Sepsis in 2017: After three decades of change, where are we now?

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The purpose of this lecture is to update the audience on recent advances in the diagnosis and treatment of sepsis. Sepsis carries a huge burden of morbidity and mortality in the present day. In this lecture, we will review the evolution of diagnostic criteria for sepsis and their validation in current practice. We will discuss the latest evidence on management of patients with sepsis under the broad categories of resuscitation, infection control, and targeted interventions against specific pathobiologic mechanisms. Finally, we will review bundles and legislative mandates in contemporary sepsis care.

Educational Objectives

At the conclusion of this lecture, the listener should be able to:
1. Understand the evolution of diagnostic criteria for sepsis.
2. Appraise the relevance of sepsis definitions in the current clinical context.
3. Apply evidence based management strategies to treat patients with sepsis and septic shock.
4. Know sepsis guidelines and mandates in practice.

Introduction

Sepsis affects more than 1 million patients in the United States annually[1,2] and more than 30 million adults worldwide.[3] The incidence of sepsis has increased substantially over the last four decades,[4,5] (Figure 1) and with $23.6 million in healthcare costs annually, it is the most expensive cause of hospitalization in the United States.[6] Although mortality rates for sepsis have declined significantly over the last decade, it continues to be high at around 20-30%.[4,5,7] Moreover, patients who survive to discharge face rapid functional and neurocognitive decline along with a long-term increased risk of mortality.[8]

Figure 1. Incidence of sepsis over three decades.
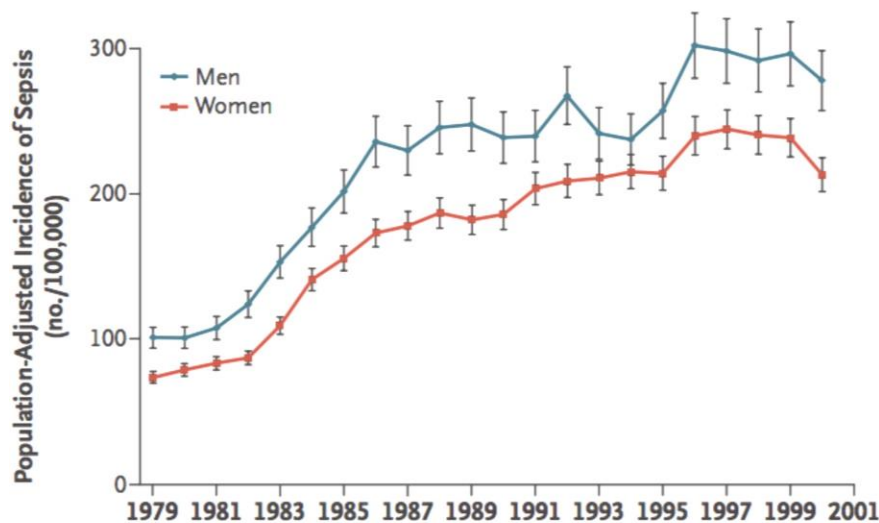
Case presentation (Adapted from NEJM Clinical Decisions[9])

"Ms. Jones is a 65-year-old woman with a history of hypertension who presents to the emergency department with a 3-day history of chills and dysuria. The only medication she is taking is amlodipine, at a dose of 10 mg daily; she had had normal electrolyte levels and renal function at a routine visit 6 weeks earlier. On arrival at the emergency department, she reports feeling dizzy. She is 165 cm (65 in.) tall and weighs 70 kg (154 lb). Her temperature is 38.6°C (101.5°F), heart rate 125 beats per minute, blood pressure 120/65 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation as measured by pulse oximetry 94% while she is breathing ambient air. A physical examination reveals dry mucous membranes; undetectable jugular venous pulsation; tachycardia without gallops, rubs, or murmurs; clear lungs; and warm extremities. She has tenderness on palpation of her suprapubic region."
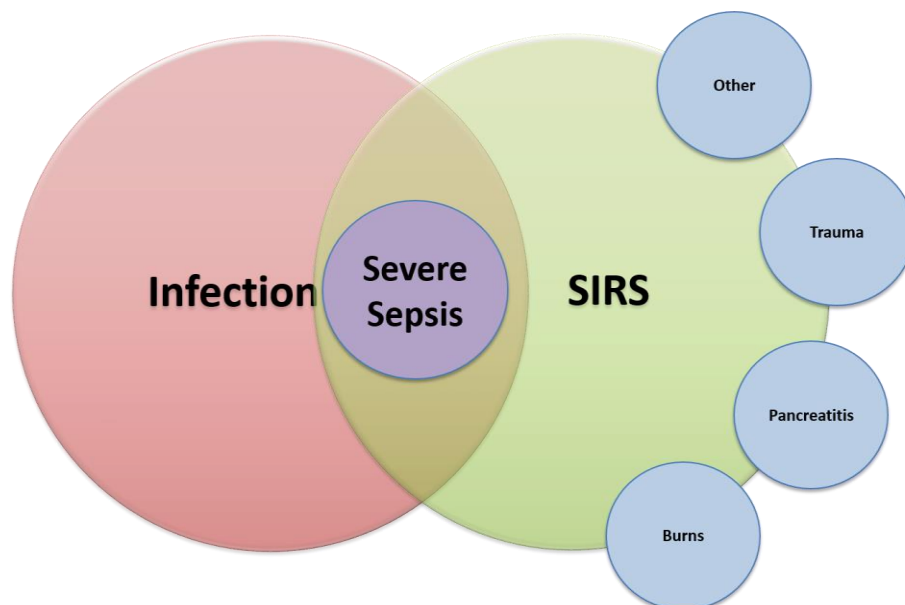
Does this patient have sepsis?

