The Management of Sepsis: What’s New in 2013

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Providence, RI
Disclosures

• Personal:
  – Financial:
    • None

• SSC
  – Financial:
    • None
    • No industry support since 2006
Projected Incidence of Severe Sepsis in the US: 2001-2050

Pathophysiology
Sepsis as Cytokine Storm

• Sepsis presentation
  – Fever, shock, respiratory failure
• Pro-inflammatory cytokines TNFα, IL-1, IL-6
  – All increased in sepsis
• Encouraging results in animal models pre-treated with therapeutics that blocked pro-inflammatory cytokines
Virulent pathogens (pneumococci, meningococcus, Group A strep, *S. aureus*, Clostridia, meningococci)

Pro-inflammatory markers—cytokines, chemokines, procoagulants, kinins, ROI, RNI, C’

Young, previously healthy patients with rapid onset septic shock - fits our animal models
TLR’s are the major pattern recognition receptors of innate immunity.
Genomic Storm

CARS

- Compensatory Anti-inflammatory Response Syndrome characteristics:
  - Predominance of Th2 and Treg responses over Th1 and T17 responses
  - CD4 lymphopenia and B lymphocyte dysfunction
  - Monocytes stimulated by PAMPs fail to produce adequate cytokines
  - Decreased expression of HLA-DR on monocytes
  - Impaired neutrophils phagocytosis
Immunosuppression

• End Stage septic patients:
  – Apoptosis-induced loss of cells of innate and adaptive immune system
    • CD4, CD8, T, B, dendritic cells
    • Occurring when clonal expansion of lymphocytes should be occurring

• Severe depletion of immune effector cells is universal finding in sepsis

Immunosuppression theory

• Initial hyperactivation of innate immune response
  – Pro-inflammatory cytokine production

• Persists for a variable period
  – Patient’s age
  – Comorbidities
  – Organism virulence
  – Other factors

• Followed by defective innate and adaptive immunity

Virulent pathogens (pneumococci, meningococcus, Group A strep, S. aureus, Clostrida spp.)

Pro-inflammatory markers - cytokines, chemokines, C, ROS, RNS, kinins, procoagulants

Early onset septic shock, MODS

Less virulent pathogens:
Stenotrophomonas, enterococci, Acinetobacter, CMV, Candida

Anti-inflammatory state - cytokines, apoptosis, LPS reprogramming, Decreased HLA DR, TNFR, TLR4, expanded Treg cells, MDSCs

Gradual deterioration and progressive organ failure fits most of our patients

Realistic view of sepsis and its pathophysiology

Sepsis-induced immunosuppression

Insult

- TLRs
- NOD-LRRs
- RLHs

Potential Imbalances

- TNF-α
- IL-1β
- IL-6
- IL-8
- IL-12
- PAF
- MIF
- HMGB-1

- $O_2^-$
- $OH^-$
- $H_2O_2$
- HOCl
- $'NO$
- $ONOO^-$

Arterioles

Endothelium

Capillary

Venules

Vasodilation

Coagulation

Leukocyte Abnormalities

Microcirculatory Dysfunction
Microcirculation: Pro-inflammatory, procoagulant state

Fibrin

Mitochondrial injury

Apoptosis

PMN elastase

Fluid shifts

Oxidant stress

NO•

O₂⁻

Capillary lumen

Swelling

Retraction

Exudation

Vasodilation

Interstitial space

PAF, IL-6, IL-8, MCP-1, E, P-selectins
Diagnosis of Sepsis
How Do We Identify Septic Patients?

