Early Septic Shock Care – Phenotypes and How We Got Here

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Financial disclosures

Delegate Editor, Annals of Emergency Medicine

My external funding past 36 months

- NHLBI – PETAL Network (PI); T32 Research Training Grant
- NIGMS - RO1 ProACT (procalcitonin in LRTI)
- Royalties from three texts (Tintinalli’s Study Guide; The Trauma Manual; ED Critical Care) and UpToDate (not sepsis related)

Expert opinions - civil
Learning Objectives

- List three reasons for the ProCESS and other two non-US trials
- Note two main outcomes
- List two similarities in design and outcome with the more recent trials
- State how different sepsis phenotypes exist and could influence actions and assessments.
Origins of sepsis

- Hippocrates (BC ~460-370)
  - Sepsis (σῆψις)
    - The process by which flesh rots, swamps generate foul airs at night, and wounds fester
    - It is rank, disease-producing, and evil
The 2000 year evolution of ‘germ theory’

- Fracastoro (1478-1553)
  - Passage of minute bodies from one person to another

- Pasteur (1822-1895)
  - Confirmation of the germ theory; vaccination

- Semmelweis (1818-1865) and Lister (1827-1912)
  - Antiseptic control

- Koch
  - Scientific basis for interrogation of mechanism of action

- Domagk, Fleming, et al (20th century)
  - Modern era of antibiotics
What do we think sepsis ‘is’?

- Patients still die DESPITE effective antibiotics
- Sepsis is a host response to infection gone awry!
  - A case of harm by friendly fire
- When organs fail, the sepsis is called ‘severe’
  - 1992 and 2003 International Consensus Definition
Sepsis accounted for 36-55% of all hospital deaths

#1 cause of hospital deaths in the US
Background

**Landmark – 11k (!!) citations on Google Scholar**

**Single center study**
- N=263

**Protocolized EGDT vs. usual care after early detection/fluid bolus**

**16% absolute mortality reduction**
- 30% vs. 46%
- Exp arm: 5L (vs 3.5 L IVF), more blood, dobutamine
Protocol-based EGDT

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

- Insert central line with oximetric port

Sedation, analgesia, +/- or paralysis (if intubated)

- 500 cc fluid bolus if CVP < 8 mmHg

CVP

- < 8 mmHg

8-12 mmHg

MAP

- < 65 mm Hg

- > 90 mm Hg

ScvO2

- < 70%

- ≥ 70%

Goals achieved?

- No

- Yes

Reassess q15-30 min

Potential PRBC and dobutamine use

Early insertion of CVC for ScvO2

Titrated to CVP, MAP and ScvO2

CVP - central venous pressure, MAP - mean arterial pressure, ScvO2 - central venous oxygen saturation, HCT - hematocrit, PRBCs - packed red blood cells
Residual questions

- Is the difference due to the act of ‘protocolizing’ or attention only to resuscitative care after early/better identification of shock?

- Are all elements of the protocol necessary?
  - Early central venous catheterization in all patients
  - CVP guided initial fluid therapy
  - ScvO₂ monitoring to guide therapy, notably red cell transfusion and dobutamine

- Are the results generalizable?
  - Now?
  - In broader multicenter setting
  - Follow-up EGDT studies often used “off/on” design with limited CVC/protocol adherence – testing attention instead of protocol?
The ProCESS trial

- **Early** septic shock in the **Emergency Department**

- **Randomization** to one of 3 arms for 6 hours of resuscitation
  - **Protocol-based** ‘Early Goal-directed Therapy’
  - **Protocol-based** standard therapy
  - **Usual** care

- **Two sequential hypotheses** …
  - Is protocol-based resuscitation superior to usual care?
  - If so, is EGDT superior to protocol-based standard therapy?

