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Unpacking the sepsis controversy

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ABSTRACT

Despite its many definitions and revisions, consensus statements and clinical guidelines, the term 'sepsis' continues to be referred to as a discrete clinical entity that is often claimed to be a direct cause of mortality. The assertion that sepsis can be defined as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection,' has led to a field dominated by failed clinical trials informed by host-centered, pathogen-agnostic, animal experiments in which animal models do not recapitulate the clinical condition. The observations from the National Health Service from England that claim that 77.5% of sepsis deaths occur in those aged 75 years or older and those from the USA indicating that most patients dying *of* sepsis have also been diagnosed with 'hospice qualifying conditions,' seem to refute the assertion that sepsis is caused by, rather than associated with, a 'dysregulated host response.' This piece challenges the current conceptual framework that forms the basis of the sepsis definition. Here we posit that as a result of both its definition and the use of inappropriate animal models, ineffective clinical treatments continue to be pursued in this field.

INTRODUCTION

That animal models of sepsis are insufficient to address the human condition is certainly not a novel concept.[1 2] Despite decades of research, no agent has yet been developed that can interrupt the clinical course of a severe, life-threatening infection. In fact, because of the inappropriate definition and modeling of sepsis, People for the Ethical Treatment of Animals has initiated a lawsuit against the National Institutes of Health, USA, which, in response, has decided to move away from animal research involving sepsis models. Whereas the term 'sepsis' has been traditionally used to indicate when a suspected infection has developed into a life-threatening systemic disorder, its definition and hence the focus of most investigations in the field consider it to be due to a 'dysregulated host response.' Although most experts agree that a clinical infection or suspected infection initiates the process of sepsis, the pathogen's role during the course of illness seems to fade into the background as 'runaway inflammation' becomes the prime target of experimental models and clinical trials. Clinically, sepsis is characterized by a high heart rate, fever, abnormal breathing and organ failure due to a suspected infection. Virtually every article and every proposal studying 'sepsis' begins with the declarative statement that the sepsis response itself kills 250 000 US patients per year and is the most common *cause* of death in modern intensive care units (ICUs). Despite compelling evidence to the contrary,[3–5] such wording suggests that most patients do not die *with* sepsis, they die *of* it. Although certainly 'a dysregulated host response' is involved in a poor outcome from infection, claiming the dysregulated host response itself to be the actual cause of death is what has led many investigators to focus on host-centered modulation as the preferred method of mitigation. A main point of controversy in this field is the observation that, many, if not most hospitalized ICU patients suffering from sepsis have 'hospice-qualifying conditions' according to one study.[3] Although it must be certainly recognized that the interaction of highly virulent pathogens with their host can lead to lethal infection (ie, meningoccocal septicemia, group B *streptococcus*, *Escherichia coli* diarrhea), the assertion that the majority of the 250 000 septic deaths in US ICUs and in societies with advanced care systems, is *caused* by the 'host response to the infection itself,' is not supported by the evidence. For example, although certainly patients can unexpectedly develop pulseless electrical activity arrest and hence die *of* asystole,[6 7] most patients die *with* asystole, not of it, as a result of an underlying heart condition or some other end-stage disease. Here it is posited that claiming 'sepsis' to be a main 'cause of death' in hospitalized ICU patients in the USA and in other advanced care systems not only biases the science used to model it, but also the approaches to treat it.[7 5]

A recent consensus panel was convened to consider a new definition of sepsis. After years of deliberations, it was defined as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection.'[8] Note use of the term '*caused*'. Given this definition, it is easy to understand the motivation of investigators to design host-targeted, immune-based therapies informed by currently available, yet inappropriate animal models (ie, cecal ligation and puncture (CLP) vida infra). For example, when the COVID-19 pandemic appeared, the condition was declared by some to be one of 'viral sepsis,' and thus amenable to treatment directed at the 'dysregulated host response.'[9] Despite numerous failed trials with this approach, including the use of steroids where the effect size was analyzed to be small and occasionally harmful,[10–13] the appearance of vaccines that could neutralize the virus and the development of drugs that killed the virus[14] emerged as most effective.[15] Although targeting the immune dysregulation was clearly less effective than eliminating or neutralizing the offending pathogen, proponents argued and continue to argue, that pathogen-directed therapy should be accompanied by some type of immune modulation as the host response to infection is clearly maladaptive[16] and can be pharmacologically

