

SEPSIS

RECOGNITION

Brian C. Peach, MSN, RN, CCRN
University of Florida
College of Nursing
PhD Candidate
bpeach01@ufl.edu

Conflict of Interest

I have no conflict of interest to report.

Objectives

- By the completion of this webinar, the learner will be able to:
 - Explain why a change in the sepsis definition was necessary.
 - Define 'Sepsis' and 'Septic Shock' according to the new Sepsis-3 definitions.
 - Identify how the new qSOFA score could be used in practice.
 - Discuss the potential implications of the new Sepsis-3 definitions and the qSOFA score on research and practice.
 - Debate the utility of the qSOFA in relation to other early warning systems

Defining Sepsis

- Sepsis 1: 1991-2001
- Sepsis 2: 2001-2016
- Sepsis 3: 2016-?

Sepsis-1 definition (1991-2001)

- Created in a consensus conference in Chicago by members of the **Society of Critical-care Medicine (SCCM)** & **The American College of Chest Physicians (ACCP)**
- They hoped to create a definition that would:
 - Help clinicians improve detection to allow for early therapeutic intervention.
 - Aid in standardizing research protocols to improve dissemination and application of research studies.
- The members recognized that the first definition was broad, but the science to define sepsis wasn't there yet.

Sepsis-1 definition (1991-2001)

- The Sepsis-1 definition was based in the **Systemic Inflammatory Response Syndrome (SIRS)**
- What is SIRS?
 - An inflammatory process related to infectious and non-infectious causes
 - Common causes of a SIRS response:
 - Infection
 - Trauma
 - Burns
 - Pancreatitis

Sepsis-1 definition (1991-2001)

- SIRS criteria:
 - $T > 100.4\text{ F}$ or $< 96.8\text{ F}$
 - $\text{HR} > 90\text{ beats/min}$
 - $\text{RR} > 20\text{ breaths/min}$
 - $\text{WBC} > 12,000$ or $< 4,000$ or $> 10\%$ bands
 - $\text{PCO}_2 < 32\text{ mmHg}$
- Sepsis-1 definition:
 - Infection + 2 or more SIRS criteria = Sepsis
 - 3 levels: sepsis, severe sepsis, and septic shock

Sepsis-1 definition (1991-2001)