The term 'sepsis': A long tortuous history

The meaning of the term 'sepsis' has evolved over time. The first use of this term can be traced back to 400 BC when Hippocrates described it as a process of biological decay.[10] Alongside the advent of germ theory, Semelweiss found higher rates of puerperal sepsis in deliveries conducted by medical students, compared with those by midwives. He also noted that medical students frequently conducted autopsies in the hours preceding these deliveries, and suggested that 'germs' may be responsible for sepsis. Lister independently made a similar observation, and demonstrated dramatic reductions in the rates of post-operative sepsis with the use of aseptic surgical procedures.[10]

However, with the expanding knowledge about the pathophysiology of sepsis, several additional factors related to the host response to infection were identified to play a role in the occurrence of this lethal syndrome. In 1991, American College of Chest Physicians and the Society of Critical Care Medicine convened an international meeting to put together the first set of consensus definitions for sepsis.[11] They proposed the term 'Systemic Inflammatory Response Syndrome', which was used to designate the clinical manifestations of the host's inflammatory response. This, in turn, could be triggered by a variety of insults, including infection.

The features of SIRS were defined as (i) a body temperature above 38°C or below 36°C; (ii) a heart rate of 90 beats per minute or higher; (iii) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a partial pressure of arterial carbon dioxide ($PaCO_2$) of less than 32 millimeters of mercury (mm Hg); and (iv) an alteration in the white blood cell count, defined by a cell count above 12,000 per cubic millimeter (mm^3), a cell count below 4,000 per mm^3, or the presence of over 10% immature neutrophils ("bands"). In this context, sepsis was defined as the systemic host response to infection, manifested by two or more of the above SIRS criteria (Figure 2). Further, the septic response was classified into three categories - sepsis, severe sepsis, and septic shock (in the order of severity of the clinical presentation, Table 1).

Figure 2. Conceptualization of SIRS, sepsis and severe sepsis

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Table 1. Sepsis, severe sepsis and septic shock (as defined by Bone *et al*. 1991)

Systemic Inflammatory Response Syndrome (SIRS)	Systemic inflammatory response to a variety of severe clinical insults. The response is manifested by 2 or more of the following conditions: (1) temperature >38 °C or <36°C; (2) heart rate >90 bpm; (3) respiratory rate > 20 breaths per minute or $PaCO_2$ of less than 32 mm Hg; and (4) an alteration in the white blood cell count, such as a count >12,000/ cu mm, a count <4,000/cu mm, or the presence of >10 percent immature neutrophils ("bands").
Sepsis	Systemic response to infection, manifested by two or more of the above SIRS criteria
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion may include, but not limited to lactic acidosis, oliguria, or an acute alteration in mental status
Septic shock	Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities.

With time, sepsis definitions were recognized to not adequately identify mechanisms underlying the clinical presentation, and a heterogeneous population of patients with respect to the source of infection, inflammatory mediators, and the pathophysiological mechanisms behind the organ dysfunction were grouped together.[12] In 2001, these definitions were revisited by a second large consensus conference. The primary task of this meeting was to redefine sepsis. However, although they were able to expand the list of signs and symptoms to aid the clinical diagnosis of sepsis (Table 2)., there was insufficient empirical evidence to guide a change in definitions, and therefore, the definitions of sepsis, severe sepsis and septic shock were not revised.[13]

Table 2. Diagnostic criteria of sepsis determined by 2001 sepsis conference

Diagnostic criteria for sepsis
Infection, documented or suspected, and some of the following:
General variables
Fever (core temperature > 38.3 °C)
Hypothermia (core temperature < 36 °C)
Heart rate > 90/ min or > 2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 hours)
Hyperglycemia (plasma glucose >120 mg/dl or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (white blood cell count > 12,000 / µL)
Leukopenia (white blood cell count <4,000 / µL)
Normal WBC count with >10% immature forms
Plasma C-reactive protein > 2 SD above the normal value
Plasma Procalcitonin > 2 SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP< 90mm of Hg, MAP < 70 or SBP decrease > 40 mm of Hg or <2 SD below normal for age)
SvO2>70%

Cardiac index > 3.5 L/min
Organ dysfunction variables
Arterial hypoxemia (PaO2/ FiO2 < 300)
Acute oliguria (urine output < 0.5 ml /kg/hr or 45 mmol/ L for at least 2 hours)
Creatinine increase > 0.5 mg/ dL
Coagulation abnormalities (INR > 1.5 or aPTT > 60 seconds)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000/ μL)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or >70 mmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

Sepsis-3

In 2014, an expert panel of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine reevaluated the sepsis construct. They identified several challenges with the existing SIRS criteria, including:

1) High sensitivity: Over 90% of all intensive care unit (ICU) patients qualify as having 'sepsis'.[14]
2) Poor discriminant validity: SIRS represents an inflammatory response to infection, and not necessarily a deleterious response. The SIRS criteria, therefore, do not effectively distinguish sepsis from uncomplicated infection.[15]
3) Poor concurrent validity: 12% of patients in the ICU with infection and organ dysfunction did not meet the SIRS criteria.[16]

