

REVIEW

Organ Dysfunction in Sepsis: An Ominous Trajectory From Infection To Death

César Caraballo^a and Fabián Jaimes^{b,c,d,*}

^aCenter for Outcomes Research and Evaluation, Yale New Haven Health, New Haven, CT, USA; ^bAcademic Group of Clinical Epidemiology, School of Medicine, University of Antioquia, Medellín, Colombia; ^cDepartment of Internal Medicine, School of Medicine, University of Antioquia, Medellín, Colombia; ^dResearch Direction, San Vicente Foundation University Hospital, Medellín, Colombia

Sepsis is a highly complex and lethal syndrome with highly heterogeneous clinical manifestations that makes it difficult to detect and treat. It is also one of the major and most urgent global public health challenges. More than 30 million people are diagnosed with sepsis each year, with 5 million attributable deaths and long-term sequelae among survivors. The current international consensus defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. Over the past decades substantial research has increased the understanding of its pathophysiology. The immune response induces a severe macro and microcirculatory dysfunction that leads to a profound global hypoperfusion, injuring multiple organs. Consequently, patients with sepsis might present dysfunction of virtually any system, regardless of the site of infection. The organs more frequently affected are kidneys, liver, lungs, heart, central nervous system, and hematologic system. This multiple organ failure is the hallmark of sepsis and determines patients' course from infection to recovery or death. There are tools to assess the severity of the disease that can also help to guide treatment, like the Sequential Organ Failure Assessment (SOFA) score. However, sepsis disease process is vastly heterogeneous, which could explain why interventions targeted to directly intervene its mechanisms have shown unsuccessful results and predicting outcomes with accuracy is still elusive. Thus, it is required to implement strong public health strategies and leverage novel technologies in research to improve outcomes and mitigate the burden of sepsis and septic shock worldwide.

*To whom all correspondence should be addressed: Dr. Fabián Jaimes, Hospital San Vicente Fundación, Calle 64 # 51 D-154, Medellín, Antioquia, Colombia; Tel: +57 (4) 2192433, Email: fabian.jaimes@udea.edu.co.

†Abbreviations: Ang-Tie, angiotensin-tyrosine kinase with immunoglobulin-like loop epidermal growth factor domain ligand-receptor; iNOS, inducible nitric oxide synthase; NO, nitric oxide; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; VCAM-1, vascular cell adhesion molecule-1; ATP, adenosine triphosphate; ARDS, acute respiratory distress syndrome; TNF- α , tumor necrosis factor alpha; PaO₂, partial pressure of arterial oxygen; FIO₂, fraction of inspired oxygen; AKI, acute kidney injury; ICAM-1, intercellular adhesion molecule-1; DIC, disseminated intravascular coagulation; APPs, acute-phase proteins; SOFA, Sequential (sepsis-related) Organ Failure Assessment.

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INTRODUCTION

Sepsis is an intricate, heterogeneous, and highly lethal syndrome that can be hard to identify and treat [1]. Defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection [2], sepsis is one of the major and most urgent public health challenges worldwide [3,4]. It is estimated that more than 30 million people globally are diagnosed with sepsis each year, leading to 5 million deaths [5], with high economic burden and long-term morbidity among survivors [6]. Particularly, annually in the United States sepsis is present in 1.7 million hospitalized patients and contributes to 270,00 deaths [7].

Prognosis in sepsis is influenced by characteristics of the patient (*e.g.* age, immunologic status, comorbidities, among others) [8-10] and characteristics of the infection (*e.g.* pathogen type, virulence, site of infection, inoculum, among others) [8,11,12]. Although combinations of such characteristics influence the clinical presentation and risk, sepsis is a common pathway from infection to death, in which progressive organ dysfunction is the mean. In this review, we present a comprehensive overview of the features found in patients with sepsis that lead to multiple organ failure and death.

