Who is the best Batman?

A: Adam West
B: Michael Keaton
C: Val Kilmer
D: George Clooney
E: Christian Bale
F: Ben Affleck
OBJECTIVES

• Briefly review the host innate response
• Tie in the innate response to the introduction of infection
• Introduce the pathophysiology of sepsis
• Discuss the challenges of therapeutic interventions directed at sepsis
• Explain current definitions of SIRS & sepsis
• Explain our best current treatment for sepsis and septic shock referencing the “Sepsis Alert”
Cytokine Initiation

- Microbes stimulate nearby macrophages
- TNF, IL-1, IL-6 and some chemokines released
- The “clinical” systemic inflammatory response syndrome (SIRS)* is initiated
- How significant the disease burden is depends on inflammatory response.

* SIRS (Systemic Inflammatory Response Syndrome) is a pattern of clinical response characterized by the onset of systemic inflammation as a response to an acute stimulus.
TNF-α Explosion

“Friendly Fire”

Low quantities (plasma conc. <10^{-9} M)
- Local inflammation
  - Endothelial cell
    - Adhesion molecule
    - IL-1, chemokines
  - Leukocyte
    - Activation

Moderate quantities
- Systemic effects
  - Brain
    - Fever
  - Liver
    - Acute phase proteins
  - Bone marrow
    - Leukocytes

High quantities (plasma conc. ≥10^{-7} M)
- Septic shock
  - Heart
    - Low output
  - Blood vessel
    - Thrombus
    - Low resistance
  - Liver
    - Hypoglycemia
Stuff that IL-1, IL-6, and TNF-α does

- Fever, hypothermia (worse)
- Release of acute-phase reactants
- Endothelial activation
- Complement activation
- Depression of cardiac contractility
- Further cytokine cascade
- Impairment of protein C anticoagulation pathway → DIC
- Direct and indirect causes of multi-organ dysfunction syndrome (MODS)
Metabolic Abnormalities

• Mainly hyperglycemia (treating glucose <180 = better)

• Promotion of gluconeogenesis
  – Endogenous glucagon
  – Increased catecholamines
  – Increased glucocorticoids (increased adrenal response)

• Rarely, the adrenal glands can undergo dysfunction, and adrenal insufficiency results
  – Hypoglycemia; must give back glucocorticoids
Endothelial Cell Activation & Injury

- Microbial components & inflammatory mediators contribute:
  - 3 major consequences
    - Thrombosis
    - Increased vascular permeability
    - Vasodilatation
- Leads to tachycardia, then hypotension
- Potentially DIC; ischemia of end-organs
Let’s treat this inflammatory response!
Let’s Treat the Sepsis Response!

• DIC major cause of morbidity/mortality in sepsis, the result of impairment of the protein C anticoagulation pathway
  – Drotrecogin alfa (Xigris): recombinant activated protein C
    • Withdrawn from market **October 2011**

• Ok then, let’s “block” TNF-α since it causes all these problems...
  – Give antibiotics to kill the bugs, give TNF-α “blockers” to blunt the host response – GENIUS!
    • Clinical trials showed patients on IL-1 antagonists and TNF-α antagonists had **higher** rates of prolonged sepsis and **higher** mortality.

• Other attempts at blocking host response unsuccessful.
Darn

Maybe we shouldn’t try to block the host’s pro-inflammatory response
• No current reliable way to control the inflammatory response to sepsis

• Treatment now guided towards:
  – Early recognition
  – Appropriate antibiotic therapy
  – Hemodynamic support to prevent end-organ injury

• “Weather the cytokine storm”
Clinical Definitions
Early Recognition: “SIRS criteria”

- Temperature > 38.0° C or < 36.0° C
- Heart rate > 90
- Respiratory rate > 20 or PaCO$_2$ < 32 mmHg
- WBC count > 12,000, < 4,000, or > 10% immature (band) forms

- At least 2 of the 4 above criteria to meet “SIRS”
Sepsis

• “SIRS criteria” + a suspected source
  – Bacteremia
  – Pneumonia
  – Urinary tract infection
  – Intra-abdominal infection
  – Cellulitis
  – Meningitis
  – UNKNOWN = 10-25%

SIRS & Sepsis

- Bacteria
- Infection
- Sepsis
- SIRS
- Fungi
- Parasites
- Viruses
- Other
- Trauma
- Burns
- Pancreatitis
- Blood born infection
Severe Sepsis

- Sepsis and SIRS associated with organ dysfunction
  - +/- Hypotension
  - Hypoperfusion (usually)
    - Kidney failure; low urine output
    - Altered mental status
    - Lactic acidosis
    - Lack of blood flow or volume sufficient for delivery of oxygen and nutrients to tissues and end organs.

