Sepsis

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Clinical Scenario

• 24 yo previously healthy female presents to ED with:
  • 2 days of fevers, chills, headaches, and cough
  • Temp 101.8°F, HR 132, BP 115/80, RR 18,
    O2 sats on 2L NC: 94%
  • WBC 7.8, Hgb 10, plt 132
  • Bicarb 19, lactate 2.2
  • INR 1.4

Sepsis

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Sepsis Background Information

- Sepsis accounts for up to 50% of hospital deaths\(^1\), and is the most expensive condition in US hospitals (~$20 billion/yr) \(^2\)
  - Most sepsis cases are admitted through the ED\(^3\)
  - Most sepsis cases identified during hospital stay were present on admission to ED\(^1\)

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2. AHRQ 2011 (https://www.hcup-us.ahrq.gov/reports/statbriefs/sb160.jsp)
Severe Sepsis Acute Implications

• Global incidence ~19 million cases (1)
  – ~5 million related deaths (1)
• Annual incidence in U.S. ~750,000 cases
  – The trend is rising (2)
• 20-30 % 90 day mortality
  – The trend has been favorable over past 10 years (3)

4. 2011 AHRQ Statistics
~215,000 deaths a year in US

~590 Deaths Every day  ~4100 Deaths Every Week

Severe Sepsis Chronic Implications

• One year mortality ~50% (1,2)
• Greater use of healthcare facilities (~100%) (2)
• Fewer days spent at home (~50%) compared to non-septic matching critically ill controls (2)


Evolution of Sepsis Diagnostic Criteria

• Initially based upon the observed changes in physiological and immune cell parameters reflecting transition from a localized to **systemic inflammatory response**:

  - Physiological Variables:
    - Tachycardia
    - Tachypnea
    - Hyperthermia
Evolution of Sepsis Diagnostic Criteria

- Initially based upon the observed changes in physiological and immune cell parameters reflecting transition from a localized to systemic inflammatory response:
  - Physiological Variables:
    - Tachycardia
    - Tachypnea
    - Hyperthermia
  - Immunological features:
    - Leukocytosis
    - Leukopenia (in some cases)

1st International Consensus Taskforce 1991

- Table 1: Criteria for SIRS, sepsis, severe sepsis, and septic shock based on the 1991 ACCP/SCCM Consensus Conference

<table>
<thead>
<tr>
<th>Term</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS*</td>
<td>2 out of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>Temperature &gt;38° C or &lt;36° C</td>
</tr>
<tr>
<td></td>
<td>Heart rate &gt;90/min</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation evidenced by respiratory rate &gt;20/min or arterial CO2 lower than 32 mmHg</td>
</tr>
<tr>
<td></td>
<td>White blood cell count &gt;12000 cells/µL or lower than 4000 cells/µL</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS criteria with presumed or proven infection</td>
</tr>
<tr>
<td>Severe</td>
<td>Sepsis with organ dysfunction</td>
</tr>
<tr>
<td>Septic</td>
<td>Septic shock with hypotension despite adequate fluid resuscitation</td>
</tr>
</tbody>
</table>

Note: *SIRS, systemic inflammatory response syndrome.

Epidemiology of severe sepsis, Florian B Mayr, Sachin Yende, Derek C Angus Virulence Vol. 5, Iss. 1, 2014

2nd International Consensus Taskforce 2001

- Table 2: Criteria for sepsis based on 2001 SCCM/ESICM/SCCM Consensus Conference

<table>
<thead>
<tr>
<th>Term</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Documented (or suspected) infection with any one of the following clinical or laboratory criteria</td>
</tr>
<tr>
<td>General</td>
<td>Fever, hypothermia, tachycardia, tachypnea, altered mental status, arterial hypotension, decreased urine output, significant peripheral edema, or positive fluid balance</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Leukocytosis, leukopenia, leukopenia, hyperferritinemia, increased C-reactive protein, pseudohyponatremia, or coagulopathy abnormalities, increased cardiac output, reduced mixed-venous oxygen saturation</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>Hypovolemia, elevated mixed venous oxygen saturation, elevated cardiac index</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Arterial hypoxemia, acute oliguria, increase in creatinine level, elevated international normalized ratio or activated partial thromboplastin time, lactic acidosis, disseminated intravascular coagulation, hypothermia</td>
</tr>
<tr>
<td>Tissue perfusion</td>
<td>Hyperlactatemia, decreased capillary refill, or mottling</td>
</tr>
</tbody>
</table>

Epidemiology of severe sepsis, Florian B Mayr, Sachin Yende, Derek C Angus Virulence Vol. 5, Iss. 1, 2014
Sepsis = "life-threatening organ dysfunction due to a dysregulated host response to infection."