Sepsis was, therefore, redefined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock as sepsis with persistent hypotension requiring the use of vasopressors to maintain a mean arterial pressure (MAP) above 65 mmHg, and a serum lactate level above 2 millimoles per liter, despite adequate volume resuscitation. The sepsis definitions suggested by Bone *et al* (Table 1) were retrospectively identified as Sepsis-1, and the 2001 consensus criteria as Sepsis-2, thereby identifying the 2016 definitions as Sepsis-3.[17]

The diagnostic criteria in Sepsis-3 were based on a carefully conducted study in a large electronic health database from 12 academic and community hospitals in the University of Pittsburgh Medical Center network between 2010 and 2012.[18] All encounters in the emergency departments, wards and/or the intensive care units with suspected infection were divided into two groups. One of these groups was used to assess the clinical features of sepsis that can predict worse patient outcomes, specifically death and a prolonged ICU hospitalization. Among others, two sets of clinical criteria/scores were evaluated in the study: the SIRS criteria and the Sequential Organ Failure Assessment (SOFA) Score. The latter is a score frequently used in the ICU setting to assess the risk of end-organ damage in critically ill adults. Further, this group of patients was used to identify a new set of criteria with a good performance in predicting a higher rate of worse outcomes. The second group of patients was used to validate the predictive accuracy of these criteria. In addition, these clinical criteria were cross-validated in four external cohorts. The study

found that among patients in the ICU setting, SOFA had a higher predictive accuracy for death and prolonged ICU stay, compared with SIRS criteria. However, among patients not in the ICU, a simple model – quick SOFA or qSOFA, comprised of altered mentation, low systolic blood pressure, and elevated respiratory rate had a greater predictive ability than both the SOFA score and the SIRS criteria. Figures 3 and 4 summarize the sepsis criteria proposed by Sepsis-3.

Figure 3. Diagnostic criteria for sepsis proposed by the sepsis consensus conference of 2015.
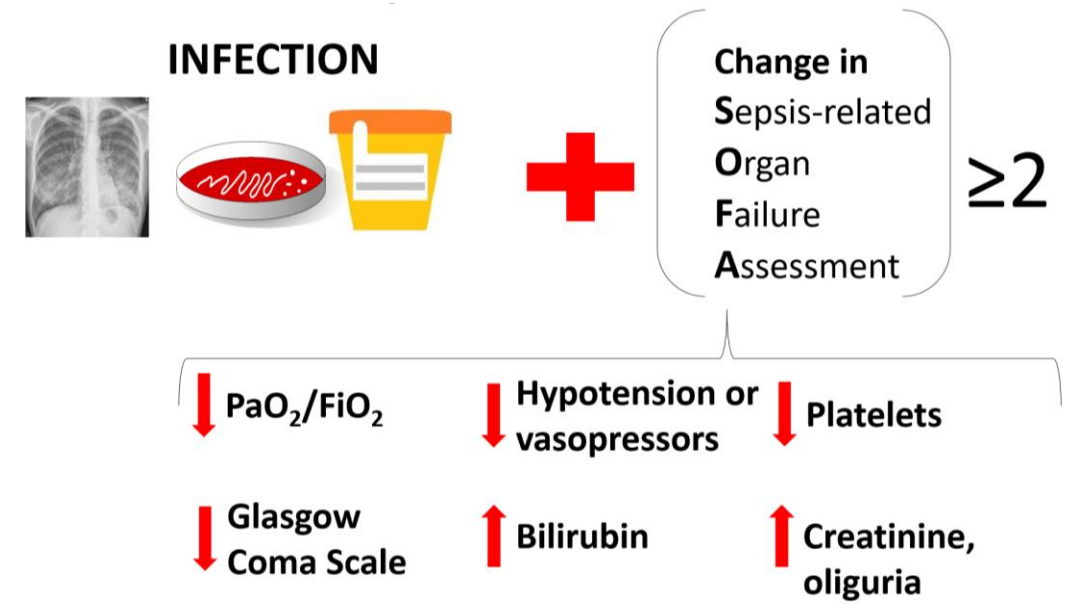
Figure 4. qSOFA as a screening tool in patients with suspected infection outside of the intensive care unit.
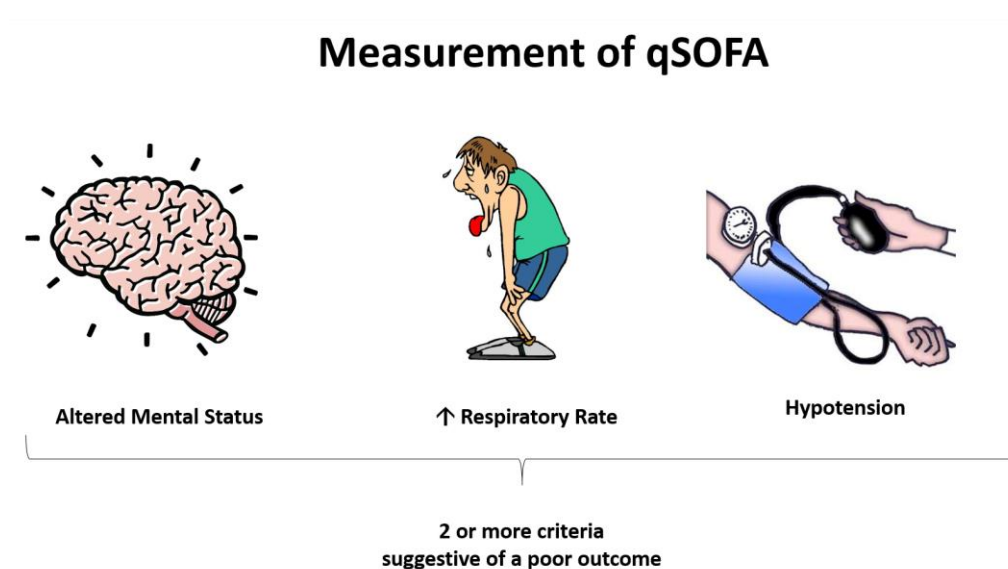
Criticism of Sepsis-3

