Tracking Progress on Preventing and Treating Sepsis

CDC’s Adult Sepsis Event Surveillance Strategy

Jefferson 4th Annual Sepsis Symposium (Sept 24th, 2019)

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Disclosures

- **Grant funding**
  - US Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality

- **Royalties**
  - UpToDate (Procalcitonin chapter)

- **Committee Membership**
  - IDSA Sepsis Task Force
  - ACEP Sepsis Management Guidelines

*No financial conflicts*
Outline

1. Why is Sepsis Surveillance Important?

2. What We “Know” About Sepsis Incidence, Mortality, and Trends

3. Limitations of Surveillance Using Sepsis Diagnoses and Administrative Data

4. A New Surveillance Paradigm Using Objective Clinical Data From Electronic Health Records
Why Is Sepsis Surveillance Important?
The High Burden of Sepsis

- Carries high risk of mortality\(^1\)
- Leading cause of death in hospitalized patients\(^2\)
- Most expensive condition treated in hospitals\(^3\)
- Survivors also at high risk for recurrent sepsis, readmission, cognitive and functional impairment\(^4\)

1. Liu, *JAMA* (2014); 312:90-92
2. Rhee, *JAMA Netw Open* 2019; 2:e187571
3. Torio, *HCUP Statistical Brief #160* 2013
The New Era of Sepsis Quality Measures

- 2013: New York State mandated sepsis protocols in all state hospitals (“Rory’s Regulations”)
  - Mandatory reporting of protocol adherence and risk-adjusted mortality
  - Other states following suit
- Oct 2015: CMS quality measure (SEP-1) implemented
  - Hospitals report compliance with a 3- and 6-hour “sepsis bundle” in patients diagnosed with sepsis (ICD-10 codes)
- Hospitals all around the country are instituting quality improvement programs
The Importance of Reliable Sepsis Surveillance

- Objective sepsis measures needed to:
  1. Understand the impact of interventions and policies
  2. Guide new programs
  3. Identify risk factors and targets for prevention
  4. Find opportunities for better care through hospital comparisons
  5. Help direct research investments

- CDC: “Surveillance and data are the foundation of public health practice”

- Cannot make progress in fighting a disease without a reliable measuring stick!
What We “Know” About Sepsis Incidence, Mortality, and Trends
A Dramatic Rise in Sepsis Incidence Over Time

Martin, NEJM 2003; 348:1546-54
Rising Sepsis Incidence: A Prevalent Claim

Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003*

Viktor Y. Dombrovskiy, MD, PhD, MPH; Andrew A. Martin, MD; Jagadeeshan Sunderram, MD; Harold L. Paz, MD


Cagan Kumar, MD; Nilay Kumar, MD, MPH; Amit Timeja, MD; Thomas Kalkel, MD; Serygei Tarima, PhD; Emily McClintey, MPH; Edgar Jimenez, MD; Anand Mohan, MD; Rumi Ahmed Khan, MD; Jeff Whittle, MD; Elizabeth Jacobs, MD, FCCP; and Rahul Nanchal, MD, FCCP, from the Milwaukee Initiative in Critical Care Outcomes Research (MICCOR) Group of Investigators

Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007

Tara Lagu, MD, MPH; Michael B. Rothberg, MD, MPH; Meng-Shiou Shieh, PhD; Penelope S. Pekow, PhD; Jay S. Steingrub, MD; Peter K. Lindnauer, MD, MSc

Kumar, Chest 2011; 140(5):1223-31
Rising Sepsis Incidence: 4 Administrative Definitions

Gaieski, *Crit Care Med* 2013; 41:1167-74
The Good News: Declining Case-Fatality Rates

Gaieski, Crit Care Med 2013; 41:1167-74
Why is Incidence Rising (and Mortality Declining)?

- **Rising sepsis incidence** typically attributed to:
  - Aging population
  - Increasing number of medical procedures
  - More immunosuppression / chemotherapy
  - Rise of MDROs, C.difficile, etc.