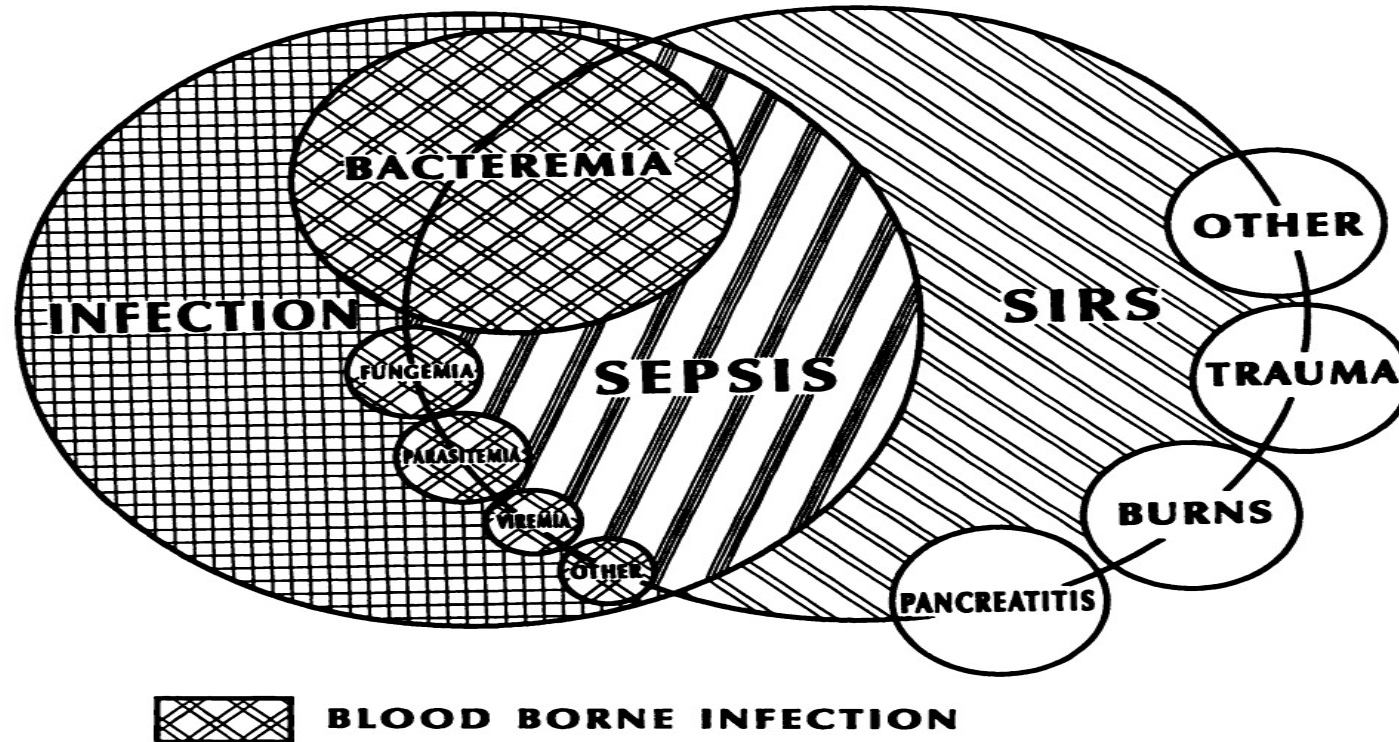


FIGURE 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.

CHEST / 101 / 6 / JUNE, 1992 1645

Figure 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection. Reprinted from "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis," by R.C. Bone et al., 1992, *CHEST*, 101(6), 1644-1655. Copyright year 1992 by "Elsevier".

Sepsis-2 definition (2001-2016)

- A 2nd consensus conference held, this time in DC w/ members from the **SCCM, ACCP + the European Society of Intensive Care Medicine (ESICM), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS)**
- Infection + SIRS is too broad
- They identified a number of biomarkers present during sepsis, but their utility in diagnosing sepsis was still unknown.
- They added clinical criteria for inadequate perfusion to the Sepsis-1 definition: **Systolic BP < 90mmHg, serum lactate levels > 4mmol, signs of end organ damage**

Sepsis-2 definition (2001-2016)



Figure 2. Sepsis Steps. Reprinted from “Sepsis—an often missed diagnosis,” by Y. Ernst, 2012.

Pathophysiology

1. An infectious agent infiltrates the body – directly into the bloodstream, or the respiratory tract, GI or GU tract, skin, etc.
2. An excessive inflammatory response leads to vasodilation, leukocyte accumulation, increased micro-vascular permeability, intravascular volume depletion, myocardial depression, and increased metabolism.
3. This unbridled response leads to an imbalance between oxygen delivery and demand, resulting in global tissue hypoxia. Patients will have abnormally high tissue oxygen needs primarily due to hyper-metabolism.
4. Tissue hypoxia->organ dysfunction/failure->DEATH

