

Early Recognition and Timely Management of Sepsis Amid Changes in Definitions

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Disclosure

I have no conflicts of interest or financial ties to any medications or devices discussed

Objectives

1. To understand the differences between old and new sepsis definitions.
2. To apply the new criteria to quickly identify patients with sepsis.
3. To manage patients with sepsis by using the new 2017 Society of Critical Care Medicine (SCCM) sepsis guidelines .

EPIDEMIOLOGY

- ▶ More than 1.5 million cases of sepsis occur in the US annually. **Approximately 70% of sepsis cases are community-acquired.**
- ▶ Approximately 215,000 patients die from sepsis in the US
- ▶ According to data from the Surviving Sepsis Campaign, mortality rates from sepsis are 41% in Europe and 28.3% in the US.
- ▶ Sepsis is the most expensive health-care problem in the US: a cost of more than \$20 billion

OBJECTIVE #1

To understand the differences
between old and new sepsis
definitions

SIRS (Systemic Inflammatory Response Syndrome)

Two or more of the following:

- Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate $>90/\text{min}$
- Respiratory rate $>20/\text{min}$ or $\text{Paco}_2 <32 \text{ mm Hg (4.3 kPa)}$
- White blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ immature bands

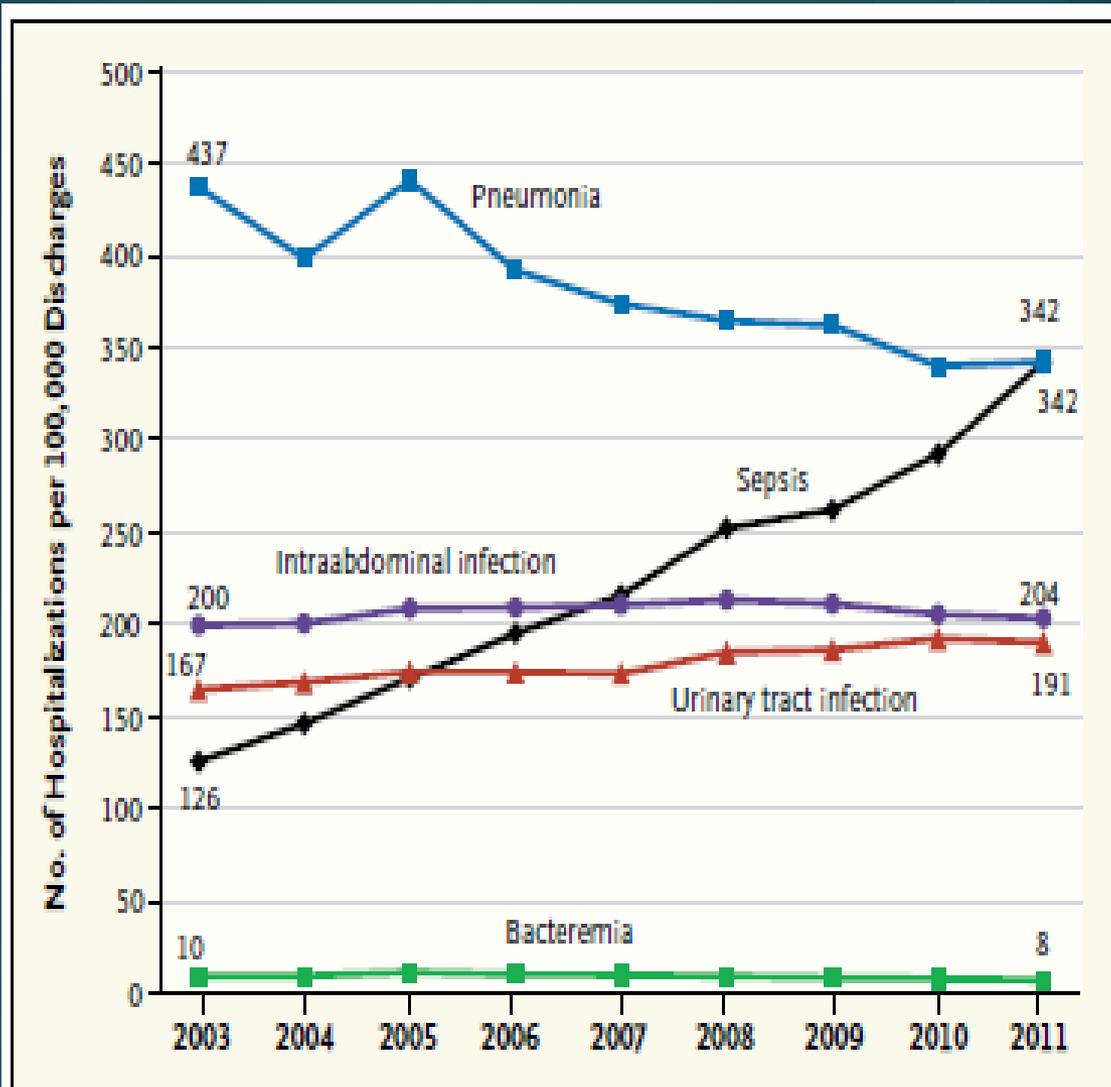
2012 Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock

- ▶ Sepsis was defined as **a systemic manifestation of infection (i.e. Systemic Inflammatory response Syndrome [SIRS] criteria) + suspected infection**
- ▶ Severe sepsis was defined as **sepsis + end organ damage**
- ▶ Septic shock was defined as **severe sepsis + hypotension not reversed with fluid resuscitation**

Dellinger RP et al. Critical Care Med 2013 Feb;41 (2):580-637.

Cont.

- However, The SIRS criteria are no longer included in the new definitions of sepsis because they do not necessarily indicate a dysregulated, life-threatening response. SIRS criteria are present in many patients who never develop infection. Therefore, they are deemed unhelpful in the diagnosis of sepsis.
- The new definitions for sepsis that will be shown in the next few slides that reflect a consensus from the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM).
- However, The Center for Medicare and Medicaid Services (CMS) continues to support the previous definition of SIRS, sepsis and severe sepsis.



Hospitalizations for Which Certain Infection Codes Were Listed as a Primary Diagnosis, 2003–2011.

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

- ▶ 2017 Guidelines Redefine sepsis as agreed upon by The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) as the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
- ▶ Sepsis: “life-threatening organ dysfunction caused by a dysregulated host response to infection.” End organ damage is identified as an acute change in total *Sequential [Sepsis-related] Organ Failure Assessment score (**SOFA**) ≥ 2 ,

OR

a quick SOFA (**qSOFA**) score ≥ 2 .
- ▶ Septic shock: A subset of sepsis “in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. These patients can be clinically identified by a vasopressor requirement to maintain a MAP ≥ 65 mmHg and serum lactate >2 mmol/L in the absence of hypovolemia”
- ▶ “Severe sepsis” category was deemed to be superfluous and is no longer recommended for clinical use

qSOFA (Quick SOFA) Criteria

- Respiratory rate ≥ 22 /min
- Altered mental status
- Systolic blood pressure ≤ 100 mm Hg

*qSOFA score ≥ 2 is associated with a greater risk of death

Sequential Organ Failure Assessment Score

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
Pao ₂ /Fio ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
	MAP ≥70 mm Hg	MAP <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 Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure; Pao₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Seymour CW et al. JAMA 2016 Feb 23;315(8):762-74

Objective/Design

- **OBJECTIVE:** To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.
- **DESIGN:** Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, those with suspected infection were identified to compare criteria.

Findings

- **EXPOSURES:** SOFA score, SIRS criteria, the quick Sequential Organ Failure Assessment (qSOFA) score were compared
- **MAIN OUTCOMES:** The discrimination for outcomes (primary: in-hospital mortality; secondary: in-hospital mortality or intensive care unit [ICU] length of stay ≥ 3 days) more common in sepsis than uncomplicated infection was determined.
- **RESULTS:** The predictive validity for in-hospital mortality was lower for SIRS (AUROC = 0.64) and qSOFA (AUROC = 0.66) vs SOFA (AUROC = 0.74). Among non-ICU encounters in the validation cohort (n = 66 522), qSOFA had predictive validity (AUROC = 0.81) that was greater than SOFA (AUROC = 0.79) and SIRS (AUROC = 0.76).
- **CONCLUSIONS:** Among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis. Among encounters with suspected infection outside of the ICU, the predictive validity for in-hospital mortality of qSOFA was statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.



Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the ED

Freund Y et al., JAMA 2017 Jan 17;317(3):301-308.

Study Findings

- **Objective:** To prospectively compare qSOFA as a mortality predictor to the previous ones.
- **Design:** A prospective study, conducted in the EDs of France, Spain, Belgium, and Switzerland between May and June 2016 for a 4-week period.
- **Exposures and Outcomes:** Measurement of qSOFA, SOFA, and SIRS. In-hospital mortality.
- **Results:** Of 1088 patients screened, 879 were included in the analysis. The qSOFA performed better than both SIRS and severe sepsis in predicting in-hospital mortality, with an area under the receiver operating curve of 0.80 vs 0.65 for both SIRS and severe sepsis
- **Conclusions:** Among patients presenting to the emergency department with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for in-hospital mortality than did either SIRS or severe sepsis.



Quick sequential organ
failure assessment
(qSOFA) compared to
systemic inflammatory
response syndrome (SIRS)
for predicting sepsis in
emergency department

qSOFA Study Findings

- **PURPOSE:** The aim of this study was to determine whether qSOFA has prognostic value when compared to SIRS in predicting organ failure in patients with a suspected infection in an ED
- **METHODS:** A retrospective observational study was conducted in an ED during a 9-year period. The ability of qSOFA compared to SIRS was analysed to predict the development of organ failure in patient using the area under receiver operating characteristic curve.
- **RESULTS:** A total of 1009 patients with suspected infection were included in the study. The predictive validity of qSOFA for organ failure was higher than that of SIRS (AUROC=0.814 vs. AUROC=0.662). qSOFA was also superior to SIRS in predicting in-hospital mortality (AUROC=0.733 vs. AUROC=0.599). qSOFA's sensitivity and specificity to predict organ failure was 75% and 82%, respectively.
- **CONCLUSIONS:** qSOFA has a superior ability compared to SIRS in predicting the occurrence of organ failure in patients with a suspected infection.



Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-hospital Mortality among adults with suspected infection admitted to the ICU

Prognostic Accuracy Study Findings

- **Objective:** To assess the discriminatory capacities of an increase in SOFA score by ≥ 2 points, 2 or more SIRS criteria, or a qSOFA score of ≥ 2 points for outcomes
- **Design, Setting, and Participants:**
 - ▶ Retrospective analysis of 184 875 patients in 182 Australian and New Zealand ICUs from 2000 through 2015. SOFA, qSOFA, and SIRS criteria data were collected within 24 hours of ICU admission.
- **Main Outcomes and Measures:**
 - ▶ The primary outcome was in-hospital mortality. In-hospital mortality or ICU length of stay (LOS) of 3 days or more was a composite secondary outcome
- **Results:** SOFA showed significant greater discrimination for in-hospital mortality than SIRS or qSOFA criteria. SOFA also outperformed the other scores for the secondary endpoint
- **Conclusions:**
 - ▶ Among adults with suspected infection admitted to an ICU, an increase in SOFA score of 2 or more had greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score. These findings suggest that SIRS criteria and qSOFA may have limited utility for predicting mortality in an ICU setting.



Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit

Finkelsztein EJ et al., Weill Cornell Medicine
Critical Care 2017 Mar 26;21:73

Comparison of qSOFA and SIRS Study Findings

- **BACKGROUND:** The authors attempted to compare the discriminatory capacity of the qSOFA versus the Systemic Inflammatory Response Syndrome (SIRS) score for predicting mortality, ICU-free days, and organ dysfunction-free days in patients with suspicion of infection outside the ICU.
- **METHODS:** The Weill Cornell Medicine Registry and Biobank of Critically Ill Patients prospectively collect biological samples and clinical information. Using such information, qSOFA and SIRS scores outside the ICU (specifically, within 8 hours before ICU admission) were calculated.
- **RESULTS:** 152 patients (67% from the ED) were included in the study. Discrimination of in-hospital mortality using qSOFA [area under the receiver operating characteristic curve (AUC)] was significantly greater compared with SIRS criteria (AUC, 0.59 $p = 0.03$). The qSOFA performed better than SIRS regarding discrimination for ICU-free days ($p = 0.04$), but not for ventilator-free days ($p = 0.19$), any organ dysfunction-free days ($p = 0.13$), or renal dysfunction-free days ($p = 0.17$).
- **CONCLUSIONS:** In patients with suspected infection who eventually required admission to the ICU, qSOFA calculated before their ICU admission had greater accuracy than SIRS for predicting mortality and ICU-free days.