Where ‘standard’ therapy does **NOT** include
- Central venous pressure and oxygen monitoring
- Latter guiding blood or dobutamine
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ABSTRACT

BACKGROUND
In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

The members of the writing committee (Donald M. Yealy, M.D., John A. Kellum, M.D., David T. Huang, M.D., Amber E. Barnato, M.D., Lisa A. Weissfeld, Ph.D., and Francis Pike, Ph.D., University of Pittsburgh, Pittsburgh; Thomas Terndrup, M.D., Ohio State University, Columbus; Henry E. Wang, M.D., University of Alabama at Birmingham, Birmingham; Peter C. Hou, M.D., Brigham and Women's Hospital, Boston; Frank LoVecchio, D.O., Maricopa...
Resuscitation from randomization to 6h

**Intravenous fluids**

<table>
<thead>
<tr>
<th></th>
<th>EGDT protocol</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous fluids</td>
<td>2.8 L</td>
<td>&lt;0.001</td>
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**Intravenous antibiotics**

<table>
<thead>
<tr>
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<th>EGDT protocol</th>
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<tr>
<td>Intravenous antibiotics</td>
<td>97.5%</td>
<td>0.90</td>
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<thead>
<tr>
<th></th>
<th>PST</th>
<th></th>
<th>Usual care</th>
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<tbody>
<tr>
<td>Intravenous fluids</td>
<td>3.3 L</td>
<td></td>
<td>2.3 L</td>
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<th>Usual care</th>
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<tr>
<td>Intravenous fluids</td>
<td>97.1%</td>
<td></td>
<td>96.9%</td>
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</tbody>
</table>
### Outcomes

#### Table 2. Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protocol-based EGDT (N=439)</th>
<th>Protocol-based Standard Therapy (N=446)</th>
<th>Usual Care (N=456)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death by 60 days: primary outcome</td>
<td>92/439 (21.0)</td>
<td>81/446 (18.2)</td>
<td>86/456 (18.9)</td>
<td>0.83$\ddagger$</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>129/405 (31.9)</td>
<td>128/415 (30.8)</td>
<td>139/412 (33.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>New organ failure in the first week — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>269/439 (61.3)</td>
<td>284/446 (63.7)</td>
<td>256/456 (56.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Respiratory</td>
<td>165/434 (38.0)</td>
<td>161/441 (36.5)</td>
<td>146/451 (32.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Renal</td>
<td>12/382 (3.1)</td>
<td>24/399 (6.0)</td>
<td>11/397 (2.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of organ support — days$\S$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.6±1.6</td>
<td>2.4±1.5</td>
<td>2.5±1.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6.4±8.4</td>
<td>7.7±10.4</td>
<td>6.9±8.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Renal</td>
<td>7.1±10.8</td>
<td>8.5±12</td>
<td>8.8±13.7</td>
<td>0.92</td>
</tr>
</tbody>
</table>

- **No difference in mortality**
  - Results unchanged when adjusting for potential site heterogeneity
  - Higher dialysis-dependent renal failure in protocol-based Std Rx arm
Mortality over time

In-hospital mortality up to 60 days

Mortality up to one year

Log rank p=0.52

90 days: p=0.70
1 year: p=0.92

Number at risk
EGDT protocol: 439, 373, 356, 348, 347, 347, 347
PST protocol: 446, 389, 376, 368, 366, 366, 365
Usual care: 456, 396, 376, 371, 371, 371, 370

Days

Protocol-based EGDT
Protocol-based Standard Therapy
Usual care
### Secondary outcomes

#### Table 2. Outcomes.

<table>
<thead>
<tr>
<th>Use of hospital resources</th>
<th>EGDT</th>
<th>PSC</th>
<th>Usual</th>
<th><strong>p-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to intensive care unit — no. (%)</td>
<td>401 (91.3)</td>
<td>381 (85.4)</td>
<td>393 (86.2)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Stay in intensive care unit among admitted patients — days</td>
<td>5.1±6.3</td>
<td>5.1±7.1</td>
<td>4.7±5.8</td>
<td><em>0.63</em></td>
</tr>
<tr>
<td>Stay in hospital — days</td>
<td>11.1±10</td>
<td>12.3±12.1</td>
<td>11.3±10.9</td>
<td><em>0.25</em></td>
</tr>
<tr>
<td>Discharge status at 60 days — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not discharged</td>
<td>3 (0.7)</td>
<td>8 (1.8)</td>
<td>2 (0.4)</td>
<td><em>0.82</em></td>
</tr>
<tr>
<td>Discharged to a long-term acute care facility</td>
<td>16 (3.6)</td>
<td>22 (4.9)</td>
<td>22 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Discharge to another acute care hospital</td>
<td>8 (1.8)</td>
<td>2 (0.4)</td>
<td>5 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Discharged to nursing home</td>
<td>71 (16.2)</td>
<td>93 (20.9)</td>
<td>88 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Discharged home</td>
<td>236 (53.8)</td>
<td>227 (50.9)</td>
<td>235 (51.5)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>13 (3.0)</td>
<td>13 (2.9)</td>
<td>18 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events — no. (%)</td>
<td>23 (5.2)</td>
<td>22 (4.9)</td>
<td>37 (8.1)</td>
<td><em>0.32</em></td>
</tr>
</tbody>
</table>