FROM INFECTION TO ORGAN DYSFUNCTION

Sepsis definition has changed over the last few decades as our understanding of it has increased [2,13,14], and its current definition emphasizes the presence of organ dysfunction (Table 1). The cornerstone of sepsis-induced organ damage is the instauration and perpetuation of a mismatch between perfusion and tissues metabolic requirements. Inflammation-induced cardiac dysfunction and systemic blood volume redistribution have pivotal roles on this, but are exacerbated by an impaired tissue oxygen utilization [15]. This sepsis-induced global hypoperfusion state has common clinical manifestations such as hypotension, decreased capillary refill time, mottled skin, and cold extremities. Besides the early initiation of antibiotic therapy and source control—which are essential for sepsis treatment and significantly reduces the risk of death [16,17]—the recommended early resuscitation strategies for patients with sepsis or septic shock intend to reestablish an adequate organ perfusion [16].

Vascular Dysfunction: the Failure of the Circuit

Several changes occur simultaneously in the systemic vascular bed in patients with sepsis, with an increasing interest in the importance of microcirculatory injury and dysfunction [18]. Capillary permeability is increased, compromising the effective vascular volume and there-

fore systemic perfusion. This paracellular leakage seems to be caused by a diffuse endothelial injury and dysfunction mediated by proinflammatory molecules [19]. Particularly, recent research underscores the important role in the imbalance of the angiopoietin-tyrosine kinase with immunoglobulin-like loop epidermal growth factor domain ligand-receptor system (Ang-Tie) in patients with sepsis. The augmented expression of Ang-2 and the inhibition of Ang-1 blocks Tie-2 receptor and increases vascular permeability, causing tissue edema [20]. Its prognostic value has been demonstrated in clinical studies where high serum Ang-2/Ang-1 ratio was associated with increased severity of organ dysfunction and higher mortality, even in early sepsis [21-23].

Although in most cases these volume distribution abnormalities can be countered by a successful resuscitation with an adequate and rational vascular volume expansion [24], some patients have a concomitant persistent vasodilatory state that impedes adequate perfusion even after achieving an euvolemic state. This clinical scenario is known as septic shock, the most severe manifestation of sepsis. Vascular smooth muscle fails to contract with neurohormonal stimulus, resulting in a profound systemic arterial and venous vasodilation [25] that reduces the pressure gradient required for venous return and, subsequently, decreases cardiac output [26]. Although the mechanisms of such a dramatic vascular dysfunction are not well understood, inflammation-induced endothelial dysfunction seems to be associated with an over-expression of an inducible nitric oxide synthase (iNOS) [27]. The subsequent excessive production of nitric oxide (NO) directly induces vascular smooth muscle cells relaxation and hyperpolarization, preventing their response to vasoconstrictors and thus perpetuating hypotension [25,28]. A deficiency of vasopressin with paradoxical simultaneous downregulation of vasoconstrictive receptors has also been described during septic shock, but its mechanism in humans is yet to be fully understood and therapies targeted directly to reverse these maladaptive mechanisms have been unsuccessful [29-32].

Cardiac Dysfunction: the Failure of the Pump

After volume resuscitation or vasopressors initiation, venous return augments and patients enter in a hyperdynamic profile characterized by high cardiac output and low systemic vascular resistance [33]. This response, however, is often accompanied by a depressed myocardial function. Pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β) and interleukin-6 (IL-6), depress cardiomyocyte contractility and induces expression of vascular cell adhesion molecule-1 (VCAM-1) in the coronary endothelium, which mediates infiltration of neutrophils to the myocardium [34,35]. Importantly, NO exacerbates

