Sepsis: Diagnosis and Treatment

Henry F. Chambers, MD

I have nothing to disclose
In theory
there is no difference
between theory and practice.
In practice, there is.

Scope of the problem

- 2-3 cases per 100 admissions
- A leading cause of death in the US
- Leading immediate cause of death in ICUs
- 1,000,000 cases annually and increasing
- 20-40% mortality
Case 1

- 77 y/o female, h/o prior stroke, lives in LTCF
- Exam
  - T = 38.1, P=105, BP=89/60, RR=20
  - HEENT: limited ROM of neck, poor dentition, PERL
  - Heart: 2/6 sem, irreg rhythm
  - Lungs: poorly cooperative, shallow breathing
  - Abd: guarding, diffusely
  - GU: foley, cloudy urine in foley bag
  - Neuro: altered, nonverbal, R hemiparesis with hand contracture, L gaze preference

Case 1

- What is the appropriate next step(s)?
- Likely source(s) of infection?
- Potential pathogen(s)?
- What antibiotic(s) would you prescribe?
What is Sepsis?

Systemic Inflammatory Response Syndrome (SIRS)

• At least two of the following
  – Temp > 38°C or < 36°C
  – RR > 20 per min or PaCO₂ < 32 torr
  – HR > 90 per min
  – WBC > 12,000 or < 4000 per mm³ or 10% bands
Pop Quiz!

SIRS criteria were developed to identify patients who have an infection.

1. True
2. False

SIRS ≠ Infection !!!

• More general term than “sepsis”
• Infection may or may not be present (e.g. pancreatitis, trauma, burns, liver disease, etc)
  – Note: SIRS may be absent and infection still present
• Described by Dr. William R. Nelson in 1983 as definition which dealt with the multiple etiologies associated with organ dysfunction and failure following circulatory shock.
• Implies systemic inflammation, remote tissue injury
Partial List: Non-infectious Causes of SIRS

- Mesenteric ischemia
- Adrenal insufficiency
- Autoimmune disorders
- Burns (all types)
- Chemical aspiration
- Vasculitis
- Dehydration
- Drug reaction
- Pulmonary embolism
- Trauma
- Surgery
- Erythema multiforme
- Hemorrhagic shock
- Heme malignancy
- MI
- Pancreatitis
- Seizure
- Substance abuse
- TEN
- UGI bleed
- Transfusion

Infection ≠ SIRS

SIRS ≠ Infection: Utility of SIRS criteria in the ED for Identifying Infection

Sensitivity = 0.69
Specificity = 0.35

+LR = Sens/(1-Spec) = 1.06
-LR = (1- Sens)/Spec) = 0.89


Assessment of Clinical Criteria for Predicting Sepsis-Related In-Hospital Mortality


<table>
<thead>
<tr>
<th>Setting</th>
<th>AUROC* (95% CI)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIRS</td>
<td>SOFA</td>
<td>LODS</td>
<td>qSOFA</td>
</tr>
<tr>
<td>ICU</td>
<td>0.64 (0.62-0.66)</td>
<td>0.74 (0.73-0.76)</td>
<td>0.75 (0.73-0.76)</td>
<td>0.66 (0.64-0.68)</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>0.76 (0.75-0.77)</td>
<td>0.79 (0.78-0.80)</td>
<td>0.81 (0.80-0.82)</td>
<td>0.81 (0.80-0.82)</td>
</tr>
</tbody>
</table>

*Area under the Receiver Operating Characteristic Curve
SOFA = Sequential Organ Function Assessment;
LODS = Logistic Organ Dysfunction System

NOTE: NONE USEFUL FOR PREDICTING INFECTION AS ALL ASSUMED TO BE INFECTED

AUROCs for Predictors of Sepsis Mortality

### New Sepsis Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>1991 and 2001 Definitions</th>
<th>2015 Definition</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Suspected or documented infection + SIRS &gt; 2 points</td>
<td>Life-threatening organ dysfx from dysregulated host response to infection</td>
<td>Suspected or documented infection + acute increase in SOFA &gt; 2 points</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis + hypotension, hypopertusion, organ dysfx</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Severe sepsis + hypotension unresponsive to fluids</td>
<td>Sepsis + major circulatory/metabolic/cellular abnormalities</td>
<td>Sepsis + pressor to keep MAP &gt; 65 + lactate &gt; 2 mmol/L after fluids</td>
</tr>
</tbody>
</table>
# SOFA Scorecard

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Resp: PaO2/FiO2</td>
<td>&gt; 400</td>
</tr>
<tr>
<td>Coag: Platelets</td>
<td>≥ 150</td>
</tr>
<tr>
<td>Liver: Bilirubin</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Cardiovascular: MAP</td>
<td>≥ 70</td>
</tr>
<tr>
<td>CNS: GCS</td>
<td>15</td>
</tr>
<tr>
<td>Renal: Creatinine</td>
<td>&lt; 1.2</td>
</tr>
<tr>
<td>Urine output</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

