

Commentary

The International Sepsis Forum's controversies in sepsis: how will sepsis be treated in 2051?

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Abstract

Sepsis, the life-threatening illness that arises from innate immunity to overwhelming infection, is treated symptomatically at the start of the 21st century. Looking ahead 50 years, one can perhaps foresee profound changes in the way we manage this disorder. A shift from a focus on eradicating microorganisms as universally inimical to one on supporting optimal host–microbial homeostasis will have a profound impact on how we treat infection, and will relegate antibiotics to a small, adjuvant role. Probiotic therapy may well be as important as antibiotic therapy. Resuscitation strategies will support microvascular flow rather than systemic pressure. Rapid genetic profiling will permit pre-emptive gene therapy for some, and titration of specific therapies directed against fundamental intracellular processes in others. We will treat diseases, not syndromes, and guide therapy by molecular staging. A fanciful victim of sepsis in 2051 illustrates how future treatments might transform sepsis from a prolonged and morbid illness to a rapidly reversed acute disease.

Keywords host–microbial interactions, infection, polymorphisms, probiotics

It is a sobering experience to be faced with a blank page and to be asked to speculate on what we might be doing 49 years from now. I will not be treating sepsis in 2051 because I won't be here. The chances are, however, that future intensivists will not really be treating 'sepsis' either. Let me explain.

By the middle of the 21st century we will finally have a definition of sepsis. For instance, this is what you might read in the 2048 edition of a medical dictionary:

sepsis (*sep-sis*). A generic term that describes a group of diseases that result from the systemic expression of acute inflammation.

By then, the epidemiology of sepsis will have changed; sepsis will be more common because it is an iatrogenic disorder – a consequence of the successes that we have had in critical care medicine. However, mortality will have decreased profoundly, partly because of new therapies and

partly because we will understand the pathophysiology better. Depending on the stage of sepsis, mortality will be no more than 5%, in large part because we will finally accept that it is legitimate to die from natural causes, and those deaths will no longer be attributed to sepsis.

Changing our perception of infection

Today our tools for the diagnosis of infection are limited to microbial cultures, radiologic investigations, and direct examination. Selecting appropriate antibiotic therapy is difficult because culture and sensitivity data are not immediately available. It is not difficult to imagine, however, that in the future we will have rapid point of care diagnostic technology based on detecting microbial products and even antibiotic resistance genes.

At present we see the microbial world as largely inimical, and we take extraordinary measures to eradicate it. In the future we will have a better understanding of 'host–microbial

symbiosis'. We will understand that the successful treatment of infection is grounded not just in eliminating a pathogen but also in supporting the indigenous flora of the host. We will administer micro-organisms as often as we will kill them. We will change the way we use antibiotics. We will understand that antibiotics kill micro-organisms, and will only use antibiotics when we have clear evidence that there are viable pathogenic organisms present. A typical course of antibiotics will last no more than 12–24 hours, and we will guide the duration of treatment by specific viability assays.

As we improve our understanding of the role that the indigenous flora play in maintaining physiologic homeostasis, we will develop the science of 'probiotics', recalling, for example, a landmark study from the late 20th century. A strain of a relatively avirulent organism was genetically engineered to produce IL-10 and was fed to mice with experimentally induced colitis [1]. When the colitis flared up, transit through the gut decreased, resulting in increased bacterial numbers. This in turn led to increased secretion of IL-10 and resolution of the acute inflammatory process. That study will have set the stage for an entire class of therapeutics, using bacteria as drug delivery systems and using the kinetics of bacterial growth as a mechanism for titrating therapy.

Yet another approach to limiting inflammation will derive from the recognition that bacteria contribute to the termination of an inflammatory response by inducing the apoptosis or programmed cell death of the neutrophil. Work from the past century established the principle. Sookhai and coworkers [2] subjected rats to intestinal ischemia/reperfusion injury, and showed improved survival when killed *Escherichia coli* were simultaneously administered down the trachea. The bacteria induced apoptosis in neutrophils that had migrated into the lung, lessening the acute lung injury and significantly enhancing survival of the animals. If infection is a potent stimulus to limit inflammation, then in the future we may well believe that patients die from the absence of infection as often as from its presence.

Image-guided surgery

Today we are witnessing the merging of two technologies with roots that are quite divergent, namely minimally invasive surgery and radiology. As these technologies advance, the distinction between them is becoming blurred. The challenge for today's surgeon is to learn how to image, whereas the challenge for today's radiologist is to learn how to perform the surgery. In the future these skills will be combined. Surgery will become less invasive as imaging techniques become more revealing.

Indeed, the next frontier in imaging will be to reveal not only anatomy but also physiology and biochemistry. In the future we will be able to image cellular metabolism noninvasively, and to make clinical decisions on the basis of dynamic visualization of cellular function.

Resuscitation

At the start of the 21st century we debated the relative merits of differing vasopressor strategies in septic shock. In the future we will shift our focus to vasodilator therapy, recognizing that normalization of blood pressure is only achieved at the cost of a profound reduction in flow in the microvasculature. We will realize that measurement of pressure is a poor surrogate for optimization of flow, and will resuscitate patients on the basis of direct visualization of flow in microvascular beds. This new philosophy of 'permissive hypotension' will be based on the recognition that the reduced peripheral vascular resistance of sepsis is an appropriate adaptive mechanism to be supported, rather than a disease to be reversed.