**Higher ICU use with EGDT**

*Possibly due to monitoring differences*
A priori subgroup analyses

- No interaction between treatment arm and ...
  - Age
  - Sex
  - Race
  - Source of infection
  - Type of shock

- True for 60d hospital mortality, 90d mortality, and 1y mortality

- Process of care hour +6-72 – no difference ("catch up" or correcting gaps not evident)
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND
Early goal-directed therapy (EGDT) has been endorsed in the guidelines of the Surviving Sepsis Campaign as a key strategy to decrease mortality among patients presenting to the emergency department with septic shock. However, its effectiveness is uncertain.

METHODS
In this trial conducted at 51 centers (mostly in Australia or New Zealand), we randomly assigned patients presenting to the emergency department with early septic shock to receive either EGDT or usual care. The primary outcome was all-cause mortality within 90 days after randomization.

RESULTS
Of the 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual-care group. Primary outcome data were available for more than 99% of the patients. The rate of primary outcome was 26.8% in the EGDT group and 32.9% in the usual-care group (odds ratio for death, 0.84; 95% confidence interval, 0.73 to 0.97; P = 0.02). The members of the writing committee (Sandra L. Peake, M.D., Ph.D., Anthony Delaney, M.D., Ph.D., Michael Bailey, Ph.D., Rinaldo Bellomo, M.D., Peter A. Cameron, M.D., D. James Cooper, M.D., Alisa M. Higgins, M.P.H., Anna Holdgate, M.D., Belinda D. Howe, M.P.H., Steven A.R. Webb, M.D., Ph.D., and Patricia Williams, B.N.) assume responsibility for the overall content and integrity of the article. Address reprint requests to Ms. Belinda Howe at the Australian and New Zealand Intensive Care Research Centre, Alfred Centre, Level 6 (Lobby B), 99 Commercial Rd., Melbourne, VIC 3004, Australia, or at anzicrc@monash.edu.

*The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial.
Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ABSTRACT

BACKGROUND
Early, goal-directed therapy (EGDT) is recommended in international guidelines for the resuscitation of patients presenting with early septic shock. However, adoption has been limited, and uncertainty about its effectiveness remains.

METHODS
We conducted a pragmatic randomized trial with an integrated cost-effectiveness analysis in 56 hospitals in England. Patients were randomly assigned to receive either EGDT (a 6-hour resuscitation protocol) or usual care. The primary clinical outcome was all-cause mortality at 90 days.

From the Clinical Trials Unit, Intensive Care National Audit and Research Centre (P.R.M., G.S.P., D.A.H., R.J., S.E.H., K.M.R.), Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine (M.Z.S., R.D.G.), and Faculty of Medicine, Imperial College London (D.B.), Department of Acute Medicine, Chelsea and Westminster Hospital NHS Foundation Trust (D.B.), and Bloomsbury Institute of Intensive Care Medicine, University College London
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators
Early, Goal-Directed Therapy for Septic Shock—A Patient-Level Meta-Analysis

The PRISM Investigators*

Abstract

Background

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISE) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to

The members of the writing committee (Kathryn M. Rowan, Ph.D., Derek C. Angus, M.D., M.P.H., Michael Bailey, Ph.D., Amber E. Barnato, M.D., Rinaldo Bellomo, M.D., Ruth R. Canter, M.Sc., Timothy J.
Conclusions

For patients presenting with early septic shock in the setting of …
- Prompt recognition
- Prompt *intravenous fluid bolus* for hypotension
- Prompt intravenous *antibiotics*

… there is *no superiority to routine* …
- *Protocol-based resuscitation* if other aggressive recognition/care exists
- *Mandatory* central line placement in all patients
- *ScvO₂* monitoring, with triggers for blood transfusion and dobutamine
Impact

- Looking early and hard, treating aggressively with antibiotics and hemodynamic support, and rechecking is more important than “how” support is done.