- **Declining sepsis case fatality rates** typically attributed to improvements in sepsis care
  - Also improvements in global ICU and hospital care
The Surviving Sepsis Campaign

SSC launched in early 2000s

Goal: Improve sepsis awareness and decrease mortality through evidence-based guidelines
  ➢ Updated every 4 years

Dellinger, Crit Care Med 2004; 32:858-73
Sepsis Mortality Rates by Duration of SSC Participation

↑Bundle compliance associated with ↓25% mortality

Levy, Crit Care Med 2015; 43:3-12
Sepsis Mortality in New York State After Rory’s Regulations

Over ~2 years:
- 3 hour bundle compliance: ↑53% to 65%
- Risk-adjusted mortality: ↓29% to 24%
- ↑Compliance associated with ↓LOS and mortality
Declines in Sepsis Mortality in NY vs 4 Control States

1 million sepsis hospitalizations identified using administrative data ("Dombrovskiy" definition)

Significantly greater decline in sepsis mortality vs control states (absolute mortality 3.2% lower than expected in quarter 10)

Kahn, JAMA 2019; 322:240-250
Limitations of Surveillance Using Sepsis Diagnoses and Administrative Data
How Reliable Are Current Sepsis Estimates?

Most studies based on administrative claims data...
(or in some cases, prospective sepsis screening)

However:

1. Sepsis is **difficult to define**
2. Diagnosing sepsis is **subjective and variable**
3. Diagnosis and coding practices are **changing over time**
What Is Sepsis, Really?

- Even today, clinicians still struggle to define it!
  - Complex, heterogeneous syndrome
  - No single confirmatory test
  - Florid cases (e.g., meningococcemia, gram-negative bacteremia with multi-organ failure) are a minority of cases
Evolving Sepsis Definitions: Sepsis-1

“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 >12k, <4k, or >10% bands
- **Sepsis** = Infection + SIRS
- **Severe Sepsis** = Sepsis + Organ Dysfunction
- **Septic Shock** = Sepsis + Refractory Hypotension

Bone, Crit Care Med 1992; 20:684-74
Sepsis-2 (2001)

- Expanded list of possible diagnostic criteria, but otherwise no significant change to this framework

<table>
<thead>
<tr>
<th>Table 1. Diagnostic criteria for sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection,</strong> documented or suspected, and some of the following:*</td>
</tr>
<tr>
<td><strong>General variables</strong></td>
</tr>
<tr>
<td>Fever (core temperature &gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;=36°C)</td>
</tr>
<tr>
<td>Heart rate &gt;90 min⁻¹ or &gt;=2 sd above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>Significant edema or positive fluid balance (&gt;20 mL/kg over 24 hrs)</td>
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<tr>
<td>Hyperglycemia (plasma glucose &gt;120 mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
</tr>
<tr>
<td><strong>Inflammatory variables</strong></td>
</tr>
<tr>
<td>Leukocytosis (WBC count &gt;12,000 μL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt;4000 μL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 sd above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin &gt;2 sd above the normal value</td>
</tr>
<tr>
<td><strong>Hemodynamic variables</strong></td>
</tr>
<tr>
<td>Arterial hypotension* (SBP &lt;90 mm Hg, MAP &lt;70, or an SBP decrease &gt;40 mm Hg in adults or &lt;2 sd below normal for age)</td>
</tr>
<tr>
<td>SVO₂ &gt;70%</td>
</tr>
<tr>
<td>Cardiac index &gt;3.5 L/min⁻¹·M⁻²³</td>
</tr>
<tr>
<td><strong>Organ dysfunction variables</strong></td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL·kg⁻¹·hr⁻¹ or 45 mmol/L for at least 2 hrs)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL</td>
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<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 secs)</td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000 μL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dL or 70 mmol/L)</td>
</tr>
<tr>
<td><strong>Tissue perfusion variables</strong></td>
</tr>
<tr>
<td>Hyperlactatemia (&gt;1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

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

- Operationalized as \( \uparrow \) in SOFA score by \( \geq 2 \) points
- SIRS criteria eliminated
- “Severe Sepsis” eliminated (=“Sepsis”)

Singer, JAMA 2016, 315:801-10
Challenges in Sepsis Diagnosis - Irrespective of Definition

- Signs are nonspecific
- Cultures positive in only a fraction of cases
- **Often difficult to know:**
  - Whether infection is present
  - Whether organ dysfunction is attributable to infection
- **No pathologic gold standard for sepsis**
Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes

Chanu Rhee1,2*, Sameer S. Kadri3, Robert L. Danner3, Anthony F. Suffredini3, Anthony F. Massaro2, Barrett T. Kitch4, Grace Lee3 and Michael Klompas1,2

- 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
  - Conducted prior to Sepsis-3 release