Table 1. Sepsis and Septic Shock Clinical Criteria Over Time

Consensus	Clinical criteria
Sepsis-1, 1991 [13]	<p>Sepsis: Systemic response to an infection, manifested by two or more of the following components of the systemic inflammatory response syndrome (SIRS): a) temperature >38°C or <36°C; b) heart rate >90 beats per minute; c) respiratory rate >20 breaths per minute or PaCO₂ <32mmHg; and d) white cell blood count >12,000 cells per mL, <4,000 cells per mL, or >10% immature forms.</p> <p>Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension.</p> <p>Septic shock: Sepsis-induced hypotension (SBP <90 mmHg or an SBP reduction ≥40 mmHg from baseline) despite adequate fluid resuscitation, or requiring vasopressor agents, along with the presence of perfusion abnormalities.</p>
Sepsis-2, 2001 [14]	<p>Sepsis: Documented or suspected infection with <i>some</i> signs of systemic inflammation, which were expanded from the SIRS criteria to include abnormalities from 5 major categories (general variables, inflammatory variables, hemodynamic variables, organ dysfunction variables, and tissue perfusion variables).</p> <p>Severe sepsis: Sepsis associated with organ dysfunction, which can be estimated with the SOFA score.</p> <p>Septic shock: Persistent arterial hypotension (SBP <90 mmHg, MAP <60 mmHg, or reduction in SBP >40 mmHg from baseline) despite adequate fluid resuscitation and unexplained by other causes.</p>
Sepsis-3, 2015 [2]	<p>Sepsis: Suspected or documented infection and acute organ dysfunction (defined as an increase of ≥ 2 points in SOFA points).</p> <p>Septic shock: Sepsis and vasopressor therapy needed to elevate MAP ≥65 mmHg and lactate >2 mmol/L despite adequate fluid resuscitation.</p>

PaCO₂: partial pressure of carbon dioxide; SBP: systolic blood pressure; MAP: mean arterial blood pressure; SOFA: Sequential Organ Failure Assessment.

mitochondrial dysfunction diminishing myocardial oxygen utilization, perpetuates release of pro-inflammatory cytokines, and downregulates β-adrenergic receptors [35,36].

Consequently, almost 1 out of 3 patients with sepsis presents reversible left ventricular systolic impairment, driven by hypokinesia and reduced ejection fraction, with unclear implication on survival [37]. On the other hand, left diastolic dysfunction is present in 1 out of 2 patients and is associated with an 80 percent increased risk of death [38]. Similarly, nearly 1 out of 2 patients with sepsis have right ventricular dysfunction, with an associated 60 percent increased risk of death [39].

Furthermore, chronotropic response, the ability to modify the heart rate according to systemic requirements, is also often impaired in sepsis [40]. A recent study found that those with low heart rate variability had nearly six times higher hazard of death [41]. On the other hand, sepsis is also associated with incidental clinical cardiac events like acute heart failure, life-threatening arrhythmias, myocardial infarction, and non-ischemic myocardial injury, among others [42-45]. In a recent study, Patel

et al. found that 13 percent of patients hospitalized due to sepsis experienced at least one incidental cardiac event and had 30 percent higher risk of death than those who did not [46].

Microcirculation and Cellular Dysfunction: the Failure in Final Oxygen Delivery and Utilization

While most therapeutic efforts are directed to solve the overt hemodynamic dysfunction, changes in the microcirculation have an important role in perpetuating the organ injury even after restoration of hemodynamic abnormalities. Various mechanisms can explain this microcirculatory failure. The endothelial dysfunction and injury over-expression of iNOS is not homogeneous thorough all organ beds, causing shunting of the flow and hypoperfusion on the underexpressed tissues [47]. This situation is aggravated by occlusion of terminal circulation vessels due to sepsis-induced erythrocyte decreased deformability, greater platelet aggregability, and microthrombi formation [27,48]. Moreover, NO has a pivotal role in the impairment of cellular oxygen utilization. Regardless of the restoration of adequate tissue perfusion

or oxygen delivery, NO inhibits mitochondrial respiration by disrupting the respiratory chain, which depletes ATP and causes cellular dysfunction and organ injury [27,49,50].

