What’s New With Sepsis?

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Clinical Pharmacy Manager
Central Washington Hospital
Confluence Health
Objectives

- Cover some basic microbiology
- Understand the new and old definitions of sepsis and septic shock
- Recognize the clinical characteristics of a patient with sepsis
- Be able to perform a qSOFA score
- Determine the appropriate management of a patient with sepsis
Microbiology: Bacteria Basics

- Single-cell microscopic organisms
- Consume nutrients from environment → grow to double their size and divide
- DNA is circular and shared regularly
- 1 trillion human cells make up your body along with 10 trillion bacterial cells
- 100 times as many bacterial genes
- Digest your food, produce vitamins, protect you
Classification

- Morphology
  - Cocci vs. bacilli vs. coccobaccili
- Gram Stain
- Growth Requirements (aerobic vs. anaerobic)
- Biochemical Reactions (lactose fermentation)
- Serotypes (streptococcus group A vs. B. vs. D)
- Antibiotic Resistance Patterns (MSSA vs. MRSA)
The Gram Stain
Normal Flora

- Skin - *Staphylococcus* spp. and *Streptococcus* spp. *Corynebacterium* spp.
- Oropharynx - Streptococci-viridans group, Neisseria (-), *Haemophilus* (coccobacilli)
- Genital tract - *Staphylococcus* spp. and *Streptococcus* spp. Enterobacteriaceae (*E. coli, Klebsiella*)
Immune System

- Physical/Chemical Barriers
  - Skin, tears, sweat, mucus, cilia, stomach acid
- Innate Immune System
  - Immediate, non-specific response
  - Inflammation (redness, swelling, heat)
  - Phagocytes
    - Macrophages, neutrophils, dendritic cells, natural killer cells
- Passive Immunity
  - Antibodies passed from mom to baby through breast milk
  - Artificial (Intravenous Immune Globulin IVIG)
  - Treatment of Ebola Virus Infection with Antibodies from Reconvalescent Donors
- Active Immunity or Adaptive
  - Production of antibodies directed against specific pathogen
  - Starts with innate immune system
  - Principle behind immunization
Antibiotic Resistance

- Selection Pressure (Darwinian)
- Spontaneous Mutation with Vertical Gene Transfer
- Horizontal Gene Transfer
- Transformation
  - Bacteria die and DNA is taken up by bacteria from external environment
    - Altered PBP
- Conjugation
  - Bacteria Sex, even other species
    - Sharing of plasmid DNA
  - Thought to be primary mechanism of bacterial resistance
- Transduction
  - Bacteriophages transfer DNA between two closely-related bacteria
Mechanisms of Antibiotic Resistance

Altered binding site

http://textbookofbacteriology.net/resantimicrobial_3.html
The New Mantra: Shorter is Better

- Almost all serious infections now have data to support short course antibiotic therapy
- This decreases the amount of resistant pathogens produced
Multi-Drug Resistant Organisms

- Methicillin Resistant *Staphylococcus Aureus* (MRSA)
- Vancomycin Resistant *Enterococcus* (VRE)
- Extended Spectrum Beta-Lactamase (ESBL)
- *Klebsiella* producing carbapenemase (KPC)
Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>MIC Dilutn</th>
<th>MIC Interp</th>
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<tr>
<td>Methicillin Resistant Staphylococcus aureus</td>
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<td>S</td>
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# Central Washington Hospital Antibiogram

## Escherichia coli
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<thead>
<tr>
<th># Isolates</th>
<th>Am</th>
<th>Ampicillin</th>
<th>Ampicillin/sulbactam</th>
<th>A/S</th>
<th>Aug</th>
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## Klebsiella pneumoniae
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Some quick terminology

- Leukocytosis: WBC >12,000 cells/ml
- Leukopenia: WBC <4,000 cells/ml
- Bandemia (AKA left shift)
  - Bands (AKA “stabs”) >10%
- Bacteremia
  - Presence of bacteria in blood culture
- Fungemia
  - Presence of fungus in blood culture
The 5 W’s

- Wind
- Walk
- Wound
- Whiz
- Wonder Drugs
Noninfectious Causes

- Central fevers
  - Stroke, intracranial bleed, severe head trauma
- Post-operative fevers
- Drug induced fevers
  - Malignant hyperthermia
  - Neuroleptic malignant syndrome
  - Immune/inflammatory reactions
Infectious Causes of Fever

- Surgical site infections
- Central nervous system infections
- Urinary catheter related infection
- *Clostridium difficile* infection (CDI)
- Intravascular line infections
- Ventilator associated pneumonia
- Sepsis
Sepsis
Sepsis: What is it?