Rhee, Crit Care 2016; 20:89
Case Vignette

- 67 year old male with severe congestive heart failure presents with several days of progressive shortness of breath, lower extremity swelling, malaise, productive cough, and subjective fevers.
- Low grade fever in ED, rapid atrial fibrillation, hypotensive, with signs of volume overload
- Labs with elevated WBC, lactate, and acute kidney injury
- Chest X-ray with pulmonary edema and possible left lower lobe infiltrate
Case Vignette, continued

- Gets fluids, diltiazem, and antibiotics
- **Decompensates into respiratory failure, shock and altered mental status, requiring intubation and vasopressors + inotropes**
- Admitted to ICU – continued on vasopressors + inotropes, antibiotics, anti-arrhythmic medications
- Improves and gets extubated. **Blood and sputum cultures negative.** Finishes course of antibiotics and discharged.
Does This Patient Have Sepsis?
**Does This Patient Have Sepsis?**

- Overall Fleiss Kappa amongst 5 vignettes = 0.29
- No difference in subset of intensivists who felt “strongly confident” in their knowledge of sepsis definitions

Rhee, *Crit Care* 2016; 20:89
Are Sepsis Diagnosis and Coding Practices Changing?

**GET AHEAD OF SEPSIS**

**JUST ASK**

“**COULD IT BE SEPSIS?**”

**Sepsis: Know the signs, save a life**

- Temperature: Higher or lower than normal
- Infection: May have signs and symptoms of an infection
- Mental decline: Confused, sleepy, difficult to rouse
- Extremely ill: “I feel like I might die,” severe pain or discomfort

**KNOW THE RISKS. SPOT THE SIGNS. ACT FAST.**
Sepsis Screens / Best Practice Alerts

Your patient may have sepsis. Please review and treat the patient.
If you think that sepsis is most likely diagnosis please investigate and treat using the Powerplans via Orders.
If you know the patient is septic from before or has an alternative dx to explain trigger, place diagnosis using confirmation button.

Is this Septic Shock?

Yes  No
Based upon the clinical indicators and treatment, please clarify if you are treating a possible or suspected:

- Sepsis
- Septic Shock
- SIRS due infection

<table>
<thead>
<tr>
<th>Present</th>
<th>Clinical Indicators Documented</th>
<th>Location in Medical Record</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔️</td>
<td>Fever or hypothermia 🌡₃₈°C</td>
<td>Progress Note 8/21</td>
</tr>
<tr>
<td></td>
<td>Tachypnea</td>
<td></td>
</tr>
<tr>
<td>✔️</td>
<td>Tachycardia 🏃️₁₁₀</td>
<td>8/21</td>
</tr>
<tr>
<td>✔️</td>
<td>WBC count ¹⁴₂</td>
<td>8/21</td>
</tr>
<tr>
<td></td>
<td>Oliguria</td>
<td></td>
</tr>
<tr>
<td>✔️</td>
<td>Hypotension 🍽₄₈/₉₂</td>
<td>8/21</td>
</tr>
<tr>
<td></td>
<td>Positive Blood Culture: 🍽️ＵＲＳＡ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>✔️</td>
<td>IV fluids</td>
<td>8/21</td>
</tr>
<tr>
<td>✔️</td>
<td>IV antibiotics</td>
<td>8/21</td>
</tr>
</tbody>
</table>

If you concur, please document in the progress notes and discharge summary.

Please let me know if you have any questions.

Thank you,

Maggie

CDR Nurse
By definition, the marginal cases are the less obvious, less sick cases. This leads to higher case counts & lower mortality rates.
Ascertainment Bias: Local QI Initiatives

Increasing Sepsis Incidence (Lower Threshold for Diagnosis)

Decrease in Sepsis Mortality (Less Severe Cases Included)
Ascertainment Bias: Local QI Initiatives

Increasing Sepsis Incidence (Lower Threshold for Diagnosis)

Decrease in Sepsis Mortality (Less Severe Cases Included)
Sepsis Mortality in NY After Mandated Reporting

Q2 2014
N=8,664 cases reported

Q2 2015
N=11,170 cases reported

30% Increase!
Sepsis Mortality in NY After Mandated Reporting

Levy, AJRCCM 2018;198:1406-12
Sepsis Mortality in NY After Mandated Reporting

Risk Adjustment Flattens the Mortality Curve
(risk adjustment model AUC 0.77)

Levy, AJRCCM 2018;198:1406-12
Ascertainment Bias: Is it Happening Globally?