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manipulated to improve outcome.[17] Although this latter concept is not disputed here, given that the 'sepsis response' is considered to be a discrete entity itself, it is not surprising that host-centered research continues. Yet a major part of this inappropriate focus is the assumption the microbial component is under control by the invariable use of antibiotics and therefore modulating the host response will lead to an improved outcome. Unfortunately, despite cultures and imaging studies being negative, no critically ill patient with a life-threatening infection is ever truly 'sterile.' The effect of the antibiotics and the role of the microbiome and its metabolites or the transition of the microbiome to a pathobiome (perhaps from antibiotic use itself) is often dismissed as relevant to outcome.[18]

Perhaps one element that promotes confusion in this field is the idea that although a pathogen may be the initial trigger of the sepsis response, it is the 'runaway inflammation' that continues to cause organ damage. Again, this assumes that the antibiotics alone are effective at eliminating the infectious agent.[9] Among those espoused to this view is the claim that 'sterile sepsis' can occur from inflammation alone.[19] This idea may have developed as severe acute pancreatitis (SAP) and other life-threatening problems (ie, non-infectious acute respiratory disease syndrome (ARDS), systemic inflammatory response syndrome (SIRS),[20] cytokine release syndrome[21]) began to be considered as classic cases of 'sterile sepsis' given that no abscess on imaging or infection by culture could be demonstrated.[22 23] A debate then centered around whether to administer antibiotics to such high-risk patients despite the absence of a focus of infection.[24] Yet declaring SAP and other disorders to be 'sterile' when patients are critically ill, administered antibiotics, invasively instrumented, mechanically supported, and regularly exposed to healthcare-associated pathogens seems untenable. Critically ill patients have been shown to develop altered gut barrier function, a propensity to harbor resistant and virulent pathogens in the gut and other tissues, and frequently develop gut-derived bacteremias.[25] These issues compelled many to empirically treat patients with SAP and other so-called 'sterile' disorders with broad-spectrum antibiotics, reasoning that the gut microbiome's transformation to a 'pathobiome[26] may play a central role in driving the sepsis response.[27] Thus declaring a state of 'sterile inflammation' when the patient is anything but sterile and when antibiotics are invariably administered seems to controvert the very claim made regarding 'sterility.' These and many other such studies do not necessarily justify the claim that the 'host response to a suspected infection' is the driving cause of the disorder, nor do they clarify the extent to which pathogen colonization of a critically ill host is a cause or consequence of the response itself.[28] Regardless, there are few, if any practitioners who would withhold antibiotics during the treatment of a so-called 'septic' critically ill patient with SAP based on the assumption that the entire process is due to 'sterile inflammation,' as is often the case after a bone marrow or stem cell transplant.[29 30]

Therefore, the time has come to challenge current definitions of sepsis and redirect and limit inappropriate experiments in animals. As such, the following is proposed:

