SEPSIS

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OBJECTIVES

Definition

History

Management

Future directions

HISTORIC SEPSIS DEFINITION

- 1991 Consensus
  - Infection plus 2 SIRS criteria:
    - T >38 or <36
    - Hr >90
    - RR >20 or PaCO2 <32
    - WBC >12K or <4K

Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med.* 2015;192(8):958-964

Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med.* 2015;372(17):1629-1638.

CHALLENGES TO DEFINITION

- Sepsis represents a clinical syndrome(s) rather than discrete illness
- 80 yo with heart failure and UTI, HR 90 and AMS vs 32yo with pneumonia, fever, HR 130
- Sepsis is the primary cause of death from infection
- Sepsis syndrome is shaped by pathogen and host factors
  - Dysregulated hoist response and organ dysfunction
- Sepsis-induced organ dysfunction may be occult
- Any organ dysfunction should raise the possibility of infection
- Local organ dysfunction may occur from infection

SOFA SCORE

Table 1. Sequential [Se

System	4
Respiration	
Pao_2/Fio_2, mm Hg (kPa)	<100 (13.3) with respiratory support
Coagulation	
Platelets, $\times 10^3/\mu L$	<20
Liver	
Bilirubin, mg/dL (µmol/L)	>12.0 (204)
Cardiovascular	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system	
Glasgow Coma Scale score[c]	<6
Renal	
Creatinine, mg/dL (µmol/L)	>5.0 (440)
Urine output, mL/d	<200

Abbreviations: Fio_2, frac … r at least 1 hour.
Pao_2, partial pressure of … gher score indicates better
[a] Adapted from Vincent …

Quick Sepsis-Related Organ Assessment (qSOFA)

Points	Respiratory Rate	Altered Mental Status	Low Blood Pressure
	≥22 breaths per min	Glasgow coma scale <15	SBP ≤100 mmHG
Points	1	1	1

qSOFA ≥2 suggests a poorer outcome and should alert clinicians of possible infection when previously not known.

Information adopted from:

Singer M, Deutschman DS, Seymour CW, Shankar-Hari M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801-810.

Third Inte … tic Shock. *JAMA* 2016;315 …

QSOFA VS CURB65

qSOFA	CURB65
Criteria • Abnormal mental status • RR ≥22 • SBP ≤ 100	**Criteria** • Confusion • RR ≥ 30 • SBP <90 *or* diastolic Bp ≤ 60 mm • BUN > 19 mg/dL • Age ≥ 65 YO
Interpretation • >1: sepsis (mortality ~10%)	**Interpretation** • 0: 0.6% mortality • 1: 2.7% mortality • 2: 6.8% mortality • 3: 14% mortality • 4-5: 28% mortality

WHAT ABOUT PROCALCITONIN AND CRP?