- Surviving Sepsis Campaign
- CMS SEP-1 Measure
- Growing Number of Publications
- High-Profile Cases in the Media
- Quality Improvement Initiatives
- Awareness Campaigns
- Better Documentation and Coding

Sepsis
National Data: Hospitalization Primary Diagnoses, 2003-2011

Source: HCUP Nationwide Inpatient Sample (AHRQ)

Rhee, NEJM 2014; 370(18):1673-76
National Data: Hospitalization Primary Diagnoses, 2003-2011

Source: HCUP Nationwide Inpatient Sample (AHRQ)

Rhee, NEJM 2014; 370(18):1673-76
Coding for Organ Dysfunction is Changing Too

Data from Massachusetts General Hospital and Brigham & Women’s Hospital

Rhee, Critical Care 2015; 19:338
Coding for Organ Dysfunction is Changing Too

Data from Massachusetts General Hospital and Brigham & Women’s Hospital

Rhee, Critical Care 2015; 19:338
Sepsis Surveillance Using Objective Clinical Data From Electronic Health Records
Can We Track Sepsis More Objectively?

- Alternate method: leverage the *increasing national uptake of EHR systems* to identify *clinical indicators of sepsis*:
  - Presumed Infection (e.g. cultures + antibiotics)
  - Concurrent Organ Dysfunction (e.g., vasopressors, mechanical ventilation, abnormal laboratory values)
Pilot CDC-funded studies using data from academic hospitals demonstrated that EHR-based surveillance is feasible, more accurate than administrative data, and yields more stable trends in sepsis incidence and mortality.

CDC convened a working group to discuss possible national approaches to sepsis surveillance using more objective clinical measures.

Broad representation from various sepsis stakeholders:
- Sepsis-3 Task Force
- SCCM
- Surviving Sepsis Campaign
- ACEP
- IDSA
- New York Department of Health
- CDC Division of Healthcare Quality Promotion
- CDC Prevention Epicenters
- (and others...)
Objectives:

- Create a surveillance definition based on the Sepsis-3 framework using objective and routinely available EHR data
- Apply the definition to diverse hospitals to generate the most credible estimates of current U.S. national sepsis burden to date
Different Sepsis Criteria for Different Purposes

- Underlying Premise to “Defining” Sepsis:
  - No true gold standard
  - No single definition can fit needs of all stakeholders

- **Real-time clinical care (Sepsis-3)**
  - **Goal:** Early identification of sepsis, trigger aggressive treatment
  - **Desirable properties:** Timely, applicable at bedside, highly sensitive

- **Retrospective surveillance (CDC)**
  - **Goal:** Rigorous case-counting for epidemiologic monitoring
  - **Desirable properties:** Objective, reproducible, specific (>sensitive), low measurement burden

  - Clinical credibility important but surveillance definitions do not need to perfectly match clinical definitions

Adapting Sepsis-3 Clinical Criteria for EHR Surveillance

- Infection criteria focused on **blood culture orders** rather than entire spectrum of clinical cultures
  - Easier to identify and standardize across datasets
  - More specific for suspected sepsis (with minimal loss of sensitivity)

- Emphasized **sustained treatment of infection (≥4 days of antibiotics)** over mere suspicion of infection (any antibiotic)
  - Eliminates patients treated empirically with antibiotics for 48-72 hours then stopped when infection no longer suspected

- **SOFA organ dysfunction criteria simplified**
Why Simplify the SOFA Score?

- SOFA is well-tested and useful for clinically characterizing septic patients at the bedside…