Indicators of Perfusion Status

The overall effect of such an inadequate systemic oxygen delivery and its impaired cellular utilization has major implications for tissues metabolism, increasing anaerobic glycolysis. This results in a higher production of lactate as a byproduct of pyruvate metabolism, as less of it enters Krebs aerobic cycle. Hyperlactatemia, defined as a serum concentration >2 mmol/L, is associated with higher risk of death in patients with sepsis, independently of hemodynamic status [51,52]. Its prognostic relevance is underscored by the fact that those with hyperlactatemia alone (*i.e.* no hypotension or need for vasopressor therapy) have a higher risk of death than those with hypotension and normal serum lactate levels [53]. This phenotype of normotension with hyperlactatemia have led to the term of “cryptic shock” [15]. Thus, lactate is commonly used as an indicator of patients’ perfusion status and its sequential measurement is included in the recommended approach to patients with sepsis as its clearance seems indicative of an effective resuscitation [16,54]. Recent studies have assessed the association between hyperlactatemia and clinical signs to assess the perfusion status and guide resuscitation, aiming to identify a bed-side option. However, an observational study found no association between lactate levels and capillary refill time [55] and a clinical trial found no statistically significant benefit in survival by using the same clinical perfusion indicator versus lactate [56].

Strategies Aimed to Restore Tissue Perfusion

The cornerstone of sepsis and septic shock initial treatment is to overcome such systemic hypoperfusion [16,24]. As mortality risk increases with the duration of hypotension [57], current guidelines recommend that at least 30 mL/Kg of crystalloids should be given during the first 3 hours of treatment, with additional fluids administration guided by a comprehensive and frequent hemodynamic status reassessment to avoid volume overload [16]. However, the strength of the recommendation is weak, and some studies suggest that such an aggressive early goal-directed therapy is not beneficial [58] and might actually increase the risk of adverse outcomes—mainly respiratory failure and death—in resource-limited settings [59-61]. As evidence suggests that a more conservative approach is effective and safe [62], there has been an increased interest in a more personalized fluid management [63,64].

For those with persistent hypotension despite ade-

quate volume resuscitation, hemodynamic drug support is recommended with the goal of achieving and maintaining a mean arterial blood pressure target of ≥ 65 mmHg [16]. Norepinephrine is the recommended first-choice vasopressor due to its effectiveness and lower rate of adverse events when compared to other options like dopamine [16,65], and its adoption as such is consistent among intensive care specialists worldwide [66]. However, a proportion of patients do not achieve the mean arterial pressure target despite high doses of this catecholamine, reflecting the high underlying heterogeneity in the pathophysiology of this syndrome. These non-responders have higher mortality risk, their optimal treatment is still not well known, and are the focus of recent research in critical care [67,68]. Recently, Chawla *et al.* proposed that in order to avoid prolonged hypotension, every patient with septic shock should be started on multiple vasopressors of different mechanism of action and de-escalated afterwards according to their response, similar to the “broad spectrum antibiotics” approach [69].

BEYOND CIRCULATORY FAILURE: SEPSIS IMPLICATIONS ON OTHER ORGANS

Given that sepsis is a continuous process of concomitant insults occurring thorough the body, its damage should not be understood as isolated events on different systems. However, for conceptualization we here describe how sepsis affects specific organs beyond the circulatory system and their prognostic implications.

Lungs

Sepsis is the most common cause of acute respiratory distress syndrome (ARDS) [70] and 40 percent of patients with sepsis or septic shock develop it [71]. ARDS is characterized by an acute respiratory failure with diffuse pulmonary infiltrates caused by alveolar injury and an increased pulmonary vascular permeability to protein-rich fluid. Although its etiology is yet to be fully understood, studies have shown that this alveolar barrier injury is mediated by proinflammatory cytokines—such as tumor necrosis factor alpha (TNF- α) or IL-1 β —the widespread endothelial barrier dysfunction, platelet activation with microthrombi formation, and neutrophils extracellular traps formation [72-74]. This edema and alveolar damage increase physiological dead space impairing gas exchange and causing severe hypoxemia and hypercapnia [75]. The severity of the condition is evaluated using the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO₂/FiO₂), as well as the mechanical ventilatory parameters required by the patient. Mortality among those with ARDS is high, ranging from 35 percent to 46 percent [76]. Furthermore, those with sepsis-related ARDS have higher 60-day mortality than those with

ARDS caused by any other reason [77]. Whereas these patients benefit from lung-protective mechanical ventilation strategies to aid respiratory muscles and maintain adequate gas exchange [78], pharmacological interventions to prevent the occurrence or mitigate the impact of ARDS on survival have been unsuccessful [79,80].

