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REVIEW
Science

From Sepsis to Pepsis

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Septic shock is a formidable medical problem, with a mortality rate of greater than 20% and the dubious distinction of being the first among all causes of death in intensive care units [1]. Although we understand that septic shock is caused by systemic infection, the molecular mechanisms by which sepsis exerts its effects in totality, including in shock, remain obscure. Therefore, virtually all of the recent clinical trials aimed at reversing septic shock pharmacologically have been unsuccessful. Thus, septic shock remains a condition stubbornly resistant to the miracles of modern medicine, with a considerable risk of death and only supportive treatment available.

He who forgets the past is doomed to repeat it; thus so any discussion of sepsis must begin with a historical perspective on the condition. It was the Egyptians some 4,000 years ago who put forth our first written history of a sepsis-like phenomenon, postulating that a dangerous substance known as "ukhedu" lived in all of our guts and could, if not kept in check, migrate through our blood vessels and even stop our hearts [2]. To stave off this deadly disease, the Egyptians set aside three days each month to give themselves purges and enemas. The Greeks took up the Egyptian concept of ukhedu and generalized it into "sepsis," which referred to putrefaction and was closely associated with things smelling bad (rotting meat, the contents of the colon). Sepsis was in tight balance with a complementary concept, "pepsis," which was associated with things smelling good (a delicious pot roast, an aromatic lemon verbena soap).

Having conceptualized sepsis, I will not linger much longer on the historical basis of our modern day understanding. However, a few highlights are too good to ignore, including a 1718 sketch of the "animalcules" that were initially proposed to cause sepsis (**Figure 1**), a sketch of an early experiment to determine the method of transmission of these animalcules that involved the incubation of various animals in a sealed barrel with putrid material ("miasma") at its base (**Figure 2**), and this description of an 1872 study of the bloodborne transmission of putrid material: "Casimir Davaine [a French physician who also discovered anthrax] injected pu-

trid blood under the skin of a rabbit; it died in 40 hours. The blood from that rabbit killed the next

Figure 1. Concept drawing of an animalcule, *adapted from [2].*

rabbit, and so on for 25 rabbits; the lethal dose became progressively smaller" [2].

These highly sophisticated experiments eventually succeeded in showing that sepsis was caused by systemic infection, helped along the way by the discovery of "bacteria." Louis Pasteur and Robert Koch set forth the germ theory of disease circa 1860, and since then, our understanding of sepsis has slowly advanced. We have come to understand that the immune stimulation by infection and the resulting immune response play important roles in inciting sepsis. For example, it was demonstrated almost 40 years ago that adoptive transfer of bone marrow from mice injected with endotoxin (a.k.a. lipopolysaccharide, or LPS) into other mice was sufficient to kill the recipient animals [3]. Follow-up work identified particular cytokines—in particular IL-1, IL-6 and TNFα—that were responsible for mediating the host inflammatory response to LPS and that could be blocked to prevent septic shock in mice [4]. Indeed, sepsis has been cured many times over in mice using anti-cytokine and anti-endotoxin approaches.

However, translation of these discoveries into treatments for human patients has yielded mostly disappointing results, and several landmark studies have been published with shockingly negative results regarding anti-cytokine therapy in sepsis. One study examined 28-day mortality following administration of an anti-TNFα monoclonal antibody in patients with septic shock, and the investigators found no association between treatment and survival [5]. Another large study administered an IL-1 receptor antagonist (IL-1ra) in the setting of sepsis and again found no effect [6]. Additional studies have taken a different track, hypothesizing that giving an immunostimulatory cytokine, such as GM-CSF, might induce proliferation of the cells required to fight sepsis (i.e., macrophages). Those results (16.6% mortality with GM-CSF versus 17.6% without GM-CSF in a meta-analysis) have been resoundingly negative as well [7]. In totality, efforts to translate our developing understanding of sepsis has perplexed investigators and significantly dampened optimism for cytokine-related therapies for sepsis.

Importantly, however, the authors of the IL-1ra study also performed a subgroup analysis of mortality by infection type and showed that IL-1ra therapy may confer a survival benefit in certain Gram-negative infections. Although such an analysis was not pre-specified and their study was not powered to conduct such a subgroup analysis, this result offered the valuable suggestion that distinct infections may operate through distinct mechanisms of sepsis. Supporting this model, a monoclonal antibody against the lipid A domain of endotoxin was shown to be efficacious in Gram-negative

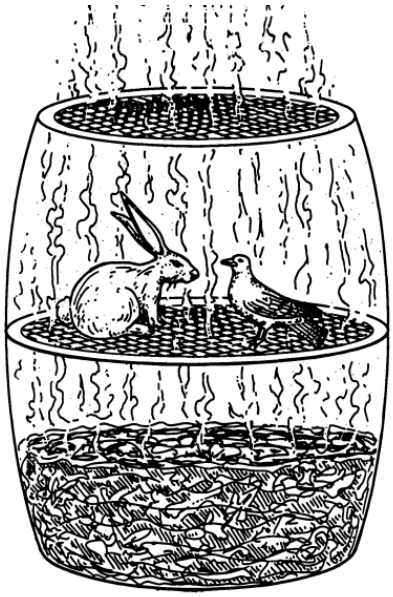

Figure 2. Animals incubating in miasma, *adapted from [2].*

bacteremia (37% mortality with the antibody versus 52% mortality without) [8]. The understanding of sepsis as a heterogeneous disease, defined uniquely by the particular infectious agent involved, has led to a new approach of addressing the problem of septic shock. While anti-IL-1, anti-TNFα, or anti-LPS drugs may be efficacious in the setting of particular pathogens, such as Gram-negative *E. coli*, they may be ineffective or even harmful in the setting of other infections, such as those caused by opportunistic *Candida* or Gram-positive *S. pneumoniae* (**Figure 3**).

