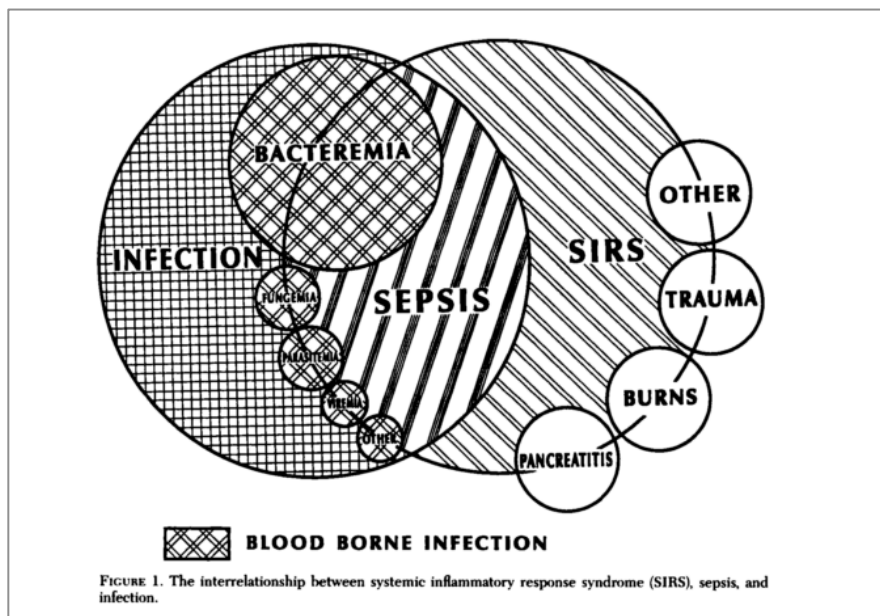


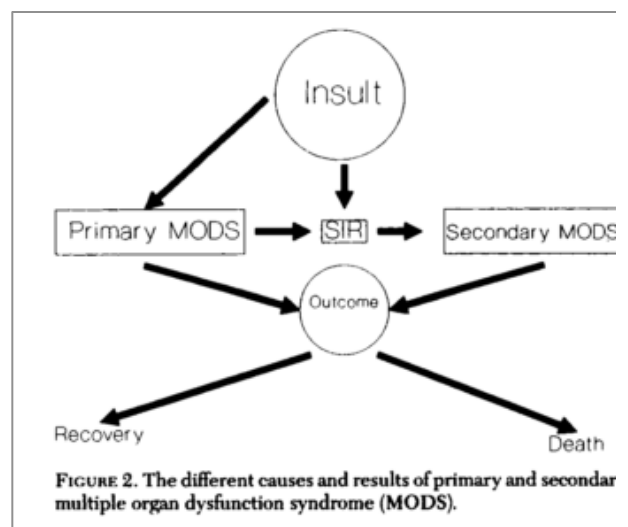
## The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

- Introduction
  - Sepsis is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection
  - Major public health concern
  - >\$20 billion (5.2%) of total US hospital costs in 2011
  - Reported incidence of sepsis is increasing, likely a reflection of:
    - Aging populations with more comorbidities
    - Greater recognition
  - True incidence unknown
- 1991
  - American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference
  - Goal: establish a set of definitions that could be applied to patients with sepsis and its sequelae
  - Proposed broad definitions:
    - To improve the ability to make early bedside detection of sepsis possible
    - Thus allowing early therapeutic intervention
    - Allow for the standardization of research protocols, with improved dissemination and application of information derived from clinical studies
      - Ability to compare protocols and evaluate therapeutic interventions



- Sepsis: implies a clinical (systemic) response arising from infection

- SIRS: a clinical (systemic) response arising from inflammation without infection
  - Body temperature greater than 38°C or less than 36°C
  - Heart rate greater than 90 beats per minute
  - Tachypnea
    - Respiratory rate greater than 20 breaths per minute
    - Hyperventilation, as indicated by a PaCO<sub>2</sub> of less than 32 mmHg
  - Alteration in the white blood cell count
    - >12,000/ cu mm
    - <4,000/cu mm
    - >10% band neutrophils
- Infection: a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
- Bacteremia: the presence of viable bacteria in the blood
  - The presence of viruses, fungi, parasites, and other pathogens in the blood should be described in a similar manner (ie, viremia, fungemia, parasitemia, etc).
- Septicemia: previously defined as the presence of microorganisms or their toxins in the blood
  - Used in a variety of ways, resulting in confusion
  - Does not adequately describe the entire spectrum of pathogenic organisms that may infect the blood
  - \*\*\*\*Eliminated term from current usage
- Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity
  - Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension
    - Septic shock: sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction
  - Sepsis-induced hypotension: systolic BP < 90mmHg, or its reduction by ≥40mmHg, in the absence of other causes for hypotension
- MODS: altered organ function in the acutely ill patient
  - A major threat to survival was not the underlying illness, or even a single complication thereof, but rather a process of progressive physiologic failure of several interdependent organ systems



- 2001
  - Gap in knowledge and understanding of sepsis and SIRS
  - No “gold standard” for sepsis or SIRS against which the diagnostic criteria can be calibrated
    - Diagnostic criteria to be judged successful if clinicians regard them as an aid for decision making at the bedside
  - SIRS can be triggered by a variety of infectious and noninfectious conditions
    - Signs of systemic inflammation occur in the absence of infection
    - Specific criteria proposed in the previous consensus definitions are too nonspecific to be of utility in diagnosing a cause of the syndrome or in identifying a distinct pattern of host response
    - 1991 consensus definitions are too nonspecific to be of utility in diagnosing a cause of the syndrome or in identifying a distinct pattern of host response
  - Sepsis
    - Sepsis to be the clinical syndrome defined by the presence of both infection and a systemic inflammatory response
    - SIRS criteria + findings such as hemodynamic instability, arterial hypoxemia, oliguria, coagulopathy, and altered liver function tests among the list of criteria that can be used to establish the diagnosis of sepsis
      - Important that as a practitioner “checks off the boxes” to establish the diagnosis of sepsis; only findings that cannot be easily explained by other causes should be included
    - Concluded that few, if any, patients in the early stages of the inflammatory response to infection are diagnosed with sepsis via four arbitrary criteria
      - A clinician at the bedside identifies a myriad of symptoms, and regardless of an evident infection declares the patient to “look septic”
  - Severe sepsis
    - Unchanged definition
    - Organ failure defined using SOFA
- Developing a staging system for sepsis

**Table 1** Diagnostic criteria for sepsis

	<b>Infection<sup>a</sup></b> Documented or suspected <i>and</i> some of the following <sup>b</sup> :  <b>General parameters</b> Fever (core temperature >38.3°C) Hypothermia (core temperature <36°C) Heart rate >90 bpm or >2 SD above the normal value for age Tachypnea: >30 bpm Altered mental status Significant edema or positive fluid balance (>20 ml/kg over 24 h) Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes  <b>Inflammatory parameters</b> Leukocytosis (white blood cell count >12,000/μl) Leukopenia (white blood cell count <4,000/μl) Normal white blood cell count with >10% immature forms Plasma C reactive protein >2 SD above the normal value Plasma procalcitonin >2 SD above the normal value  <b>Hemodynamic parameters</b> Arterial hypotension <sup>b</sup> (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age) Mixed venous oxygen saturation >70% <sup>b</sup> Cardiac index >3.5 l min <sup>-1</sup> m <sup>-2c,d</sup> <b>Organ dysfunction parameters</b> Arterial hypoxemia (PaO <sub>2</sub> /FIO <sub>2</sub> <300) Acute oliguria (urine output <0.5 ml kg <sup>-1</sup> h <sup>-1</sup> or 45 mM/l for at least 2 h) Creatinine increase ≥0.5 mg/dl Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s) Ileus (absent bowel sounds) Thrombocytopenia (platelet count <100,000/μl) Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 μmol/l)  <b>Tissue perfusion parameters</b> Hyperlactatemia (>3 mmol/l) Decreased capillary refill or mottling
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<sup>a</sup> Defined as a pathological process induced by a micro-organism

<sup>b</sup> Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

<sup>c</sup> Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

<sup>d</sup> Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

- Proposed PIRO
  - Stratifies patients on the basis of their:
    - Predisposing conditions
    - Nature and extent of the insult (in the case of sepsis, infection)
    - Nature and magnitude of the host response
    - Degree of concomitant organ dysfunction
  - \*\*PIRO concept is rudimentary; extensive testing and further refinement are needed before ready for routine application in clinical practice
- SUMMARY
  - Expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience, and no evidence exists to support any change in the definitions
- 2016
  - The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
  - Improved Understanding of Sepsis Pathobiology
    - Sepsis is a multifaceted host response to an infecting pathogen that may be significantly amplified by endogenous factors
    - SIRS criteria focuses on proinflammatory effects