- Heart Attack
  - EKG
  - Cardiac Enzymes
    - CPK
    - MB
  - Troponin
  - CRP
  - BNP
  - Echocardiogram
  - Cardiac Catheterization

- Sepsis
  - Signs and symptoms
    - Fever, chills, elevated WBC, difficulty breathing
  - “Look sick”
  - Objective measurements........
# SSC Interactive Database

## Evaluation for Severe Sepsis Screening Tool

1. **Is the patient's history suggestive of a new infection?**
   - Pneumonia/empyema
   - Urinary tract infection
   - Acute abdominal infection
   - Meningitis
   - Soft tissue infection
   - Bone/joint infection
   - Wound infection
   - Blood stream catheter infection
   - Endocarditis
   - Implantable device infection
   - Other infection

2. **Are any two of the following signs and symptoms of infection both present and new to the patient?**
   - Hyperthermia >38.3°C (101.0°F)
   - Influenza with rigors
   - Tachycardia >90 bpm
   - Tachypnea >20 bpm
   - Leukocytosis (WBC count >12,000 µL⁻¹)
   - Leukopenia (WBC count <4000 µL⁻¹)
   - Hyperglycemia (plasma glucose >120 mg/dL in absence of diabetes)
   - Acutely altered mental status

3. **Are any of the following organ dysfunction criteria present at a site remote from the site of the infection that are NOT considered to be chronic conditions? Notes: in the case of bilateral pulmonary infiltrates the remote site stipulation is waived.**
   - SBP < 90 mm Hg or MAP < 65 mm Hg
   - SBP decrease > 40 mm Hg from baseline
   - Creatinine > 2.0 mg/dL (176.8 mmol/L) or urine output < 0.5 ml/kg/hour for 2 hours
   - Bilirubin > 2 mg/dL (34.2 mmol/L)
   - Platelet count < 100,000
   - Lactate > 2 mmol/L (18.0 mg/dL)
   - Coagulopathy (INR > 1.5 or aPTT > 60 secs)
   - Bilateral pulmonary infiltrates with PaO2/FiO2 ratio < 300
   - Bilateral pulmonary infiltrates with a new or increased oxygen requirement to maintain SpO2 > 95%

If the answer is Yes to all 3 items above, then severe sepsis is present. Enter date and time of diagnosis.

<table>
<thead>
<tr>
<th>Date:</th>
<th>Time:</th>
</tr>
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</table>

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Sepsis Management
Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012

R Phillip Dellinger MD1; Mitchell M. Levy MD2; Andrew Rhodes MD BS3; Djillali Annane MD4; Herwig Gerlach MD PhD5; Steven M. Opal MD6; Jonathan E. Sevransky MD7; Charles L. Sprung MD8; Ivor S. Douglas MD9; Roman Jaeschke MD10; Tiffany M. Osborn MD MPH11; Mark E. Nunnally MD12; Sean R. Townsend MD13; Konrad Reinhart MD14; Ruth M. Kleinpell PhD RN-CS15; Derek C. Angus MD MPH16; Clifford S. Deutschman MD MS17; Flavia R. Machado MD PhD18; Gordon Dr. Rubenfeld MD19; Steven A. Webb MB BS PhD20; Richard J. Beale MB BS21; Jean-Louis Vincent MD PhD22; Rui Moreno MD PhD23; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

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Intensive Care Med. 2013 Feb;39(2):165-228
Current Surviving Sepsis Campaign Guidelines Sponsors

- American Association of Critical-Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- Australian and New Zealand Intensive Care Society
- Asia Pacific Association of Critical Care Medicine
- American Thoracic Society
- Brazilian Society of Critical Care (AIMB)
- Canadian Critical Care Society
- Chinese Society of Critical Care Medicine
- Chinese Society of Critical Care Medicine of Chinese Medical Association
- European Respiratory Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Society of Pediatric and Neonatal Intensive Care
- German Sepsis Society
- Infectious Diseases Society of America
- Indian Society of Critical Care Medicine
- Japanese Association for Acute Medicine
- Japanese Society of Intensive Care Medicine
- Latin American Sepsis Institute
- Pan Arab Critical Care Medicine Society
- Pediatric Acute Lung Injury and Sepsis Investigators
- Society Academic Emergency Medicine
- Society of Critical Care Medicine
- Society of Hospital Medicine
- Surgical Infection Society
- World Federation of Critical Care Nurses
- World Federation of Societies of Intensive and Critical Care Medicine
Diagnosis

1. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antimicrobial therapy is administered as long as such cultures do not cause significant delay (>45 minutes) in antimicrobial administration, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hr.) inserted (Grade 1C).
Initial Resuscitation

1. We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

   • Central venous pressure (CVP): 8–12mm Hg
   • Mean arterial pressure (MAP) ≥ 65mm Hg
   • Urine output ≥ 0.5mL.kg–1.hr –1
   • Central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65%, respectively

(Grade 1C)
Initial Resuscitation

2. In patients with elevated lactate levels as a marker of tissue hypoperfusion we suggest targeting resuscitation to normalize lactate as rapidly as possible (grade 2C).