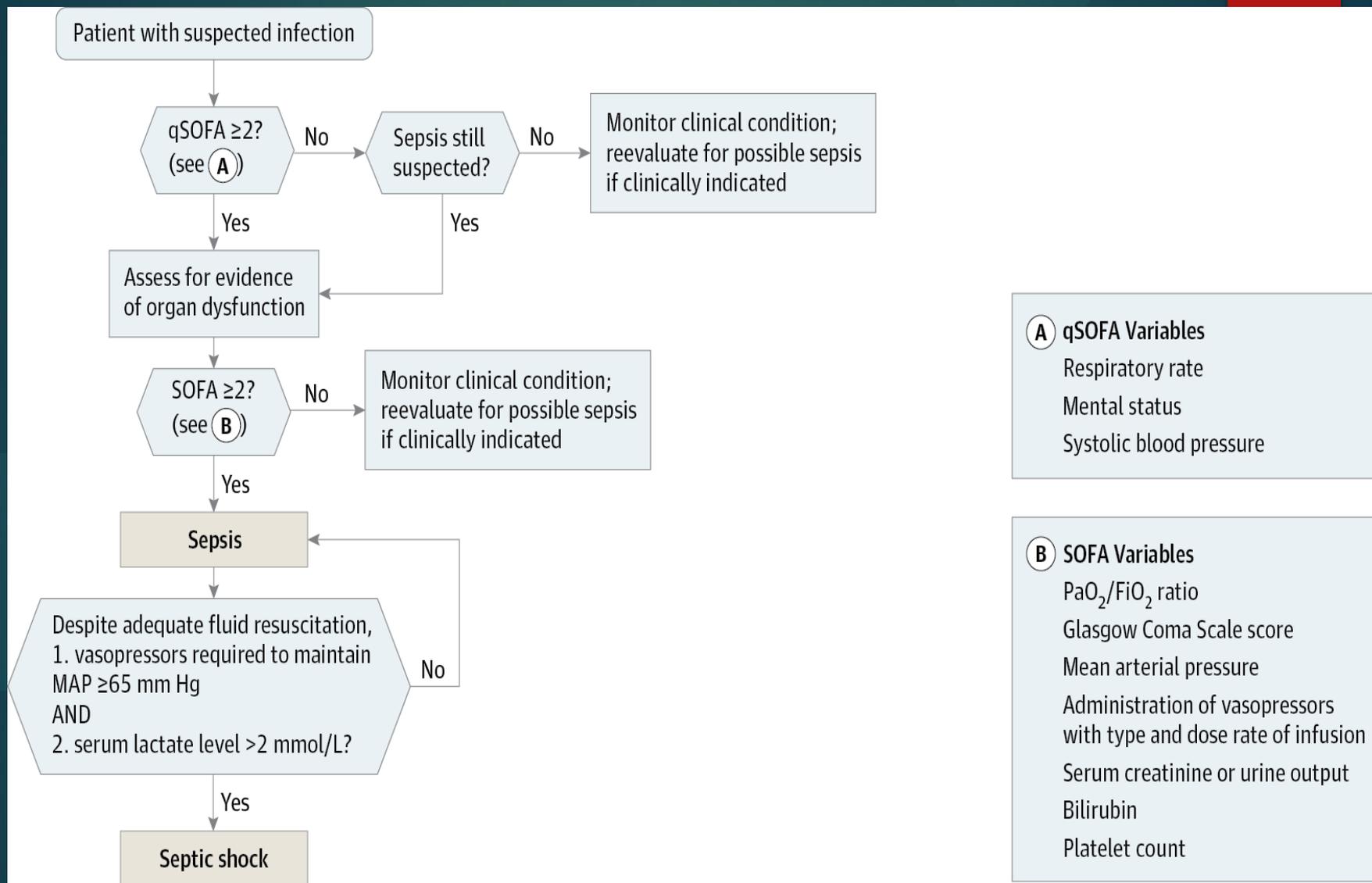
SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS

	2012	2016
SEPSIS DEFINITION	Systemic manifestation of infection + suspected infection Severe sepsis: sepsis + organ dysfunction	Life threatening organ dysfunction caused by dysregulated response to infection No severe sepsis category
INITIAL RESUSCITATION	at least 30 cc/kg in first 3 hours Crystalloid fluid (no recommendations on 0.9% NaCl vs balanced solution) Albumin if patients require "substantial" fluids (weak)	
	Protocolized care including CVP ScVO2 Normalize lactate	Use dynamic resuscitation markers (passive leg raise) Target MAP of 65mmHg Reassess hemodynamic status to guide resuscitation Normalize lactate
VASOPRESSORS	target MAP of 65 mmHg 1. Norepinephrine 2. Epinephrine if not at target MAP OR vasopressin to reduce norepinephrine requirement 3. Avoid dopamine in most patients	
STEROIDS	Only indicated for patients with septic shock refractory to adequate fluids and vasopressors	
ANTIBIOTICS	One or more antibiotics active against presumed pathogen Combination therapy (double coverage) for neutropenic patients and pseudomonas	Initial broad spectrum antibiotics (ex: vancomycin + piperacillin-tazobactam) Against combined therapy (i.e. do not double cover pseudomonas) May use procalcitonin to guide de-escalation
SOURCE CONTROL	Achieve within 12 hours, if feasible	Achieve as soon as medically and logically feasible
VENTILATOR	6 cc/kg tidal volume prone patients with severe ARDS (P/F <150 in 2017 guidelines)	
	no recommendation	Against high frequency oscillatory ventilation (HFOV)
	weak recommendation for noninvasive ventilation in select patients with sepsis induced ARDS	Unable to make recommendation on noninvasive ventilation

OBJECTIVE #2

To apply the new criteria
to quickly identify patients
with sepsis

Algorithm of Clinical Criteria Identifying Patients with Sepsis and Septic Shock



- A** qSOFA Variables
- Respiratory rate
 - Mental status
 - Systolic blood pressure

- B** SOFA Variables
- PaO₂/FiO₂ ratio
 - Glasgow Coma Scale score
 - Mean arterial pressure
 - Administration of vasopressors with type and dose rate of infusion
 - Serum creatinine or urine output
 - Bilirubin
 - Platelet count

Bacteremia vs. Septicemia

1. DO NOT EQUATE BACTEREMIA WITH SEPSIS

BACTEREMIA means the presence of viable bacteria in the blood. Patients with bacteremia are at risk of developing sepsis but not always.

2. AVOID USING THE TERM “SEPTICEMIA”

SEPTICEMIA means “Blood poisoning”. This outdated term should be avoided because it is vague in meaning and easily confused with the terms sepsis and bacteremia

OBJECTIVE #3

To manage patients with sepsis by using the new 2017 Society of Critical Care Medicine (SCCM) sepsis guidelines

Case Study

In 2012, Rory Staunton, a 12-year-old boy from New York died from sepsis after his physicians reportedly misinterpreted warning signs—a high fever and vomiting but also a cut on his arm.

Staunton's death inspired the passage of Rory's Regulations

All hospitals in New York State were required to follow Rory's Regulations in 2013

- ▶ Three-hour bundle
 1. Serum lactate test
 2. Administration of broad-spectrum antibiotic after obtaining blood cultures
- ▶ Six-hour bundle that includes fluid resuscitation for patients with hypotension or elevated lactate levels.



Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, Univ of Pittsburgh,
N. Eng J Med 2017;376:2235-44

Time to Treatment Study Findings

- **METHODS:** Data from patients with sepsis and septic shock that were reported to the New York Dept of Health from April 1, 2014 to June 30, 2016 were studied.
- **RESULTS:** Among 49,331 patients at 149 hospitals, 40,696 (82.5%) had the 3-hr bundle completed within 3 hours. A longer time to the completion of the 3-hr bundle was associated with higher in-hospital mortality, as was a longer time to the administration of antibiotics, but not a longer time to the completion of intravenous fluids.
- **CONCLUSIONS:** More rapid completion of 3-hr bundle of sepsis care & rapid administration of antibiotics, but not rapid completion of an initial bolus of IV fluids, were associated with lower risk-adjusted in-hospital mortality.



