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Subtypes and Mimics of Sepsis

John A. Kellum, MD, MCCM[a,b,*], **Cassandra L. Formeck, MD, MS**[a,c,d], **Kate F. Kernan, MD**[a,b,d], **Hernando Gómez, MD**[a,b], **Joseph A. Carcillo, MD**[a,b,d]

[a]Center for Critical Care Nephrology, University of Pittsburgh, Pittsburgh, PA 15213, USA

[b]Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

[c]Division of Nephrology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

[d]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA 15224, USA

SUMMARY

Inflammation is central to many acute conditions across the spectrum, from infection to sterile tissue injury to rheumatic diseases and to drug/toxin reactions. The molecular basis for this nonspecific response involves various receptors and immune effector cells and has been elucidated, at least in part, in recent years. Sepsis is a heterogenous and imprecise syndrome that likely includes multiple phenotypes, some of which may be amenable to specific therapies. Progress in developing new therapies for sepsis almost certainly will require focusing on specific subsets of patients. Furthermore, careful evaluation of patients for sepsis mimics and for treatable diseases manifesting within the clinical classification of sepsis is key to improving care. Because sepsis is a common condition, it is easy to overlook unusual causes of organ failure and to succumb to confirmation bias about the nature of a patient's illness. Careful attention to past medical and family histories and specific use of an array of diagnostic testing and subspecialty input can help identify potentially treatable diseases masquerading as typical sepsis. The increasing use of artificial intelligence to sift through patterns of clinical characteristics also may help advance research into this complex area.

Keywords

Endotoxin; Endotoxemia; Polymyxin B; Blood purification; Macrophage activation syndrome; Atypical hemolytic uremic syndrome

INTRODUCTION

The "Third International Consensus Definitions for Sepsis and Septic Shock" define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Other causes of life-threatening organ dysfunction, however, can be present in patients with

[*]Corresponding author. Center for Critical Care Nephrology, 3347 Forbes Avenue, Suite 220, Pittsburgh, PA 15213. kellum@pitt.edu, Twitter: kellumja (J.A.K.).

known or suspected infection. Some are sepsis mimics in that a patient does not have sepsis but has another syndrome that is mistaken for sepsis (eg, noninfectious febrile conditions, such as malignant hyperthermia and serotonin syndrome—see “Common presentations of rare drug reactions and atypical presentations of common drug reactions” in this issue). In other instances, a patient technically meets criteria for sepsis but has dysfunction that is not directly attributable to infection. Because the host response is not routinely measured directly and cannot easily determine the presence of a dysregulated state, it is a matter of conjecture as to the cause of organ dysfunction in a patient with infection. Consider the common scenario where a patient presents with fever, cough, and infiltrates on chest radiograph, a presentation most often consistent with pneumonia. If that patient then develops acute kidney injury (AKI), the combination of organ dysfunction and presumed infection meets criteria for sepsis. Suppose, however, that the patient has heart failure and an upper respiratory tract infection? Suppose the AKI is related to the heart failure or its treatment? These clinical uncertainties, in which the organ dysfunction may not be directly attributable to the host response to infection, happen regularly. In a study of 2029 patients admitted to a hospital with a clinical diagnosis of community-acquired pneumonia, a diagnosis of pneumonia subsequently was ruled out in 134 patients (6.6%).[2]

In addition to these sepsis mimics, there also are instances when patients indeed may have sepsis but have an unusual subtype that may be amenable only to therapy specific for that subtype. This review considers this latter group of rare and not-so-rare conditions that may be responsible for a disproportionally high number of deaths from sepsis. Importantly, existing and emerging therapies are available for these subtypes. Although controversial, these therapies offer potential benefit in some patients currently labeled as having typical sepsis.

PATHOPHYSIOLOGY OF SEPSIS

The pathophysiology of sepsis is complex and incompletely understood.[3] Sepsis currently is conceptualized as a result of an imbalance in the systemic inflammatory response that affects immune function, the neuroendocrine axis, and coagulation, ultimately resulting in organ injury. Inflammation plays a critical role in the pathogenesis of sepsis, beginning with—in response to invasive pathogens—an initial release of cytokines, damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs) (Table 1). PAMPs stimulate monocytes to release procoagulants and other mediators to activate platelets, neutrophils, and endothelial cells. DAMPs—comprising histones, chromosomal DNA, mitochondrial DNA, nucleosomes, and a variety of proteins—are released from neutrophils and activate inflammation and coagulation. Damaged endothelial cells further promote coagulation through disruption of the glycocalyx and expression of von Willebrand factor. Shedding of the glycocalyx leads to exposure of E-selectin and other adhesion molecules, leading to adhesion of platelets and neutrophils, causing thrombus and fibrin formation.

Because inflammation is not specific to infection, inflammatory diseases most easily are confused with infection. This includes many rheumatic diseases as well as conditions associated with extensive tissue injury, such as polytrauma, burns, pancreatitis, and chemical

pneumonitis. These conditions release various DAMPs into the circulation, engaging the molecular machinery that produces the same cardinal features of infection, including fever, increased capillary permeability, and activation of immune effector cells.

