The role of the gut in sepsis

Marcel Gatt

Abstract

Sepsis is defined as the systemic inflammatory response syndrome (SIRS) associated with suspected or confirmed infection. As such, it is implicit that two components are necessary in the causation of surgical sepsis: a source of infection as well as a SIRS response by the patient. In recent years, the management of patients with sepsis has been aided by a much better understanding of the underlying pathophysiological processes which occur. In particular, we have a better perception of the complex interactions between the host and the invading organisms as well as a better appreciation of the cellular and extracellular pathways involved, including, but not confined to the complexly intertwined roles of the immunological system, the complement cascade and the coagulation pathway, as well as the role of the gut in driving this process. Given the plethora of homeostatic functions of the gastrointestinal tract, it is self evident, albeit somewhat poorly represented in the medical literature, that this organ plays a central role in the process. This article reviews the role played by the gut in the development of sepsis with a particular emphasis on the surgical patient. The passage of viable bacteria or its components across the gut barrier in a process known as bacterial translocation as well as other mechanisms are also discussed.

Keywords Critically ill; gut failure; gut function; intestinal failure; mortality; multi-organ failure; multiple organ dysfunction syndrome; nutrition; sepsis; surgery; systemic inflammatory response syndrome

Introduction

The word 'sepsis' is derived from Greek and means to decay or to make rotten. In modern practice, the phrase sepsis has come to represent a catch-all term referring to the changes observed when living organisms are subjected to an insult of an infectious nature. There have been many attempts to define sepsis more systematically[1,2] and this has introduced a dizzying array of seemingly synonymous albeit novel and distinct concepts. Terms such as the systemic inflammatory response syndrome (SIRS), severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) carry specific meanings and are often a source of confusion. For purposes of clarity, these and other relevant terms are summarized in Table 1.

Despite numerous advances in clinical care, sepsis is widely recognized as a primary cause of morbidity and mortality in hospitalized patients. This is particularly true in the critically ill and the surgical patient. The diagnosis of infection and underlying sepsis in such patients can be complex, and the challenge is often intensified by multiple coexisting disease processes. The signs of sepsis suggested by the Sepsis Conference of 2001 and summarized in Table 2 are a useful guide to diagnosis in such situations, but none of the signs are specific enough to be pathognomonic on their own. A high degree of suspicion is required and the possibility of sepsis should be entertained when these signs are present.

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Pathophysiology of sepsis

Homeostasis is maintained in vivo by a complex interplay of a number of mechanisms aimed at maintaining the status quo of the internal milieu. Such mechanisms include the immune system (with both its innate and adaptive components), as well as the complement and coagulation cascades. With respect to the immune system, a tightly maintained balance between opposing yet complimentary pro-inflammatory and anti-inflammatory mediators maintains health and homeostasis. Any upset in this tightly controlled balance may result in disease.

The clinical manifestations of sepsis result from the complex interactions between the immune and other systems of the host and the infecting microorganisms. Cells of the host's innate immune system recognize microorganisms and initiate responses to these microbes or their products. This response is mediated through a number of host cell surface receptors and proteins and a battery of microbe antigens. Host cell surface receptors include the so-called pattern recognition receptors (PRRs) and toll-like receptors (TLRs). These are expressed by cells of the innate immune system, which in turn employs a limited number of germline-encoded PRRs that recognize invariant pathogen-associated microbe antigens including small molecular motifs conserved within different classes of microbes known as pathogen-associated molecular patterns (PAMPs). Better known examples of PAMPs include lipopolysaccharides (LPS, endotoxins) expressed by virulent Gram-negative bacteria, peptidoglycan, lipopeptides, lipoteichoic acid (a component of gram-positive bacterial cell walls), flagellin and bacterial DNA. While it is beyond our scope to review the complexities of the immune system and other homeostatic pathways, it should suffice to say that activation of a variety of complex metabolic systems, including the immune and coagulation cascade pathways result from host—antigen interaction, culminating in what is recognized as the septic response.

With the involvement of such complex pathways and with the contribution of so many intermediate substances, one may be forgiven to think that the level of one or more of these intermediaries may be used to diagnose sepsis with some certainty or accurately monitor its progress. In the last few decades more than 170 biomarkers have been studied both as diagnostic markers as well as prognostic indicators for sepsis, but none of them have been found to have sufficient sensitivity or specificity on their own to be used routinely in clinical practice. CRP and procalcitonin (PCT) have been used most widely, but they both have their limitations when used to distinguish sepsis from other inflammatory conditions as well as when they are used as prognostic indices.