Specific therapy for sepsis

We will have a large number of adjuvant therapies that target the host response. However, rather than target individual mediators, we will treat the underlying cellular derangements of critical illness: the balance between proinflammatory and anti-inflammatory mediators; the balance between procoagulant and anticoagulant mechanisms; and the balance between cell growth and apoptosis.

Inflammatory mediators

Genetic predisposition plays a significant role in defining the response to an infectious stimulus and in determining the outcome following an intervention [3]. The capacity to detect genetic polymorphisms reliably and rapidly, for example in cytokine promoter sequences or in Toll-like receptors (TLRs), is not far off. Such an ability will enable us to manage patients pre-emptively, rather than reactively, and thus prevent disease, rather than treat its sequelae. Moreover, if we can identify potentially deleterious genetic polymorphisms, then we will be able to modulate the expression of the involved genes using specific gene therapies.

We will also be able to perform biochemical response profiling, simultaneously detecting changes in the expression of thousands of genes and in the proteins that they encode. Sequential assay of the interactions of hundreds of different proteins creates enormous challenges in data capture and interpretation, but will permit individualization of therapy and real-time monitoring of changes in biology. We will move from the familiar model of one molecule producing one biologic effect to a model based on complexity theory [4], in which the unexpected perturbations that result from apparently insignificant interactions can be detected and modulated.

The coagulation cascade

The role of modulation of the coagulation cascade will shift from that of an ill-defined partner in the pathogenesis of dysregulated inflammation to a discrete biochemical process that jeopardizes oxygen delivery to tissues by disrupting microvascular flow. Treatment will be monitored using

intravital microscopy both to detect flow through the microvasculature and to quantify the nature of interactions between circulating blood elements and the endothelium.

Apoptosis

In the late 20th century we learned that cells die not only through the inadvertent, destructive process of necrosis, but also through an exquisitely orchestrated process of cellular suicide, known as apoptosis. Deranged apoptosis contributes to degenerative disorders such as Alzheimer's disease, as well as to diseases of uncontrolled cell growth such as cancer. Derangements in the normal expression of apoptosis – both excessive cell death [5] and, in the case of neutrophils and other cells of the innate immune system, inadequate apoptosis [6] – will be found to be the final common pathway to organ dysfunction for all of the acute diseases of critical illness. The ability to intervene to alter the expression of programmed cell death will be the basis for a wide spectrum of new therapies in the intensive care unit (ICU).

However, therapeutic agents will rarely target any specific inflammatory mediators. Rather we will attempt to modify intracellular processes using interventions that target signalling, kinases, transcription factors, and the spectrum of mechanisms that maintain normal intracellular homeostasis. Furthermore, rather than using expensive recombinant proteins, we will be using synthetic, small molecules.

A typical intensive care unit admission in 2051?

So here, then, is a typical ICU admission in the middle of the 21st century.

The patient, a 20-year-old man, is admitted to the ICU with pneumococcal pneumonia and a blood pressure of 70/40 mmHg following resuscitation in the emergency department. He and his family are known to have a TLR2 polymorphism that results in a hyperactive response to Gram-positive bacteria. He was previously counselled about the benefits of gene therapy but refused to undergo treatment.

We were alarmed at his blood pressure, and immediately started him on a course of vasodilator therapy to lower his blood pressure to a more reasonable 30/20 mmHg, and confirmed using intravital magnetic resonance microscopy that he had excellent flow in all of the vital vascular beds, including the heart, brain, gut, and liver. We gave him penicillin, which is still highly effective against streptococcal pneumonia because, in contrast to the practices of the past, we use only a single dose of the drug. We selected a potent anti-inflammatory agent that has good microvascular anticoagulant activity, namely intravenous acetylsalicylic acid, which was demonstrated so convincingly to improve survival when it was finally formally evaluated back in 2030. We also administered heparin as an adjuvant anticoagulant.

We fully understood that a septic state such as he manifested leads to profound changes in the gut, despite the use of permissive hypotension. Therefore, we fed him an *E. coli* strain that was engineered to produce recombinant human IL-11 in order to protect his gastrointestinal epithelium, and recombinant IL-10 in order to sustain the counter-inflammatory activity of the gut-associated immune tissues. We started a caspase-1 inhibitor with a view to blocking apoptosis in gut epithelial cells and lymphocytes. Finally, we gave him an aqueous suspension of *Aeromonas* in the fluid being used for liquid ventilation, in order to accelerate apoptosis of the neutrophils that intravital magnetic resonance microscopy had shown to be infiltrating the lung.

We classified his disease process as stage 3b 'Aktosis' – a consequence of dysregulation of signalling through the Akt pathway. We therefore also gave him a single dose of an Akt inhibitor, to neutralize the downstream signaling consequences of PI3 kinase activation.

He was discharged home the next day and is doing well.

Competing interests

JCM has been a paid consultant for a number of companies involved in developing mediator-directed therapy for sepsis. He is also an avowed antibiotic minimalist. PST received an honorarium from the International Sepsis Forum for helping to write this commentary.

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