How do you define sepsis?
Sepsis Definitions

- 1991 Definition (Sepsis I): Focus on inflammatory response of the host immune system
- 2001 (Sepsis II): Sepsis Task Force had recognized some of the limitations of the definition but didn’t change definition
The new and improved(?) sepsis definition

- **Sepsis is now defined as** life-threatening organ dysfunction caused by a dysregulated host response to infection
- **Septic Shock**: persistent hypotension requiring vasopressors to maintain MAP $\geq 65$ mmHg AND having a serum lactate level $> 2$ mmol/L despite adequate volume resuscitation
  - Mortality in excess of 40%
Old Definition: SIRS Criteria

<table>
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<tr>
<th>Two or more of the following</th>
<th>Temp</th>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>CBC</th>
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<tr>
<td></td>
<td>&gt;38.3°C</td>
<td>HR &gt;90</td>
<td>RR &gt;20</td>
<td>WBC &gt;12,000</td>
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<tr>
<td></td>
<td>&lt;36°C</td>
<td>SBP &lt;90</td>
<td>PaCO₂&lt;32</td>
<td>WBC &lt;4,000</td>
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<tr>
<td>Not explainable through other diagnosis</td>
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+ Attributed to an infectious source
Sepsis, Severe Sepsis and Septic Shock

- **Sepsis** = SIRS + infection

- **Severe Sepsis** = sepsis-induced hypoperfusion or organ dysfunction

- **Septic Shock** = sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia
But What is Sepsis?

- Dysregulated host response
  - Cytokines wreak havoc on the body
- Imbalance between oxygen delivery and demand
  - Hypovolemia, decreased vasomotor tone, decreased arterial oxygen content, myocardial depression, increased metabolic demands, impairment of oxygen utilization
- Critical decrease in systemic oxygen delivery followed by increase in systemic oxygen extraction ratio → $\text{ScVO}_2$ ↓
Sepsis Pathobiology

Shock Syndromes Related to Sepsis
What Causes Sepsis?
Underlying Infection: Source

- Underlying Infection: Source
  - Pneumonia
    - Most common cause of sepsis ~ 50%
  - Intra-abdominal infection
  - Urinary tract infection

- Cultures
  - Blood, urine, pleural fluid, abscess fluid
  - Ideally before abx, as long as they don’t delay the administration

Andrew Rhodes, MB BS, MD(Res) (Co-chair); Laura E. Evans, MD, MSc, FCCM (Co-chair); Walied Alhazzani, MD, MSc, FRCP (methodology chair); Mitchell M. Levy, MD, MCCM; Massimo Antonelli, MD; Ricard Ferrer, MD, PhD; Anand Kumar, MD, FCCM; Jonathan E. Sevransky, MD, FCCM; Charles L. Sprung, MD, JD, MCCM; Mark E. Nunnally, MD, FCCM; Bram Rochwerg, MD, MSc (Epi); Gordon D. Rubenfeld, MD (conflict of interest chair); Derek C. Angus, MD, MPH, MCCM; Djillali Annane, MD; Richard J. Beale, MD, MB BS; Geoffrey J. Bellinghan, MRCP; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD; Craig Coopersmith, MD, FACS, FCCM; Daniel P. De Backer, MD, PhD; Craig J. French, MB BS; Seitaro Fujiwara, MD; Haruia Carlsoh, MPA, MD, PhD; Jorge Luis Hidalgo, MD, MACP, MCCM.
2016 Surviving Sepsis Guidelines and JAMA series

- 31 Endorsing societies
  - NOT American College of Chest Physicians, American College of Emergency Physicians
- Differentiated sepsis from an uncomplicated infection
- Updated definitions
- Identify clinical criteria for identifying all the components of sepsis
  - Infection, Host Response, Organ Dysfunction
- Called out the lack of a validated diagnostic tests leading to variability in incidence and mortality rates
- Better reproducibility of studies (including epidemiological)
Quick –sofa (qSOFA): Bedside Measurement