In moderate to severe sepsis the inflammatory response causes an imbalance of procoagulants and anticoagulants, which culminates in disseminated intravascular coagulation (DIC). The formation of clots eventually cause thrombosis of small vessels and impaired tissue perfusion. The higher levels of cytokines and the secondary mediators in severe sepsis lead to hypotension due

Definitions (adapted from[3,4])

Infection	A pathologic process caused by suspected or proven invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms or a clinical syndrome associated with a high probability of infection
Systemic inflammatory response syndrome (SIRS)	Presence of at least two or more of the following, one of which must be abnormal temperature or white blood cell (WBC) count in children: • Core temperature >38.3°C, >38.5°C in children, or <36°C • Heart rate >90 beats/minute or in children a mean heart rate >2 standard deviations (SD) above normal for age, or in children <1 year of age bradycardia defined as a mean heart rate <10th percentile for age • Respiratory rate >20 breaths/minute or $PaCO_2$ <32 mmHg, or in children >2 SD above normal for age; or need for mechanical ventilation • WBC count >12,000/mm^3 or <4000/mm^3, or >10% immature (band) forms, or in children elevated or depressed level for age
Sepsis	Systemic inflammatory response syndrome associated with suspected or confirmed infection, positive blood cultures are not necessary
Severe sepsis	Sepsis complicated by cardiovascular organ dysfunction or acute respiratory distress syndrome or dysfunction of two or more other organs
Septic shock	Cardiovascular collapse related to severe sepsis despite adequate fluid resuscitation characterized by hypotension defined as systolic blood pressure (SBP) <90 mmHg (in children a pressure <2 SD below normal for age), mean arterial pressure (MAP) <60 mmHg or a reduction of >40 mmHg on baseline SBP
Multiple organ dysfunction syndrome (MODS)	The presence of altered organ function in a patient who is acutely ill and homeostasis cannot be maintained without intervention. The criteria are: • Hypoxaemia (PaO_2/FiO_2 <300) • Acute oliguria (urine output <0.5 ml/kg/hour for 2 hours) or creatinine >2.0 mg/dl • Coagulopathy (platelet count <100,000, international normalized ratio >1.5 or partial thromboplastin time >60 seconds • Ileus • Plasma bilirubin >4 mg/dl

Table 1

to systemic vasodilation, diminished myocardial contractility, and systemic leucocyte adhesion due to widespread endothelial damage and activation as well as diffuse alveolar capillary damage in the lung. MODS ensues from these combined effects, most notably affecting the liver, kidneys and the central nervous system. In this situation, the patient can succumb rapidly unless the underlying infection (and the resulting LPS overload) is brought under control.[2] It is increasingly recognized that the gut plays a pivotal role in both the initiation as well as the propagation of this septic response.

Sepsis and the gut

It is well established that the primary function of the gastrointestinal (GI) tract is that of nutrition, being involved in the digestion and absorption of nutrients, fluids and trace elements from the diet. The gut, however, is a highly complex organ and it satisfies a plethora of additional functions. Amongst other roles, it is also involved in the production of numerous hormones with both local and systemic effects, and participates in the excretion of waste by-products of metabolism. Its gut-associated lymphoid tissue (GALT) is the single largest immunological organ and cytokine producer in the body.

The normal GI tract harbours large numbers of both aerobic and anaerobic bacteria which exist in symbiosis with man. Typically, the numbers are lower in the stomach due to the hostile environment here. A low pH and slow transit promote the killing of ingested microbes. Ordinarily the proximal small bowel has fewer microbes than the distal small bowel and the number of microorganisms gets exponentially higher distal to the ileocaecal valve. The gut also serves as a barrier against luminal microbes and other antigens, essential in separating self from non-self; the so-called 'intestinal barrier function' of the gut.

This barrier role of the gut is highly effective. The fact that luminal contents in the caecum have a bacterial concentration of the order of 10^{12} organisms/ml of faeces, whilst portal blood, mesenteric lymph nodes (MLN) and indeed tissues one cell deep to the intact intestinal mucosa are usually sterile, dramatically illustrates the efficacy of this barrier. Anaerobes are the predominant flora in the GI tract, outnumbering aerobes by approximately two orders of magnitude. The adherence of the resident gut microflora to endothelial cells, mucus and to each other creates a highly anaerobic environment which helps to prevent adherence, proliferation, overgrowth and invasion of pathogens. This phenomenon associated with the physical barrier is termed 'colonization resistance'.[5]

The barrier role of the gut serves to manage luminal antigens, encouraging the symbiotic relationship between man and enteric bacteria without which humans could not survive, while ensuring that the internal milieu remains sterile. Breakdown or