PAMPs produce the same proinflammatory effects as DAMPs. Endotoxin, the most important and well-characterized PAMP, is particularly well suited to causing systemic inflammation, activating the immune response through multiple pathways, including some shared by DAMPs. Responses to endotoxin vary throughout the animal kingdom, with mammals generally the most sensitive; humans are exquisitely sensitive to endotoxin compared with other mammals.[4] The gastrointestinal (GI) tract is an enormous reservoir for endotoxin—some estimates suggest that enough endotoxin is present inside the gut of a single human to kill an entire city if given intravenously.[5] For this reason, any condition that jeopardizes intestinal barrier function from inflammatory bowel disease to ischemic enteritis can produce endotoxemia. COVID-19 infection also is a cause of endotoxemia, presumably from the GI tract.[6]

Because inflammation on a systemic level is dangerous, endogenous mechanisms to regulate inflammation exist and are vital for survival. Both proinflammatory and anti-inflammatory cytokines are released, and engagement of complement and coagulation cascades have built-in braking mechanisms to ensure the system is controlled as much as possible. Sepsis is the most common form of dysregulated inflammation, but others also exist. This review considers 3 syndromes that can mimic sepsis or exist as subtypes of sepsis. These syndromes are macrophage activation syndrome (MAS), atypical hemolytic uremic syndrome (aHUS), and endotoxemic shock. Finally, the overlap between these syndromes and what recent studies using artificial intelligence reveal about subtypes of sepsis and how they might relate to these syndromes are examined.

EVIDENCE FOR PHENOTYPIC AND GENETIC VARIATION IN SEPSIS

Sepsis may cause a wide range of organ failures, both in terms of which organs are involved and the severity that is observed (Fig. 1). There is no clear connection between the severity of organ failure and the number of organs failing. For example, a patient may have severe, even refractory shock but remain on room air with only mild dysfunction of the kidneys and brain. Conversely, some patients develop severe AKI or acute respiratory distress syndrome (ARDS) but maintain appropriate hemodynamics. Hospital mortality does correlate with the number of organs affected as well as the severity, but enormous heterogeneity exists.

In adults, sepsis disproportionally affects older patients, many of whom may have underlying organ dysfunction. Classifying organ dysfunction in sepsis in the presence of underlying chronic disease is challenging: classification systems for sepsis-associated organ failure like the sepsis-related organ failure assessment (SOFA) conflate acute and chronic organ dysfunction.[7] For example, the score for a patient with chronic kidney disease, hepatic cirrhosis, and home oxygen therapy for chronic lung disease could start at 6 points or 8 points prior to assessing any acute illness-related features. Although many investigators are careful to exclude points for chronic disease, it often is difficult to know what was present prior to sepsis, especially if a patient has not had regular medical attention. To make matters

worse, interventions for sepsis can add to organ dysfunction. For example, patients given large amounts of fluids for shock may develop respiratory failure and require mechanical ventilation. They also may require sedation to tolerate mechanical ventilation, and this may, in turn, worsen shock. Antibiotics and other medications can be nephrotoxic or lead to thrombocytopenia or liver dysfunction. Thus, in any given patient, some degree of organ dysfunction may be from the treatment of sepsis rather than the sepsis itself.

Some amount of phenotypic variation also may come from genetic differences. A Danish study showed a near 6-fold increase in the risk of death from infection before age 50 for adoptees whose biological parents also died from infection under 50 years of age.[8] Despite great variation in host responses, identifying genetic variants contributing to sepsis outcomes has proved challenging. Most genomic studies in sepsis have treated all patients as a single group, assuming shared genetic risk factors. They also have focused on correlations between common polymorphisms and sepsis outcome with limited functional studies to support associations.[9,10] Recently, the authors performed whole-exome sequencing (WES) on a small number of adults with sepsis[11] taken from a large cohort enrolled in the Protocolized Care for Early Septic Shock (ProCESS) trial.[12] The hypothesis was that certain genetic variants implicated in the pathogenesis of MAS and aHUS, as well as conditions like cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever, might be more common in patients with sepsis manifesting extreme inflammation. Using serum ferritin greater than 7000 ng/mL as a screen, the authors performed WES on 6 patients. All 6 exhibited 1 or more gene variants associated with these conditions (Table 2).

Although all the variants associated with MAS and aHUS reported in this study have been classified as pathogenic or likely pathogenic, they may or may not have been causal. Moreover, even if genetic variation played a role in the extreme phenotypes exhibited in these cases, the application of immunomodulatory therapies to septic individuals with these variants is of unclear benefit or harm. These findings provide evidence, however, that screening select sepsis patients can identify unappreciated heritable disease and could facilitate genome-driven precision medicine in the treatment of sepsis.

MACROPHAGE ACTIVATION SYNDROME

MAS is life-threatening complication of systemic inflammatory disorders, most commonly systemic juvenile idiopathic arthritis (sJIA), adult-onset Still disease, and systemic lupus erythematosus. Clinical and laboratory features of MAS include sustained fever, hyperferritinemia, pancytopenia, fibrinolytic coagulopathy, and liver dysfunction.[13] Thus, MAS looks much like sepsis, especially in cases where pancytopenia is absent or when only thrombocytopenia manifests. Typically, an underlying history of rheumatic disease makes a diagnosis easier, but MAS easily can be confused with sepsis. To make matters worse, certain infections can lead to MAS, notably Epstein-Barr virus (EBV), and, more recently recognized, severe cases of COVID-19.[14] The initial reports of cytokine storm in COVID-19 prompted many of the trials testing immune-modulating therapies for affected patients. Given that sepsis often is bacterial culture–negative, patients who develop clinical features of sepsis rarely have a diagnosis of sepsis challenged or affirmatively disproved. If a patient gets better on antibiotics, confirmation bias about the cause of the disease is succumbed to.

Likewise, if a patient does not improve, confirmation bias leads to assuming that the sepsis was refractory to therapy, rather than sepsis not being the cause of the patient's illness.

