Surviving Sepsis: Early Management Saves Lives

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Objectives

• Understand the incidence of sepsis
• Discuss the difference between sepsis, severe sepsis and septic shock
• Define an early recognition process for severe sepsis
• Discuss the evidence based interventions for severe sepsis
Sepsis is an Epidemic

- Affects >1 million Americans per year
- 3rd leading cause of death in the US
- Sepsis occurs in just 10% of U.S. hospital patients, but it contributes to as many as half of all hospital deaths
- US spends $24 billion per year to treat

> 700 people die each day from sepsis in the U.S.- one every 2 minutes


Sepsis: CDC Vital Sign

https://www.cdc.gov/vitalsigns/sepsis/August 2016

- 80% of sepsis begins outside the hospital
- 7 out of 10 patients with sepsis had recently used health services or had chronic dx requiring frequent care
- 4 types of infections most connected to sepsis; lung, urinary tract, skin and gut
- HCP: think sepsis & act fast
Common Causes of Hospitalization Adults aged 85 and over: U.S.

<table>
<thead>
<tr>
<th>First-listed diagnosis</th>
<th>Rate of hospitalization per 1,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>48</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>51</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>19</td>
</tr>
<tr>
<td>Septicemia</td>
<td>15</td>
</tr>
<tr>
<td>Stroke</td>
<td>37</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>28</td>
</tr>
</tbody>
</table>

1Percent change for each diagnosis is significant from 2000 through 2010 (p < 0.05).

NOTE: First-listed diagnosis is considered to be the main cause or reason for the hospitalization. The diagnoses were chosen because they were the top six first-listed diagnoses in 2010.


Sepsis Impact on Mortality in Hospitals

In KPNC 2012 subset, patient meeting criteria for EGDT comprised 32.6% of sepsis deaths & patients with sepsis, normal BP & lactate < 4 comprised 55.9% of sepsis deaths.

Chang DW; Tseng CH; Shapiro MF. Critical Care Medicine. 43(10):2085-93, 2015 Oct.
### Proportion & Cost of Unplanned 30 day Readmissions after Sepsis (2013 Nationwide Readmission Database)

#### Table: Length of Stay and Cost for Unplanned 30-Day Readmissions After an Index Admission for Sepsis, Acute Myocardial Infarction, Heart Failure, Pneumonia, and Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>National Readmission Data*</th>
<th>Weighted Proportion of Cases in the United States</th>
<th>Percentage of Total Estimated Cost of All Readmissions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions associated with 30-day readmission</td>
<td>1187697</td>
<td>6.4 (6.4-6.5)</td>
</tr>
<tr>
<td><strong>Primary Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>147084</td>
<td>7.4 (7.3-7.4)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15001</td>
<td>5.7 (5.6-5.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>79480</td>
<td>5.4 (6.4-5.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>59378</td>
<td>6.6 (6.6-6.7)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>54395</td>
<td>6.0 (5.9-6.0)</td>
</tr>
<tr>
<td><strong>Sensitivity Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>89280</td>
<td>7.6 (7.6-7.7)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>21281</td>
<td>6.0 (5.9-6.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>236636</td>
<td>6.5 (6.5-6.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>130504</td>
<td>6.9 (6.9-7.0)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>201867</td>
<td>6.3 (6.3-6.4)</td>
</tr>
</tbody>
</table>

Mayr FB, et al. JAMA, 2017, Jan 22nd published online

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### Michigan All Cause Readmission to any hospital

- **Title**: All-Cause Readmission Within 30 Days of Index Discharge to Any, Same and Other Hospital by Top 10 Diagnosis Related Group (DRG), Michigan Medicare (FFS) Beneficiaries [July 1, 2016 – June 30, 2017]