3. We suggest that during the first 6 hrs of resuscitation of severe sepsis or septic shock, if ScvO2 <70% (or SvO2 equivalent of <65%), respectively persisted with fluid resuscitation to the central venous pressure target, then transfusion of packed red blood cells to achieve a hematocrit of 30% and/or administration of a dobutamine infusion (up to a maximum of 20 μg·kg⁻¹·min⁻¹) be used to achieve this goal (grade 2C).
Antibiotic therapy

1. We recommend that intravenous antimicrobial therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (grade1C).
Relationship between Shock, Antibiotic Timing, and Mortality

Each hour of delay: survival ↓ 7.6%

### Hospital Mortality by Time to Antibiotics

#### Table 11: Adjusted hospital mortality odds ratio for continuous time to ABX based on a GEE population-averaged model comparing severe sepsis to septic shock. Adjusted for the number of baseline organ failures, infection type, and geographic region

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<th>Time to ABX¹, hrs</th>
<th>OR²</th>
<th>95% CI</th>
<th>p-value</th>
<th>Probability of mortality³</th>
<th>95% CI</th>
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## Time to Antibiotics: Wards vs. ED

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<th>Time to ABX, hrs</th>
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<th>p-value</th>
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¹Time to ABX is based on 11,101 observations that are greater than or equal to zero
4. We suggest the use of low procalcitonin levels to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found (grade 2C).
Fluid therapy

1. We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

2. We recommend against the use of hydroxy ethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).

3. We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require repeated boluses of crystalloids (grade 2C).
Fluid therapy

4. We recommend that initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemic be started with $\geq 1000$ mL of crystalloids (to achieve a minimum of 30ml/kg of crystalloids in the first 4 to 6 hours). More rapid administration and greater amounts of fluid, may be needed in some patients (see Initial Resuscitation recommendations) (Grade 1B).

5. We recommend that a fluid challenge technique using incremental fluid boluses be applied wherein fluid administration is continued as long as the hemodynamic improvement either based on dynamic (e.g. delta pulse pressure, stroke volume variation...) or static (eg, arterial pressure, heart rate) variables continues (Grade 1C).
Vasopressors

1. We recommend that vasopressor therapy initially target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).

2. We recommend norepinephrine as the first choice vasopressor (Grade 1 B).

3. We recommend epinephrine (added or substituted) when an additional agent is needed to maintain adequate blood pressure (Grade 2B).

4. We suggest vasopressin 0.03 units/minute can be added to and subsequently potentially substituted for norepinephrine (Grade 2A).

5. We suggest dopamine as an alternative vasopressor agent to norepinephrine in highly selected patients at very low risk of arrhythmias and with low cardiac output and/or low heart rate. (Grade 2C).
Corticosteroids

1. We suggest not using intravenous corticosteroids in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy is able to restore hemodynamic stability. In case this is not achievable we recommend a daily dose of 200 mg intravenous hydrocortisone given by continuous intravenous infusion (Grade 2C).

2. We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B).

3. We suggest that patients with septic shock receive hydrocortisone rather than other steroids (Grade 2B). Further we recommend that hydrocortisone alone be used instead of hydrocortisone plus fludrocortisone (Grade 1B).
Licensed Therapeutic Agents for Sepsis

• Antibiotics
Recent Failed Clinical Trials in Sepsis

- TNFα
- Activated Protein C
- TLR4 inhibitor
- Talectoferrin
- Tissue Factor Pathway Inhibitor
- 25 Failed clinical trials for immunomodulation
Clinical Research with anti-inflammatory or anti-coagulant agents for sepsis: “Good” ideas and preclinical data