A definitive diagnosis of MAS can be elusive, although careful physical examination and directed laboratory evaluation can establish a diagnosis. Cardinal features of MAS include persistently high fevers, hepatosplenomegaly, hyperferritinemia, pancytopenia, increased liver enzymes, increased fibrinogen, and hypertriglyceridemia (Table 3). Bone marrow biopsy that reveals macrophage hemophagocytosis also is suggestive, especially if there increased CD163 staining. To calculate the probability of MAS from these findings, an HScore has been developed,[15,16] and on-line calculators are available (such as at mdcalc.com).

Pathogenesis and Pathophysiology of Macrophage Activation Syndrome

Several recent reviews have characterized the pathogenesis of MAS in detail.[17,18] The prototype disease is familial hemophagocytic lymphohistiocytosis (fHLH), a constellation of rare autosomal recessive immune disorders resulting from homozygous deficiency in cytolytic pathway proteins.[19] In fHLH, defects in natural killer (NK) cell and cytotoxic T-cell function result in uncontrolled expansion of macrophages and T cells,[19,20] which leads to unregulated hypersecretion of cytokines, resulting in hematologic alterations and organ damage (Fig. 2).[21] The term *cytokine storm* often is used in this context but it is important to appreciate that the strikingly high levels of cytokines reported in many studies of fHLH pale in comparison to what can be seen in typical cases of sepsis. For example, Henter and colleagues[22] reported levels of interleukin (IL)-6 between 25 pg/mL and 130 pg/mL in the plasma of children with active fHLH; other studies have reported only modest elevations in IL-6 and tumor necrosis factor levels (226 pg/mL and 24 pg/mL, respectively) in patients with clinically defined MAS in the setting of COVID-19.[23] Meanwhile, patients with bacterial sepsis may have levels of these cytokines many times higher.[24] Expression of cytokines in the periphery, however, may belie the degree of cytokine activation in the tissue (eg, liver), leading to local organ damage.[25] In addition, the efficacy of certain anticytokine therapies (discussed later) strongly argues for an important role of cytokines in the pathobiology of MAS. Whether the defects in NK-cell and T-cell cytolytic function in MAS are acquired or are related to genetic susceptibility is unknown. MAS and fHLH may share some of the same genetics. For example, the same biallelic pathogenic variants in the *UNC13D* gene reported in fHLH have been identified in some patients with MAS in the setting of sJIA.[26] Genetic polymorphisms in the interferon regulatory factor 5 (*IRF5*) gene also have been found to be risk factors for MAS.[27] In other patients, however, no such cytolytic dysfunction or genetic linkages have been found.

Management of Macrophage Activation Syndrome

Definitive clinical trials for MAS are lacking and, therefore, treatment largely is empiric. Historically, high-dose corticosteroids and/or cyclosporine have been used, and in extreme cases etoposide.[18] Plasma exchange also has been tried with variable results. With recent development of specific anticytokine therapies, many more potential treatments for MAS exist (Table 4). Definitive evidence as to which of these agents is most effective, however, still is lacking. COVID-19 has afforded an opportunity to test various immune-modulating

drugs in the setting of infection-triggered inflammation, and some cases of COVID-19 resemble MAS. The RECOVERY trial randomized patients with COVID-19 to receive tocilizumab and used C-reactive protein (CRP) levels above 15.0 mg/dL as an indication of severe inflammation rather than MAS itself,[28] showing a mortality benefit, whereas a majority of other trials were either neutral or suggested harm. A recent follow-up analysis of the CORIMUNO-TOCI-1 trial[29] found a statistical interaction with CRP, such that patients with levels above 15.0 mg/dL experienced a large benefit in terms of 90-day mortality (9% with tocilizumab vs 35% with usual care; hazard ratio 0.18; 95% CI, 0.04–0.89) whereas no benefit was observed when CRP was below this threshold. Other immune-modulating therapies are being actively tested in COVID-19; whether the use of CRP for patient selection will prove useful is unknown.

Sepsis with Macrophage Activation Syndrome Features

An infectious trigger often is detected in sJIA patients with MAS, and EBV is the most common causative agent.[18] Even in patients without underlying rheumatic disease, however, there is a key question as to whether MAS could be triggered by sepsis in a small number of patients with particularly aggressive disease.[30] Prompt recognition and increasing compliance to best practices have reduced in-hospital mortality from sepsis for most patients over the past decade.[31–33] Some patients appear to be refractory to standard therapy, however, and some experts have hypothesized that MAS or a MAS-like condition might complicate some cases. One line of evidence in support of this hypothesis comes from a study by Shakoory and colleagues,[34] in which a post hoc analysis was performed on a randomized clinical trial investigating the effect of anakinra on mortality in sepsis. The investigators hypothesized that anakinra would improve survival in the subset of patients with sepsis who also presented with features of MAS, defined by concomitant hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC). The investigators demonstrated that compared with placebo, anakinra resulted in a 50% relative risk reduction in mortality only in the subset of patients with features of MAS (approximately 6%) whereas the drug had no effect on the remaining patients.[35] The clinical phenotype of HBD plus DIC as a screen for MAS has the advantage that it is simple and objective and has been used as a more practical strategy for identifying patients with features of MAS during sepsis that may respond to anakinra.[11,35,36,37]