The new sepsis and septic shock definitions have been widely debated in the critical care and emergency medicine communities. While endorsed by the Society of Critical Care Medicine and the American Thoracic Society, they have not been supported by the American College of Chest Physicians, the Infectious Disease Society of America or the American College of Emergency Physicians. A few major concerns regarding the new criteria include:

1. An emphasis on organ failure can delay the early recognition and treatment of sepsis.[19]
2. This change in definition was not prompted by any new scientific breakthrough or new clinical evidence for sepsis.[20]
3. The qSOFA score was derived using a data driven approach in a single study from one country[21].
4. Since SIRS represent the current clinical criteria, their lower discriminative ability for worse outcomes may reflect their use in the recognition and initiation of early treatment of sepsis leading to improved patient outcomes.[22]
5. Several other predictive scoring systems were not considered.[23]

Validation of Sepsis-3

The scoring systems SOFA and qSOFA have been subsequently validated in other cohorts (Table 3). They appear to have superior predictive ability for in-hospital mortality, compared with SIRS, consistent with the results of the primary study supporting the Sepsis-3 criteria. However, a study that evaluated the predictive validity of SOFA and qSOFA against the modified and the national early warning scores (MEWS, NEWS) found the latter to be marginally superior (Table 3).

Table 3. Predictive validity of SOFA and/or qSOFA compared to other scoring systems.

Study	Design and Time period	Patient population	Primary outcome	Area under the receiver operating characteristic curve (95% CI)				
				SIRS	SOFA	qSOFA	MEWS	NEWS
Churpek et al 2016 (PMID: 27649072)	Retrospective cohort 2008-2016	Patients with suspected infection in ED or wards (n=30,677)	In-hospital mortality	0.65 (0.63-0.66)	-	0.69 (0.67-0.70)	0.73 (0.71-0.74)	0.77 (0.76-0.79)
Raith et al 2017 (PMID: 28114553)	Retrospective cohort 2000-2015	Patients with infection – related primary diagnosis in ICU (n=184,875)	In-hospital mortality	0.59 (0.58-0.59)	0.75 (0.75-0.76)	0.61 (0.60-0.61)	-	-
Freund et al 2017 (PMID: 28114554)	Prospective cohort 5/2016-6/2016	Patients with suspected infection in ED (n=879)	In-hospital mortality	0.65 (0.59-0.70)	0.77 (0.71-0.82)	0.80 (0.74-0.85)	-	-

| Study	Design / Years	Population	Outcome					
Park et al 2017 (PMID: 28647650)	Retrospective cohort 2007-2016	Patients with suspected infection in ED (n=1,009)	Development of organ failure (Change in SOFA≥2)	0.66 (0.58-0.75)	-	0.81 (0.72-0.91)	-	-
Ranzani et al 2017 (PMID: 28613918)	Retrospective cohort 2009-2011	Patients with community-acquired pneumonia in ED (n=6,874)	In-hospital mortality	0.58 (0.55-0.60)	-	0.70 (0.67-0.72)	-	-
Siddiqui et al 2017 (PMID: 28575814)	Retrospective cohort 2015	Patients with diagnosis of sepsis in ICU (n=52)	In-hospital mortality	0.71	-	0.69	-	-
Donnelly et al 2017 (PMID: 28268067)	Retrospective cohort (REGARDS) 2003-2012	Patients with infection requiring ED visit or hospital admission (n= 30,239)	In-hospital mortality	0.72	0.76	0.76	-	-
Singer et al 2017 (PMID: 28110990)	Retrospective cohort 2014-2015	Patients in the ED with all vital sign data (n=4,149)	In-hospital mortality	-	-	0.75 (0.71-0.78)	-	-
Wang et al 2016 (PMID: 27321936)	Retrospective cohort	Patients diagnosed with infection in ED (n=477)	28-day mortality	-	0.73 (0.68-0.78)	0.67 (0.61-0.72)	-	-

Abbreviations: MEWS: Modified Early Warning Score, NEWS: National Early Warning Score

Road to Treatment: Understanding the Pathobiology of Sepsis

Our understanding of the pathobiology of sepsis has evolved substantially over the last decade. While initially considered a state of uninterrupted inflammation in response to an infectious agent, sepsis is now identified to be a consequence of complex interactions between excess inflammation, immunosuppression, and coagulation disturbances, that together contribute to the damage observed in patients suffering with this condition (Figure 5). Pathogen-associated molecular proteins (PAMPs) activate pattern recognition receptors, such as the Toll-like receptor 1 and the interleukin (IL)-1 receptor, triggering a cascade of pro-inflammatory cytokines, particularly, TNFα, IL-1β, IL-12 and IL-16. These mediators result in an inflammatory state through trafficking of leukocytes, endothelial damage, and activation of the coagulation cascade. In addition, microbial invasion also activates the complement pathway that independently mediates endothelial damage and activation of the coagulation pathway. Coagulation factors, like thrombin and tissue factor/VIIa complex, further perpetuate inflammation and lead to disseminated intravascular coagulation (DIC). Concurrently, the host response leads to immunosuppression through (i) an increase in the number of immature neutrophils and myeloid derived suppressor cells that produce anti-inflammatory cytokines, like TGF-β and IL-10, and have defective antimicrobial activity, (ii) a reprogramming of antigen-presenting cells that leads to reduced HLA‑DR expression, and (iii) the expression of PDL1 (programmed cell death ligand 1), leading to increased T-cell apoptosis.