1. *Coding of sepsis in the medical record.* Coding all patients who are in an ICU or similar situation with a life-threatening state and organ failure as being diagnosed with 'sepsis' must be changed. More appropriate descriptions such as 'Life-threatening infection with organ failure' with 'end-stage cancer' might be better. Explicitly qualifying the patients underlying comorbidities, end-of-life issues, futile care, or 'hospice qualifying conditions' is needed before claiming 'sepsis' to be the cause of death. Although death records and administrative claims data are important sources of this information, they provide different estimates of sepsis-related mortality versus deaths from the sepsis process itself.[31] The blurry lines between cytokine response syndrome, SIRS and ARDS, when all conditions are simply coded as 'sepsis,' remain problematic. This is especially the case when an offending pathogen(s) is neither suspected nor isolated or when an unrecoverable injury (ie, postcardiac arrest ischemia-reperfusion injury, profound hemorrhagic shock with multiple organ failure (MOF), *in extremis* trauma-related MOF) is present.[32]
2. *Pathogen genotyping.* A more in-depth understanding of the molecular characteristics, antibiotic resistance genes and phenotype of the microbes involved in the sepsis continuum is needed. This includes those pathogens foreign to the host as well as those intrinsic to the patient's native microbiota. Although often unavoidable, the empirical use of broad coverage antibiotics in critically ill patients with a suspected diagnosis of 'sepsis' can disrupt the gut microbiome in ways that may adversely affect outcome.[33] Although the worldview of sepsis is that it is an immunologic host-centered disorder that is pathogen-agnostic, an overlooked fact is that in the USA and other Western countries, most patients without a fatal underlying disorder (ie, >80%), actually survive the infectious episode with antibiotics and supportive care.[34 35]
3. *Reconsidering the CLP model as representative of human sepsis.* Declaring the CLP model in rodents to be most representative of the human disorder remains highly problematic. Despite its many criticisms, this model remains actively in use today, and its results continue to be published in high-impact journals.[36] Unfortunately, the field continues to insist that use of the CLP model can uncover host-directed targets that will modify outcome despite acknowledging its failure to inform effective therapy for the human condition.[37] Despite the knowledge that the CLP model exposes rodents to commensal rodent microbes (not human microbes) extruded into the peritoneum, and despite the knowledge that a necrotic/infected cecum is left in place which would never be allowed in a patient, that these aspects neither represent the pathogens to which critically ill patients are exposed[38] nor the standard of care by which they are treated,[39 40] remains unchallenged. The forming abscess from the puncture site is not drained, neither imaging nor surgery is performed, cultures are not taken and the appropriate antibiotics are not administered in line with culture and sensitivity data.[41] Therefore, suggesting that interrogating immune and inflammatory pathways with the CLP model will be an effective approach to inform how to treat the human condition seems ill-advised.[39] Dismissing the role of the microbiome in the response to infection also is a major flaw in this approach.[18] Finally, rodents feed on a plant-based, high-fiber, low-fat, low-carbohydrate diet, unlike most patients in the ICU with a life-threatening infection/injury.[42] Breeding of rodents raised in a laboratory under specific pathogen-free conditions differs significantly from those raised in the wild.[43] Diet-dependent metabolites from the gut microbiome enrich the plasma with agonists that target the aryl hydrocarbon receptor (AhR) resulting in enhanced heart, lung, liver, and kidney function,[44] and enhanced survival in mice after peritoneal infection.[4546] Critically ill patients have been demonstrated to become depleted of important gut microbiota-derived metabolites that activate the AhR, such as tryptophan.[47] Unfortunately, host-directed therapies that are discovered to rescue mice from CLP models, as currently employed, invariably fail in human trials.[48]

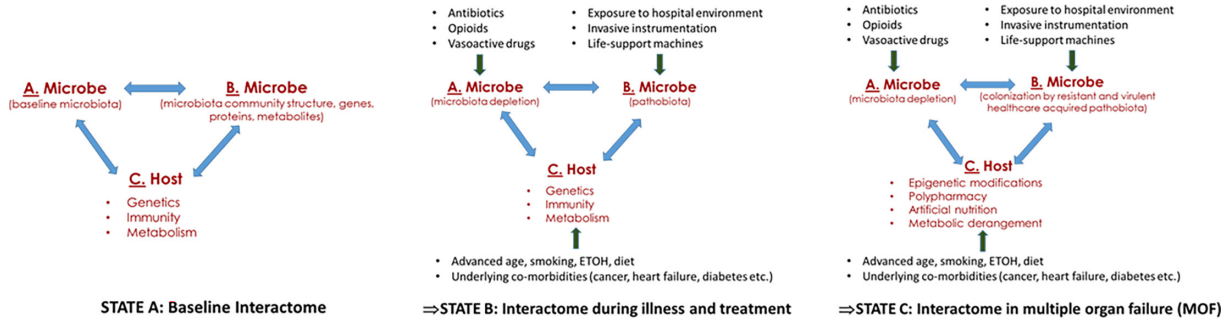

Figure 1 The sepsis 'Interactome.' Critically ill patients hospitalized and cared for in the intensive care unit (ICU) undergo a rapid alteration in their gut microbiome that shifts to a 'pathobiome' from exposure to hospital-associated pathogens, the initial insult itself, the invariable exposure to multiple antibiotics, polypharmacy, invasive procedures, surgery, hyperoxia, indwelling catheters, etc. Bidirectional molecular communication across multiple compartments, species and kingdoms (termed telesensing[65]) has been described and creates a highly complex, stochastic and fluid ecosystem that is challenging to categorize, track and modulate towards recovery. Attempting to unbundle the various components to uncover a single druggable target belies the matchless web of dense dynamic interactions that occur when individual cases are considered to be unique based on the prior and current exposure to pathogens, the pharmacologic agents being used, and the response of the host along the continuum of the interaction. ETOH, Alcohol.

4. *Expanding the definition of virulence*. Perhaps a more holistic approach to infectious disease and sepsis pathobiology would be useful. Considering 'virulence, harmfulness or clinical infection' to be neither a property of the pathogen nor that of the host, but rather it is a property of their interaction, as others have suggested, may advance the field.[49 50] Such a view requires accounting for all genes, be they host or microbial, proteins or metabolites within the 'hologenome,' including those that occur during the course of the sepsis continuum as the patient's microbiome transitions to a pathobiome.[51–53] In addition, the application of the 'molecular' Koch's postulates of infection pathogenesis may also be useful when framing the process of sepsis due to a major infection.[54] The notion that pathogen-agnostic approaches will suffice as they target the 'dysregulated host response' needs to be reconsidered.[55] Clinicians treating the protean manifestations of sepsis understand that managing the complex and dynamic multidirectional, interspecies and interkingdom interactions is challenging and often involves treatment based on incomplete information[56] (see figure 1).
5. *The emergence of antibiotic resistance*. Finally, the escalating use of empirical broad-spectrum antibiotics in all patients with the diagnosis of 'sepsis'[40] is not an evolutionarily stable strategy, to quote Professor Richard Dawkins.[57] Although withholding antibiotics in critically ill, 'septic-appearing' patients is extremely challenging when faced with a patient *in extremis*, overprescribing antibiotics carries the long-term problem of promoting the emergence of antibiotic-resistant organisms.[58]
6. *A plea to use human pathogens to model human infection*. Given that each and every infection-related pathogen is evolutionarily unique given the genes it acquires during its life history, the very pathogens that infect humans must be introduced into experimental models. For example, intraperitoneal injection of a cecal slurry admixed with human healthcare-associated pathogens (ie, *Pseudomonas aeruginosa*, *Stappylococcus aureus*, *Enterobacteriaceae spp*) could provide a more relevant infection-related stress compared with the standard CLP model.[59] Use of non-inbred wild mice in such experiments could be exposed to the same antibiotics to which critically ill infected humans are exposed. Additionally, mice (or other animals) in these experiments could easily be exposed to high concentrations of oxygen (as occurs clinically and is known to eliminate key health-promoting obligate anaerobes).[60] Animals could also be made to consume a liquid, sterile, fiber-free diet (as occurs clinically).[42] Finally, animals could be implanted with a slow-release opioid pellet (as others have shown directly enhances bacterial virulence and suppresses immunity).[59 61] In some cases, tumor-bearing mice could be used to recapitulate an underlying comorbidity, which others have shown has a major influence on the outcome from CLP.[62]

In summary, a breakthrough in sepsis research is possible were its host-centric worldview recognized to be dependent on, and directly influenced by human-relevant pathogens, the disrupted and evolving microbiome, the underlying disorder of the patient and its environmental exposures.[56 63] Using the term 'sepsis' to include any patient with a serious life-threatening infection and ignoring the care they are receiving and the underlying comorbidities they harbor, introduces major survivability bias.[64] In conclusion, unpacking the sepsis controversy will require a rethinking of how this complex clinical disorder is experimentally modeled and how it can be improved.

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