ATYPICAL HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome (HUS) is characterized by hemolysis and renal failure. Typical HUS is caused by strains of bacteria (mainly *Escherichia coli*) producing Shiga toxins (STEC-HUS),[38] whereas an atypical form (aHUS) is associated with genetic or acquired disorders leading to dysregulation of the complement system.[39,40] Unlike typical HUS, aHUS occurs in the absence of Shiga toxin–producing bacterial infection and may be triggered by atypical infectious, drug, or environmental exposures, leading to microangiopathy, thrombocytopenia, and AKI. Cases of HUS can be familial or sporadic, and it is estimated that between 40% and 60% of affected patients harbor a rare variant that constitutes a genetic risk for disease.[41] More than 120 variants affecting various complement components and regulators have been described to date, accounting for 50%

to 60% of cases.[42] Importantly, aHUS is thought to be an extremely rare disease, affecting fewer than 1 in 1 million adults and 3.5 per million children.[43] As a result, the disease rarely is considered, especially in patients with plausible alternate explanations for AKI, thrombocytopenia, and multiorgan failure, such as sepsis. The authors have discovered that more than 20% of patients in their center with sepsis and AKI develop severe thrombocytopenia (<50,000/mL) during their hospital course and yet only approximately 1% are diagnosed with aHUS or thrombotic thrombocytopenic purpura (TTP). As discussed previously, the authors also have identified genetic variation in some adults with septic shock known to be consistent with aHUS.[11]

Elsewhere in this issue, aHUS is discussed in detail, along with other forms of thrombotic microangiopathy in the context of uncommon causes of AKI—see Formeck and colleagues. Like MAS, aHUS is a disease of multiorgan failure that can be triggered by infection. Thus, it is difficult to distinguish from sepsis, a disorder that commonly causes AKI and thrombocytopenia (see Table 3). aHUS, however, causes thrombotic microangiopathy distinct from DIC and TTP. With DIC, coagulopathy also is present and the international normalized ratio (INR) usually is increased above 1.5. aHUS should be suspected in patients with sepsis and AKI when thrombocytopenia is unexplained by DIC, especially when there is evidence of hemolysis (eg, increased lactate dehydrogenase). Evidence of microvascular hemolysis on peripheral blood smears (eg, schistocytes) can be helpful but may be absent or episodic. aHUS can be distinguished from TTP on the basis of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) enzyme activity measurement.

ENDOTOXEMIC SHOCK

Endotoxin, also known as lipopolysaccharide (LPS), is a stabilizing molecule in the outer membrane of the cell wall of gram-negative bacteria. Endotoxin is highly immunostimulatory in mammals, especially humans, despite the fact that enormous quantities of it are carried around in the intestines—more than a million times the lethal dose if given intravenously.[5] Endotoxin can trigger all of the cardinal feature of sepsis on its own and likely is a modulating factor during the syndrome. This, in part, likely explains why the molecule and particular types of gram-negative bacteria have dominated sepsis experimental models and drug development for decades. Humans are especially sensitive to endotoxin, more so than any of their cousins in the animal kingdom.[4] This exquisite sensitivity leads to a variety of responses, including activation of immune cells, which produce inflammatory proteins (eg, cytokines) that also are cytotoxic and whose actions result in the release of various DAMPs (see Table 1). This process ensures that even if the endotoxin exposure is transient, there will be a robust immune response lasting for some time.

In 1993, a laboratory technician self-administered 1 mg of Salmonella endotoxin, dissolved in sterile water, intravenously, in an attempt to treat a recently diagnosed tumor.[44] The patient presented 2.5 hours later in profound shock. Although the patient ultimately recovered, over the course of the next 72 hours, all the cardinal features of sepsis developed, including fever, tachycardia, increased cardiac output, leukocytosis with up to 45% immature neutrophils, thrombocytopenia with evidence of DIC, AKI, elevated hepatic

transaminases, and mild hypoxemia requiring supplemental oxygen. Remarkably, the serum lactate concentration was only 2.0 mmol/L. The patient received a 100-mg dose of HA-1A antibody (Centoxin, Centocor, Malvern, Pennsylvania), a human IgM antibody for the lipid A domain of endotoxin, 23 hours after the endotoxin injection. The patient ultimately made a complete recovery and appeared to resolve the illness rather rapidly. Although fever remained for 60 hours and vasopressors were required for almost as long, sustained organ failure did not occur. The inflammatory response was attenuated substantially from its peak already at 24 hours after endotoxin injection, although it was still very abnormal and subsequent testing was not performed. The discrete, nonsustained nature of the exposure, perhaps helped by the HA-1A antibody, resulted in a relatively mild case of sepsis. The patient, however, developed rather severe shock, receiving 2 vasopressors and more than 15 L of resuscitation fluid. It is intriguing to speculate whether a different predisposition or a more sustained exposure would have resulted in a different outcome.

Endotoxin as a Trigger for Macrophage Activation Syndrome and Atypical Hemolytic Uremic Syndrome

Endotoxin is a potent activator of macrophages (see Fig. 2) and is the classic stimulus used in vitro. The patient, described previously, with self-administered endotoxemic shock had a serum IL-6 concentration of 263,510 pg/mL measured 6.8 hours after the injection.[44] Compared with the so-called cytokine storm reported in many patients with MAS, this is several orders of magnitude higher. Could ongoing exposure to endotoxin produce an MAS picture? Although persistent exposure to low doses of endotoxin induces a phenomenon known as endotoxin tolerance,[45] continuous infusions of high doses are required to induce sepsis in nonhuman primates[4] and a more sustained exposure to endotoxin might be expected to lead to irreversible organ failure in humans.