Kidneys

The renal system is another common target of this progressive organ dysfunction. Sepsis is the most common contributing factor for acute kidney injury (AKI) in critically-ill patients, [81] and more than half of patients with sepsis or septic shock develop it [82,83]. AKI is defined as a serum creatinine increase of ≥ 0.3 mg/dl in 48 hours, 50 percent increase from baseline in 7 days or urine output < 0.5 ml/kg/h for more than 6 hours [84]. Patients with sepsis-associated AKI have 62 percent and 36 percent higher risk of in-hospital mortality compared to those with sepsis without AKI [85] and to those with non-sepsis associated AKI, respectively [86]. Despite its high frequency, the underlying mechanisms of sepsis-associated AKI are not completely understood. Renal hypoperfusion leading to acute tubular necrosis has been the paradigm, but current evidence suggests an even more important role of the local microcirculation and inflammatory signals, including ischemia-reperfusion injury, oxidative stress, and tubular apoptosis [87,88]. Moreover, sepsis treatment can also contribute to AKI by the usage of nephrotoxic drugs and excessive or less-physiological fluid resuscitation. Volume overload increases central venous pressure, which also increases renal vascular pressure, causing subsequent organ edema, increased intracapsular pressure and decreased glomerular filtration rate [89,90]. There is a recent interest in the role of resuscitation fluid selection in the development of sepsis-associated AKI. When compared to balanced crystalloids (*e.g.* lactated Ringer's solution), evidence suggests that the high concentration of chloride in normal saline (0.9% sodium chloride) might be associated with worse renal outcomes and survival [91-95].

Coagulation System

Pro-inflammatory cytokines also increase the endothelial luminal expression and serum circulation of intercellular adhesion molecule-1 (ICAM-1) and VCAM-1, contributing to platelet adhesion and coagulation cascade activation. Additionally, the anticoagulant mechanisms are downregulated by the same proinflammatory cytokines. Endothelial production of thrombomodulin—a glycoprotein that inhibits conversion of fibrinogen to fibrin by binding thrombin—is severely impaired, reducing activation of Protein C, a strong anticoagulant with fibrinolytic properties [96,97]. Interestingly, this seems to

be propagated by neutrophils extracellular traps, which induce platelet aggregation, thrombin production, and fibrin clots formation [98]. Then, microthrombi formation in small vessels further impairs perfusion and oxygen delivery, causing organ injury and dysfunction [23].

Overall, this procoagulant up-regulation causes platelet consumption and coagulation factors depletion, leading to the classical sepsis-associated thrombocytopenia and overt disseminated intravascular coagulation (DIC), especially with expression of tissue factor and secretion of von Willebrand factor when monocytes and endothelial cells are activated to the point of cytokine release following injury [99]. Among patients with sepsis and septic shock, up to 55 percent and 61 percent have thrombocytopenia and/or DIC, respectively [100,101]. Both of these conditions are associated with worse outcomes such as higher risk of major bleeding events and death [97,101-105]. The current treatment of these coagulation abnormalities consist on prevention and treatment of major bleeding events [106], whereas therapies aimed to intervene the pathophysiology of this condition have been unsuccessful [107-109].