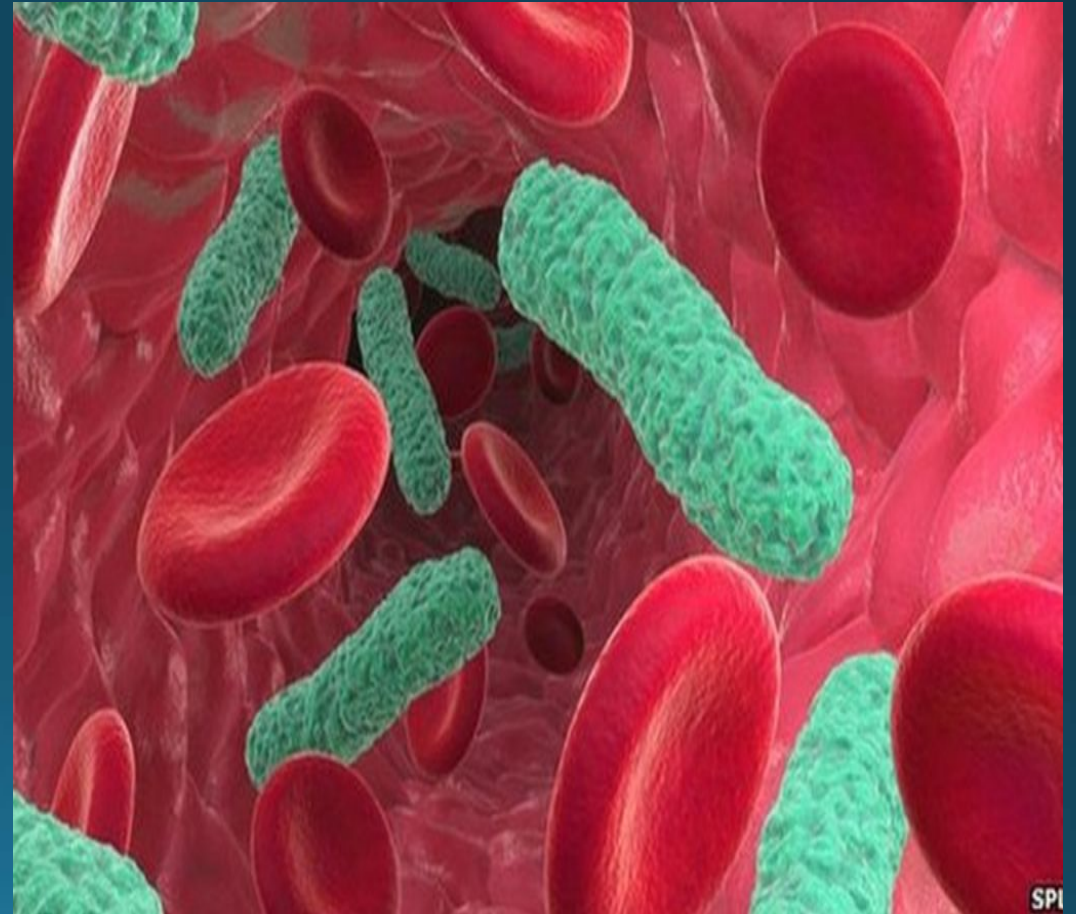


Figure 3. Bacteremia. Reprinted from “World Sepsis Day” by T. Sandle, 2014.

Newer findings

- Sepsis involves activation of both **pro-** and **anti-inflammatory responses** (Hotchkiss, Monneret, & Payen, 2013)
- Recent research has uncovered **endogenous factors** that rapidly change the **cardiovascular, neurological, endocrine, and hematological systems** in response to infection and the body's inflammatory response (Deutschman & Tracey, 2014; Singer, De Santis, Vitale, & Jeffcoate, 2004).
- These endogenous factors can “**amplify**” the host response (Singer et al., 2016, p. 804).
- Other factors like the **source of infections** and **comorbidities** may have a significant impact on the body's response to infection

Alarmins

- A family of endogenous molecules passively secreted from necrotic tissue cells, injured tissue, activated leukocytes, and epithelia
- Mediate inflammation, and are now one of the targets of therapy research
- Link innate and active immunity
- May prove to be valuable biomarkers in terms of diagnostic and prognostic utility
- Being investigated in relation to autoimmune disorders
- Examples: high-mobility group protein B1 (HMGB1), S100 proteins, and heat shock proteins (HSPs)