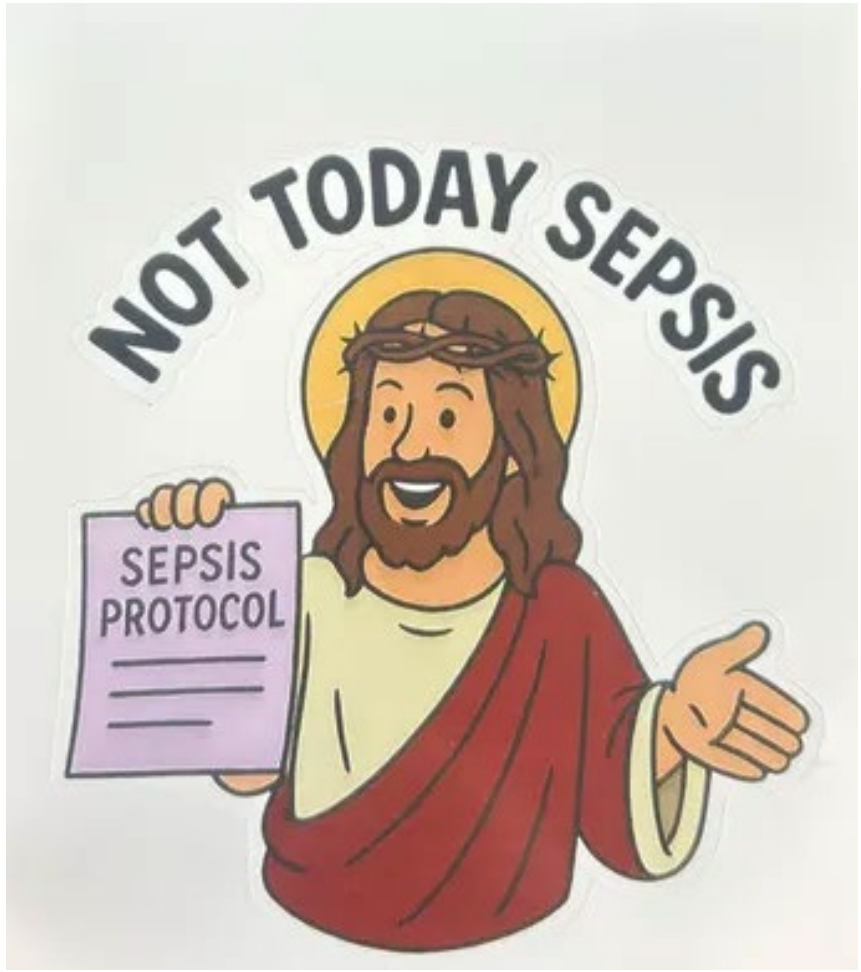
- Procalcitonin rises within 4 hrs
  - Peak 12-48 hrs
- Falsely low in immune suppression, chronic infections, atypical bacteria
- False positive in renal failure, methamphetamine, pancreatitis, surgery, burns, ischemic bowel

- CRP rises within 6hrs
  - Peak 12-48hrs
- Falsely low in liver failure
- Elevated in viral infections, Lupus flare, pancreatitis, fat emboli, post-ROSC

SEPTIC SHOCK

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]