**Organ Dysfunction Criteria**

(At least 2 of these)

- PaO₂/FiO₂ ratio
- Glasgow Coma Scale score
- Mean arterial pressure, mm Hg
- Administration of vasopressors with type/dose/rate of infusion
- Serum creatinine, mg/dL, or urine output, mL/d
- Bilirubin, mg/dL
- Platelet count, 10⁹/L

**Alternative qSOFA approach**

- Respiratory Rate > 22
- Any change in mental status (GCS < 15)

**Implications**

Pre-2016

Infection

Sepsis

Severe Sepsis

Septic Shock
Implications

Infection

Pre-2016

Sepsis

Severe Sepsis

Septic Shock

Infection

Post-2016

Sepsis

Sepsis: Pathogen Profile

Epidemiology of severe sepsis, Florian B Mayr, Sachin Yende, Derek C Angus

Epidemiology of severe sepsis, Florian B Mayr, Sachin Yende, Derek C Angus

Sepsis Source

Site of infection

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Frequency (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Respiratory</td>
<td>41.8</td>
<td>35.8</td>
</tr>
<tr>
<td>Bacteremia, site unspecified</td>
<td>21.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10.3</td>
<td>18.0</td>
</tr>
<tr>
<td>Abdominal</td>
<td>8.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Device-related</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Wound/soft tissue</td>
<td>9.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Others/unspecified</td>
<td>6.7</td>
<td>8.6</td>
</tr>
</tbody>
</table>

- Every hour delay of appropriate antibiotics = 7.6% lower survival

Kill the Infection!!

- Every hour delay of appropriate antibiotics = 7.6% lower survival

---

Pathogenesis:
A Battle of Host vs. Pathogen

<table>
<thead>
<tr>
<th>PAMP Detection by TLRs and Other PRRs</th>
<th>Species</th>
<th>PAMPs</th>
<th>TLR Usage</th>
<th>PRRs Involved in Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria, mycobacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>Bacteria, mycobacteria</td>
<td>LPS</td>
<td>TLR4</td>
<td></td>
</tr>
<tr>
<td>lipoproteins, LTA, PGN, lipomannan</td>
<td>Bacteria, mycobacteria</td>
<td>lipoproteins, LTA, PGN, lipomannan</td>
<td>TLR2/1, TLR2/6</td>
<td>NOD1, NOD2, NALP3, NALP1</td>
</tr>
<tr>
<td>flagellin</td>
<td>Bacteria, mycobacteria</td>
<td>flagellin</td>
<td>TLR5</td>
<td>IPAF, NAIP5</td>
</tr>
<tr>
<td>DNA</td>
<td>Bacteria, mycobacteria</td>
<td>DNA</td>
<td>TLR9</td>
<td>AIM2</td>
</tr>
<tr>
<td>RNA</td>
<td>Bacteria, mycobacteria</td>
<td>RNA</td>
<td>TLR7</td>
<td>NALP3</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>Viruses</td>
<td>DNA</td>
<td>TLR9</td>
<td>AIM2, DAI, IFN-γ</td>
</tr>
<tr>
<td>RNA</td>
<td>Viruses</td>
<td>RNA</td>
<td>TLR3, TLR7, TLR8</td>
<td>NLR1, MDA5, NALP3</td>
</tr>
<tr>
<td>structural protein</td>
<td>Viruses</td>
<td>structural protein</td>
<td>TLR2, TLR4</td>
<td></td>
</tr>
</tbody>
</table>

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A Battle of Host vs. Pathogen