# Glasgow Coma Score

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Opens to verbal command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Opens to pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Verbal</td>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused conversation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Motor</td>
<td>Obey commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Purposeful movement to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Withdraws from pain</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Decorticate posture to pain</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Decerebrate posture to pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>
**SOFA Calculator**

http://clincalc.com/IcuMortality/SOFA.aspx

**qSOFA**

- Criteria (1 point for each)
  - Altered mental status
  - Respiratory rate ≥ 22 per minute
  - Systolic BP ≤ 100 mm Hg
- Score ≥ 2 associated with 3-14 fold increase in-hospital mortality for patients with suspected infection
### qSOFA Glasgow Coma Scoring

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<th>Score</th>
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<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Motor</td>
<td>Obeys commands</td>
<td>6</td>
</tr>
</tbody>
</table>

Altered mentation unless all of above are present

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**Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department**

JAMA 317:301, 2017
Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit

JAMA 317:290, 2017


Diagnosis of Sepsis

- Clinical diagnosis
- Blood cultures positive in 20-30% of cases
- Focus of infection never identified in a quarter of cases

Sources of Sepsis

- Urinary tract: 33%
- *Intraabdominal: 15%
- *Lung: 10%
- Skin, soft tissue: 10%
- Unknown: 30%

*Major sources in patients with severe sepsis and septic shock
Approach to the Patients with Suspected Infection

Work-up of Infection

• History
  – Fever, chills, sweats, localizing symptoms, ROS
  – Exposures, occupations, surgeries
  – Medications
• Physical Exam: Vital signs, focused at first
• Labs
  – CBC: WBC >12,000 or <4,000, ≥ 10% bands
  – As appropriate
    • CXR, urinalysis/culture
    • electrolytes, metabolic, liver panel, lactate
    • LP, other imaging
    • Blood and other cultures before antibiotics
Biomarkers for Sepsis: Procalcitonin as an Example

Meta-Analysis of Procalcitonin as a Biomarker for Sepsis

Sensitivity = 0.77  
(95% CI 0.72-0.81)

Specificity = 0.79  
(95% CI 0.74-0.84)

ROC-AUCs for Prediction of Infection

LBP = lipopolysaccharide binding protein
PCT = procalcitonin
CRP = C-reactive protein
IPS = Infection probability score


Risk Factors for Poor Outcome

• Age
• Underlying disease
• APACHE II score
• Shock vs. no shock
• Appropriate vs inappropriate antibiotics
Life-Saving Power of Antibiotics in Sepsis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>OR</th>
<th>NNT to prevent 1 death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA for MI</td>
<td>1.30</td>
<td>41</td>
</tr>
<tr>
<td>Low MW heparin</td>
<td>1.16</td>
<td>63</td>
</tr>
<tr>
<td>Appropriate antibiotics by 48h</td>
<td>1.6</td>
<td>10</td>
</tr>
</tbody>
</table>


Factors to Consider in Antibiotic Selection

- Community vs. Hospital Onset
- Healthcare associated
- Immune status, comorbidities
- Prior antibiotics
- Neutropenia
- Site of infection
### Bacteria that Can Kill Quickly

<table>
<thead>
<tr>
<th>Organism</th>
<th>Drug(s) of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococcus</td>
<td>Penicillin</td>
</tr>
<tr>
<td><em>E. coli</em>, gram-neg rods</td>
<td>Beta-lactam or FQ*</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Nafcillin or vanco</td>
</tr>
<tr>
<td>Group A strep</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Penicillin or ceftriaxone</td>
</tr>
<tr>
<td>Rickettsia (RMSF)</td>
<td>Doxycycline</td>
</tr>
</tbody>
</table>

### Microbiology of Sepsis

- **Gram-negatives**
  - *E. coli*, *Klebsiella* sp., enterics: 65%
  - Resistant GNR: 20%
  - Mixed/anaerobic: 15%
- **Gram-positives**
  - *S. aureus*: 50-75%
  - Streptococci: 25%
- **Other**: Candida, viral
Possible Empirical Regimens for Sepsis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Holes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone 1-2 g qd</td>
<td>MRSA, enterococcus, pseudomonas, ESBL/carbapenemase producers, <em>B. fragilis</em>, atypicals</td>
</tr>
<tr>
<td>Cefepime 2g q8-12h</td>
<td>MRSA, enterococcus, some ESBL producers, carbapenemase producers, <em>B. fragilis</em>, atypicals</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>MRSA, carbapenemase producers, atypicals</td>
</tr>
<tr>
<td>Pip/tazo 4.5 g q8h</td>
<td>MRSA, ESBL/carbapenemase producers, atypicals</td>
</tr>
<tr>
<td>Vanco 1-2 g q12 + cipro 400 mg q8-12</td>
<td>Anaerobes (Gram-neg), FQ-resistant GNRs</td>
</tr>
</tbody>
</table>