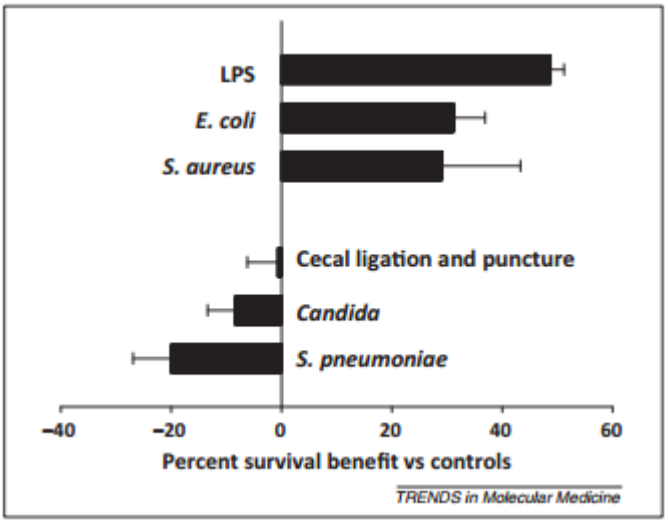

Figure 3. Meta-analysis of mortality in eight different preclinical models of sepsis following treatment with an anti-TNF antibody, *adapted from [12]*.

The challenge, then, is to unravel the molecular mechanisms of the immune response to particular pathogens and to systematically develop drugs that specifically target the molecular basis of sepsis. For example, in the case of LPS, recent immunological research has delved deeply into how LPS is sensed and how that signal is transduced into the production of pro-inflammatory cytokines. One important class of mediators is the inflammasome, a large oligomeric complex that forms in response to an innate immune stimulus. A series of recent studies in mice have demonstrated that LPS can activate a particular NOD-like receptor (NLR) inflammasome known as NLRP3, expressed in macrophages and dendritic cells, via an initial priming event and a successive, direct activation event [9]. NLRP3 then oligomerizes and cleaves a downstream activator, caspase-1, to produce an active protease that goes on to cleave IL-1β and IL-18 into their active forms. Importantly, caspase-1 also cleaves a protein called gasdermin D (GSDMD), which forms pores in the cell's plasma membrane and allows for release of the now-activated proinflammatory cytokines into the extracellular milieu [10]. These findings have rounded out our biological understanding of how inflammation results from infection—LPS stimulates NLRP3, stimulating caspase-1 cleavage, GSDMD production, and IL-1β/IL-18 release into the blood—thus allowing a more coherent understanding of the altered biological state in sepsis and identifying new targets for intervention (i.e., an NLRP3 oligomerization inhibitor if we want to turn down inflammation, or increased GSDMD production if we wish to turn it up). GSDMD activation has been shown to be effective in controlling both *E. coli* and *S. aureus* infection [10], both of which were also responsive to anti-TNF therapy in the setting of sepsis (**Figure 3**), offering a compelling link between the clinical picture of sepsis and our molecular understanding of infection and the immune response.

Altogether, our understanding of the NLRP3 inflammasome offers a compelling model for how we might approach infectious triggers of sepsis in general. One might expect, for example, that exploring other inflammasomes that have not been well characterized (there are 34 different genes coding NLR inflammasomes in the mouse genome) may hold the key to understanding how the immune system senses and responds to distinct infections. If we can identify the particular immune mediators produced in response to particular pathogens as well as the mechanistic basis for said production, we may very well be able to intervene rationally to inhibit or promote production of these mediators as appropriate, thereby effectively controlling sepsis.

This strategy does bring about unique complications. Future clinical trials investigating therapies for septic shock will need to stratify patients by infection type in order to generate appropriate data. To enable such a stratification, improved diagnostics must be developed to identify particular types of infections within a clinically actionable timeframe for septic shock, much in the same way that we culture microbes to understand which anti-

biotics may be efficacious for a given infection. A major key is the clinically actionable timeframe: targeted therapies for septic shock, an acutely deadly condition, will not work if there is a need to culture out infections for a week prior to initiating treatment. Additionally, many episodes of sepsis are not uncomplicated, monogenic infections but rather mixed infections with several different pathogenic organisms with which to contend. In such cases, the appropriate therapies may not be immediately evident, and additional research into more complex models will be necessary. Cecal ligation and puncture, a leading mouse model of sepsis where the mouse's cecum is closed off and punctured within the abdominal cavity to induce systemic infection [11], has so far proved resistant to cytokine therapies and poses a clear illustration of the challenges of complex infections (**Figure 3**).

Still, the first step towards solving these difficult problems is by answering the easier ones. Better definitions of the molecular stimuli, mechanisms, and mediators of inflammation in response to infection will be an important stride toward improving outcomes for patients with distinct and heterogeneous septic manifestations—helping to move patients, as the Greeks might say, from sepsis to pepsis.

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