- “EGDT” vs ‘egdt’ (one set of specific goals vs. concepts)

- The durable message from Rivers through ProCESS – septic shock is deadly, and early care matters.

- Not an anomaly though still opportunity - outcomes match other reports (Jones *JAMA* 2010; Kakonen *JAMA* 2014)
So, buckets of volume then pressor, right?

- Maitland (*NEJM* 2010) – those with more fluids did worse than rest

- Andrews (*JAMA* 2017) – same story
  - Patients (children/acute and chronic illnesses)
  - Ancillary care (esp. ICU, ventilation)
  - Pathogens
  - Antimicrobial therapy

**CLOVERS** – NHLBI trial through PETAL network – RCT of early fluids vs early pressor in US sepsis care. All get @ 2L IV, then restrict/pressor or more fluids.
Antibiotics

- All US/European/Australian trials gave early (inside hours)

- How early is early enough?

- Before resuscitation?
  - Lab data conflict

- Best human data – Seymour et al *NEJM*, NY state observational cohort
  - Earlier matters – but crude measure (time to complete 3 hr bundle – better if done < 12 hrs)
  - Each hour delay increases mortality
  - Later giving sites do worse
JAMA | Original Investigation

Association Between State-Mandated Protocolized Sepsis Care and In-hospital Mortality Among Adults With Sepsis

Jeremy M. Kahn, MD, MS; Billie S. Davis, PhD; Jonathan G. Yabes, PhD; Chung Chou H. Chang, PhD; David H. Chong, MD; Tina Batra Hershey, JD, MPH; Grant R. Martsolf, PhD, MPH, RN; Derek C. Angus, MD, MPH

**IMPORTANCE** Beginning in 2013, New York State implemented regulations mandating that hospitals implement evidence-based protocols for sepsis management, as well as report data on protocol adherence and clinical outcomes to the state government. The association between these mandates and sepsis outcomes is unknown.

**OBJECTIVE** To evaluate the association between New York State sepsis regulations and the outcomes of patients hospitalized with sepsis.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study of adult patients hospitalized with sepsis in New York State and in 4 control states (Florida, Maryland, Massachusetts, and New Jersey) using all-payer hospital discharge data (January 1, 2011-September 30, 2015) and a comparative interrupted time series analytic approach.

**EXPOSURES** Hospitalization for sepsis before (January 1, 2011-March 31, 2013) vs after (April 1, 2013-September 30, 2015) implementation of the 2013 New York State sepsis regulations.

**MAIN OUTCOMES AND MEASURES** The primary outcome was 30-day in-hospital mortality. Secondary outcomes were intensive care unit admission rates, central venous catheter use, *Clostridium difficile* infection rates, and hospital length of stay.
Results

- The mandated efforts improved outcomes – mortality and others
- Outcomes improved in non-mandated settings also, but not as much relatively
- Which parts are less clear – recognition and antibiotics still key, latter = sooner
- Who benefits the most from what? Phenotypes…
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Li, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visveswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

**IMPORTANCE**  Sepsis is a heterogeneous syndrome. Identification of distinct clinical phenotypes may allow more precise therapy and improve care.

**OBJECTIVE**  To derive sepsis phenotypes from clinical data, determine their reproducibility and correlation with host-response biomarkers and clinical outcomes, and assess the potential causal relationship with results from randomized clinical trials (RCTs).

**DESIGN, SETTINGS, AND PARTICIPANTS**  Retrospective analysis of data sets using statistical, machine learning, and simulation tools. Phenotypes were derived among 20,189 total patients (16,552 unique patients) who met Sepsis-3 criteria within 6 hours of hospital presentation at 12 Pennsylvania hospitals (2010-2012) using consensus k means clustering applied to 29 variables. Reproducibility and correlation with biological parameters and clinical outcomes were assessed in a second database (2013-2014; n = 43,086 total patients and n = 31,680 unique patients), in a prospective cohort study of sepsis due to pneumonia (n = 583), and in 3 sepsis RCTs (n = 4,737).