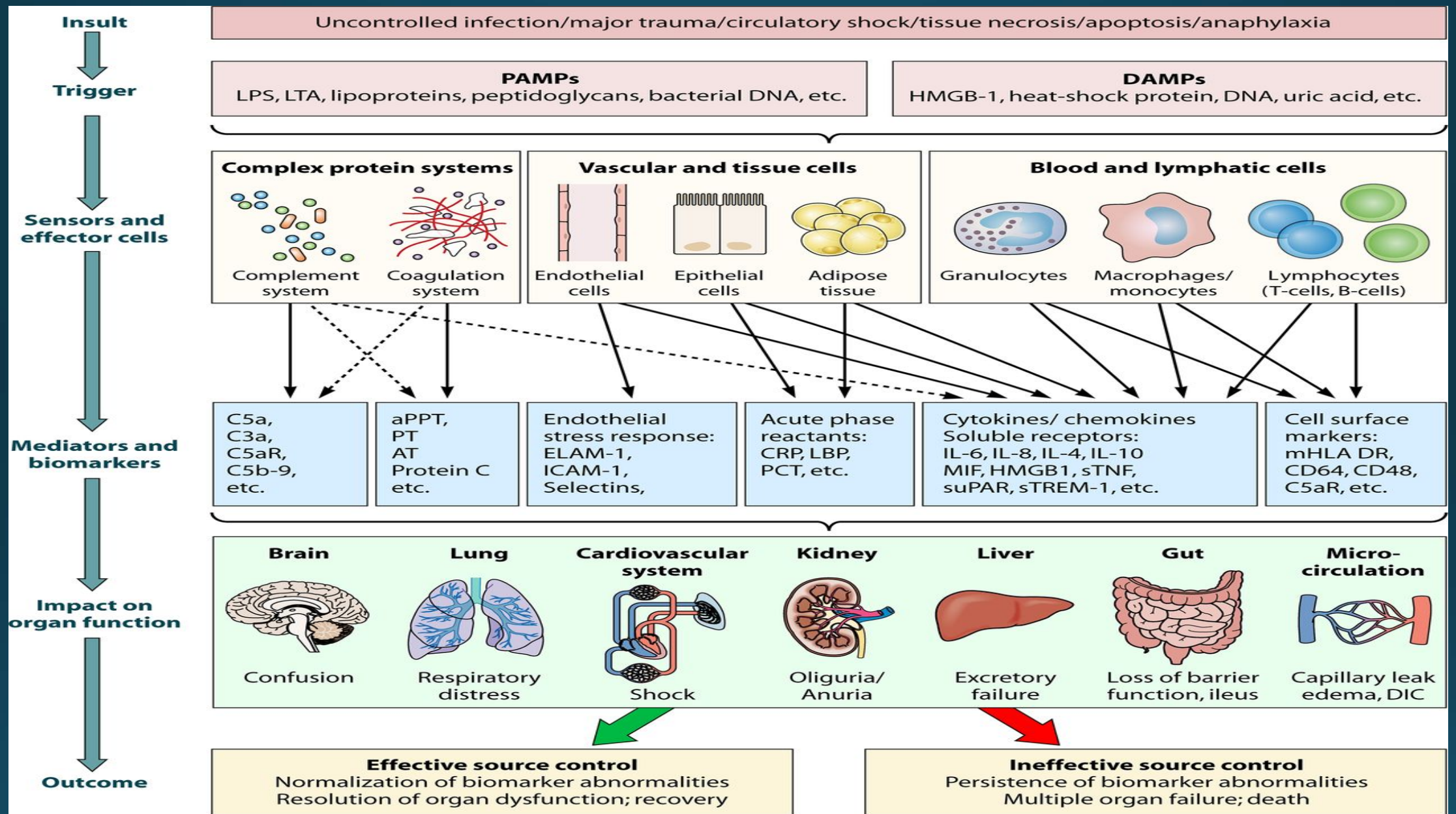


Figure 4. Sepsis Cascade. Reprinted from Immune system error creates vulnerability to sepsis. K. Marker, 2016.

We have a new sepsis definition...



Figure 5. Redefining Sepsis. Reprinted from “PulmCrit-top ten problems with the new sepsis definition, “ by J. Farkas, 2016.

The Sepsis-3 definition

- In February 2016, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) announced a monumental change to the sepsis definition at the SCCM annual conference in Orlando, and it was published that same week in the Journal of the American Medical Association (JAMA).
- Why the change?
 - 1. Excessive focus on inflammation
 - 2. Misleading model that sepsis follows a continuum from severe sepsis to septic shock
 - 3. Inadequate specificity and sensitivity of the SIRS criteria
 - 4. Multiple definitions are currently used for sepsis, septic shock, and organ dysfunction, which leads to discrepancies in reported incidence and observed mortality.
 - 5. The term “severe sepsis” is redundant.

New Sepsis-3 definition (as of 02/2016)

“Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more.”

(Singer et al., 2016, p. 802)

New Septic Shock definition (as of 02/2016)

“A subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater AND serum lactate level greater than 2mmol/L (>18mg/dL) in the absence of hypovolemia.”

(Singer et al., 2016, p. 802)

What is SOFA?

- A morbidity severity score AND a mortality estimation tool
- Developed from a study of 1,449 patients from 40 intensive care units throughout the world (Vincent et al., 1998).
- The SOFA score is composed of 6 variables, each representing an organ system.
- Each organ system is assigned a point value from 0 (normal) to 4 (high degree of dysfunction/failure).
- The SOFA score ranges from 0 to 24.
- SOFA is superior to the SIRS criteria in terms of predictive validity for in-hospital mortality (Seymour et al., 2016).

What is SOFA?

- Other scoring systems like the **Acute Physiologic and Chronic Health Evaluation (APACHE)** and **Simplified Acute Physiologic Score (SAPS)** have only been validated in the first 24 hours of admission, and only to predict mortality (Vincent & Moreno, 2010).
- SOFA should be calculated **24 hours after admission AND every 48 hours** thereafter to assess progress (Vincent & Moreno, 2010).
- The **mean** and **highest** scores are most predictive of mortality (Ferreira, Bota, Bross, Melot, & Vincent, 2001)

SOFA

Table 1. The Sequential Organ Failure Assessment (SOFA) Score*

Variables	SOFA Score				
	0	1	2	3	4
Respiratory Pao ₂ /Fio ₂ , mm Hg	>400	≤400	≤300	≤200†	≤100†
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 Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio₂, fraction of inspired oxygen.