Endotoxin also is a potent activator of complement and is capable of activating both the classical and alternative complement pathways.[46] aHUS is a disorder of complement activation and it known that endotoxin can trigger aHUS in susceptible hosts. Typical HUS is caused by Shiga toxin, and, although it originates from some of the same species of bacteria, Shiga toxin and endotoxin are quite distinct. The patient described previously certainly had complement activation, although it was rapidly brought under control. It is plausible that sustained endotoxemia might provoke aHUS, even in humans without a genetic predisposition, because approximately 40% of cases have no known genetic association.[42]

Sources of Endotoxin in Sepsis

Although endotoxin is ubiquitous in the environment, in the soil, in food, and on skin,[5] endotoxemia rarely comes from such sources. Gram-negative infections may result in endotoxemia and antibiotics may release it as they kill bacteria. Each person carries, however, a massive reservoir of endotoxin in the intestines. Estimates of the amount of endotoxin present in GI tracts are as high as 10 g to 50 g.[5]

In the GI tract, the chemical barrier of the mucosal layer and the cellular immune system maintains a symbiotic relationship with commensal bacteria.[47] Tight junction

proteins are required for the maintenance of epithelial barrier integrity. The intracellular signaling transduction system and several extracellular stimuli, including cytokines, small GTPases, and post-translational modifications, dynamically modulate the tight junction protein complexes. An imbalance in these regulators leads to compromised barrier integrity and is linked with pathologic conditions.[47] Bacterial products, chiefly endotoxin, can cross the dysfunctional barrier and result in endotoxemia.

Humans and other mammals tend to be most sensitive to endotoxin from commensal gram-negative bacteria—organisms that constitutively live on or inside the host. These organisms have 6 acyl chains on the lipid A portion of the molecule (hexa-acylated lipid A) and these forms of endotoxin are most immunostimulatory in mammals, whereas LPS with fewer acyl chains is less so. Endotoxin with hexa-acylated lipid A is found in mainly bacteria that live in the lung and gut mucosa of mammalian hosts, such as commensal *Enterobacteriaceae* (eg, *Escherichia coli*, *Klebsiella*, and *Salmonella*).[4]

Management of Endotoxemia

Efforts to neutralize endotoxin began in the 1970s and accelerated as the molecular structure of endotoxin was characterized.[48] Various antibodies to endotoxin have been studied, including the HA-1A antibody used in the case discussed previously. Clinical trials testing these therapies have been discouraging. Few studies, however, have examined the effect of these treatments in patients with detectable endotoxemia.[49,50] An analysis of HA-1A found that this monoclonal antibody reduced mortality among 27 patients with detectable endotoxemia but not for 55 patients without detectable endotoxemia.[50] In general, however, results in the endotoxemia-positive subgroups of patients have not been positive.[51] The reasons for the disconnect between strong preclinical data, biologic rationale, and negative trials have been pondered in multiple reviews.[48] Potential explanations include problems with the agents themselves, study populations, and timing of therapy.

An alternative strategy to pharmacologic neutralization of endotoxin is removal of the molecule using hemoperfusion. Polymyxins are a group of cyclic cationic polypeptide antibiotics that have well characterized endotoxin binding. Although toxicity limits the clinical use of polymyxin B as an antibiotic, polymyxin B can be bound to a hemoperfusion column, and circulating endotoxin can be removed effectively through exposure to immobilized polymyxin B without the systemic toxicity. This method has been available in Japan since 1994 and received CE mark approval in Europe in 1998. More than 100,000 patients have been treated in more than a dozen countries.[52] Analyses of clinical data from a national Japanese database using propensity matching and other techniques has demonstrated benefit in the range of 3% to 7% absolute risk reduction for hospital mortality.[53,54] No clinical trials have been adequately powered to find an effect size in this range. The 2 largest trials to date, the ABDOMIX trial in France[55] and the EUPHRATES trial in the United States,[56] did not find a survival benefit for polymyxin B hemoperfusion. The EUPHRATES trial, however, was significantly different in design compared with other trials. Midway through the trial, enrollment was restricted to patients with multiple organ dysfunction score (MODS) of 9 or less (MODS range, 0–24, with 24 the worst possible score),[57] and the MODS group with a greater than 9 score became the primary analysis.

This change was prompted by evidence that any benefit appeared to be limited to patients with greater organ dysfunction. A similar conclusion recently was reached by Fujimori and colleagues[54] in an analysis of more than 4000 patients from Japan. In this analysis, the therapy was most effective for patients with more organ failure.

Another significant difference between the EUPHRATES trial and other studies was the use of the endotoxin activity assay (EAA). EAA is an immunoassay that uses anti–lipid A monoclonal antibody and whole blood. Endotoxin in the blood sample binds with the antibody, and this antibody-antigen complex stimulates neutrophils that also are in the sample. Reactive oxygen species produced by neutrophils then are measured by the luminol chemiluminescence reaction. Basal and maximally stimulated samples are measured in parallel as negative and positive controls, and endotoxin activity in the sample is expressed as a relative value (EAA level).[58] A level of 0.60 or higher is considered the threshold for high endotoxin activity and is associated with increased intensive care unit (ICU) mortality.[59] Enrollment into the EUPHRATES trial was restricted to patients with septic shock who were found to have EAA 0.60 or higher.

Overall, the EUPHRATES trial showed that even in the per protocol analysis restricted to patients with a MODS greater than 9, 28-day mortality was 33% with hemoperfusion versus 36.4% with sham, a difference that was not statistically significant.[56] The EA, however, cannot quantify circulating endotoxin precisely when EAA levels are 0.90 or greater and values in this range may not represent treatable levels. A reanalysis of the EUPHRATES trial data revealed that 17% of patients had EAA greater than or equal to 0.90. When these patients are removed, 28-day mortality was 26.1% for polymyxin B hemoperfusion versus 36.8% for sham (risk difference 10.7%; odds ratio 0.52, 95% CI, 0.27–0.99; $P = .047$).[60] These findings prompted the design of an ongoing trial in the United States.

SEPSIS AND ARTIFICIAL INTELLIGENCE

Sepsis is a heterogeneous syndrome; identification of distinct clinical phenotypes could allow for more precise therapy and improve care. Machine learning is a branch of artificial intelligence based on the notion that systems can learn from data, identify patterns, and make decisions without human intervention. If the input data are comprehensive, the results can be considered unbiased, and discovery using these approaches can complement more directed hypothesis testing and help generate new hypotheses. Seymour and colleagues[61] used machine learning and simulation to derive clusters of clinical characteristics (ie, phenotypes) from patients meeting the Sepsis-3 criteria[1] within 6 hours of hospital presentation. *k*-Means clustering was applied to all clinical and laboratory variables in the electronic health records (29 in all) from 16,552 patients and then validated in a second database (n = 31,160) and in prospective cohorts from observational studies and randomized controlled trials (n = 5320). Optimal fit was obtained with 4 derived phenotypes (α, β, γ, and δ) and host-response biomarkers (eg, cytokines); organ failure patterns and survival varied considerably across phenotypes (Table 5). Although all phenotypes included some dysfunction across organs, kidney, liver, and coagulation abnormalities tended to cluster in 1 phenotype (δ phenotype), and pulmonary involvement tended to be greatest in the γ phenotype. The δ phenotype was present in 10% to 15% of patients across data sets and was

associated with a dramatically higher mortality rate (32% in-hospital mortality compared with 2% for the α phenotype.

Given the distributions of organ failures and hyperinflammation seen in the δ phenotype and the associated mortality, it is likely that patients with sepsis who develop MAS and/or aHUS-like conditions would be included mainly in this phenotype. It is equally tempting to posit that endotoxemia may be a driver of this phenotype in many patients. Because endotoxin is not routinely quantified and because MAS and aHUS often are missed, further research is needed to confirm or refute the hypothesis that these conditions are driving the δ phenotype.

DISCLOSURE

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KEY POINTS

- Inflammation is central to many acute conditions, ranging from infection to sterile tissue injury to rheumatic diseases and to drug/toxin reactions. These conditions easily can be confused with one another.
- Sepsis is extremely heterogenous at both the clinical and molecular levels. Emerging evidence points to various subphenotypes with divergent pathophysiology.
- Macrophage activation syndrome is a life-threatening complication of systemic inflammatory disorders, most commonly systemic juvenile idiopathic arthritis, adult-onset Still disease, and systemic lupus erythematosus.
- Atypical hemolytic uremic syndrome is associated with genetic or acquired disorders that lead to dysregulation of the complement system and thrombotic microangiopathy, resulting in multiple organ failure.
- Endotoxemic shock occurs in approximately half of patients with septic shock and often is refractory to standard therapy. The source of endotoxin often is loss of gut barrier function.

CLINICS CARE POINTS

- Sepsis can be missed in patients with underlying chronic organ dysfunction and always should be considered in any patient with infection, regardless of prior medical history.
- Sepsis also be may over-diagnosed: up to 10% of patients initially diagnosed with sepsis have an alternate diagnosis.
- aHUS should be considered when thrombocytopenia and intravascular hemolysis present along with AKI.
- A sepsis phenotype that includes liver dysfunction and DIC may occur in up to 10% of patients with sepsis. The condition appears to have features in common with MAS, including extremely high ferritin and poor survival.
- Endotoxin activity greater than 0.6 identifies a subset of sepsis patients with increased ICU mortality.