Liver

The liver is far from a bystander in sepsis: it is a regulator of the inflammatory process and a target of host response. When exposed to lipopolysaccharides, Kupffer cells increase the release of IL-1 β , IL-6, and TNF- α [110,111]. In response to the proinflammatory cytokines, hepatocytes release acute-phase proteins (APPs) into systemic circulation, with widespread proinflammatory and anti-inflammatory effects [112]. Thus, it has been hypothesized that hepatocytes, via APPs, have a pivotal role in balancing the immune response in sepsis, preventing an excessive inflammatory or immunosuppressed state [111]. This regulatory role gains importance when considering that up to 46 percent of patients with sepsis have concomitant hepatic dysfunction [113], which has been associated with a higher 28-day mortality [114]. Two major mechanisms seem to explain the liver injury and subsequent dysfunction in sepsis: hypoxic hepatitis and sepsis-induced cholestasis. Hypoxic hepatitis is commonly defined as a clinical setting that leads to reduced oxygen delivery or utilization by the liver (*e.g.* cardiac, respiratory, or circulatory failure), with an increase of at least 20-fold the upper limit of normal serum aminotransferase levels, and without other potential causes of liver injury [115,116]. In sepsis, the profound hemodynamic alterations, microthrombi formation, sinusoidal obstruction, and endothelium dysfunction impairs liver perfusion leading to subsequent injury and hypoxic hepatitis [112]. In a recent study that included 1116 critically ill patients with this condition [117], sepsis was the second leading predisposing factor of hypoxic hepatitis, with an in-hos-

pital mortality of 53 percent, only behind cardiac failure.

On the other hand, the definition of sepsis-induced cholestasis is not as well standardized, its etiology is still to be elucidated, and its prognostic relevance is not clear. Sepsis-induced cholestasis is understood as an impaired bile formation and defective flow caused by a non-obstructive intrahepatic insult [112], and its diagnosis is commonly made by an elevation of total serum bilirubin greater than 2 mg/dl and aminotransferases greater of at least 2-fold the upper normal limit [118]. Animal models have suggested that proinflammatory cytokines alter the hepatocytes expression of bile acids transporters, reverting the normal bile acid transport into the blood. Furthermore, pro-inflammatory cytokines and NO lead to ductular cholestasis by inhibiting cholangiocytes secretion [119,120].

Central Nervous System

Up to 70 percent of critically-ill patients with sepsis have any degree of sepsis-associated encephalopathy [121]. Beyond the direct infections of the brain and its surrounding tissues (*e.g.* encephalitis or meningitis), sepsis injures the central nervous system by a wide range of mechanisms, with the mismatch of systemic perfusion over metabolic requirements having an essential role. The severe systemic hemodynamic instability can overcome the central nervous system finely tuned perfusion regulation mechanisms, leading to critical brain ischemic lesions [122]. Additionally, the onset of cardiac arrhythmias and sepsis-induced coagulopathy may further explain the increased the risk of ischemic and hemorrhagic stroke among patients with sepsis [123-126]. On the other hand, the marked inflammatory response contributes to microcirculatory failure and disruption of the blood-brain barrier, allowing inflammatory mediators and neurotoxins into brain tissue [127]. Importantly, the increased NO diffuses even through the intact blood-brain barrier causing oxidative stress, which can lead to neuronal dysfunction and apoptosis [128]. The disruption of cholinergic and dopaminergic neurotransmission also play a key role in this acute brain dysfunction [129,130], which can range from delirium to seizures and coma [127]. Moreover, when critical areas—like the brainstem—are compromised by these insults, the autonomic dysfunction is exacerbated, perpetuating the hemodynamic instability and increasing the risk of death [129,131].

ESTIMATING THE MAGNITUDE AND IMPORTANCE OF THE ORGAN DYSFUNCTION

Standard and accurate criteria for organs dysfunction are of great importance in critical care since it helps clini-

cians to systematically follow patients' progress throughout the hospitalization and adjust treatment accordingly. Since the different potential organ dysfunction we have mentioned so far does not occur on a strictly linear or isolated manner but are part of a highly complex and integrated process—and not all occur in every patient—the challenge for the clinicians and researchers has been to objectively assess the true magnitude or “*amount*” of organ failure for each patient. Accordingly, in 1996 Vincent *et al.* [132] presented the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score, with the goal of objectively estimating the degree of organ dysfunction over time in patients with sepsis. SOFA evaluates the respiratory, hematologic, cardiovascular, hepatic, renal, and central nervous system of each patient, assigning each system a value from 0 (normal organ function) to 4 (most abnormal organ function). Therefore, SOFA score ranges from 0 to 24 (Table 2).