Early goal-directed therapy in the treatment of severe sepsis and septic shock

Rivers E. et al.

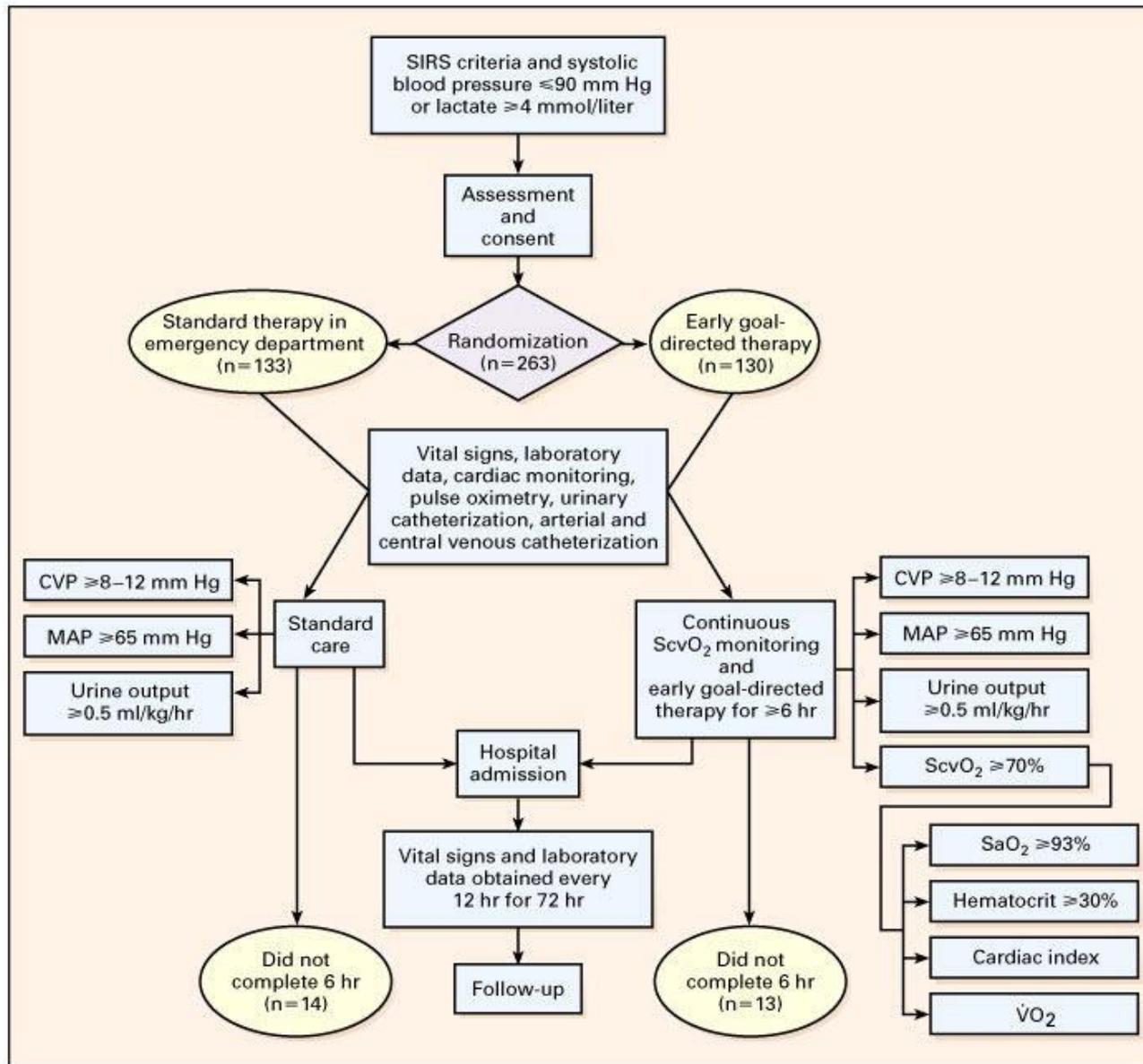
Henry Ford Health System, Detroit

New Engl J Med 2001 Nov 8;345(19):1368-77

Early Goal-directed Therapy Study Findings

- **BACKGROUND:** The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the ICU
- **METHODS:** We randomly assigned patients who arrived at an ED with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy as a control before admission to the ICU. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and (APACHE II) scores were obtained serially for 72 hours
- **RESULTS:** Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy. In-hospital mortality was 30.5 % in the group assigned to early goal-directed therapy, as compared with 46.5 % in the group assigned to standard therapy ($P = 0.009$). Mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0 ± 6.3 vs. 15.9 ± 6.4 , $P < 0.001$).
- **CONCLUSIONS:** Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

Overview of patient enrollment and hemodynamic Support





**Duration of hypotension
before initiation of
effective antimicrobial
therapy is the critical
determinant of survival in
human septic shock**

Duration of Hypotension Study Findings

- **OBJECTIVE:** To determine the prevalence and impact on mortality of delays in initiation of antibiotics from initial onset of septic shock.
- **DESIGN/SETTING:** A retrospective cohort study performed between July 1989 and June 2004. Fourteen ICUs in Canada and the US
- **PATIENTS:** Medical records of 2,731 adult patients with septic shock
- **RESULTS:** The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients who received effective antibiotics only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 , $p < .0001$). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.
- **CONCLUSIONS:** Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock.

Early, Goal-Directed Therapy for Septic Shock-A Patient-Level Meta-Analysis

The PRISM Investigators
N Engl J Med 2017;376:2223-34

*PRISM stands for Protocolized Resuscitation in Sepsis
Meta-Analysis

Patient-Level Meta-Analysis Study Findings

- **BACKGROUND:** A meta-analysis of 3 multicenter trials (ProCESS, ARISE, ProMISe) to explore the effect of early, goal-directed therapy (EGDT) in reducing mortality from septic shock.
- **METHODS:** A meta-analysis of the above 3 multicenter trials. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs.