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</thead>
<tbody>
<tr>
<td><strong>Fungus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zymosan, l-glucan</td>
<td>Fungus</td>
<td>zymosan, l-glucan</td>
<td>TLR2, TLR6</td>
<td>Def-1, NALP3</td>
</tr>
<tr>
<td>mannan</td>
<td>Fungus</td>
<td>mannan</td>
<td>TLR2, TLR4</td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td>Fungus</td>
<td>RNA</td>
<td>TLR7</td>
<td></td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-gp1 (Trypanosoma)</td>
<td>Parasites</td>
<td>K-gp1 (Trypanosoma)</td>
<td>TLR2</td>
<td></td>
</tr>
<tr>
<td>glycosphosphatidylinositol (Trypanosoma)</td>
<td>Parasites</td>
<td>glycosphosphatidylinositol (Trypanosoma)</td>
<td>TLR4</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>Parasites</td>
<td>DNA</td>
<td>TLR9</td>
<td></td>
</tr>
<tr>
<td>hemozoin (Plasmodium)</td>
<td>Parasites</td>
<td>hemozoin (Plasmodium)</td>
<td>TLR9</td>
<td>NALP3</td>
</tr>
<tr>
<td>profilin-like molecule (Toxoplasma)</td>
<td>Parasites</td>
<td>profilin-like molecule (Toxoplasma)</td>
<td>TLR11</td>
<td></td>
</tr>
</tbody>
</table>

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Dramatic Changes in Immune System During Sepsis and Related Complications

Treatment Implications of Immune Response?

Hotchkiss et al. Nat Med 2009
Early Immune Suppression

Delayed Treatment with Immune Activators

No Benefit

Investigations Underway
**Summary**

- Sepsis is a leading cause of morbidity and mortality
- Early and effective antibiotic treatment!

**Summary**

- Sepsis is a leading cause of morbidity and mortality
- Sepsis is a leading healthcare cost
- Immune modulation therapies?
Summary

- Sepsis is a leading cause of morbidity and mortality
- Sepsis is a leading healthcare cost
- Early and effective antibiotic treatment!
- Immune modulation therapies?
- Organ failure management

Sepsis

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What is sepsis?

- Sepsis represents a syndrome
  - No 1 diagnostic test
    - Variability in identification
  - Various manifestations at presentation
    - Variability in identification by providers
  - No process to operationalize the definition
    - Variability in incidence and mortality rates

What is sepsis?

- Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection
  - Utilization of SOFA score
    - More defined diagnostic criteria
  - Septic shock: sepsis +
    - Persistent hypotension requiring vasopressors for MAP ≥ 65 mmHg and
    - Serum lactate > 2 mmol/L despite resuscitation
Recognizing Sepsis

- Increase awareness of signs/symptoms among healthcare providers
- Assessment of EMR tools to aid in diagnosis
- Evaluation of Sepsis alerts / rapid response teams
- Increase community awareness of sepsis

MEWS

Modified Early Warning Score (MEWS)
- a single-weighted “risk” score
  - 5 parameters: HR, SBP, RR, Temp, RASS

<table>
<thead>
<tr>
<th>Score</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>&lt;70</td>
<td>71-80</td>
<td>81-100</td>
<td>101-109</td>
<td>≥110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>-</td>
<td>30-40</td>
<td>41-50</td>
<td>51-100</td>
<td>101-110</td>
<td>111-129</td>
<td>≥130</td>
</tr>
<tr>
<td>Respiratory rate (RPM)</td>
<td>-</td>
<td>&lt;9</td>
<td>9-14</td>
<td>15-20</td>
<td>21-29</td>
<td>≥30</td>
<td></td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>-</td>
<td>&lt;95</td>
<td>95-101</td>
<td>101-105</td>
<td>≥101.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>RASS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+1 to 0</td>
<td>-1 to -3</td>
<td>-4</td>
<td>-5</td>
</tr>
</tbody>
</table>

MEWS and sepsis recognition
- Evidenced-based proactive identification for clinical deterioration
- Most adverse events preceded by early warning signs of clinical instability
  - MEWS shown predictive
    - ICU admission within 72hrs, ERT call within 72hrs, cardiac arrest, hospital mortality
- MEWS does not replace Clinical Judgment
- Ongoing research using MEWS for sepsis screening

Treating sepsis

1 Maupin, Janice. AHRQ Health Care Innovations Exchange, Nov. 23, 2011
Within 3 hours of presentation

- Measure lactate
- Obtain blood cultures (ideally prior to antibiotics)
- Administer broad spectrum antibiotics
- Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

Septic shock mortality in relation to time to effective antibiotic from onset of shock