  But poses challenges for implementing **objective and consistent EHR-based surveillance across hospitals**
<table>
<thead>
<tr>
<th>Organ System</th>
<th>SOFA Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>1 - Mean Arterial Pressure &lt;70 mmHg</td>
<td>Spurious vital signs and transient escalation of vasopressor doses common and difficult to account for in electronic surveillance</td>
</tr>
<tr>
<td>2 - DA ≤ 5 mcg/kg/min or Dobutamine (any dose)</td>
<td></td>
</tr>
<tr>
<td>3 - DA &gt; 5 or EPI ≤ 0.1 or NE ≤ 0.1 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>4 - DA &gt; 15 or EPI &gt; 0.1 or NE &gt; 0.1 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>1 - PaO2/FiO2 300-399</td>
<td>ABGs not routinely measured; difficult to distinguish arterial vs venous sample and identify FiO2 at time ABG drawn</td>
</tr>
<tr>
<td>2 - PaO2/FiO2 200-299</td>
<td></td>
</tr>
<tr>
<td>3 - PaO2/FiO2 100-199 and ventilated</td>
<td></td>
</tr>
<tr>
<td>4 - PaO2/FiO2 ratio &lt;100 and ventilated</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>1 - Creatinine 1.2-1.9 mg/dL</td>
<td>Urine output inconsistently measured and documented</td>
</tr>
<tr>
<td>2 - Creatinine 2.0-3.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td>3 - Creatinine 3.5-4.9 mg/dL or UOP &lt;500 cc/day</td>
<td></td>
</tr>
<tr>
<td>4 - Creatinine &gt;5.0 mg/dL or UOP &lt;200 cc/day</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
</tr>
<tr>
<td>1 - Bilirubin 1.2-1.9 mg/dL</td>
<td></td>
</tr>
<tr>
<td>2 - Bilirubin 2.0-5.9 mg/dL</td>
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<td></td>
</tr>
<tr>
<td>4 - Bilirubin &gt;12.0 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
</tr>
<tr>
<td>1 - Platelets 100-149 cells/µL</td>
<td></td>
</tr>
<tr>
<td>2 - Platelets 50-99 cells/µL</td>
<td></td>
</tr>
<tr>
<td>3 - Platelets 20-49 cells/µL</td>
<td></td>
</tr>
<tr>
<td>4 - Platelets &lt; 20 cells/µL</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td></td>
</tr>
<tr>
<td>1 - Glasgow Coma Scale score 13-14</td>
<td>Subjective, not routinely measured, and difficult to assess in sedated patients</td>
</tr>
<tr>
<td>2 - Glasgow Coma Scale score 10-12</td>
<td></td>
</tr>
<tr>
<td>3 - Glasgow Coma Scale score 6-9</td>
<td></td>
</tr>
<tr>
<td>4 - Glasgow Coma Scale score &lt;6</td>
<td></td>
</tr>
<tr>
<td>Organ System</td>
<td>SOFA Score</td>
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<tr>
<td>--------------</td>
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4 - \(DA > 15\) or \(EPI > 0.1\) or \(NE > 0.1 \text{ mcg/kg/min}\) |
| Pulmonary | 1 - \(\text{PaO}_2/\text{FiO}_2\) 300-399  
2 - \(\text{PaO}_2/\text{FiO}_2\) 200-299  
3 - \(\text{PaO}_2/\text{FiO}_2\) 100-199 and ventilated  
4 - \(\text{PaO}_2/\text{FiO}_2\) ratio <100 and ventilated |
| Renal | 1 - Creatinine 1.2-1.9 mg/dL  
2 - Creatinine 2.0-3.4 mg/dL  
3 - Creatinine 3.5-4.9 mg/dL or \(UOP < 500 \text{ cc/day}\)  
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2 - Platelets 50-99 cells/\(\mu\)L  
3 - Platelets 20-49 cells/\(\mu\)L  
4 - Platelets <20 cells/\(\mu\)L |
| Neuro | 1 - Glasgow Coma Scale score 13-14  
2 - Glasgow Coma Scale score 10-12  
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4 - Glasgow Coma Scale score <6 |
<table>
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<tr>
<th>Organ System</th>
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<th>eSOFA</th>
<th>Vasopressor initiation</th>
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4 - DA > 15 or EPI >0.1 or NE >0.1 mcg/kg/min | Vasopressor initiation |  |
| **Pulmonary** | 1 - PaO2/FiO2 300-399  
2 - PaO2/FiO2 200-299  
3 - PaO2/FiO2 100-199 and ventilated  
4 - PaO2/FiO2 ratio <100 and ventilated | Mechanical ventilation initiation |  |
| **Renal** | 1 - Creatinine 1.2-1.9 mg/dL  
2 - Creatinine 2.0-3.4 mg/dL  
3 - Creatinine 3.5-4.9 mg/dL or UOP <500 cc/day  
4 - Creatinine >5.0 mg/dL or UOP <200 cc/day |  |  |
| **Hepatic** | 1 - Bilirubin 1.2-1.9 mg/dL  
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2 - Platelets 50-99 cells/µL  
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| **Neuro** | 1 - Glasgow Coma Scale score 13-14  
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3 - Glasgow Coma Scale score 6-9  
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| **Renal** | 1 - Creatinine 1.2-1.9 mg/dL  
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<tr>
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<td></td>
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<td></td>
<td>3 - Platelets 20-49 cells/µL</td>
<td></td>
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<td>4 - Platelets &lt;20 cells/µL</td>
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</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2 - Glasgow Coma Scale score 10-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 - Glasgow Coma Scale score 6-9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 - Glasgow Coma Scale score &lt;6</td>
<td></td>
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</tr>
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| Neuro | 1 - Glasgow Coma Scale score 13-14  
2 - Glasgow Coma Scale score 10-12  
3 - Glasgow Coma Scale score 6-9  
4 - Glasgow Coma Scale score <6 | Neurologic Dysfunction Not Assessed  
Lactate ≥2.0 mmol/L |
EHR Surveillance for Sepsis Event