- However it is now know that sepsis involve early activation of both pro- and anti-inflammatory responses and major modifications in nonimmunologic pathways (such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation)
  - All have prognostic significance
- Sepsis
  - The current use of 2 or more SIRS criteria to identify sepsis was unanimously considered by the task force to be unhelpful
  - Defined as life-threatening organ dysfunction caused by a dysregulated host response to infection
    - Nonhomeostatic host response to infection, the potential lethality that is considerably in excess of a straight forward infection, and the need for urgent recognition
  - No current clinical measures reflect the concept of a dysregulated host response
  - Diagnosis
    - SOFA change >2

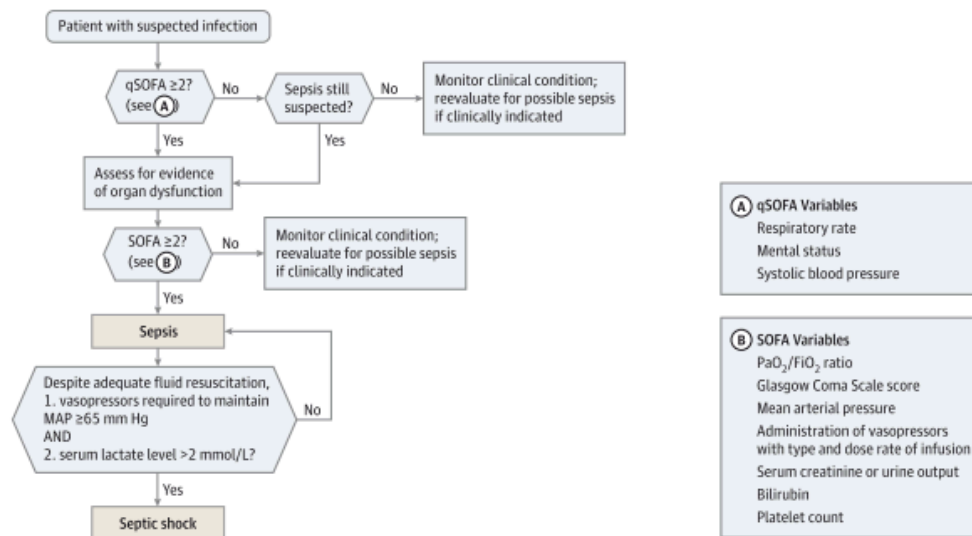
SOFA score	1	2	3	4
<b>Respiration<sup>a</sup></b>				
PaO <sub>2</sub> /FIO <sub>2</sub> (mm Hg)	<400	<300	<220	<100
SaO <sub>2</sub> /FIO <sub>2</sub>	221-301	142-220	67-141	<67
<b>Coagulation</b>				
Platelets ×10 <sup>3</sup> /mm <sup>3</sup>	<150	<100	<50	<20
<b>Liver</b>				
Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
<b>Cardiovascular<sup>b</sup></b>				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
<b>CNS</b>				
Glasgow Coma Score	13-14	10-12	6-9	<6
<b>Renal</b>				
Creatinine (mg/dL) or urine output (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

- qSOFA
  - Simple bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes
  - Altered mentation, systolic blood pressure of 100mmHg or less, and respiratory rate of 22/min+

Box 4. qSOFA (Quick SOFA) Criteria
Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≤100 mm Hg

- SOFA score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient
  - qSOFA criteria should be used to prompt clinicians to:
    - Further investigate for organ dysfunction
    - Initiate or escalate therapy as appropriate
    - Consider referral to critical care
    - Increase the frequency of monitoring
    - Prompt consideration of possible infection in patients not previously recognized as infected
  - Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality
    - Broader view than 1991 definition
    - To differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities
    - Septic shock should reflect a more severe illness with a much higher likelihood of death than sepsis alone
    - Identified if septic AND persisting hypotension requiring vasopressors to maintain MAP > 65 mmHg AND lactate > 2 mmol/L despite adequate volume resuscitation
    - Identified a subset of patients with a hospital mortality rate of more than 40%
  - Severe sepsis
    - Superfluous