*Assuming 130,000 septic shock cases per year*

<table>
<thead>
<tr>
<th>Time to Effective Antibiotic</th>
<th>Percentage of Patients (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2h</td>
<td>26.8</td>
<td>26.7</td>
</tr>
<tr>
<td>&gt;2-3h</td>
<td>9.0</td>
<td>36.1</td>
</tr>
<tr>
<td>&gt;3-4h</td>
<td>7.8</td>
<td>36.6</td>
</tr>
<tr>
<td>&gt;4-6h</td>
<td>12.8</td>
<td>46.8</td>
</tr>
<tr>
<td>&gt;6-12h</td>
<td>18.8</td>
<td>62.3</td>
</tr>
<tr>
<td>&gt;12h</td>
<td>24.9</td>
<td>83.1</td>
</tr>
</tbody>
</table>

Adapted from Kumar et al. Crit Care Med 2006; 34: 1589-96.

Optimal sepsis treatment

- Utilization of protocolized treatment / sepsis bundle
  - Resuscitation
  - Diagnostic procedures
  - Antimicrobial treatment
  - Source Control
  - Infection Prevention

Surviving Sepsis Campaign. Crit Care Med 2013;41;580
Septic shock mortality in relation to time to effective antibiotic from onset of shock

Adapted from Kumar et al. Crit Care Med 2006; 34: 1589-96.

*Assuming 130,000 septic shock cases per year*

<table>
<thead>
<tr>
<th>Time to Antibiotic (h)</th>
<th>% of Mortality</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2h</td>
<td>26.8</td>
<td>26.8</td>
</tr>
<tr>
<td>&gt;2-3h</td>
<td>36.1</td>
<td>9.0</td>
</tr>
<tr>
<td>&gt;3-6h</td>
<td>36.6</td>
<td>7.8</td>
</tr>
<tr>
<td>&gt;6-12h</td>
<td>46.8</td>
<td>12.8</td>
</tr>
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</tr>
<tr>
<td>&gt;12h</td>
<td>83.1</td>
<td>24.9</td>
</tr>
</tbody>
</table>

By getting shock-to-antibiotic times of <2h for ALL septic shock patients, we would save 32,360 lives per year. (89 people a day) (3.7 people an hour) (3.5 times the effect of STEMI intervention)

Adapted from Kumar et al. Crit Care Med 2006; 34: 1589-96.

Antibiotics and sepsis

- Effective antimicrobials within 1 hour of recognition:
  - Initial empiric anti-infective therapy with ≥ 1 drug with activity against all likely pathogens
  - Daily reassessment for potential de-escalation
    - Consider procalcitonin
  - Combination therapy recommended for:
    - Neutropenic patients
    - History of multidrug resistant organisms

Initial Resuscitation and Sepsis

- CVP 8-12 mmHg
- MAP ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg/hr
- Mixed venous oxygen saturation (Svo₂) ≥ 65%
- SVC ≥ 70%

Surviving Sepsis Campain. Crit Care Med 2013;41;580
Assessment of resuscitation

- **ProCESS trial**
  - Compared Early Goal Directed Therapy protocol to protocolized standard therapy
  - Fluid resuscitation followed by clinical reassessment (no CVP monitoring)
  - No protocolized transfusions
  - No defined inotropic role

**Process Trial**

Usual care was associated with:
- Less PRBC transfusion
- Less dobutamine
- Less overall Vasopressor use

Initial Resuscitation and Sepsis

- Crystalloids as initial fluid of choice (1B)
- Albumin in patients who require substantial amounts of crystalloids (2C)
- Fluid challenge 30ml/kg of crystalloid (1C)

- But that was in 2012…
What is ideal resuscitation fluid

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

JAMA 2012;308:1566

What is ideal resuscitation fluid

Chloride-poor fluids use was associated with:
- Less AKI (OR 0.52 [0.37-0.75] p<0.001)
- Less RRT (OR 0.52 [0.33-0.81] p<0.001)
- No difference in mortality or LOS

Lactated Ringers (109 mEq) or Plasmalyte 148 (98 mEq)
(154 mEq in 0.9 NS & 120 mEq in 4% albumin)

What is ideal resuscitation fluid?