BLOOD CULTURE

Hospital Day 1 2 3 4 5 6 7

Antibiotic Rx ≥4 Days*

+-/2 Day Window

Acute Organ Dysfunction (≥1 eSOFA Criteria)

- New Vasopressor
- New Mechanical Ventilation
- ↑2x Cr or ↓50% eGFR
- ↑2x Bilirubin to ≥2.0 mg/dL
- ↓50% Plts to <100 cells/μL
- Lactate ≥2.0 mmol/L

Presumed serious infection

SEPSIS EVENT

*<4 antibiotic days allowed if death, hospice, or hospital transfer occurs before 4 days
Distribution of Study Hospital Characteristics vs All AHA Hospitals

Study Hospitals (n=409)  AHA Hospitals (n=4810)

Geographic Region

- Northeast
- South
- Midwest

2014 Study Cohort:
~2.9 million adult encounters
(~10% of all U.S. adult hospitalizations)

Teaching Status

- Teaching
- Nonteaching

Large (≥500 beds)
Sepsis Patients: Clinical Characteristics

- 173,690 adult sepsis cases in cohort in 2014
  - 6% prevalence among hospitalized patients
  - 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
How Many Patients Who Die In-Hospital Have Sepsis?

Sepsis was present in ~35% of all in-hospital deaths.

Total Study Cohort Deaths:
- Total Cohort Deaths: n=75,969
- Sepsis Deaths: n=26,278 (34.6%)
## 2014 National Projection: Sepsis Cases and Deaths by Strata

<table>
<thead>
<tr>
<th>Region</th>
<th>Size</th>
<th>Teaching Status</th>
<th># AHA Hospitals</th>
<th># Study Hospitals</th>
<th>Study Admissions</th>
<th>Study % of AHA Admissions</th>
<th>Study Adult Sepsis Cases</th>
<th>Study Adult Sepsis Incidence</th>
<th>Study Adult Sepsis Deaths</th>
<th>Study Adult Sepsis Mortality</th>
<th>Projected Sepsis Cases</th>
<th>Projected Sepsis Deaths</th>
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<tbody>
<tr>
<td>NE</td>
<td>L</td>
<td>N</td>
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<td>2</td>
<td>8,771</td>
<td>5.3%</td>
<td>448</td>
<td>5.1%</td>
<td>69</td>
<td>15.4%</td>
<td>8,516</td>
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<td>56</td>
<td>6</td>
<td>157,039</td>
<td>7.6%</td>
<td>8,052</td>
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<td>1,596</td>
<td>19.8%</td>
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<td>2,241</td>
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<td>14.2%</td>
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<td>771,130</td>
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<td>41,957</td>
<td>6.3%</td>
<td>5,592</td>
<td>14.3%</td>
<td>291,261</td>
<td>41,596</td>
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<td>65</td>
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<td>13,760</td>
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<td>1,797</td>
<td>13.1%</td>
<td>68,147</td>
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<td>100,711</td>
<td>38.6%</td>
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<td>649</td>
<td>14.2%</td>
<td>11,855</td>
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<td>0</td>
<td>0</td>
<td>0.0%*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>10,037</td>
<td>6.7%</td>
<td>1,523</td>
<td>15.2%</td>
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<td>9,838</td>
<td>9.3%</td>
<td>1,562</td>
<td>15.9%</td>
<td>157,628</td>
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<td>5,916</td>
<td>4.3%</td>
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<td>4.2%</td>
<td>15</td>
<td>7.3%</td>
<td>4,760</td>
<td>348</td>
</tr>
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</table>