Add ons: vanco, clindamycin, metronidazole, FQ, aminoglycoside

Empirical Therapy

- **Urosepsis**: FQ; 3rd gen cephalosporin, carbapenem; aminoglycoside
- **Intra-abdominal**: pip/tazo; FQ or 3rd gen ceph + metronidazole; carbapenem
- **SSTI**: vancomycin + 3rd gen ceph or pip/tazo or carbapenem or FQ + clindamycin
- **Community-acquired pneumonia**: ceftriaxone + macrolide or doxy, FQ (vancomycin?)

*Gram-neg and anaerobic coverage for necrotizing infections, severe sepsis*
Therapy of Sepsis

- Support breathing
- Support blood pressure (norepi is pressor of 1st choice if needed) and perfusion (crystalloid)
- Administer antibiotics (goal of 1-3 h)
- Anticipate and manage complications
- Source control

Surviving Sepsis Campaign Bundles

- Within 3 hours of presentation
  - Measure lactate
  - Blood (and other) cultures before antibiotics
  - Administer broad spectrum antibiotics (target 1h)
  - Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
- Within 6 hours
  - Pressors to keep MAP ≥ 65 mm Hg
  - If persistent hypotension after fluid or if lactate ≥ 4, reassess volume status and perfusion (VS, capillary refill, repeat lactate if > 2 etc)

http://www.survivingsepsis.org/About-SSC/Pages/default.aspx
Antimicrobial Therapy

• Initial broad coverage for likely pathogens within 1-3 h, taking into account
  – Severity of illness
  – Host factors (age, comorbidities, immunocompromise, IVDU, etc)
  – Possibility of resistant organisms (e.g., HCA)
• Combination therapy: neutropenia, MDR Gram-negatives, Pseudomonas bacteremia
• De-escalate when possible, treat 7-10 days?
• D/C antibiotics after 3-5 days if no infection (procalcitonin useful here?)
• SOURCE CONTROL!!!!!
Effect of Time on Outcome

Seymour, et al. NEJM 376:2235, 2017

Effect of Time on Outcome

Seymour, et al. NEJM 376:2235, 2017
**Initial Management**

Likely: having a high probability of occurring or being true; very probable

Probable: supported by evidence strong enough to establish presumption but not proof

- Find the source of infection and eliminate it

**Pathogenesis of Sepsis**

- Overstimulated immune system
  - “Cytokine storm” hypothesis
- Dysfunctional immune system
  - Phasic illness
    - Early: Inflammatory response
    - Late: Immunosuppression
Dynamic View of Sepsis

Parrillo, NEJM 328:1471, 1993
Adjunctive Therapies

- **Steroids**
  - Venkatesh. NEJM, Jan 19, 2018 DOI: 10.1056/NEJMoa1705835
  - Hydrocortisone dose 200 mg/d
  - No mortality benefit, no MV benefit
  - May reduce duration of shock by about a day
- **IVIG**: not recommended
- **Glucose control**: 140-180 mg/dl
- **No HCO3**: for pH > 7.15*
- **Establish goals of care!**

* weak recommendation

Case 2

• 27 y/o female, h/o UTIs, most recent episode one month ago treated with cipro
• Presents with N, V, abdominal pain
• T = 38.1, P=98, BP=119/64, RR=18, 98% sat (RA)
• EXAM: RLQ, R flank tenderness to palpation
• CBC: WBC 15,900, Serum Cr 1.7
• UA: 50-100 WBCs, Urine Gram stain: GNRs
• CT-abd: R hydrenephrosis, bilateral kidney stones

Case 2: Management

• You order blood cultures and IV fluids
• What would you do next?
  1. Start ceftriaxone IV, urgent urology consultation
  2. Start levofloxacin IV, urgent urology consultation
  3. Start vancomycin + pip/tazo, urgent urology consultation
  4. Start ertapenem, urgent urology consultation
  5. Start vancomycin + ertapenem, urology consultation the next morning
Key References

- JAMA 315:762, 2016: Assessment of SOFA and qSOFA as predictors of mortality in sepsis
- JAMA 315:801, 2016: New definitions for sepsis, septic shock
- JAMA 315:775, 2016: Definition, clinical criteria for septic shock
- JAMA 315:739, 747,757, 2016: Editorials pertaining to above
- JAMA 314:708, 2015: Review of septic shock Dx and Rx
- Critical Care Medicine March 2017, Vol 45 No 3: