Sepsis-3
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(One Personal Disclosure: I am an ID physician)

Objectives
• Contrast new with old definitions of sepsis and septic shock
• Apply qSOFA and SOFA
• Highlight some management strategies from Surviving Sepsis Campaign (SSC) 2016
• Understand some of the controversy surrounding Sepsis 3 and SSC 2016

The Burden of Sepsis in the U.S. is High
• #1 cause of death in the non coronary ICU
• May contribute to 30-50% of hospital deaths
• Most expensive condition treated in hospitals
• Survivors also at high risk for recurrent sepsis, readmission, cognitive and functional impairment
• There is no gold standard diagnostic test for sepsis-sepsis is a complex, heterogeneous syndrome
• Most studies are observational and not risk adjusted and subject to bias
• Reporting national mortality without severity and covariate adjustment can lead to misleading results
• Early recognition and timely evidenced-based interventions probably reduces mortality. The Surviving Sepsis Campaign has done a lot of good by focusing attention on early diagnosis and optimal treatment

History of Sepsis Definitions:
“Sepsis-1”

The Surviving Sepsis Campaign has done a lot of good by focusing attention on early diagnosis and optimal treatment.

Bone et al., Chest 1992; 101:1644

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References
1. Minino et al, NCHS Data Brief (2012)
2. Liu et al, JAMA (2014)

History of Sepsis Definitions:
“Sepsis represents the systemic inflammatory response to the presence of infection”

• SIRS + 2 of: Temperature >38.0 or <36.0; Heart Rate >90 bpm; Respiratory Rate >20/min; WBC >12, <4, or >10% bands
• Septic + Infection + SIRS
• Severe Sepsis = Sepsis + Organ Dysfunction
• Septic Shock = Sepsis + Refractory Hypotension (despite fluids)
Why a New Definition?

- SIRS criteria are problematic:
  - Nonspecific for infection/sepsis - poor specificity
  - May miss 1 in 8 patients with serious infection + organ dysfunction
  - Sepsis = dysregulated host response to infection, but SIRS is actually physiologic
  - Organ dysfunction is key
  - Confusing nomenclature: "sepsis" and "severe sepsis" used interchangeably
  - Unclear definition for "organ dysfunction"

Pathobiology of Sepsis: Self destruction

The consequence of unbalanced pro- and anti-inflammatory response
Conceptual Changes

“Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection”

“Septic shock is 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.”

→ SIRS criteria removed from definition
→ "Severe Sepsis" removed from definition (replaced by "Sepsis")

The Third International Consensus
Development of Definition and Clinical Criteria

• Sepsis and Septic Shock definitions should reflect pathobiology, allow consistency for epidemiologic and clinical studies and facilitate more timely management
• Shankar-Hari et al used task force of 19
  • systematically reviewed 44 sepsis studies (166,479 pts) to identify various constellations of clinical criteria and mortality associated
  • Described variability of that review then found consensus via a Delphi study (3 surveys/discussions)
  • then used cohort studies of various EHR data bases to test (mortality as outcome measures): n=28,150 from Surviving Sepsis Campaign 2005–2010; n=1,309,025 Univ Pitt Med Ctr 2010-2012; n= 1,847,165 Kaiser Permanente Northern California 2009–2013

SEPSIS-3

• Singer et al article outlines the consensus definitions agreed upon by the 19 member expert panel combining the Seymour “Assessment” and Shankar-Hari “Development”
• Recognizes sepsis as a syndrome without a validated criterion standard diagnostic test; defines sepsis by describing what it "is"
• Lay terms: “Sepsis is a life-threatening condition that arises when the body’s response to infection injures its own tissues and organs”
• Acknowledges that culture-positive "sepsis" is only observed in 30% to 40%.
• Calls the updated definitions a "work in progress"

Sepsis Clinical Criteria

• Sepsis
  • Suspected or documented infection and an acute increase ≥ 2 SOFA points or a qSOFA of ≥ 2

• Septic Shock
  • Sepsis with vasopressor therapy needed to elevate MAP ≥ 65 mmHg and lactate > 2 mmol/L, after adequate hydration

Sepsis-3: Operational Clinical Criteria

• Sepsis = Infection + increase in SOFA score by ≥ 2 points from baseline
Sepsis-3: Operational Clinical Criteria

qSOFA-"HAT"

- Hypotension-SBP<100
- Altered mental status-GCS < 15 (GCS 15 requires)
  a) spontaneous eye opening
  b) accurate orientation person/place/time
  c) appropriate motor response to commands
- Tachypnea-RR>22

Third International Consensus Definitions

SEPSIS
- Life threatening organ dysfunction due to dysregulated host response to infection
- Infected non-ICU with 2/3 qSOFA *
- Infected ICU with SOFA increase >2
- Lactate not additive
- In-hospital mortality >10%, ICU stay > 3 days