~1.7 million adult hospitalizations with sepsis

~270,000 sepsis-associated deaths
Trends Comparisons: “Explicit” vs “Implicit” Administrative Definitions

1. **“Explicit Codes”**
   - Severe sepsis (995.92) or Septic shock (785.2) codes
   - Some also use Septicemia (038x) codes
   - *High PPV, low sensitivity, captures severely ill patients*

2. **“Implicit Codes”** (ex: Angus method)
   - Infection + Organ dysfunction codes
   - *Higher sensitivity, but lower PPV; captures less sick patients*
Sepsis Incidence Trends, 2009-2014

Implicit or Explicit Codes: +10%/y (p<0.01)

Explicit Codes: +7%/y (p<0.01)
Sepsis Incidence Trends, 2009-2014

- **Implicit or Explicit Codes:** +10%/y (p<0.01)
- **Clinical Surveillance Definition:** +4%/y (p=0.02)
- **Explicit Codes:** +7%/y (p<0.01)
Sepsis Incidence Trends, 2009-2014

Adjusted Sepsis Incidence

- Implicit or Explicit Codes: $+10\%\text{/y (p<0.01)}$
- Clinical Surveillance Definition: $+4\%\text{/y (p=0.02)}$
- Clinical Surveillance Definition Without Lactate: $+0.6\%\text{/yr (p=0.67)}$
- Explicit Codes: $+7\%\text{/y (p<0.01)}$
In-Hospital Mortality

Explicit Codes: -7%/y (p<0.01)

Implicit or Explicit Codes: -7%/y (p<0.01)
In-Hospital Mortality

Adjusted Sepsis Mortality

Explicit Codes: -7%/y (p<0.01)

Clinical Surveillance Definition: -5%/y (p<0.01)

Implicit or Explicit Codes: -7%/y (p<0.01)
In-Hospital Mortality

Explicit Codes: -7%/y (p<0.01)

Clinical Surveillance Definition Without Lactate: -3%/y (p<0.01)

Clinical Surveillance Definition: -5%/y (p<0.01)

Implicit or Explicit Codes: -7%/y (p<0.01)
In-Hospital Death or Discharge to Hospice

Explicit Codes: -5%/y (p<0.01)

Implicit or Explicit Codes: -4%/y (p<0.01)
In-Hospital Death or Discharge to Hospice

Adjusted Rate of Death or Discharge to Hospice

Explicit Codes: -5%/y (p<0.01)

Clinical Surveillance Definition: -2%/y (p=0.03)

Implicit or Explicit Codes: -4%/y (p<0.01)
In-Hospital Death or Discharge to Hospice

Explicit Codes: -5%/y (p<0.01)

Clinical Surveillance Definition Without Lactate:

-1%/y (p=0.19)

Clinical Surveillance Definition: -2%/y (p=0.03)

Implicit or Explicit Codes: -4%/y (p<0.01)

Inclusion of Hospice Discharges Attenuates Apparent Improvement in Sepsis Outcomes Over Time
Validation of EHR Surveillance Definition vs Sepsis-3 Criteria

506 medical record reviews across 5 academic and community hospitals

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<thead>
<tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>70%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
</tr>
<tr>
<td>PPV</td>
<td>70%</td>
</tr>
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<td>NPV</td>
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<td>76%</td>
<td>31%</td>
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<tr>
<td>NPV</td>
<td>98%</td>
<td>96%</td>
<td>98%</td>
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If sepsis was defined as *clinically suspected infection* + organ dysfunction → PPV = 88%
CDC National Sepsis Surveillance Study: Summary

- **Sepsis is common:**
  - ~ 6% of adult hospitalizations
  - ~ 1.7 million U.S. cases annually

- **Sepsis is deadly:**
  - >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

- **Sepsis trends have been fairly stable from 2009-2014:**
  - Mild rise in incidence if including lactate criteria (likely due to more testing)
  - Hospital-mortality rates have declined slightly, but attenuated when considering discharge to hospice
  - *Clinical data contrast with claims-based trends*

- **EHR-surveillance compares well with medical record reviews**
  - Imperfect but better than claims-based methods
CDC’s Adult Sepsis Event Definition