TREATMENT

Fluids

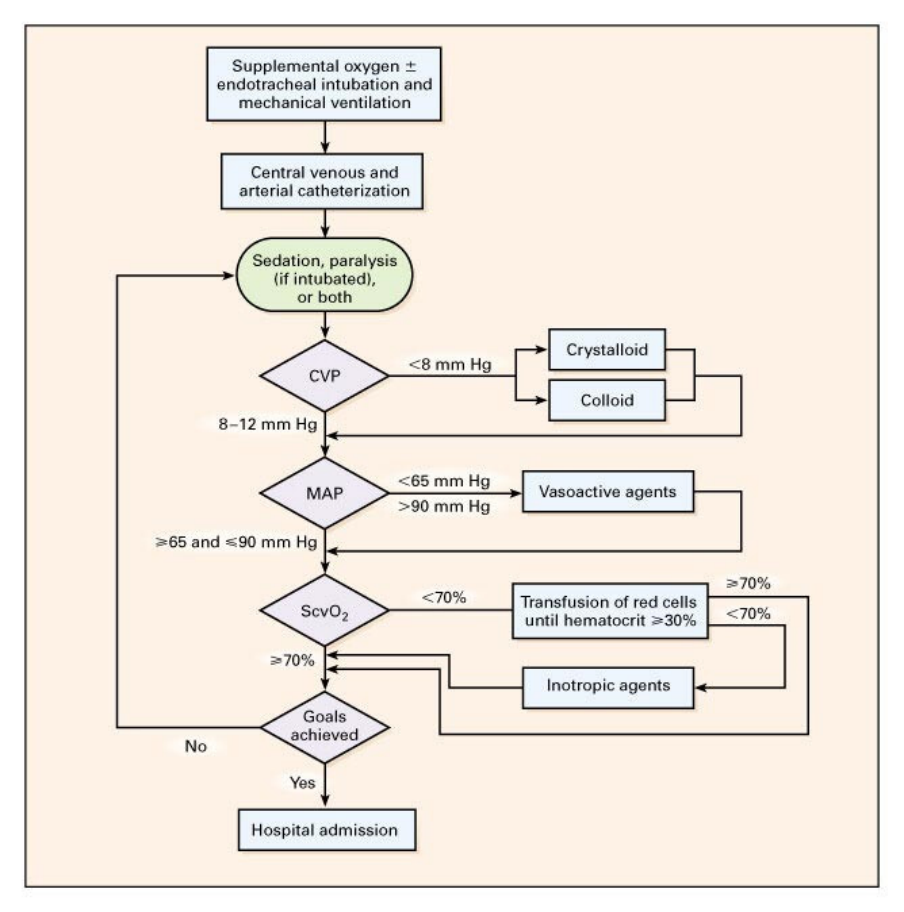
Vasopressors

Antibiotics

Source control

Steroids

RIVERS TRIAL



Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77

SURVIVING SEPSIS CAMPAIGN

- IDSA did not endorse Guidelines
  - Difficulty identifying if infection is present
  - Difficulty determining if infection the cause of organ dysfunction
  - Up to 40% of ICU admissions for sepsis later determined to not have infection*
  - Multiple definitions
  - One-size–fits–all recommendations
  - Timing of antibiotics
  - Multidrug and combination therapy recommendations

Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care 2015; 19:319.

2018 SSC

Bundle Element	Grade of Recommendation and Level of Evidence
Measure lactate level. Remeasure if initial lactate >2 mmol/L	Weak recommendation; low-quality evidence
Obtain blood cultures before administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive	Strong recommendation, moderate quality of during or after fluid resuscitation to maintain evidence
Mean arterial pressure ≥65 mm Hg	

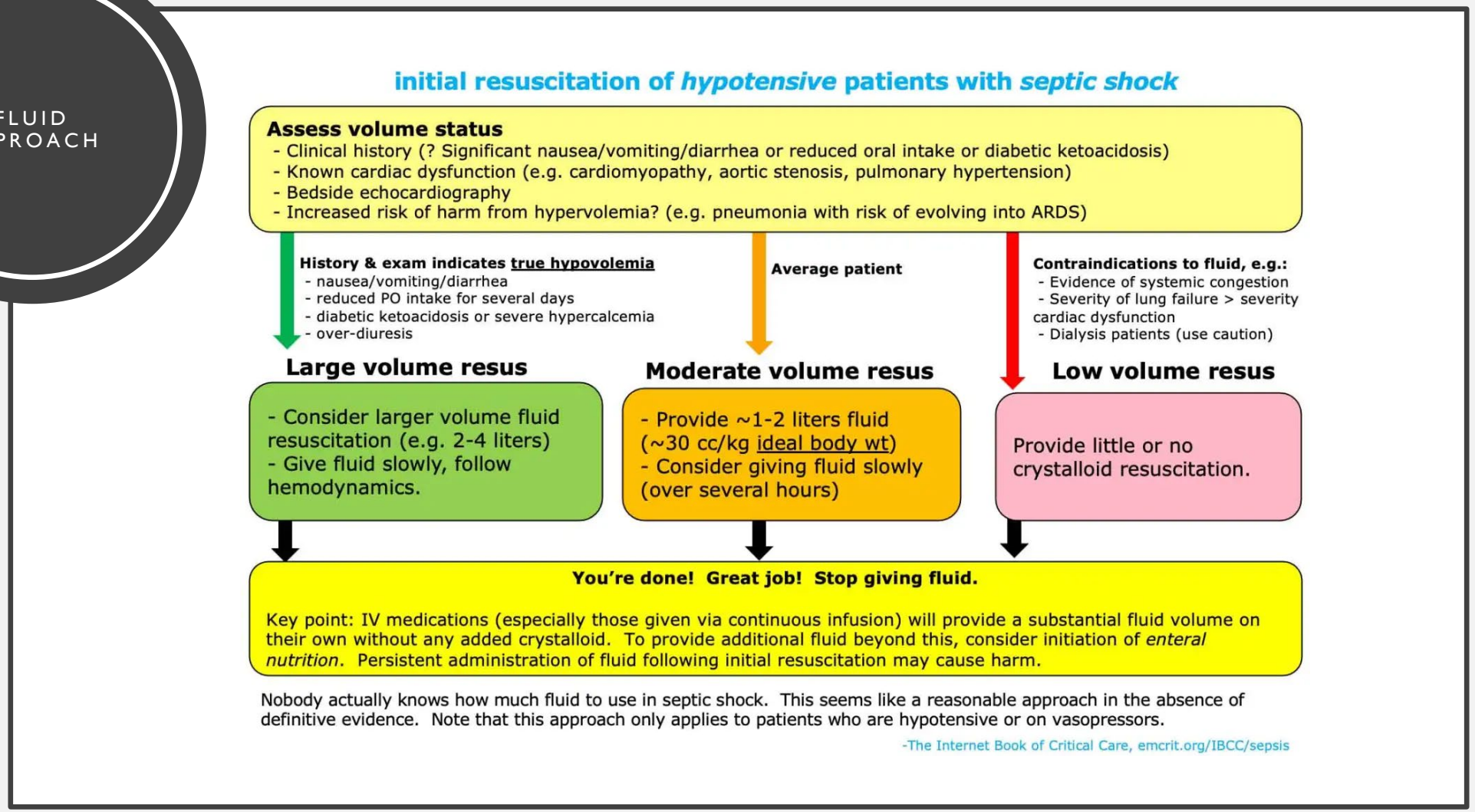
Point: Should the Surviving Sepsis Campaign guidelines be retired? Yes
Chest. 2019; **155**:12-1

FLUID

- 30ml/kg LR
  - Blood volume 5-6liters
- Primary dysfunction is vasodilatation
  - Component of cardiac dysfunction and microvascular effects
- No high-quality evidence that large volume resuscitation is associated with improved outcome
- Only ~1/2 critically ill patients fluid responsive
- Benefits to cardiac output offset by hemodilution
- Effects transient due to extravasation of fluid
- Increased risk of intubation, renal failure, and mortality

Comparison of fluid compartments and fluid responsiveness in septic and non-septic patients. *Anaesth Intensive Care*. 2011;39(6):1022-1029

FLUID APPROACH



https://emcrit.org/ibcc/sepsis/

VASOPRESSORS

- Peripheral use acceptable
- Earlier use in hypotensive patients
- Sequential addition of vasopressors
  - Norepinephrine, vasopressin epinephrine
- VANISH trial suggested less use of renal replacement therapy may be lower with initial use of vasopressin vs norepinephrine
- A comparison of epinephrine to norepinephrine found similar results in achieving MAP goals,
  - No difference in mortality
  - 12.9% Epi group dropped due to metabolic side effects
- Avoid dopamine

SOURCE CONTROL

- Nephrolithiasis
- Cholangitis
- Bowel perforation
- Necrotizing fasciitis
- Urologic
- Hardware

Association between time to source control in sepsis and 90-day mortality. Jama Surgery, 2022;157(9):817-826

ANTIBIOTICS

- Given as soon as possible after sepsis or septic shock identified
- Directed to expected source of infection
- 33% of patients with suspected sepsis turn out to have non-infectious mimics
- Balancing timing and appropriateness

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.

Cooperative antimicrobial therapy of septic shock database research group initiation of inappropriate antimicrobial therapy results in fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.

Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis 2010;50:814-20.

ANTIBIOTICS

- Local antibiogram
- Patient factors
  - Prior culture results
  - Prior antibiotic exposure
  - Immune compromise
  - Indwelling or drainable sources
- Adequate tissue penetration for suspected source
- Antifungals and antivirals

MULTIDRUG AND COMBINATION THERAPY

- Multidrug regimens recommended for septic shock
  - Broader spectrum coverage
  - High consequence
- More targeted regimen for hemodynamically stable patients
- Combination
  - More than one drug with activity against presumed pathogen
  - No clear evidence for improved survival or faster reversal of shock
  - May have role in septic shock patients with increases risk of multidrug resistant infections

STEROIDS IN SHOCK

- Stress dose
  - 50mg hydrocortisone q6h
- Does not increase risk for superinfection or myopathy
  - Does increase blood glucose
- Lower duration of shock, mechanical ventilation and ICU stay

Intensive Care Med. 2018 Jul;44(7):1003-1016.

Crit Care Med. 2015 Nov;43(11):2292-302.

FUTURE DIRECTIONS

- Improved definitions
- Prevention
- AI
- Biomarkers
- Molecular testing
- Genetic and immunotherapy
- Novel antimicrobials
- Adaptive platform trials testing multiple parameter
  - Enrollment adapts to ongoing results