- **State of Michigan**

- **Rank** | **DRG** | **Title** | **% all** | **% all** | **% all** | **% all** | **% all** | **% all** | **% all** |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>871</td>
<td>NEPTICEMIA OR SEVERE SEPSIS W/O MV W/HOURS W MCC</td>
<td>5.14</td>
<td>17,474</td>
<td>3,765</td>
<td>21.55</td>
<td>2,890</td>
<td>16.31</td>
<td>918</td>
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<tr>
<td>2</td>
<td>885</td>
<td>PSYCHOSIS</td>
<td>3.93</td>
<td>13,300</td>
<td>3,196</td>
<td>23.92</td>
<td>905</td>
<td>6.77</td>
<td>2,293</td>
</tr>
<tr>
<td>3</td>
<td>291</td>
<td>HEART FAILURE &amp; SHOCK W/MC</td>
<td>3.16</td>
<td>10,756</td>
<td>3,003</td>
<td>37.82</td>
<td>2,261</td>
<td>21.02</td>
<td>743</td>
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<tr>
<td>4</td>
<td>392</td>
<td>NEPHRITIS, GASTROENT &amp; MISC URINARY TRACT DISORDERS W/O MCC</td>
<td>2.09</td>
<td>7,110</td>
<td>1,167</td>
<td>16.41</td>
<td>834</td>
<td>11.73</td>
<td>333</td>
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<tr>
<td>5</td>
<td>189</td>
<td>PULMONARY EDEMA &amp; RESPIRATORY FAILURE</td>
<td>1.93</td>
<td>6,555</td>
<td>1,003</td>
<td>24.45</td>
<td>1,261</td>
<td>19.24</td>
<td>342</td>
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<tr>
<td>6</td>
<td>262</td>
<td>HEART FAILURE &amp; SHOCK W/CC</td>
<td>1.76</td>
<td>5,964</td>
<td>1,485</td>
<td>24.77</td>
<td>1,092</td>
<td>18.22</td>
<td>363</td>
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<tr>
<td>7</td>
<td>683</td>
<td>RENAL FAILURE W/CC</td>
<td>1.72</td>
<td>5,049</td>
<td>1,277</td>
<td>21.83</td>
<td>974</td>
<td>16.65</td>
<td>303</td>
</tr>
<tr>
<td>8</td>
<td>196</td>
<td>CHRONIC OBSTRUCTIVE PULMONARY DISEASE W MCC</td>
<td>1.70</td>
<td>5,765</td>
<td>1,372</td>
<td>23.72</td>
<td>1,055</td>
<td>18.24</td>
<td>317</td>
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<tr>
<td>9</td>
<td>472</td>
<td>NEPTICEMIA OR SEVERE SEPSIS W/O MV W/HOURS W MCC</td>
<td>1.50</td>
<td>5,046</td>
<td>792</td>
<td>15.54</td>
<td>546</td>
<td>11.69</td>
<td>148</td>
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<tr>
<td>10</td>
<td>662</td>
<td>RENAL FAILURE W MCC</td>
<td>1.46</td>
<td>4,980</td>
<td>1,380</td>
<td>27.71</td>
<td>1,022</td>
<td>20.52</td>
<td>356</td>
</tr>
</tbody>
</table>
## Discharge Disposition After Sepsis

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Septicemia or sepsis</th>
<th>Other diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>Transfer to other short-term care facility</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Transfer to long-term care institution</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Died during the hospitalization</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Other or not stated</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Difference is statistically significant at the 0.05 level. SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.*

## Impact on the Elderly

- Age itself independent risk factor for death
- More likely admitted to ICU
- Highest mortality in the old elderly (85+)
- Prolonged hospitalization

**Post Sepsis Impact**
- Contributes to Cognitive decline
- Contributes to Physical long term disabilities (walking, ADLs, and IADLs)
Sepsis Awareness
study done by Sepsis Alliance annually

- Sepsis awareness has significantly increased at 58% over 55% in 2016.
  - This means more than 7 million more adults are aware of sepsis in 2017 compared to 2016
  - Those under 45 are significantly more likely to have heard the term sepsis than over (62% vs. 53%)
- Almost one-quarter of Americans believe that sepsis only happens in hospitals (23%)
- An alarming 39% of Americans believe that sepsis is contagious
- Nearly three-quarters of Americans say they can identify the symptoms of someone having a stroke, whereas less than 1% can correctly identify all of the most common sepsis symptoms
- More Americans have never heard of sepsis (27%) than Ebola (5%), a nearly non-existent condition in the U.S.
- Nearly 58 million adults believe if you are healthy, an infection isn’t anything you need to worry about (24%)

Time Sensitive Diseases
Changing the Paradigm of Practice

- AMI
- Stroke
- Trauma

AMI: < 10%
Stroke: < 10%
Trauma: < 5%

Undiagnosed heart attacks
Severe Sepsis: Defining a Disease Continuum

Infection → SIRS → Sepsis → Severe Sepsis

Adult Criteria
A clinical response arising from a nonspecific insult, including ≥ 2 of the following:
- Temperature: > 38°C or < 36°C
- Heart Rate: > 90 beats/min
- Respirations: > 20/min
- WBC count: > 12,000/mm³, or < 4,000/mm³, or > 10% immature neutrophils

SIRS with a presumed or confirmed infectious process
Sepsis with ≥1 sign of organ dysfunction, hypoperfusion or hypotension.
- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Shock

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

**Neurological**
- Altered level of consciousness (unrelated to primary neuro pathology)

**Cardiovascular**
- Tachycardia
- SBP < 90 mmHg

**Respiratory**
- Increased O₂ requirements
- SaO₂ < 90%

**Renal**
- UO < 0.5 ml/kg per hr (despite fluid)

**Metabolic**
- Unexplained metabolic acidosis
  - pH < 7.30 or Base deficit ≥ 5.0 mEq/l
  - Lactate > 4

**Hematologic**
- Platelets < 80,000/mm³
- Decline in platelet count of 50% over 3 days
Definitions

• Infection
• Sepsis: infection plus 2 or more SIRS
• Severe Sepsis: infection plus 2 or more SIRS plus new organ dysfunction
• Septic Shock: severe sepsis with a lactic acid greater than or equal to 4mmol/L OR continued hypotension (systolic BP<90 or 40mmHg decrease from their baseline) after initial fluid bolus (30ml/kg)

Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

Sir William Osler – 1904
The Evolution of Modern Medicine
Homeostasis is unbalanced in severe sepsis

Coagulation

Inflammation

Fibrinolysis


Inflammation, Coagulation and Impaired Fibrinolysis in Severe Sepsis

Reprinted with permission from the National Initiative in Sepsis Education (NISE).
Microcirculation of Septic Patient: Othogonal Polarization Spectral Imaging

- BP: 120/80 Hg
- SaO₂: 98%

Microcirculation of Septic Shock Patient: Othogonal Polarization Spectral Imaging

- Resuscitated with fluids and dopamine
  - HR: 82 BPM
  - BP: 90/35 mm Hg
  - SaO₂: 98%
  - CVP: 25 mm Hg

Key Components of Sepsis Care

- Infection prevention
- Early identification
- Early and aggressive management (bundles)
- Avoid iatrogenic harm (discuss on different webinar)
  - Understand post sepsis syndrome and how to minimize its impact
  - Prevent sepsis readmissions

*ALL of these must be provided across the continuum of care*

Infection Prevention

- Implement evidence based strategies to prevent hospital acquired infections (HAIs): CLABSI, CAUTI, VAP, non-vent PNA, c-diff, SSI
- Measure rates/SIR for infection
- Audit prevention strategies
- Learn from each infection (defect) that occurs
- Multidisciplinary team

*This needs to be done across the continuum: SNFs, home care, medical home, and for patients in their homes*
SEPSIS (SEVERE SEPSIS) AND SEPTIC SHOCK ARE MEDICAL EMERGENCIES, AND WE RECOMMEND THAT TREATMENT AND RESUSCITATION BEGIN IMMEDIATELY

2016 Surviving Sepsis Guidelines Best Practice Statement

TO SAVE LIVES.....

Early identification

Early antibiotics

Early fluid resuscitation
Early Identification

- Surviving Sepsis Campaign Guidelines recommends screening to early identify patients
  - Results in earlier treatment and improved mortality.
  - Routine screening upon admission, every shift and with change in condition.
  - EMR alerts can be used in addition to routine screening

- Go beyond the hospital
  - Screening by EMS, in SNFs, home care and in PCP offices

The Importance of Early Detection

- Efforts to **just treat recognized sepsis** alone is not enough.
- A critical aspect of **mortality reduction** has been pushing practitioners to identify sepsis early.
  - It may well be that **earlier recognition** accounts for much of the signal in mortality reduction and partially explains sharply increasing incidence.
  - Without recognition that the **clock is ticking**, there is simply no incentive to recognize a challenging diagnosis early.


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Going beyond the hospital walls
*it's all about the early*

- **Partner with EMS**
  - Have them screen and begin fluids for hypotension, possibly draw lactic acid

- **Partner with PCPs** and medical and surgical homes to educate on severe sepsis
The importance of the EMS role

- A study from Colorado looked at the role of pre-hospital care providers in the treatment of sepsis.
  - Paramedics were trained to recognize sepsis in the field through identification of SIRS criteria and alert the hospital in advance, similar to a STEMI notification.
  - Patients whose caregivers provided those alerts had a median arrival-to-antibiotic time of 24 minutes less than those whose caregivers didn’t.
  - While 24 minutes may seem unimpressive, in the context of previous research demonstrating a 7.6% increase in mortality for every one hour delay to antibiotics, it becomes more significant.