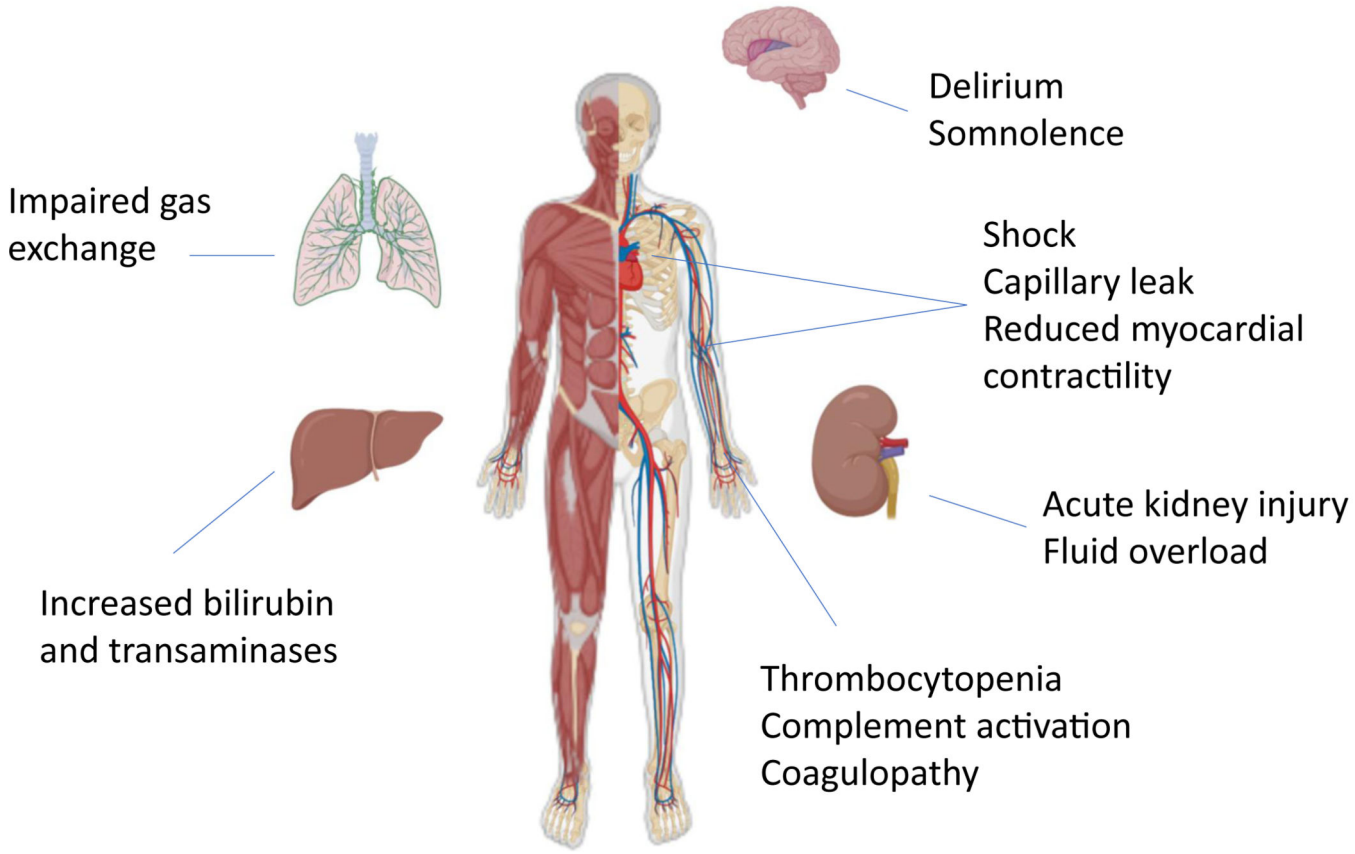

Fig. 1.
The spectrum of organ failure seen in sepsis.

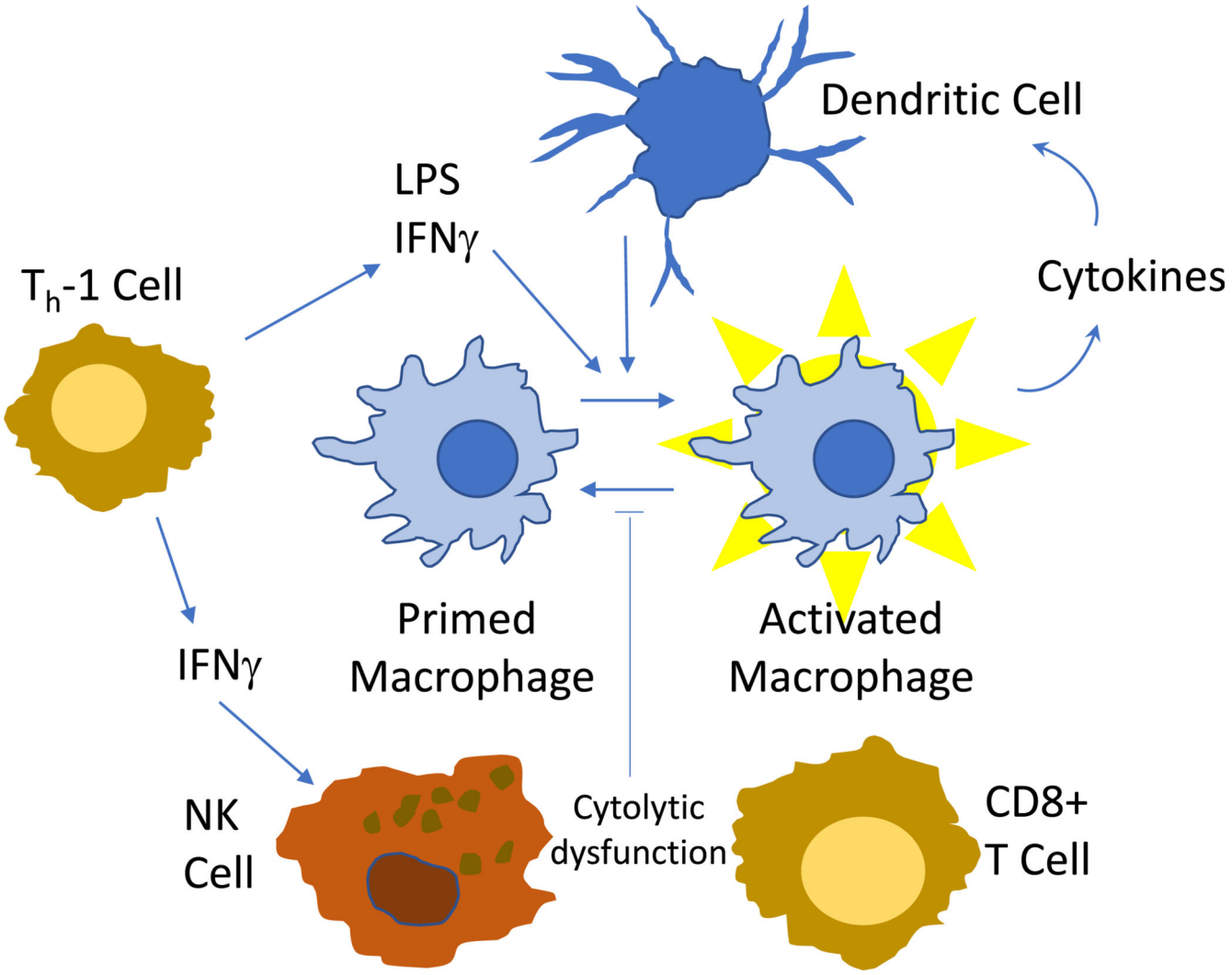

Fig. 2.
Pathogenesis of MAS. IFNg, interferon gamma; T_h-1, type 1 helper T cells.