†Values are with respiratory support.

‡To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

§Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

||To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

Table 1. The Sequential Organ Failure Assessment (SOFA) Score Adapted from “Serial evaluation of the SOFA score to predict outcome in critically ill patients,” by Ferreira, et al., 2001, *JAMA*, 286(14), 1754-1758. Copyright year 2001 by “American Medical Association”.

Differences between old and new definitions

- The focus is now on organ dysfunction instead of inflammatory markers
- The baseline SOFA score is assumed to be 0 in the absence of known organ dysfunction.
- Instead of 3 categories, 'sepsis', 'severe sepsis', and 'septic shock', there are just 2 (no more 'severe sepsis')

Predicting SEPSIS-related mortality

Maximum SOFA score during ICU stay	Mortality
0-6	<10%
7-9	15-20%
10-12	40-50%
13-14	50-60%
15	>80%
16-24	>90%

Note. Based on the results of 2 prospective studies, SOFA can be used to estimate mortality in patients with sepsis.

Table 2. SOFA Score and Associated Mortality. Adapted from “Serial evaluation of the SOFA score to predict outcome in critically ill patients,” by Ferreira, et al., 2001, *JAMA*, 286(14), 1754-1758. Copyright year 2001 by “American Medical Association”.

Predicting SEPSIS-related mortality

Score Trend (after first 48 hours)	Mortality
Increasing	>50%
Unchanged	27%-35%
Decreasing	<27%

Table 3. SOFA Trend and Associated Mortality Adapted from “Serial evaluation of the SOFA score to predict outcome in critically ill patients,” by Ferreira, et al., 2001, *JAMA*, 286(14), 1754-1758. Copyright year 2001 by “American Medical Association”.

qSOFA

“In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quick SOFA (qSOFA): **respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100mmHg or less.**”

(Singer et al., 2016, p. 802)



Figure 6. qSOFA. Reprinted from “Conferencia Internacional de Consenso en Sepsis y Shock Séptico...¡¡y van tres!! qSOFA scoring.” by R. Gonzalez de Castro, 2016.

QSOFA

qSOFA criteria be used to: “prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken.” (Singer et al., 2016, p. 808)