36 novel agents for sepsis tested in clinical trials: 32 no clear benefit; 3 worsened outcome; 1 +/- success (rhAPC), now withdrawn
Future Immunomodulatory Approaches

• Block inflammatory cytokines briefly and early
  – Biomarker directed
• Augment host (adaptive) immunity late
  – IL-7
  • Induces proliferation of T cells
  • Increase CD4 and CD8 T cells
  • Reverses lymphopenia
  • Increases cell-adhesion molecules
  • Decreased sepsis-induced apoptosis
New approaches to immunotherapy

• Individualization
  – Genome, proteome targeted therapy

• Focused targeting of immune response
  – Biomarkers
  – Timing
  – Predominance of inflammation or immune suppression
1) Treat very early and try to abort the process before immune suppression develops

2) Reverse immune depression after initial resuscitation and promote recovery

3) Tissue hibernation, mitochondrial sparing, repair pro-resolution and regeneration strategies

Can we rapidly determine the immune status of the patient and intervene appropriately?

Glucose control

1. We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose ≤ 180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (Grade 1A).
The Surviving Sepsis Campaign

A Performance Improvement Initiative in Sepsis Using Sepsis Bundles to Improve Care
SSC Methodology: Multifaceted Intervention

- National/regional/network “launch meetings”
  - Identify local champions
  - Introduce sepsis bundles
  - Educational tools
    - SSC manual
    - SSC slides
  - Staff support for coordinating sites
  - Regular conference calls

- Website
  - SSC and IHI website
  - Sepsis list-serve

- Interactive database
  - Automated uploading to SSC server
  - Technical support
  - Local audit and feedback capabilities
Change in Compliance Over Time

Change in Mortality Over Time

Surviving Sepsis Campaign: Data Analysis January 2005-December 2009

• First analysis:
  – 2 years
  – 15,000 pts
  – January 2005-December 2006

• Current analysis:
  – 4 years
  – 28,150 pts
SSC: Demographics

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### Mortality: Site Quarter

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<td>15</td>
<td>319</td>
<td>29.2</td>
<td>28.0</td>
</tr>
<tr>
<td>16</td>
<td>189</td>
<td>27.5</td>
<td>28.2</td>
</tr>
</tbody>
</table>

- Mortality over 4 year study period
  - 36.7% to 27.5%
  - **ARR: 9.2%**
  - **RRR: 25.0%**
    - P=0.005
SSC:
Association between compliance and Mortality
Table 1: Hospital mortality by sepsis admission source (ward vs. ED) for North America based on generalized estimating equation (GEE) population-averaged logistic regression model

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted for sepsis severity score</th>
<th>Mortality odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward vs. ED</td>
<td>No</td>
<td>1.64</td>
<td>1.52 – 1.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ward vs. ED</td>
<td>Yes</td>
<td>1.18</td>
<td>1.10 – 1.28</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
### Table 3: Hospital mortality by resuscitation performance and ward vs. ED

<table>
<thead>
<tr>
<th>Sepsis admission source</th>
<th>Low resuscitation performance</th>
<th>High resuscitation performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED, N (percent mortality)</td>
<td>4,149 (27.3%)</td>
<td>8,049 (23.2%)</td>
</tr>
<tr>
<td>Ward, N (percent mortality)</td>
<td>1,659 (38.2%)</td>
<td>3,105 (33.1%)</td>
</tr>
</tbody>
</table>
What’s Next?
The Surviving Sepsis Campaign: Government involvement

- Sepsis metrics (from SSC) now approved by National Quality Forum (US)
- New York State department of health programs
- CMS
  - Multiple sepsis projects
Conclusions:

• Complex, redundant mechanisms of inflammation and immune suppression
  • Likely balance between hyperimmune response and prolonged immune suppression

• Early identification of sepsis is key to therapy
  – Rapid administration of appropriate antibiotics
  – Early, aggressive resuscitation

• All trials for immunotherapy have failed
  – There are no “new” agents for sepsis

• Increased compliance with performance metrics is associated with improved survival