Hypotension
Systolic BP
<100 mmHg

Altered
Mental
Status

Tachypnea
RR >22/Min

Score of 22 Criteria Suggests a Greater Risk of a Poor Outcome

http://rebelem.com/sepsis-3-0/
### Sequential Organ Failure Assessment: SOFA

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<tr>
<th>Organ system</th>
<th>Score</th>
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<tr>
<td>Respiratory: PaO₂/FiO₂</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Renal: Creatinine (mg/dl)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Hepatic: Bilirubin (mg/dl)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Cardiovascular: Hypotension</td>
<td>No hypotension</td>
</tr>
<tr>
<td>Hematologic: Platelet count (10⁹/mcL)</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Neurologic: Glasgow coma scale score</td>
<td>15</td>
</tr>
</tbody>
</table>

Adrenergic agents administered for at least 1 h (doses given are in μg/kg/min). FiO₂ = Fractional inspired oxygen, MAP = Mean arterial pressure, PaO₂ = Arterial oxygen tension, SOFA = Sequential organ failure assessment.
Patient with Suspected Infection

qSOFA ≥ 2? NO

Assess for Evidence of Organ Dysfunction

SOFA ≥ 2? NO

Sepsis Still Suspected?

YES Monitor Clinical Condition; Reevaluate for Possible Sepsis if Clinically Indicated

NO

YES

NO

Despite Adequate Fluid Resuscitation:
1. Vasopressors Required to Maintain MAP ≥ 65mmHg AND
2. Serum Lactate Level > 2mmol/L?

YES

Septic Shock
Management of Sepsis (nutshell)

- Fluid resuscitation
  - Crystalloids or colloids IV
  - 30 ml/kg for shock patients

- Vasopressors
  - Norepinephrine +/- Vasopressin targeting a Mean Arterial Pressure ≥ 65mmHg

- Corticosteroids
  - Consider if fluid and vasopressors not effective
  - Doses ≤ 300mg hydrocortisone/day
Empiric Antibiotics

- Within 1hr of sepsis diagnosis
  - ↑ mortality 7.6%/hr without abx
- Suspected infectious etiology
  - Community, healthcare, nosocomial (hospital) acquired
  - Source control → surgery?
- Bacterial sensitivities
  - Local Antibiogram
  - Prior antibiotic classes utilized
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

ABSTRACT

Background  Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods  We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment.

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock. Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock. An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death. The transition to serious illness occurs during the critical “golden hours,” when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may
Early Goal-Directed Therapy

- Single Center Study showing decreased mortality with EGDT
- Systematic Approach (like for an AMI)
- Involved placement of CVC and monitoring of ScVO$_2$ and CVP
  - Guided use of IV fluids, vasopressors, inotropes and PRBC
- CVP < 8 = fluids
- CVP 8 but MAP < 65 mmHg = vasoactives
- CVP 8 but MAP < 65 mmHg and ScVO$_2$ < 70% = PRBC
Early Goal-Directed Therapy

- Became standard of care for severe sepsis
- Prompted “Think Sepsis” and give Abx and Fluids early
- Now under scrutiny
  - Dobutamine ≠ improved microvascular perfusion in septic shock
  - Transfusion to Hct 30% appears harmful
  - Lactate can probably be used as effectively as invasive ScVO$_2$ to assess perfusion
Fluid and Multiple Organ Failure

Adapted from: Benes, J et al. Fluid Therapy: Double-Edged Sword during Critical Care? BioMed Research International. 2015. Figure 3.
Fluid Resuscitation in Sepsis

Antibiotic Management

- Reassess daily
  - Reduce toxicity, costs, prevent resistance
- Combination therapy
  - (Think resistant gram negatives)
    - Known or suspected *pseudomonas*
    - Neutropenic patients
    - At most 3-5 days
- Total duration 7-10 days
- Slow improvement → longer courses
Controversies

- Will redefining sepsis improve patient care?
- Subjectivity: “suspected infection”
  Infection is in the differential for many workups
- SOFA designed to predict mortality in all critically ill patients, not designed to define sepsis
- Discrepancy between CURB-65 and qSOFA
Take Homes

- Sepsis is still sepsis
- qSOFA is the new bedside tool for assessment
- We are better at treating sepsis, but we still have a lot to learn about the distinct phenotypes
References and Suggested Reading