Algorithm using the new sepsis definition

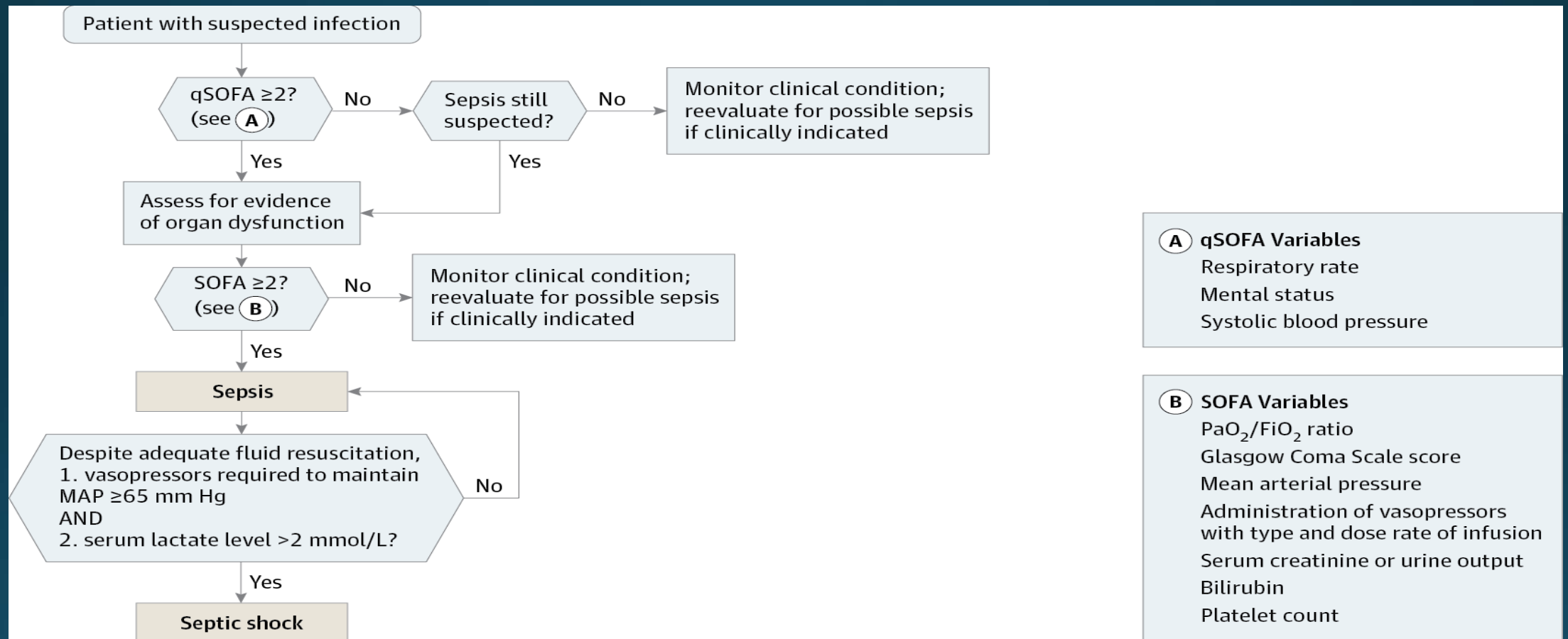


Figure 7. Sepsis 3 Algorithm. Reprinted from “The third international consensus definitions for sepsis and septic shock (Sepsis-3),” by M. Singer et al., 2016, *JAMA*, 315(8), 801-810 . Copyright year 2016 by “American Medical Association”.

Area Under Receiver Operating Characteristic (AUROC)

- Measures **discrimination**: the ability of the test to correctly classify who has disease, and who does not.
- The AUROC tells us a test's ability to **correctly classify from randomly drawn cases**.

Area Under Receiver Operating Characteristic (AUROC)

AUROC	Level of Discrimination
.90-1	Excellent
.80-.90	Good
.70-.80	Fair
.60-.70	Poor
.50-.60	Fail

Table 4. AUROC Scores

Early Validation Results for the qSOFA

- Moskowitz et al. (2017), Critical Care Medicine
- Retrospective cohort: 24,164 patients with suspected infection admitted into a single center ED over a 4 year period
- The AUROC of qSOFA for prediction of a need for critical care intervention was 0.74 [95% CI, 0.73-0.74) vs. 0.69 for SIRS criteria. The sensitivity of qSOFA for predicting critical care intervention was 38%. In terms of predicting in-hospital mortality, the AUROC for qSOFA was 0.71 [95% CI, 0.69-0.72] vs. SIRS (0.66).
- Conclusion: qSOFA outperforms the SIRS criteria in predicting critical care intervention and in-hospital mortality in patients admitted through an ED with suspected infection, however its low sensitivity and discrimination in identifying sicker patients makes its utility in EDs questionable.

Early Validation Results for the qSOFA

- Churpek et al. (2017), American Journal of Respiratory and Critical Care Medicine
- Retrospective cohort: 30,677 patients suspected of having an infection who were admitted to non-ICU floors over a 7 yr period in a single center
- SIRS vs. qSOFA vs. NEWS vs. MEWS in predicting in-hospital mortality
- NEWS found to be the best performing tool (AUROC 0.77; 95% CI 0.76–0.79), followed by the MEWS (AUROC 0.73; 95 % CI, 0.71–0.74), qSOFA (AUROC 0.69; 95% CI, 0.67–0.70), and SIRS (AUROC 0.65; 95% CI, 0.63–0.66) ($p=0.01$). SIRS highest in sensitivity (91%), but poor in specificity (13%). NEWS scored well for sensitivity (67%) and specificity (66%). MEWS average for sensitivity (59%) and well (70%) for specificity, and qSOFA average sensitivity (54%) and well sensitivity (67%).
- Conclusion: qSOFA is superior to the SIRS criteria, but should not replace the NEWS or MEWS in clinical settings

Early Validation Results for the qSOFA

- Raith et al. (2017), JAMA
- Retrospective cohort: 184,875 patients with an infection-related primary admitting diagnosis in 182 Australian and New Zealand ICUs over a 15 year period
- After adjusting for these baseline predictions of mortality, SOFA (AUROC 0.815 [99% CI, 0.811-0.818]) outperformed both SIRS (AUROC 0.755 [99% CI, 0.752-0.759]) and qSOFA (AUROC 0.762 [99% CI, 0.758-0.765]) in predicting in hospital mortality in ICU settings
- Conclusion: The qSOFA outperformed the SIRS criteria in predicting in-hospital mortality, but it is inferior to the more-variable laden SOFA score in ICU settings.

Questions?

Thank you for attending
this session!

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