- **RESULTS:** 3723 patients in 138 hospitals in 7 countries were studied. Mortality at 90 days was similar for EGDT and usual care (24.9% vs 25.4%). Average costs were higher with the EGDT group.
- **CONCLUSIONS:** EGDT did not result in better outcomes than usual care and was associated with higher cost.

CDC initiative promotes early detection, rapid treatment of sepsis

- ▶ Sepsis is an unrecognized killer. It has a mortality rate of between 15% and 30% in the 1 million to 3 million patients who are diagnosed with it each year. Approximately 70% of sepsis cases are community-acquired
- ▶ CDC has launched *Get Ahead of Sepsis*, a national educational initiative that highlights the importance of early detection and rapid treatment of sepsis.
- ▶ *Get Ahead of Sepsis* provides resources for health care professionals and patients such as fact sheets, brochures, social media and shareable videos, so they can understand the risks and recognize the signs and symptoms of sepsis and act quickly to begin treatment.
- ▶ Signs and symptoms of sepsis can include confusion, shortness of breath, elevated heart rate, fever, chills, extreme pain/discomfort and clammy or sweaty skin.
- ▶ Health care professionals, patients, and their family members can work as a team to prevent infections and be alert to the signs of sepsis.

Brenda Fitzgerald, MD

<https://www.cdc.gov/sepsis>

GET AHEAD

OF SEPSIS

KNOW THE RISKS. SPOT THE SIGNS. ACT FAST.



“Could this infection be leading to sepsis?”

GET AHEAD
OF SEPSIS



Summary

- ▶ Sepsis is newly defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”. The SIRS criteria are no longer included in the new definitions of sepsis. SOFA score seems to perform better than SIRS and qSOFA among ICU patients in predicting in-hospital mortality, whereas qSOFA seems to be a better tool than SOFA and SIRS to identify patients with infection who might progress to sepsis.
- ▶ Awareness Programs e.g. CDC’s *Get Ahead of Sepsis* should be provided to health care workers, patients and relatives to recognize sepsis and to understand it as a true time-critical medical emergency.
- ▶ Early Goal-Directed Therapy (EGDT) is no longer recommended for treatment of sepsis
- ▶ Begin broad spectrum, empiric antibiotic therapy within 1 hour in patients with sepsis

References

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