Table 1

Damage-associated and pathogen-associated molecular patterns

Damage-associated Molecular Patterns	Pathogen-associated Molecular Patterns
• HMGB1	• Endotoxin
• Heat-shock proteins	• Flagellin
• Hyaluronan fragments	• Lipoteichoic acid (gram-positive bacteria)
• Uric acid	• Peptidoglycan
• Heparin sulfate	• Nucleic acid variants (viruses) for example, double-stranded RNA, unmethylated CpG motifs
• DNA	

Abbreviation: HMGB1, high mobility group box 1 protein.

Table 2

Potentially pathologic variants identified in patients with septic shock

Subject	Gene	Variant	Amino Acid Change	Disease	Minor Allele Frequency[a]	Putative Therapy
1	*C3*	c.1407G>C NM_000064.2	p.Glu469Asp	aHUS	0.00394	Eculizumab
	UNC13D	c.1579C>T NM_199242.2	p.Arg527Trp	HLH	0.00523	IL1-RA
2	*CD46*	c.1058C>T NM_172359.2	p.Ala353Val	aHUS	0.01532	Eculizumab
	CFHR5	c.832G>A NM_030787	p.Gly278Ser	aHUS	0.00729	
3	*UNC13D*	c.2782C>T NM199242.2	p.Arg928Cys	HLH	0.02986	IL1RA
4	*NLRP3*	c.2113C>A NM_004895.4	p.Gln705Lys	CAPS	0.0495	IL1RA
	MEFV	c.250G>A NM_000243.2	p.Glu84Lys	FMF	0.00012	IL1RA
5	*UNC13D*	c.2983G>C NM_199242.2	p.Ala995Pro	HLH	0.00096	IL1RA
		c.2542A>C. NM_199242.2	p.Ile848Leu		0.00090	
6	*CD46*	c.1058C>T NM_172359.2	p.Ala353Val	aHUS	0.01532	Eculizumab
	MEFV	c.2084A>G NM_000243.2	p.Lys695Arg	FMF	0.00550	IL1RA

Previously reported pathogenic variants identified during WES analysis of sepsis patients with extreme hyperferritinemia. Numbers 1 to 6 indicate individual study subjects, whereas rows represent identified variants. Columns indicate genes with variants identified, specific variant, and genetic disorder associated with them.

Abbreviations: FMF, familial Mediterranean fever; HLH, hemophagocytic lymphohistiocytosis.

[a]Putative targeted therapies have been suggested based on the identification of these variants in other clinical contexts.

Adapted from Kernan, K.F., Ghaloul-Gonzalez, L., Shakoory, B. et al. Adults with septic shock and extreme hyperferritinemia exhibit pathogenic immune variation. Genes Immun 20, 520–526 (2019). https://doi.org/10.1038/s41435-018-0030-3; with permission.

Table 3

Clinical feature of typical sepsis versus macrophage activation syndrome and atypical hemolytic uremic syndrome

Characteristic	Sepsis	Macrophage Activation Syndrome	Atypical Hemolytic Uremic Syndrome
Fever	++	+++	+
Hepatomegaly, splenomegaly lymphadenopathy	±	+++	−
Encephalopathy	++	++	+++
ARDS	++	−	−
AKI	++	±	+++
ESR	↑↑	↓	↑↑
White blood cell count	↑↑	↓	↑
Increased AST	±	++	−
DIC	±	++	−
Thrombocytopenia	±	++	+++
Hypertriglyceridemia	−	++	−
Increased lactate dehydrogenase	−	+	+++
Increased ferritin	±	+++	±

Abbreviations: AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate.

Table 4

Potential immune-modulating therapies for macrophage activation syndrome

Agents	Target	Mechanism
Available agent		
Anakinra, canakinumab	IL-1	Receptor antagonist
Tocilizumab	IL-6	Anti–IL-6R monoclonal Ab
Abatacept	CD28	CTLA4-Ig
Tofacitinib	JAK1/2	JAK inhibitor
Theoretic/investigational		
	IL-18	IL-18 binding protein
	IL-10	Recombinant IL-10 protein
	IL-33	Anti–IL-33R monoclonal Ab
	IFN-γ	Anti–IFN-γ monoclonal Ab

Abbreviations: Ab, antibody; CTLA4, cytotoxic T-lymphocyte–associated protein 4; IFN-γ, interferon gamma; Ig, immunoglobulin; JAK, Janus kinase; R, receptor.

Adapted from Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol. 2019;10:119. Published 2019 Feb 1. https://doi.org/10.3389/fimmu.2019.00119; with permission.

Table 5

Characteristics of sepsis phenotypes identified by artificial intelligence

		Phenotype			
Characteristic	**Total**	**α**	**β**	**γ**	**δ**
Proportion of patients		33%	27%	27%	13%
Increased cytokines		+	+	++	+++
Coagulopathy		+	+	+	++
Liver dysfunction		+	+	+	++
AKI		+	++	+	+++
Days of mechanical ventilation, median (IQR)	5 (2–10)	4 (2–9)	4(2–9)	6 (3–13)	4(2–9)
Days of vasopressors, median (IQR)	3 (2–5)	2 (2–4)	3(2–4)	3 (2–5)	3 (2–5)
Admitted to ICU	45%	25%	32%	63%	85%
In-hospital mortality	10%	2%	5%	15%	32%

Abbreviation: IQR, interquartile range.

Data from Seymour CW, Kennedy JN, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. JAMA. 2019;321(20):2003–2017. https://doi.org/10.1001/jama.2019.5791.