20% albumin versus crystalloid in severe sepsis
- Targeted serum albumin of 30 g/L
- No survival difference at 90 days

NEJM online March 18, 2014

NEJM online March 18, 2014

Within 6 hours of presentation

- Start vasopressors if MAP < 65 mmHg despite IVF
- Re-measure lactate if initial lactate is elevated
- Reassess volume status
  - Focused exam or 2 or more of:
    - CVP
    - ScvO₂
    - Bedside ultrasound
    - Passive leg raise or fluid challenge

Surviving Sepsis Campaign. Crit Care Med 2013:41;580

Sepsis and Vasopressors

- N = 1,679
- MAP < 70 or systolic blood pressure < 100 despite > 1 L crystalloid or > 500 ml colloid and signs of hypoperfusion
- Excluded if on vasopressors for > 4 hr

NEJM 2010;362:799-89

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Norepinephrine</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>50.2%</td>
<td>45.9%</td>
<td>1.19 (0.98 – 1.44)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>59.4%</td>
<td>56.6%</td>
<td>1.12 (0.92 – 1.37)</td>
</tr>
<tr>
<td>6 mo mortality</td>
<td>63.8%</td>
<td>62.9%</td>
<td>1.06 (0.86 – 1.31)</td>
</tr>
<tr>
<td>12 mo mortality</td>
<td>65.9%</td>
<td>63.0%</td>
<td>1.15 (0.91 – 1.46)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressor-free days</td>
<td>12.6</td>
<td>14.2</td>
<td>0.007</td>
</tr>
<tr>
<td>RRT-free days</td>
<td>12.8</td>
<td>14.0</td>
<td>0.07</td>
</tr>
<tr>
<td>ICU-free days</td>
<td>8.1</td>
<td>8.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>24.1%</td>
<td>12.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin ischemia</td>
<td>6.5%</td>
<td>4.1%</td>
<td>0.09</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>2.7%</td>
<td>2.4%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

NEJM 2010;362:799-89

Sepsis and hemodynamic support

- Norepinephrine is vasopressor of choice
- Epinephrine may be added to NE
- Vasopressin 0.03 units/minute may be added to NE
- Trial of Dobutamine in certain cardiac conditions

NEJM 2010;362:799-89
### Lactate and sepsis

- Check upon suspicious for sepsis
  - If elevated monitor for clearance
    - repeat in 4-6 hours
- Predictor of hospital mortality
  - LR 1.4-2 if ≥ 2.5mmol/L; 2.6-6.3 for > 4 mmol/L
  - Early normalization and clearance are predictors of survival (odds ratio 5.2 and 4 respectively)

### Steroids and Sepsis

- Corticosteroids should NOT be given in absence of shock
- Do not use ACTH stim test to determine steroid use
- 200mg/day Hydrocortisone if unable to achieve hemodynamic stability with IVF and vasopressors

### Supportive Phase

- Identify organ failures
- Customize antibiotics based on cultures/sensitivities
- Additional diagnostic testing
- Goals of care discussions
- Limited transfusions
  - Hgb ~ 7, Plt > 20 if bleeding otherwise > 10
  - No routine use of FFP for coagulopathy

### Supportive Phase

- Vent management in ARDS
  - 6ml/kg Vt
  - Plateau Pressure ≤ 30 cm H₂O
  - PEEP
  - Early consider for prone ventilation
  - SBTs
Supportive Phase

- Sedation interruptions (if sedation is needed)
- Glucose $\leq 180$ mg/dL
- NOT using bicarb if pH $\geq 7.15$
- DVT prophylaxis
- Stress ulcer prophylaxis
- Nutrition
- Mobility

Minimize additional harm to patient
Avoid nosocomial complications and new infections!

Clinical Scenario

- Was admitted and started on broad spectrum antibiotics
- Developed ARDS was intubated and underwent prone ventilation
  - Too hypoxic for initial bronchoscopy evaluation
  - Received empiric course of antibiotics and antivirals
  - Was extubated after 12 days
- Discharged to home with physical therapy after 21 hospital days

Summary

- Sepsis is common
- Sepsis is a life threatening organ dysfunction due to dysregulation in host response to infection
- Early recognition is crucial
- Early antibiotics decreases mortality
- A standardized process with re-evaluation is needed
- Norepinephrine is vasopressor of choice
- Prevent further harm