The development of disseminated intravascular coagulation in severe sepsis is a predictor of death and the development of multi-organ failure.

Table 1.1  Some examples of pro-inflammatory and anti-inflammatory cytokines.

<table>
<thead>
<tr>
<th>Pro-inflammatory</th>
<th>Anti-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 1β (IL-1β)</td>
<td>Interleukin 1 receptor antagonist (IL-1ra)</td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>IL-4</td>
</tr>
<tr>
<td>Interleukin 8</td>
<td>IL-6</td>
</tr>
<tr>
<td>Tumour necrosis factor (TNF)-α</td>
<td>IL-10</td>
</tr>
<tr>
<td>Transforming growth factor (TGF)-β</td>
<td>IL-11</td>
</tr>
<tr>
<td>Transforming growth factor (TGF)-β</td>
<td>IL-13</td>
</tr>
<tr>
<td>Soluble TNF receptors (sTNFR)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic challenges in sepsis

Despite advances in our understanding of the disease’s mechanisms, it remains difficult to apply these lessons clinically towards early diagnosis and treatment. Addressing this dilemma is paramount given the availability of life-saving interventions, interventions that lose their mortality benefit when delivered late. As the host’s initial compensatory mechanisms are overwhelmed and a patient moves through the disease spectrum, tissue beds become hypoxic and injury occurs at the microvascular level. The resultant tissue hypoperfusion, which characterizes severe sepsis and septic shock, can occur despite normal clinical parameters including vital signs and urine output, and may continue following initial resuscitation. Failure to recognize the patient with sepsis and intervene at this stage, prior to or early in the development of organ dysfunction, results in increased morbidity and mortality. Poor outcomes in severe sepsis have been correlated to the development of organ failure on as early as Day 1 following presentation.
Introduction

Lipopolysaccharide on microbe recognized by TLRs

Neutrophil/T-cell activation

Cytokine release

Monocyte/macrophage activation

Phagocytosis, cell lysis release of exotoxins

Cytokine release

Innate immunity

Adaptive immunity

Accelerated inflammation

Hyperimmune response

Shock and organ impairment

Immune paralysis

Multiple organ dysfunctions

Phagocytosis, cell lysis release of exotoxins

Nitric oxide synthesis

Vaso-dilatation

Endothelial cell damage

Intravascular thrombus formation

Capillary leakage, oedema, absolute hypovolaemia

Intravascular thrombus formation

Impaired O₂ extraction

Acidosis

Myocardial impairment

H+ (Cardiac depressant factor – not identified)

Microcirculatory collapse

Multiple organ dysfunctions

Figure 1.3 Schematic representing stages in the natural course of sepsis and their interactions. Note that multiple organ dysfunctions can also occur in the absence of overt shock through similar mechanisms.

↑ Coagulation
↑ Inflammation
↑ Homeostasis
↓ Fibrinolysis
COAGULATION
INFLAMMATION
HOMEOSTASIS
FIBRINOLYSIS

Antithrombin III
Protein C
Protein S
Tissue factor pathway inhibitor

Figure 1.4 Disturbance of the normal balance between pro- and anti-thrombotic tendency seen in severe sepsis. Adapted from Carvalho AC, Freeman NJ. How coagulation defects alter outcome in sepsis. Survival may depend on reversing procoagulant conditions. Journal of Critical Illness 1994; 9: 51–75.

Translating research into clinical practice

Knowledge transfer in medicine remains a difficult and perplexing challenge. All of us, researchers and clinicians alike, have struggled with how and when to incorporate research from the literature into bedside practice. There are numerous obstacles that stand in the way of translating research into bedside practice: first, especially in critical care, clinicians are conservative by nature – which is both good and bad news. The good news is that it means that strategies that have only been partially tested do not regularly get to the bedside and therefore needless harm is prevented for patients. The bad news is that it takes clinicians a long time to incorporate proven strategies to the bedside.

The second obstacle is that, as busy clinicians, our ability to critically appraise the literature to separate out the mediocre data from the robust randomized control data with good methodology is limited, so there is a lag time between the publication of good data and the implementation of that data.

The publication of several randomized control trials demonstrating mortality reduction with certain interventions in severe sepsis, along with the desire to integrate evidence-based medicine into clinical practice, led to the development of the Surviving Sepsis Campaign (SSC) guidelines. In partnership with the Institute for Healthcare Improvement, the SSC designed the resuscitation and management bundles in an effort to facilitate knowledge transfer and establish best practice guidelines. Phase III of the SSC is a global quality improvement effort to establish a minimum standard of care for the management of critically ill patients with severe sepsis.

Future directions

The future management of sepsis will most likely involve therapies directed at newer inflammatory targets. Several such molecules are currently under investigation and include, among others: TLR4; the receptor for advance glycation end products (RAGE); and high mobility group box 1 (HMGB-1), a cytokine-like molecule that promotes TNF release from mononuclear cells. HMGB-1 is actively secreted by immunostimulated macrophages and enterocytes and is also released by necrotic but not apoptotic cells. HMGB-1 is now recognized as a pro-inflammatory cytokine.
The use of biomarkers to diagnose, stage and risk assess is another important new field of study. Procalcitonin, C-reactive protein, IL-6 and other mediators may be used in combination to develop an ‘electrocardiogram’ (ECG) of sepsis that may ultimately help guide clinicians to early diagnosis and assist in determining appropriate treatment strategies.

Another important area of ongoing and future research lies in endothelial cells and the microcirculation. Better insight into endothelial cell and microcirculatory dysfunction may direct interventions that will facilitate enhanced restoration of tissue perfusion; a primary pathophysiologic lesion in the inflammatory process that contributes to multi-organ failure and cellular dysfunction in sepsis.

Conclusion
Severe sepsis and septic shock is common and increasing among the critically ill. The opportunity now exists for clinicians to adopt an evidence-based approach to diagnosis and management. Mortality may be reduced by focusing on early diagnosis, targeted management and standardization of the care process.

Further reading