Sepsis-3: Criticisms and Limitations

- Concern that focus on qSOFA / organ dysfunction may delay early recognition and treatment of severe infection-not a screening tool
- Will these changes reverse decades of quality improvement efforts with old definitions?
- SOFA mainly developed as a research tool rather than for clinical use
- Not easy to memorize or readily available at the bedside
- Definitions are not harmonized with SEP-1 CMS reporting measure
- Creates confusion

Reasons for Caution: Deficiencies in Surveillance and Diagnosis

- Current surveillance using ICD-9/ICD-10 codes are less reliable because:
  - Rising awareness of sepsis
  - Financial pressures to code for greater patient complexity (e.g. MS-DRG system)
  - Compounded by subjectivity in sepsis diagnosis
    ("suspected infection," attributing organ dysfunction to sepsis)

- 5 case vignettes of patients with suspected or confirmed infection and possible organ dysfunction distributed to 94 academic intensivists
  >> Respondents classified cases as SIRS alone, sepsis, severe sepsis, septic shock, or none of the above

Crit Care 2016; 20:89
Instead of claims data, can we track clinical indicators of sepsis using more consistent and uniform criteria?

- Presumed infection (e.g., cultures, antibiotics) +
- Organ dysfunction (e.g., vasopressors, mechanical ventilation, changes in baseline laboratory values)

Goals:

1. Create an objective sepsis surveillance definition based on clinical data that can be applied across different EHR systems
2. Apply this definition to diverse hospitals from across the U.S. to generate credible estimates of current national sepsis burden and trends

Sepsis Clinical Surveillance Definition

**Presumed Serious Infection**

- Blood cultures obtained +
- ≥4 Antibiotic Days (starting within +/-2 days of blood culture day)

**Acute Organ Dysfunction** (any within +/-2 days of blood culture day):

- Cardiovascular: Initiation of a vasopressor
- Respiratory: Initiation of invasive mechanical ventilation
- Renal: Doubling in serum creatinine or decrease by 50% of eGFR relative to baseline (excluding patients with ESRD)
- Hepatic: Total bilirubin ≥ 2.0 mg/dL and increase by 100% from baseline (excluding patients with ESRD)
- Hematologic: Platelet count <100 cells/µL and ≥ 50% decline from baseline (baseline must be ≥100 cells/µL)
- Perfusion: Serum lactate ≥ 2.0 mmol/L

Standardized rules implemented for calculating “baseline” laboratory values.
173,690 adult sepsis cases
→ Overall 6% incidence
• 87% present-on-admission, 13% hospital-onset
• 55% admitted to ICU
• 17% had positive blood cultures
• 15% had septic shock (vasopressors + lactate ≥2)
• 15% died in-hospital

Higher mortality for hospital-onset sepsis (26%) vs sepsis present-on-admission (14%)

Summary
• Sepsis is common:
  • ~ 6% of adult hospitalizations
  • ~ 1.7 million U.S. cases annually
• Sepsis is lethal:
  • >1 in 5 sepsis patients died or discharged to hospice
  • Present in >1/3 of all hospitalizations that culminated in death
  • Potentially contributes to ~270,000 U.S. deaths annually
  • Mortality rates have declined slightly, but no significant change when considering discharge to hospice
• Sepsis trends have been fairly stable from 2009-2014:
  • Incidence rates stable (mild rise if including lactate criteria, likely due to more testing)
  • Clinical data contrast with claims-based trends
• EHR-surveillance compares well with medical record reviews
  • Imperfect but better than claims-based methods

The CMS “SEP-1” Core Measure
• In October 2015, the Centers for Medicare and Medicaid Services began requiring hospitals to report compliance rates with the “SEP-1” sepsis core measure
  • Requires 3 and 6 hour bundles of care adapted from the Surviving Sepsis Campaign Guidelines for patients diagnosed with severe sepsis / septic shock
  • Many hospitals around the country are now devoting substantial resources to meeting and abstracting the measure

Surviving Sepsis Campaign 2016 Management Guidelines
• An update of the 2012 based upon lit review/expert panel
• Old definitions of sepsis, severe sepsis, septic shock
• Working groups for five sections: hemodynamics, infection, adjunctive therapies, metabolic and ventilation made 93 recommendations
• Graded recommendations were voted upon by the panel
Summary and Conclusions

• Most sepsis patients received care that was non-compliant with SEP-1
• Failure to measure lactates accounted for 40% of failures
• Cases that failed SEP-1 were very different than those that passed
• More septic shock, hospital-onset sepsis, and vague symptoms
• Crude mortality rates were higher in cases that failed SEP-1, but there was no significant difference after adjusting for clinical characteristics
• Delays in appropriate antibiotics (>3 hours) were associated with higher mortality rates but only accounted for 15% of SEP-1 failures

SEP-1 may not clearly differentiate between high- and low-quality care, and detailed risk adjustment is necessary to properly interpret associations between SEP-1 compliance and mortality.