• “Adult Sepsis Event” toolkit released in March 2018

• Goal to help motivated hospitals more reliably track their sepsis rates and outcomes using objective data

www.cdc.gov/sepsis
A New Frontier with Objective
EHR-Based Sepsis Surveillance?
New Insights into Sepsis Epidemiology and Risk Factors

Epidemiology of Hospital-Onset Versus Community-Onset Sepsis in U.S. Hospitals and Association With Mortality: A Retrospective Analysis Using Electronic Clinical Data

Chanu Rhee, MD, MPH; Rui Wang, PhD; Zilu Zhang, MS; David Fram, BA; Sameer S. Kadri, MD, MSc; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program

Does Obesity Protect Against Death in Sepsis? A Retrospective Cohort Study of 55,038 Adult Patients*

Dominique J. Pepper, MD; Cumhur Y. Demirkale, PhD; Junfeng Sun, PhD; Chanu Rhee, MD; David Fram, PhD; Peter Eichacker, MD; Michael Klompas, MD; Anthony F. Suffredini, MD; Sameer S. Kadri, MD

Rhee, Crit Care Med 2019; 47(9):1169-76
More Objective Hospital Comparisons

Variation in Identifying Sepsis and Organ Dysfunction Using Administrative Versus Electronic Clinical Data and Impact on Hospital Outcome Comparisons

Chanu Rhee, MD, MPH; Maximilian S. Jentzsch, MS; Sameer S. Kadri, MD, MS;
Christopher W. Seymour, MD, MSc; Derek C. Angus, MD, MPH; David J. Murphy, MD, PhD;
Greg S. Martin, MD, MSc; Raymund B. Dantes, MD, MPH; Lauren Epstein, MD, MS;
Anthony E. Fiore, MD, MPH; John A. Jernigan, MD, MS; Robert L. Danner, MD;
David K. Warren, MD, MPH; Edward J. Septimus, MD; Jason Hickok, MBA;
Russell E. Poland, PhD; Robert Jin, MS; David Fram, BA; Richard Schaaf, SM;
Rui Wang, PhD; Michael Klompas, MD, MPH; for the Centers for Disease Control
and Prevention (CDC) Prevention Epicenters Program

Development and Evaluation of a Machine Learning Model for the Early Identification of Patients at Risk for Sepsis

Ryan J. Delahanty, PhD; JoAnn Alvarez, MS; Lisa M. Flynn, MD; Robert L. Sherwin, MD; Spencer S. Jones, PhD*
Conclusions

- Sepsis is a major public health problem and now the target of national quality initiatives
- However, sepsis is difficult to define, diagnose, and track
- Traditional surveillance using administrative claims data is prone to **ascertainment bias** and **misleading estimates** of sepsis trends and hospital comparisons
- The increasing uptake of EHRs allows for more objective surveillance using consistent clinical criteria
Conclusions, continued

- CDC’s Adult Sepsis Event definition adapts Sepsis-3 and the SOFA score to use routinely available and objective EHR data
  - More accurate than administrative data
  - Application across nationally representative set of U.S. hospitals suggests sepsis incidence and outcomes are more stable than previously believed

- Objective surveillance will help hospitals, policy makers, and researchers:
  - More reliably track local and national sepsis incidence and outcomes
  - Better interpret the impact of sepsis interventions
  - Gain insight into sepsis epidemiology and risk factors
  - Facilitate comparisons to peer institutions

→ *Ultimately drive further innovation and improvements in sepsis care and outcomes*
Acknowledgements

Co-Investigators and Collaborators:
- CDC: Lauren Epstein, Raymund Dantes, John Jernigan, Tony Fiore
- UPMC: Chris Seymour, Derek Angus
- Emory: David Murphy, Greg Martin, Elizabeth Overton
- Washington University: David Warren
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Questions?
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Future Directions

- Pediatric Sepsis Events and National Pediatric Sepsis Burden
- Risk-Adjustment Tools for Adult Sepsis Events to Facilitate Hospital Outcome Comparisons
- Trends in Sepsis Treatment and Outcomes after SEP-1 Implementation
- Further Insight into Epidemiology and Outcomes of Sepsis:
  - Previously Healthy vs Comorbid Patients
  - Patients with Cancer
  - Patients with Opioid Use Disorders
  - And more…
- Antibiotic Resistance in Sepsis
- Association Between Empiric Antibiotic Regimens and Outcomes
- Elucidating Clinical Phenotypes and Differential Treatment Responses
- Better Time Zero Definitions for Measuring Processes of Care