EMS sepsis identification and management

Been in place since 2012, just updated in 2016
Partner with Skilled Nursing Facilities

- Educate them on infection prevention, sepsis, early identification and initial management
- Help them put in routine screening
- SNF sepsis toolkit available

Home Care

- Home care association of New York state in partnership with IPRO
- [https://hca-nys.org/stop-sepsis-at-home](https://hca-nys.org/stop-sepsis-at-home)
Surviving Sepsis Campaign Guidelines: 2016

- Consensus committee of 55 international experts presenting 25 international organizations
- Used GRADE system to guide assessment of quality of evidence from high to very low and to determine the strength of recommendations as strong or weak
- Utilized Best Practice Statements: Ungraded, strong recommendations

SEP-1

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION †:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

† “time of presentation” is defined as the time of earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.
SEXP-1

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg

6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to table 1.

7. Re-measure lactate if initial lactate elevated.

TABLE 1

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

Either

• Repeat focused exam(after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse and skin findings.

Or two of the following:

• Measure CVP
• Measure ScvO2
• Bedside cardiovascular ultrasound
• Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
Definitions (used by CMS and coders)

• **Infection**

• **Sepsis**: infection plus 2 or more SIRS

• **Severe Sepsis**: infection plus 2 or more SIRS plus new organ dysfunction

• **Septic Shock**: severe sepsis with a lactic acid greater than or equal to 4mmol/L OR continued hypotension (systolic BP<90 or 40mmHg decrease from their baseline) after initial fluid bolus (30ml/kg)

Sepsis 3:
*Singer et al, JAMA 2016. PMID: 26903338*

• **Sepsis** is: ‘life-threatening organ dysfunction caused by a dysregulated host response to infection’
  – Sepsis-3 does away with:
    • SIRS criteria (sepsis is pro- and anti-inflammatory)
    • Severe sepsis (sepsis = the old severe sepsis)
    • Antiquated concepts: sepsis syndrome; septicemia

• Sepsis-3 codifies the quantification of organ dysfunction through the SOFA score (Sequential Organ Failure Assessment)

• **Septic shock**: vasopressor-dependent hypotension + lactate >2

  Sepsis-3 includes clinical criteria to predict life-threatening disease
Developing new criteria

- Focus on timeliness, ease of use
- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality

New Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. (>2 SOFA points above baseline or outside the ICU—2 or more qSOFA)
- Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.
  - Patient who is vasopressor dependent to keep MAP >65 with a lactate >2

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory PsO₂/FIO₂ ratio (mmHg)</td>
<td>&gt;400</td>
<td>&gt;400</td>
<td>≤ 300</td>
<td>≤ 200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Renal Creatinine (mg/dL) or urine output (mL/d)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–3.4</td>
<td>3.5–4.9 or &lt;500mL/d</td>
<td>≤ 5.0 or &lt;200mL/d</td>
</tr>
<tr>
<td>Hepatic Bilirubin (mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–5.9</td>
<td>6.0–11.9</td>
<td>12.0</td>
</tr>
<tr>
<td>Cardiovascular Mean arterial pressure (mmHg)</td>
<td>No hypotension</td>
<td>MAP &gt;70</td>
<td>Dopamine ≤5 or dobutamine (any dose)</td>
<td>Dopamine &gt;5 or epinephrine ≤0.1</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1</td>
</tr>
<tr>
<td>Haematological Platelet count (×10⁹/mm³)</td>
<td>&gt;150</td>
<td>≤ 150</td>
<td>≤ 100</td>
<td>≤ 50</td>
<td>≤ 20</td>
</tr>
<tr>
<td>Neurological Glasgow coma score</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt; 6</td>
</tr>
</tbody>
</table>

1 With ventilatory support; 2 Adrenergic agents administered for at least 1h (doses in mcg/kg/ min).
Challenges with New Sep-3 Definitions

• SIRS not part of the definition:
  – the most appropriate use for SIRS is that its presence prompts an immediate search for both infection, as its possible source, and organ dysfunction, as its possible companion
• Late recognition
  – “sepsis is a problem only when life-threatening organ dysfunction is already present fails to recognize the spectrum of the illness, minimizes the importance of infection to its evolution and as its principal driver and devalues systemic host response as a harbinger of the onset of organ failure”
• Doesn’t recognize ‘cryptic shock’
• People will begin to use qSOFA as a screening tool
  – qSOFA and SOFA are predictors of mortality; they are not test of early sepsis at risk to progress to organ failure
• Only their predictive ability for morality and prolonged ICU stay have been evaluated, not their utility in reducing mortality


Five hundred years ago, the political writer, Niccolo Machiavelli said:

“As the physician say of hectic fever, that in the beginning of the malady it is difficult to detect but easy to treat, but in the course of time, having been neither detected nor treated in the beginning, it becomes easy to detect but difficult to treat”

Early Goal Directed Therapy

**Methodology**: 263 severe sepsis patients

- **Early Goal-Directed Therapy (EGDT)**
  - Continuous ScvO2 monitoring & tx with fluids, blood, inotropes &/or vasoactives to maintain:
    - ScvO2 > 70%, SaO2 ≥ 93%, Hct ≥ 30%, CI/VO2
    - CVP ≥ 8-12
    - MAP ≥ 65
    - UO ≥ .5ml/kg/hr

- **Standard Therapy**
  - CVP ≥ 8-12
  - MAP ≥ 65
  - UO ≥ .5ml/kg/hr


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**Early Goal-Directed Therapy Results**

**28-day Mortality**

- **Standard Therapy**
  - n=133
  - 49.2%
  - P = 0.01*

- **EGDT**
  - n=130
  - 33.3%

*NNT = 7–8*

*Key difference was in sudden CV collapse, not MODS*

• 3723 patients at 138 hospitals in seven countries (all patients from the PROCESS, PROMIS and ARISE trials)
• Prior to randomization >92% of patients were identified early, and provided the 3 hour bundle (including 2L of fluid and antibiotics—given within 70 minutes of presentation to ED)
• No difference in 90 day mortality between EGDT and Usual Care groups
• Authors stated: “It remains possible that general advances in the provision of care for sepsis and septic shock, to the benefit of all patients, explain part or all of the difference in findings between the trial by Rivers et al. and the more recent trials”

NEJM, March 21, 2017

• In 2013, New York began requiring hospitals to follow protocols for the early identification
• April 2014 to June 30, 2016
• 49,331 patients at 149 hospitals
• 82.5% had the 3-hour bundle completed within 3 hours (median time was 1.3 hrs)
• Longer time to completion of the 3 hour bundle was associated with higher risk-adjusted in-hospital mortality as well as longer time to administration of antibiotics (14% higher for both)
Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

- Objective: determine the impact of the initiation of inappropriate antimicrobial therapy on survival to hospital discharge of patients with septic shock
- Retrospective review of 5,715 patients from 22 different hospitals in Canada, US and Saudi Arabia
- Data collected from 1996-2005

Kumar A. et al. Chest, 2009; 136; 1237-1248

Initiation of Inappropriate Antimicrobial Therapy Result in a 5-Fold Reduction of Survival in Human Septic Shock

- 5,715 patients in septic shock in three countries
- 55% of cases were from community acquired infection
- Decrease in survival with inappropriate initial antibiotics was fivefold

Kumar A. et al. Chest, 2009; 136; 1237-1248
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

*2,154 septic shock patients

*Effective antimicrobial administration within the 1st hour of documented hypotension was associated with increased survival in patients with septic shock.

*Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6% (range 3.6-9.9%)

CCM 2006 Vol. 34 No.6

Antibiotics and Early Fluid Resuscitation are Key

Each elapsed hour between presentation and antibiotic administration was associated with a 9% increase in the odds of mortality with sepsis of all severity strata

Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients

Bristol B. Whiles, BS1; Amanda S. Deis, MS1; Steven Q. Simpson, MD2


Each hour until initial antimicrobial administration was associated with a 8% increase in progression to septic shock.

Patients who progressed to shock had significant increase in hospital LOS (18.7 days vs 9.66 days) and mortality (30.1% vs 7%)
Antibiotics and Early Fluid Resuscitation are Key

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality
A Retrospective Cohort Study
Sarah J. Lee, MD, MPH; Kannan Ramar, MBBS, MD; John G. Park, MD, FCCP; Ognjen Gajic, MD, FCCP; Guangxi Li, MD; and Rahul Kashyap, MBBS
CHEST OCTOBER 2014]

After adjusting for confounders, the higher proportion of total fluid received within the first 3 hrs was associated with decreased hospital mortality.

Decrease in hospital mortality was observed primarily in patients with heart and/or kidney failure (p<0.04) who received at least 2 Liters fluid resuscitation for severe sepsis with lactate between 2.1-3.9

Early fluid initiation (30-120 minutes) was associated with significantly lower hospital mortality, mechanical ventilation, ICU admission, LOS and ICU days. No harm seen to the patients.
Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate ≥ 4 mmol/L
(Based on SSC bundle and CMS threshold)

1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema.
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy:
   - Blood pressure/heart rate response,
   - Cardiac output monitoring,
   - Central venous pressure,
   - CVP, ScVO2,
   - Pulse pressure variation,
   - Lactate dehydrogenase-normalization or dynamic measurement such as response of fluid bolus or passive leg raising.
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg.

6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to table 1.

7. Re-measure lactate if initial lactate elevated.
TABLE 1
DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

Either
• Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse and skin findings.

Or two of the following:
• Measure CVP
• Measure ScvO2
• Bedside cardiovascular ultrasound
• Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Reassessment for Volume Status and Perfusion

➢ Team decide how to support all options in table 1
➢ Focused exam—templated notes? Specific form? Making sure it is done between after fluid bolus and before 6 hours
➢ Do you have all the correct equipment and tools and training for:
  ➢ CVP (IJ, Subclav or femoral)
  ➢ ScvO2 (intermittent vs continuous)
  ➢ Bedside cardiovascular ultrasound
  ➢ Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge (must be able to monitor CI, SV—pulse contour technology, non-invasive or PA catheter,)
**Optimize Cardiac Performance**

**Fluid Bolus to define place on curve:**
- Record SV
- Give 250-500 NS bolus over 15 minutes
- Record SV
- If see greater than a 10% increase in SV — pt is on steep portion of curve and will still respond to fluid (fluid responsive)

![Figure 1. Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The "normal" operating point is at a LVEDP of ~8 mm Hg and a SV of ~70 ml/beat.](image)

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**Passive Leg Raise**

- Meta-analysis of 21 studies of 991 patients whom 995 fluid challenges were performed, found changes in cardiac output induced by a passive leg raise test highly reliable in predicting fluid responsiveness

![Figure 2. Family of Frank-Starling curves. Changes in afterload and inotropic shift the Frank-Starling curve up or down.](image)

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Sensitivity of .85 & specificity .91
Passive Leg Raise (PLR)

- 150 – 300 ml volume
- Effects < 30 sec. Not more than 4 minutes
- Self-volume challenge
- Reversible

Severe Sepsis/Septic Shock Checklist
What is the current performance nationally on sepsis bundles?

**SEP-1 Initial Patient Population**

- > 99% of hospitals successfully submitted SEP-1 data
  - Q4 2016 (1st qtr of reporting) 99.9% of participating hospitals submitted data
  - Q1 2016 – Q3 2016 100% submitted data
  - Q4 2016 99.97% of participating hospitals submitted data

*Defined administrative contraindication to care between severe sepsis and septic shock cases*
All or none compliance

3 hour bundle compliance (lactate, blood culture, antibiotics)
3 hour bundle compliance
(lactate, blood culture, antibiotics)

6 hour Severe Sepsis bundle compliance
(repeat lactate)
Septic Shock 3-Hour bundle compliance (30ml/kg fluid bolus)

Septic Shock 6-Hour bundle compliance (vasopressors)
Septic Shock 6-Hour bundle compliance (reassessment)

Severe Sepsis/Septic Shock Mortality

Breakdown by SEP-1 Bundles: Septic Shock 6-Hour Bundle – Assessment

CMS Sep-1 Presentation, Nov, 2017

SEP-1 Mortality Rate Trend* for Eligible Population

CMS Sep-1 Presentation, Nov, 2017
Severe sepsis/Septic shock Mortality

Summary

• Sepsis affects >1 million people a year
• One person dies every 2 minutes in the U.S. from sepsis
• 80% of sepsis starts outside of the hospital
• Key to saving lives is early detection and early aggressive intervention with antibiotics and fluids
Questions?