Although it was not originally intended as a predictive model, the association between organ dysfunction and death has inspired research about the usage of SOFA to predict mortality in patients with sepsis, showing good predictive performance [133-137]. Notably, the latest consensus complemented the conceptual definition of sepsis by defining life-threatening organ dysfunction as an acute change in total SOFA score ≥ 2 points consequent to the infection [2], since such change was associated with approximately 10 percent increased mortality risk [137]. A pending issue, however, is the improvement of the cardiovascular component of SOFA, as it does not directly measure that organ dysfunction, but the requirement of specific interventions that have changed in the last years [138].

The components of SOFA require tests and resources that might not be readily available at bedside outside intensive care units (ICU), which limits its application on other settings. Given that nearly half of patients with sepsis present in the emergency department [139], alternative tools have been developed for early sepsis detection outside the ICU. Commonly used scores that use bedside-only measures with this intention are the Modified Early Warning Score (MEWS) [140], the National Early Warning Score (NEWS) [141], and the quick SOFA (qSOFA) [137]. MEWS considers patients systolic blood pressure, heart rate, respiratory rate, temperature, and level of consciousness, whereas NEWS also considers the SpO₂. On the other hand, qSOFA was introduced in the latest sepsis consensus and assess for abnormalities in respiratory rate, systolic blood pressure, and mental status. However, it has performed worse than MEWS and NEWS identifying critically-ill infected patients [142,143], despite the fact that these were not developed to screen for sepsis but to identify patients with high-risk of major in-hospital complications or ICU admission. The leverage of novel

Table 2. Sequential Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiratory					
PaO ₂ /FIO ₂ , mm Hg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation					
Platelets, ×10 ³ /μl	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dl	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
Mean arterial pressure or adrenergic agent administered for at least 1 hour	≥70 mm Hg	<70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma score	15	13-14	10-12	6-9	<6
Renal					
Creatinine or urine output	<1.2 mg/dl	1.2-1.9 mg/dl	2.0-3.4 mg/dl	3.5-4.9 mg/dl or <500 ml/day	>5.0 mg/dl or <200 ml/day

PaO₂: partial pressure of arterial oxygen; FIO₂: fraction of inspired oxygen.

^aAdapted from Vincent JL *et al.* [132]

^bDoses are presented as μg/kg/min

research methods and digital resources, such as artificial intelligence and electronic health records, have shown promise in improving the accuracy of personalized risk estimation [144]. In a remarkable example of this, Delahanty *et al.* [145] used machine learning methods to identify patients at high risk of sepsis in more than 2 million medical encounters, developing a new sepsis screening tool that outperformed the rest.

FUTURE PERSPECTIVES TO REDUCE THE GLOBAL BURDEN OF SEPSIS

Even though sepsis is recognized as an urgent health challenge worldwide [4], its current global burden may be underestimated due to scarcity of information available from lower and middle-income countries, where most cases of sepsis might occur [146,147]. Thus, to address this disparity in representation, the improvements in acute and individual treatment of sepsis need to be backed-up by strong public health strategies that improves its understanding worldwide. The African Sepsis Alliance signed the Kampala Declaration in 2017 and the Latin-American Institute of Sepsis signed the São Paulo Declaration in 2018, both calling for urgent national and international actions to improve the prevention, diagnosis, and treatment of sepsis and to dedicate human and financial resources to these goals [148,149]. Hopefully, these calls for action will resonate and the increased understanding of sepsis burden in lower and middle-income

regions will help design strategies that improve care and survival.

CONCLUSION

Sepsis is a highly complex and lethal syndrome with a convoluted pathway from infection to death consisting of multiple organ dysfunction. Each organ injury contributes to the patient's risk of death, with an intricate cross-talk among the whole system. Despite its high prevalence and intensive research, the vast underlying heterogeneity of sepsis might be the reason for the failure of interventions beyond supportive measures—including infection control—in improving outcomes. A more personalized approach is needed, and the recent advances using novel research methodologies have provided promising results in this regard. This research and subsequent interventions will need the support from strong public health initiatives worldwide. All these efforts will continue to help patients with sepsis to change their trajectory away from death and towards recovery.

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