Management Cornerstones

- Initial Resuscitation
- Source Control
- Antibiotics

Adequate resuscitation - FLUIDS

- Fluids
- 30 ml/kg of IV crystalloid fluid; albumin may be used in patients requiring large amounts of fluid
- Monitoring and hemodynamic status (MAP, HR, BP, O2 sat, RR, temp, UO)
- Target MAP of 65 mmHg
- Decreasing serum lactate (goal <2 mmol/L)

Vasopressors

- Norepinephrine is first line
- Goal is MAP 65 mmHg
**Vasopressor Support**

- Norepinephrine is recommended first line
- Vasopressin added to norepinephrine (JAMA 2018 meta analysis of 23 trials) although no change in mortality, lower rate of A fib and possibly protective of arrhythmia
- Dobutamine may be initiated in patients with persistent hypoperfusion despite fluids and vasopressors
- Epinephrine may be added but is a second catecholamine

**IDSA's concerns with 2016 SSC**

1. Failure to acknowledge practical difficulties in diagnosis of sepsis citing a 2015 study in CCM w/40% ICU “sepsis” admissions without infection
2. Rigid 1 hour initiation broad antibiotic to lead to over use/CMS std of care,etc vs proposal for sepsis equivalent of htn urgency and septic shock of htn emergency
3. Unclear guidance regarding catheter removal
4. Combination and Multidrug references are unclear; better guidance could have been given and some guidance is just incorrect
   - Multidrug several days past clinical improvement

**IDSA’s concerns with 2016 SSC**

1. Multiple statements imply most with sepsis or septic shock harbor antimicrobial resistant pathogens and this is not the case
2. Procalcitonin rises within 4-6 hours in invasive bacterial infection; this guideline does not specify how to best use
3. Operationalization of optimizing pharmacokinetics/pharmacodynamics needs to be specified
4. Infection prevention is not addressed
5. Duration of therapy suggested is longer than necessary
6. IDSA is disappointed disagreements could not be resolved prior to release

**Surviving Sepsis Campaign 2018 Mandate**

- Treat first and then evaluate later
The Surviving Sepsis Campaign Bundle: 2018 update

- Measure lactate: Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate >4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP 65±5 mm Hg.

**“Time zero” or “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.**

Revision of the SSC bundles is that the 3-h and 6-h bundles have been combined into a single “hour-1 bundle” with the explicit intention of beginning resuscitation and management immediately.

Inconvenient Truths

- High rate of overdiagnosis
- Approach promotes excess antimicrobial use and increases unintended consequences
  - C difficile infections
  - Acute kidney injury and other side effects (e.g. ↑ UT, rash, hemolytic)
  - Missed culture opportunities (antibiotics administered before appropriate cultures obtained)
  - Selection for MDROs
  - Alteration of microbiome-dysbiosis
- Up to 40% of patients admitted to ICU with admitting diagnosis of sepsis did not have an infection. ([Crit Care Med 2015; 19:319])
- Cultures positive in only a minority of cases leading to diagnostic uncertainty which increases broad spectrum antimicrobial use and duration

Raising Concerns About Sepsis-3 Definitions

- The Global Alliance for Infections in Surgery: 78 authors from around the world
- Biggest concern: no prospective validation in a generalizable population
- qSOFA not as diagnostic but rather as warning of poor outcome
- Continuum idea is helpful and should not be eliminated
- Distinguish screening tool from risk stratification tool—feel we still need a screening tool
Pulmonary Critical Care Community Blogs

- Online petition to retire SSC guidelines
- SSC guideline was originally sponsored by Eli Lily and Edwards Life Sciences
- Recommendations unsupported by good quality of evidence becoming standard of care
- "Bundling" elevates unhelpful elements
- 2018 update "1 hour bundle" is dangerous
  - Becomes core measure or state mandate
  - Eliminates thoughtfulness (wrt fluid overload, inappropriate abs)
  - Over-treatment is likely

New Definitions...Much Still To Be Done

- Sepsis is a syndrome, not a specific disease—there is no sepsis trigger
- Infection cannot always be confirmed (despite PCR, MALDI-TOF, etc)
- Organ system dysfunction may not be infection (trauma, pancreatitis)
- Cellular dysfunction is heterogeneous
- Precision medicine using specific biomarkers (cell receptors, intracellular pathways, genomic alterations) are not yet possible

Where do we go from here?

- Reassess the 1 hour bundle for sepsis without shock. Should the need to rapidly and aggressively treat patients be determined by the severity of illness and certainty of diagnosis rather than applied to all patients?
- Integration of biomarkers and rapid/molecular testing
- Move to an objective clinical surveillance diagnosis for sepsis
- Develop a true predictive model to alert clinicians to patients at risk for progression especially not POA
- Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?
- Research to determine the predictors of long-term morbidity and mortality and interventions to prevent long-term morbidity and mortality for patients who survive sepsis (societal $$$)
- Use risk adjustment to evaluate most effective interventions and outcomes
- What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?
- What is the optimal fluid for sepsis resuscitation?
- What is time zero?

Measurement

- Outcome oriented
- Risk adjusted
- Cost of measurement
- Unintended consequences
OLD
Antibiotics as miracles
("No downside risk, so why not try?")

New
Antibiotics: Good when used well, better when used thoughtfully