**EXPOSURES**  All clinical and laboratory variables in the electronic health record.

**MAIN OUTCOMES AND MEASURES**  Derived phenotype (α, β, γ, and δ) frequency, host-response biomarkers, 28-day and 365-day mortality, and RCT simulation outputs.
Findings

4 derived/validated phenotypes in > 60k episodes:

- the α phenotype was the most common (n = 6625; 33%) and included patients with the lowest administration of a vasopressor;

- in the β phenotype (n = 5512; 27%), patients were older and had more chronic illness and renal dysfunction;

- in the γ phenotype (n = 5385; 27%), patients had more inflammation and pulmonary dysfunction;

- and in the δ phenotype (n = 2667; 13%), patients had more liver dysfunction and septic shock
So what?

- In the derivation cohort, cumulative 28-day mortality was:
  - 287 deaths of 5691 unique patients (5%) for the α phenotype;
  - 561 of 4420 (13%) for the β phenotype;
  - 1031 of 4318 (24%) for the γ phenotype;
  - and 897 of 2223 (40%) for the δ phenotype.

- Across all cohorts and trials, 28-day and 365-day mortality were highest among the δ phenotype vs the other 3 phenotypes ($P < .001$).
Sepsis Phenotypes – what next?

- Are there genotypic or other patient based observations – at any level – that tie to these phenotypes? Can they be measured in a useful way?

- Are phenotypes stable, and when can one be assigned?

- How do the common interventions interact with outcome across phenotypes?

- What should we do when assessing quality or mandating care with phenotypic information?
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

**IMPORTANT** Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

**OBJECTIVE** To evaluate and, as needed, update definitions for sepsis and septic shock.

**PROCESS** A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

**KEY FINDINGS FROM EVIDENCE SYNTHESIS** Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

**RECOMMENDATIONS** Sepsis should be defined as life-threatening organ dysfunction caused
Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunekhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

IMPORTANCE The Third International Consensus Definitions Task Force defined sepsis as “life-threatening organ dysfunction due to a dysregulated host response to infection.” The performance of clinical criteria for this sepsis definition is unknown.

OBJECTIVE To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

DESIGN, SETTINGS, AND POPULATION Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706,399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

EXPOSURES Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) criteria, Logistic Organ Dysfunction System (LODS) score, and a new model derived using multivariable logistic regression in a split sample, the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score (range, 0-3 points, with 1 point each for systolic hypotension [≤100 mm Hg], tachypnea [≥22/min], or altered mentation).

MAIN OUTCOMES AND MEASURES For construct validity, pairwise agreement was assessed. For predictive validity, 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 were expressed as the fold-change in outcome per decile of baseline risk of death and are under the receiver.

Editorial page 757
Author Audio interview at jama.com
Related articles pages 775 and 801
Supplemental content at jama.com
SEP-3 and EM

- **No participation** – acute, early view under-represented

- **Benefits vs harm**
  - Simpler gradation – no “severe sepsis” any more
  - Septic shock now *only* with elevated lactate and vasopressor use (restrictive)
  - ? More reproducible

- **Sensitivity vs specificity, validation**
  - qSOFA robust
  - In ED – unknown performance vs “old way” (SIRS plus old definitions, or gestalt) – likely *limited sensitivity in early stages*
  - Overall effect (change # with “sepsis” and “septic shock”, and deaths attributed – but will fewer die with infections?)
The “New one-hour bundle” from SSC

- Released 2018

- Three from SSC group created this new bundle (even more selective)

- Targets one hour actions – notably volume + antibiotics
  - Time 0 = arrival
  - Starting vs finishing
  - “Aspirational” and “we know the starting time is wrong”

- Impact?
  - Overuse
  - Use in non-sepsis
  - Is all sepsis the same?
Our take away

- **Sepsis kills**, still

- Key is looking *early and often* – not “one test/thing”.
  - The field *and* the ED matters

- **Use tools** to aid – order sets, complimentary tests

- *Trying* matters – ATB and restoring perfusion (LR or pressors) more than specific steps – *assess and re-assess*

- **Sepsis** and care *has many faces* – soon, we will tailor care better – even the simple things like volume, antibiotics and pressors.
Questions ?