- Severe sepsis can often be managed on the floor
Septic Shock

- Essentially a high degree of severe sepsis
- Persistent symptoms of severe sepsis (namely hypotension) despite initial fluid resuscitation $\approx 4-6 \text{ L}$?
- Requiring vasopressors = septic shock

- Septic shock managed in ICU (unless comfort care)
Multi-Organ Dysfunction Syndrome

• Multiple end-organs affected by sepsis
  – 2 or more for official “MODS” status
  – Mortality increases with number of involved organs
• Altered mental status
• Respiratory failure / ARDS (acute respiratory distress syndrome)
• Acute renal failure
• Cardiovascular collapse
• Liver failure
• GI dysfunction: ileus, breakdown in barrier function
• DIC (Disseminated intravascular coagulopathy)
• Adrenal insufficiency
Lactate

- Product of **anaerobic** metabolism
  - Marker of poorly perfused tissues/organs
  - Can cause elevated respiratory rate

- ↑ Lactate does NOT automatically mean “sepsis”
  - Dehydration
  - Liver Failure
  - Other “non-septic” shock
  - Medications (metformin)
  - Hemolyzed blood sample
Blood Cultures

• Ideally, 2 sets of blood cultures obtained from two different peripheral veins
• Obtain prior to antibiotics to guide therapy
  – “pre-treated” cultures can mask a bacteremia and make decision for antibiotics and duration of therapy difficult
• Culture other stuff quickly if you can
  – Urine, sputum, wound, abscess, CSF, ascites

This is 1 “set” of cultures (2 bottles, 1 anaerobic, 1 aerobic). In adults, we typically get “2 sets” or 4 total bottles; in children, we usually get 1 set
Treatment

• Antibiotics
  – The earlier, the better the outcomes
  – Choice dependent on several factors
    • Suspected source of infection
    • Severity of illness
    • Immunosuppression; recent hospitalization

• “Early Goal-Directed Therapy”
  – Adjustments of the cardiovascular system to try and balance oxygen delivery with oxygen demand
  – Shown to significantly reduce mortality in severe sepsis and septic shock
Hemodynamic Support

• “Isotonic crystalloid”
  – Normal [0.9% NaCl] saline (NS)
  – Lactated Ringers (LR)
• Colloid fluids not shown to be any better
• Most patients with sepsis should get a trial of at least 2-4 liters of initial volume resuscitation “30 mL/kg” (bolused)
  – If it doesn’t work, it might be time for vasopressors
• Septic shock may require up to 10-12 L in first 24 hours
Later stages of sepsis

• They get better, OR...

• Lots of potential complications (try to prevent)
  – New infection
  – Clotting events: MI, PE, DVT
  – Side effects of treatment
  – Profound weakness (PT/OT, activity important)

• Weakened immune response immediately after the innate, pro-inflammatory response
  – Depressed cytokines?
  – Large area of study
A 67-year-old man presents to clinic with cough and shortness of breath. V/S: T 38.2°C, HR 104, RR 18, BP 132/76, SpO₂ 91% on room air. Exam reveals inspiratory and expiratory crackles over the right lower lobe. Lactate is 1.5. What clinical classification is most accurate for this patient’s presentation?

A. SIRS  
B. Sepsis  
C. Severe sepsis  
D. Septic shock

<table>
<thead>
<tr>
<th>CBC w/differential</th>
<th>VALUE</th>
<th>NORMAL RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>12.6</td>
<td>3.2 – 10.6 K/µL</td>
</tr>
<tr>
<td>% neutrophils</td>
<td>70</td>
<td>44 – 76 %</td>
</tr>
<tr>
<td>% bands</td>
<td>11</td>
<td>3 – 5 %</td>
</tr>
<tr>
<td>% lymphocytes</td>
<td>13</td>
<td>15 – 43 %</td>
</tr>
<tr>
<td>% monocytes</td>
<td>4</td>
<td>4.0 – 8.9 %</td>
</tr>
<tr>
<td>% eosinophils</td>
<td>2</td>
<td>0 – 6 %</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>15.1</td>
<td>14.6 – 17.8 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>45.5</td>
<td>40.8 – 51.9 %</td>
</tr>
<tr>
<td>Platelets</td>
<td>396</td>
<td>177 – 406 K/µL</td>
</tr>
</tbody>
</table>
A 67-year-old man presents to clinic with cough and shortness of breath. V/S: T 38.2°, HR 104, RR 18, BP 132/76, SpO₂ 91% on room air. Exam reveals inspiratory and expiratory crackles over the right lower lobe. Lactate is 1.5. What clinical classification is most accurate for this patient’s presentation?