Figure 5. Schematic representation of the mechanisms of inflammation, immunosuppression and pro-coagulation in sepsis
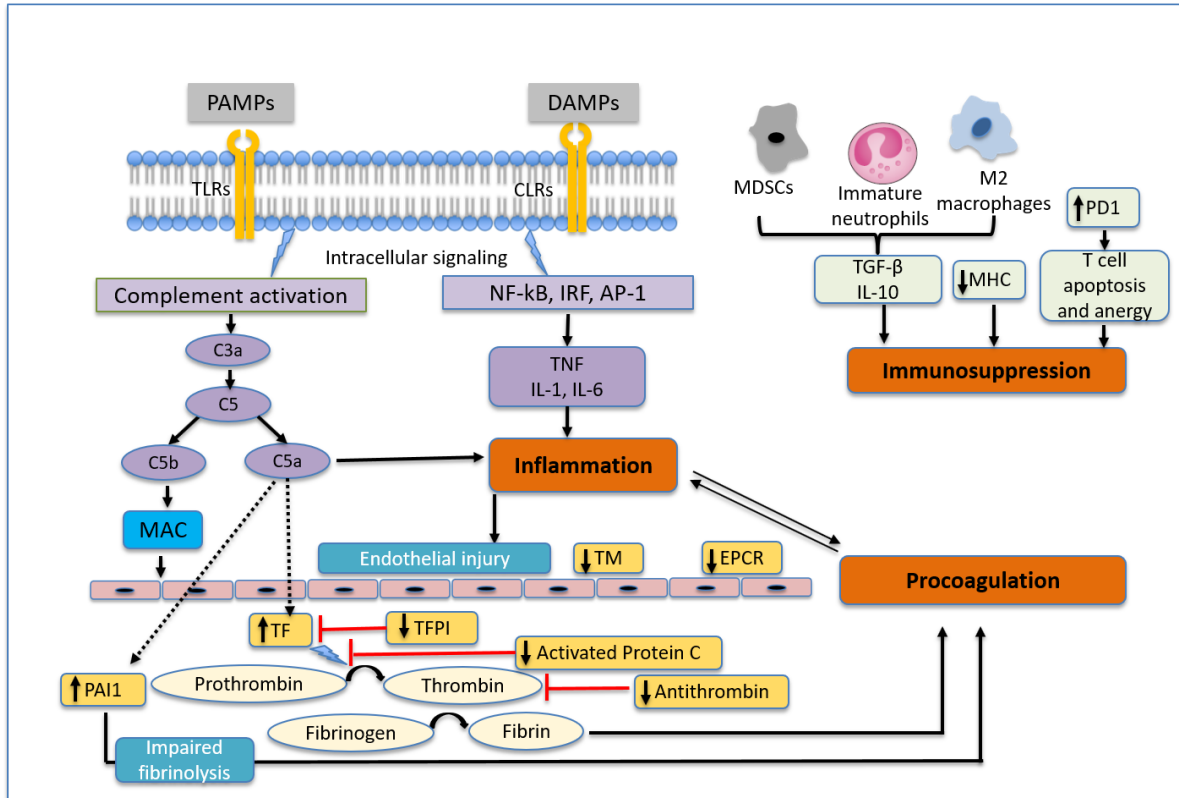

Management of Sepsis

The current management of sepsis primarily involves early resuscitation, and infection control (Figure 6). Therapeutic strategies that target specific aspects of the pathophysiology of sepsis are under active investigation.

Figure 6. Cornerstones of management of sepsis and septic shock

Resuscitation

Case presentation (continued)

".....Her vital signs over the next few hours are significant for a BP of 90/60 mm of Hg and respiratory rate of 22 breaths/ minute. Laboratory testing shows a creatinine level of 1.8 mg/dL (normal range, 0.5 to 1.1 mg/dL, blood urea nitrogen 76 mg/dL (normal range, 7 to 20 mg/dL), white-cell count 20,000/ mm³ (normal range, 4500 to 11,000),
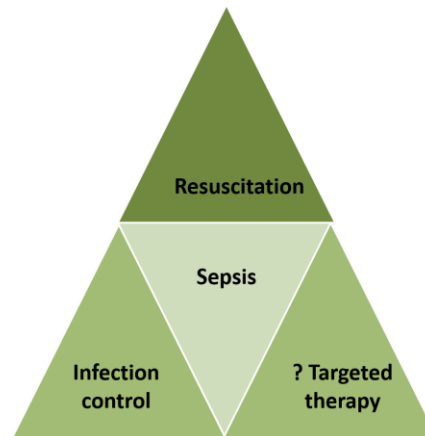
lactate 2 mg/dL and hemoglobin 9.0 g/dL (normal range, 12.0 to 15.5). Urinalysis shows 3+ leukocyte esterase, >100 white cells per high-power field, and abundant bacteria. You make a presumptive diagnosis of sepsis from a urinary source."

What is the evidence-based approach for resuscitating this patient?

In 2001, in a single-center randomized controlled trial of patients with severe sepsis and/or septic shock, Rivers *et al* found a 16% absolute reduction in in-hospital mortality with a resuscitation strategy focused on addressing cardiac preload, afterload, contractility, and the oxygen carrying capacity of blood to achieve a balance between oxygen demand and delivery. The latter was measured using mixed venous oxygen saturation (Figure 7). [24]

Figure 7. Early goal directed therapy protocol. Adapted from Rivers et al NEJM 2001.[24]
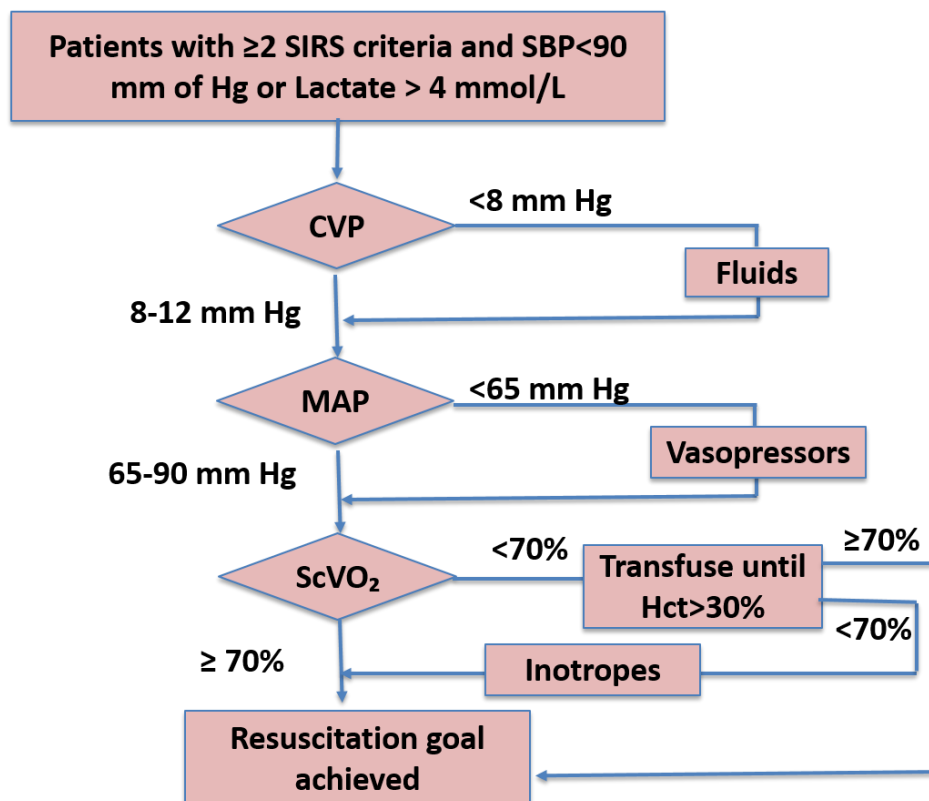
The protocol was subsequently adopted worldwide, and incorporated into sepsis care bundles. However, given the single-center nature of this study, there were significant concerns regarding its generalizability, and the efficacy of the specific components of this treatment strategy. In 2014-2015, three large multicenter trials – the Protocolized Care for Early Septic Shock (ProCESS) trial in the US[25], the Protocolised Management in Sepsis (ProMISE) trial in the UK[26], and the Australasian Resuscitation in Sepsis Evaluation

(ARISE) study in Australia and New Zealand,[27] evaluated the efficacy of EGDT, compared with usual care. Each of these trials, as well as their patient-level meta-analysis (PRISM),[28] found no benefit of EGDT for in-hospital or 90-day mortality. It is unclear if these differences reflect changes in the usual care of severe sepsis over the 15 years between the Rivers's study and these three PRISM trials. The results of these studies have guided the most recent guidelines for the management of sepsis - Surviving Sepsis Campaign Guidelines (2016). These guidelines now do not require the use of EGDT in the management of severe sepsis, however, do not recommend against its use.

The use of crystalloids at a dose of 30 milliliters per kilogram of body weight within 3 hours of identification of sepsis, is recommended for the initial resuscitation of patients with severe sepsis. While there is no empirical evidence to support this recommendation, this is now considered usual practice.[29] To determine responsiveness to fluids, dynamic measures like passive leg-raising and fluid challenges with concurrent assessments of stroke volume are preferred over static measures like CVP. Further, variations in pulse pressure and/or stroke volume with changes in intrathoracic pressure secondary to mechanical ventilation can also be used.[29]

A MAP target of 65 mmHg or higher that has been traditionally used in clinical settings is supported by evidence from a randomized controlled trial, SEPSISPAM. This was a large, open-label, multicenter trial of 776 patients with septic shock that found no difference in 28-day mortality with a target MAP of 80-85 mmHg compared with a target of 60-65 mmHg (36.6% in the high-target group vs. 34.0% in the low-target group). Notably, however, patients with chronic hypertension had a lower requirement for renal replacement therapy when treated to higher MAP targets.[30]

Types of Fluids: Crystalloids are preferred over colloids for fluid resuscitation, with a weak recommendation for the use of 4% albumin in patients needing a large volume of crystalloids for resuscitation. In a randomized controlled trial of 7,000 critically ill patients, the Saline versus Albumin Fluid Evaluation (SAFE) study, there was no difference in 28-day all-cause mortality with the use of either 4% albumin or normal saline.[31] More recently, the Albumin Italian Outcome in Sepsis (ALBIOS) study compared 20% albumin supplementation to target serum albumin concentration >30g/L in 1800 patients with severe sepsis or septic shock and found no difference in 28-day or 90-day mortality, compared with the group receiving only crystalloids.[32]

Among crystalloids, evidence examining balanced salt solutions against normal saline is limited. The recent Saline versus Plasma-Lyte 148 for Intensive care unit fluid Therapy (SPLIT) trial did not find a reduction in the risk of acute kidney injury with the use of plasmalyte, compared with normal saline, in a heterogeneous population of critically ill patients or in the subset of patients with sepsis.[33] The current guidelines do not recommend a specific crystalloid solution.

Vasopressors: Vasopressors are necessary for septic shock that is refractory to fluid resuscitation. Norepinephrine is the recommended initial pressor of choice. It has been compared to dopamine in 6 RCTs, with evidence for a lower risk of mortality (RR, 0.89; 95% CI, 0.81–0.98, high-quality evidence) and arrhythmias (RR 0.48; 95% CI, 0.40–0.58. high-quality evidence) compared with dopamine, in a pooled meta-analysis of these studies. However, comparisons between norepinephrine and other vasopressors have not

been assessed, except for a few studies, and have not suggested the superiority of norepinephrine.[29] The VASST trial compared norepinephrine alone to norepinephrine + vasopressin at 0.03U/ min and found no difference in 28-day mortality with the addition of low dose vasopressin[34]. The use of combination vasopressors has limited support from scientific studies, but is frequently needed given limited alternative options in patients with shock refractory to single agents. The current guidelines therefore recommend norepinephrine as the initial pressor, with a suggestion to add either vasopressin (up to 0.03 U/min) or epinephrine to further augment the MAP if a target of 65 mmHg is not met with norepinephrine alone. Recently, angiotensin II was evaluated in patients with vasodilatory shock already receiving high doses of pressors. Compared with placebo, angiotensin II was associated with a significant increase in MAP, and a decrease in the requirement for other vasopressors.[35]

Blood transfusions: While it is plausible that the oxygen carrying capacity of blood increases with an increase in hemoglobin concentration, iatrogenic correction of anemia in patients with septic shock has not translated into improved outcomes. In the Transfusion Requirements In Septic Shock (TRISS) trial, patients with septic shock admitted to the ICU treated to a transfusion threshold of 7 grams per deciliter (g/dL), compared with 9 g/dL, had similar rates of 90-day mortality, ischemic cardiovascular events, and the use of life support. The current guidelines, therefore, recommend a threshold of 7 g/dL for patients with septic shock.

Infection Control

Infection control is a cornerstone of sepsis treatment. This includes both the identification and control of the source of infection as well as adequate antimicrobial therapy. The selection of antibiotics depends on the suspected source of infection as well as host factors including immune status, previous antibiotic therapy, and comorbidities. Empiric antibiotic therapy selection should, therefore, be guided by a patient's risk for bacterial and fungal pathogens, and be broad enough to include all potential pathogens.[29] Combination therapy, defined as the use of two or more antimicrobial agents from different classes of drugs, is recommended for patients with septic shock. However, the routine use of combination antibiotics for the treatment of sepsis is not recommended. While antimicrobial stewardship efforts are encouraged at institutions locally, these should not prevent optimal and broad-spectrum coverage for patients with sepsis initially. It is prudent to de-escalate antibiotics based on culture results and potentially, the use of procalcitonin.

Timing of antibiotics has been identified as a crucial factor determining mortality in sepsis and septic shock in multiple retrospective cohort studies. A large study by Kumar et al found a nearly 8% decrease in survival with each hour of delayed antibiotic use after the onset of hypotension.[36] However, this effect was not observed in certain other observational studies.[37] Subsequently, multiple large cohort studies, including data from the surviving sepsis campaign,[38] and the New York state department of health,[39] have found an association between early antibiotic administration and improved patient survival. These studies emphasize the importance of prompt antibiotic administration in patients with sepsis.

Targeted therapy

Over the last few decades, many agents have been developed to modulate the host response in sepsis and while several showed a benefit in animal models, they have failed to translate into clinical practice. Targeted therapies for sepsis can be broadly classified into three categories – 1) Strategies that target bacterial infection: Besides antimicrobial therapy, this includes targeting endotoxins in gram negative sepsis. However, two anti-endotoxin monoclonal antibodies, and an endotoxin neutralizing agent, failed to show benefit in clinical studies; 2) Strategies that target inflammation: antagonists to TNFα, IL-1β, IL-6, platelet-activating factor, bradykinin and C5a receptor antagonist have been tried without success in clinical trials, and 3) Strategies that target the coagulation pathway: recombinant antithrombin, recombinant tissue factor pathway inhibitor, and human recombinant activated protein C (drotecogrin-α) have also assessed in clinical trials. The drug, drotecogrin-α received approval from the US Food and Drug Administration for use in severely ill patients with sepsis. However, subsequent studies failed to reproduce its benefit, with a signal for higher mortality risk. Therefore, it was subsequently withdrawn from the market. Immune system stimulating drugs have also been considered, with IFN-gamma, IL-7 and Il-15 as potential targets. Finally, allogeneic mesenchymal stem cells are also being evaluated in clinical trials.[40]

Combining Elements of Sepsis Therapy: Bundles and Mandates

In addition to making recommendations about individual components of therapeutic strategies for sepsis and septic shock, in the year 2004, the Surviving Sepsis Campaign launched "sepsis care bundles". These "bundles" are a set of interventions targeted to improve the delivery of care in patients with presumed sepsis. The original bundles were (1) a 6-hour early resuscitation bundle comprising lactate measurement, blood cultures before initiating antibiotic therapy, and early fluid resuscitation with a minimum of 20 ml/kg of intravenous fluids, with or without vasopressors, with close measurement of central venous pressures and mixed venous oxygen saturations, and (2) a 24-hour bundle that consisted of strict glucose control, and the administration of low-dose steroids and activated protein C in selected patients. However, as new data emerged to refute some of these mandated practices, the 24-hour bundle was discontinued in 2012, and sepsis-care bundles were reorganized into a 3-hour bundle, and a second 6-hour to focus solely on the first 6 hours of resuscitation care. With the publication of the PRISM trials, the bundles were further revised in 2015 to include dynamic measures and physical exam to guide re-assessment for fluid resuscitation (Figure 8).

In the last 5 years, there has been legislative support for improved sepsis care through the use of sepsis care protocols. In the year 2013, following the death of a 12-year-old boy with sepsis, the state of New York adopted "Rory's regulations" that require all hospitals in the state to both adopt and report adherence to sepsis protocols. The Rory Staunton Foundation, the nonprofit organization that championed these regulations in New York, has been working to promote legislative action requiring protocolized sepsis care in every state. In the year 2015, the Center for Medicare and Medicaid Services also adopted

the above surviving sepsis bundles, with a requirement for mandatory reporting of their use in all acute care hospitals.

Figure 8. Surviving Sepsis Campaign bundles for patients with severe sepsis
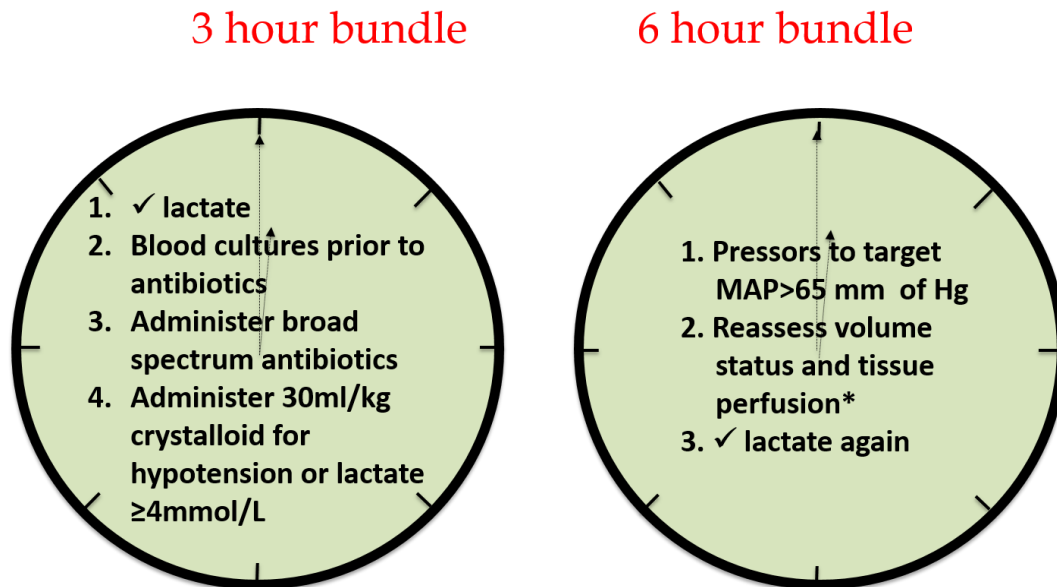
3 hour bundle

1. ✓ lactate
2. Blood cultures prior to antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

6 hour bundle

1. Pressors to target MAP>65 mm of Hg
2. Reassess volume status and tissue perfusion*
3. ✓ lactate again

Figure footnote: *Either 1) Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings, or two of the following: 1) Measure CVP, 2) Measure ScvO2, 3) Bedside cardiovascular ultrasound, 4) Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

The use of these care bundles and sepsis protocols is supported in observational studies with secular improvements in sepsis outcomes. However, these data lack adequate controls. Therefore, while compliance with sepsis bundles has been associated with improved patient outcomes, it is impossible to identify if these are a result of a general improvement in care over time, or a direct benefit of sepsis-care bundles or some of their individual components.[39,41,42] However, these mandates come at a cost, both to the patients and to the healthcare system. Given the paucity of evidence supporting the sepsis care bundles, it is unclear if their use lead to adverse patient outcomes, including diarrheal illnesses secondary to clostridium difficile infection due to broad spectrum antibiotic therapy and/or complications of invasive diagnostic or therapeutic procedures. Further, health systems may face an additional burden to comply with these mandates, including a high rate of ICU bed utilization, and auditing and reporting their compliance with the metrics included in the mandate.

While the care of patients with sepsis has evolved over the last several decades, several questions remain unanswered. It is essential that our efforts towards improving sepsis outcomes are rooted in science.

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