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

## Criticisms of Sepsis 3

### **The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients**

Sarah A. Sterling, MD<sup>1</sup>; Michael A. Puskarich, MD<sup>1</sup>; Andrew F. Glass, MD<sup>1</sup>;  
Faheem Guirgis, MD<sup>2</sup>; Alan E. Jones, MD<sup>1</sup>

- 57% of patients meeting old definition for septic shock did not meet Sepsis-3 criteria
- Sepsis-3 criteria identified a group of patients with increased organ failure and higher mortality, those patients who met the old criteria and not Sepsis-3 criteria still demonstrated significant organ failure and 14% mortality rate

### **The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients**

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- Secondary analysis of two clinical trials of early septic shock resuscitation in large academic emergency departments in the United States
- Inclusion criteria: patients with suspected infection, more than or equal to two systemic inflammatory response syndrome criteria, and systolic blood pressure less than 90mmHg after fluid resuscitation (sepsis 2.0 septic shock criteria)
  - Further characterized as Sepsis-3 septic shock if they demonstrated hypotension, received vasopressors, and exhibited a lactate greater than 2 mmol/L
- Compared in-hospital mortality in patients who met the old definition only with those who met the Sepsis-3 criteria
- The majority of patients who met the old definition for septic shock did not meet the Sepsis-3 criteria
- Sepsis-3 criteria identified patients with more organ failure and higher mortality those patients who did not meet the new criteria

- Patients identified only by old sepsis still carry a significant mortality risk
- In conclusion, although Sepsis-3 identifies a group of patients at greater risk of worse clinical outcomes, it misses a large proportion of subjects with significant disease burden that may benefit from early resuscitative therapy

**TABLE 2 . Results of In-Hospital Patient Outcomes**

Variable	"New" Septic Shock Criteria (Sepsis-3) (n = 200)	"Old" Septic Shock Criteria (1991 Only) (n = 270)	p
Mortality, n (%) <sup>a</sup>	57 (28.5); 95% CI, 22–35	39 (14.4); 95% CI, 10–19	< 0.001
Length of stay (IQR)			
Vasopressors days	1.3 (0.9–4); 95% CI, 2.3–4.2	1 (0–2); 95% CI, 0.9–1.4	< 0.001
Total hospital days	8 (5–16); 95% CI, 9.8–12.7	8 (4.5–12); 95% CI, 9.6–12.2	0.466
Total ICU days	3.2 (1.8–7); 95% CI, 4.9–7.1	2.5 (1–5); 95% CI, 3.6–5.1	0.006

IQR = interquartile range.

<sup>a</sup>Primary outcome.

**TABLE 3. Quick Sequential Organ Failure Assessment Scores and Mortality**

qSOFA Score and Mortality Rate	Septic Shock Criteria		p
	"New" Septic Shock Criteria (Sepsis-3) (n = 200)	"Old" Septic Shock Criteria (1991 Only) (n = 270)	
qSOFA < 2; mortality, n (%)	73; 11 (15)	133; 18 (14)	0.926
qSOFA ≥ 2; mortality, n (%)	127; 46 (36)	137; 21 (15)	< 0.001

qSOFA = quick Sequential Organ Failure Assessment.

- Sepsis 3 remains subjective
  - Diagnosis hinges on whether the patient has 'suspected infection'
- SOFA and qSOFA are mortality predictors, not sepsis-specific tests
  - qSOFA may be misunderstood as a sepsis screen
- Sepsis 3 is less specific for infection than sepsis 2
  - Sepsis 2: suspected infection + SIRS
  - Sepsis 3: suspected infection + qSOFA + SOFA
- qSOFA may be less specific in diseases that directly cause altered mentation, tachypnea and hypotension
- qSOFA and SOFA have not been evaluated in combination
- Sepsis 3 is not a consensus guideline
  - Endorsed by the Society of Critical Care Medicine, the American Thoracic Society, and the American Association of Critical Care Nurses
  - Not endorsed by the American College of Chest Physicians, the Infectious Disease Society of America, any of the Emergency Medicine societies, or any of the hospital medicine societies



## QUESTIONS

1. Do you think the recommended meeting 2/4 SIRS criteria for diagnosis of sepsis is unhelpful?
2. What are the three proposed common mechanisms for the vasodilatation and resistance to vasopressors that occur in most types of vasodilatory shock?
3. Do you think the recommended alterations to the diagnosis of sepsis will impact your clinical practice? If so, how? If not, why?