A. SIRS
B. Sepsis (due to pneumonia)
C. Severe sepsis
D. Septic shock
A 28-year-old woman is admitted for a recurrent bout of alcoholic pancreatitis. V/S: T 37.4°, HR 134, RR 28, BP 132/76, SpO₂ 91% on room air. Labs show an elevated lipase. Lactate is 2.5. What clinical classification is most accurate for this patient’s presentation?

A. SIRS
B. Sepsis
C. Severe sepsis
D. Septic shock
A 28-year-old woman is admitted for a recurrent bout of alcoholic pancreatitis. V/S: T 37.4°, HR 134, RR 28, BP 132/76, SpO₂ 91% on room air. Labs show an elevated lipase. Lactate is 2.5. What clinical classification is most accurate for this patient’s presentation?

A. SIRS (from pancreatitis)
B. Sepsis
C. Severe sepsis
D. Septic shock
18-year-old girl presents with 2 days of malaise, but in the last 24 hours, vomiting, and a blanching rash on her hands and feet. Vital signs show T 39.4° C, HR 132, RR 26, BP 86/48
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Lactate is 3.5 and she has a creatinine of 2.35. How should this presentation be classified at this point?

A. SIRS
B. Sepsis
C. Severe sepsis
D. Septic shock
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Lactate is 3.5 and she has a creatinine of 2.35. How should this presentation be classified at this point?

A. SIRS
B. Sepsis
C. Severe sepsis (elevated lactate + end-organ dysfunction [kidneys])
D. Septic shock – this is incorrect because there is no mention of attempted fluid resuscitation yet
“Newer” Sepsis Recognition: SOFA

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3 (26.7) with respiratory support</th>
<th>4 (13.3) with respiratory support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg (kPa)</td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200</td>
<td>&lt;100 (13.3)</td>
<td></td>
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<tr>
<td>Coagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Platelets, ×10³/µL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
<td></td>
<td></td>
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<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (µmol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
<td>&gt;5.0 (440)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FiO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen. Catecholamine doses are given as µg/kg/min for at least 1 hour. Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Adapted from Vincent et al.²⁷
qSOFA – “quick SOFA”

• Sequential [Sepsis-related] Organ Failure Assessment

• Respiratory rate ≥ 22
• Altered mentation (GCS < 15)
• Systolic blood pressure ≤ 100 mmHg

• 2 of 3 of these criteria suggest 10% higher mortality
Severe Sepsis Alert Tip Sheet - Acute Nursing

Content Owner: Jan Orton  Last Modified: 8/23/2016 5:07 PM

Sepsis Alerting in iCentra

Why do we have Sepsis alerting?
Sepsis affects nearly 750,000 Americans annually resulting in a mortality rate of 28.6%. Each case of Sepsis extends the patient length of stay by an average of 11 days. Early goal-directed therapy and the Surviving Sepsis Campaign have demonstrated and promoted best practices for management of sepsis patients. Mortality from sepsis has fallen accordingly from at least 30% prior to 2010 to below 20% in 2014. Intermountain has reduced our mortality over the last 10 years by over 50%. Building upon the national and local experiences, we seek early detection of sepsis patients. Cerner has validated a sepsis alert algorithm, and it is in use at institutions across the country and the world.

What data will trigger a sepsis alert?

Two or more criteria for SIRS (Systemic Inflammatory Response Syndrome)

- Glucose Level between 140 & 200
- Heart Rate ≥ 95
- Temperature ≤ 36 or ≥ 38.5
- Respiratory Rate ≥ 22
- WBC ≤ 4.0 or ≥ 12
- Band Man ≥ 10

AND

One or more indicators of organ dysfunction:

- SBP ≤ 90
- MAP ≤ 65
- Bilirubin Total between 2 and 10
- Lactic Acid Level ≥ 2
- Creatinine increase > 0.5 over last 72 hours

Severe Sepsis Alert Suppression Criteria

12 hours suppression

- Infection not suspected at this time
- Continue Monitoring, Reassess Vital Signs Q2, Reassess as needed
- Physician/LIP notified
- Will begin sepsis treatment per orders/protocol
- RRT/MET notified

24 hour suppression

- Continue Sepsis Treatment per orders/protocol

72 hour suppression

Sepsis PowerPlans (will suppress the Sepsis Alert for 72 Hours if Initiated)
Thank You!