Sepsis Management: Past, Present, and Future

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Tennessee ACP Meeting
October 28, 2017
Learning Objectives

• Identify the most updated definition and clinical criteria for sepsis

• Describe the recent updates in sepsis research

• Discuss the most recent recommendations for sepsis management
What is sepsis?

Overly exuberant inflammation in the setting of infection

Life threatening organ dysfunction caused by a dysregulated host response to infection
Proinflammatory response

Excessive inflammation causing collateral damage (tissue injury)

Pathogen factors
- Load
- Virulence
- Pathogen-associated molecular patterns

Perpetuation of inflammation
- Cytokines
- Proteases
- Reactive oxygen species
- Complement products
- Coagulation proteases

Leukocyte activation

Complement activation

Coagulation activation

Necrotic cell death

Damage-associated molecular patterns

Host-pathogen interaction

Neuroendocrine regulation
- Brain
- Vagus nerve
- Celiac ganglion
- Spleen
- Liver, intestine
- Norepinephrine
- Acetylcholine
- Inhibition of proinflammatory cytokine production
- Adrenal gland
- Catecholamines
- Cortisol

Imbalanced function of immune cells
- Apoptosis of T, B, and dendritic cells
- Expansion of regulatory T and myeloid suppressor cells

Inhibition of proinflammatory gene transcription
- Antiinflammatory cytokines
- Soluble cytokine receptors
- Negative regulators of TLR signaling
- Epigenetic regulation

Host factors
- Environment
- Genetics
- Age
- Other illnesses
- Medications

Antiinflammatory response
- Immunosuppression with enhanced susceptibility to secondary infections

NEJM August 2013
Most common sources of sepsis

<table>
<thead>
<tr>
<th>Site of infection — no. (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>657 (35.4)</td>
<td>620 (33.0)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>172 (9.3)</td>
<td>163 (8.7)</td>
</tr>
<tr>
<td>Blood</td>
<td>172 (9.3)</td>
<td>172 (9.1)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>28 (1.5)</td>
<td>19 (1.0)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>154 (8.3)</td>
<td>153 (8.1)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>356 (19.2)</td>
<td>371 (19.7)</td>
</tr>
<tr>
<td>Other</td>
<td>113 (6.1)</td>
<td>149 (7.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>196 (10.6)</td>
<td>218 (11.6)</td>
</tr>
<tr>
<td>Determined ultimately to have no infection</td>
<td>9 (0.5)</td>
<td>15 (0.8)</td>
</tr>
</tbody>
</table>
How to Identify a Patient with Sepsis

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

- Patient with suspected infection
  - qSOFA ≥2? (see A)
    - Yes
    - Assess for evidence of organ dysfunction
      - SOFA ≥2? (see B)
        - Yes
        - Sepsis
          - Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥65 mm Hg AND 2. serum lactate level >2 mmol/L?
            - Yes
            - Septic shock
  - No
  - Sepsis still suspected?
    - Yes
    - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
    - No
    - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

JAMA Feb 2017
The SOFA score and qSOFA

- Sepsis-related Organ Failure Assessment
- SOFA > 2 over baseline in the ICU portends a mortality rate of 10%
- quickSOFA (qSOFA) replaces SIRS as sepsis screening tool
  - Respiratory Rate > 22 breaths per minute
  - Systolic BP < 100 mmHg
  - Altered Mental Status (GCS < 15)
- These tools are still controversial
## SOFA Score

**Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score**

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P_{a}O_2/F_iO_2), mm Hg (kPa)</td>
<td>(\geq 400 (53.3))</td>
<td>(&lt; 400 (53.3))</td>
<td>(&lt; 300 (40))</td>
<td>(&lt; 200 (26.7)) with respiratory support</td>
<td>(&lt; 100 (13.3)) with respiratory support</td>
<td></td>
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<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Platelets, (\times 10^3/\mu L)</td>
<td>(\geq 150)</td>
<td>(&lt; 150)</td>
<td>(&lt; 100)</td>
<td>(&lt; 50)</td>
<td>(&lt; 20)</td>
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<tr>
<td><strong>Liver</strong></td>
<td></td>
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<tr>
<td>Bilirubin, mg/dL ((\mu mol/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><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MAP (\geq 70) mm Hg</td>
<td>MAP (&lt; 70) mm Hg</td>
<td></td>
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<tr>
<td>Dopamine (&lt; 5) or dobutamine (any dose)</td>
<td></td>
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<tr>
<td>Dopamine (5.1-15) or epinephrine (\leq 0.1) or norepinephrine (\leq 0.1)</td>
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<tr>
<td>Dopamine (&gt; 15) or epinephrine (&gt; 0.1) or norepinephrine (&gt; 0.1)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score(^c)</td>
<td>(15)</td>
<td>(13-14)</td>
<td>(10-12)</td>
<td>(6-9)</td>
<td>(&lt; 6)</td>
<td></td>
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<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Creatinine, mg/dL ((\mu mol/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>
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<tr>
<td>Urine output, mL/d</td>
<td></td>
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<td></td>
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<td>(&lt; 500)</td>
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</tbody>
</table>

Abbreviations: \(F_iO_2\), fraction of inspired oxygen; MAP, mean arterial pressure; \(P_{a}O_2\), partial pressure of oxygen.

\(^{a}\) Adapted from Vincent et al.\(^{27}\)

\(^{b}\) Catecholamine doses are given as \(\mu g/kg/min\) for at least 1 hour.

\(^{c}\) Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
9SOFA

Hypotension
Systolic BP
<100 mmHg

Altered
Mental
Status

Tachypnea
RR >22/Min

Score of 22 Criteria Suggests a Greater Risk of a Poor Outcome
The Burden of Sepsis

• More than 1.6 million people in the U.S. are diagnosed annually
• 258,000 people die from sepsis every year in the U.S.
• Leading cause of death in hospitalized patients
• Half are treated in the ICU
• Mortality about 25% for Septic Shock
  – 30 years ago, 80% mortality

A Recent History of Sepsis Milestones

- First Consensus Statement: 1992
  - SIRS is born, Severe Sepsis, Septicemia
- “Early Goal Directed Therapy” 2001
- Surviving Sepsis Campaign 2004
- 2\textsuperscript{nd} Consensus Statement 2005
- 3 EGDT Randomized Controlled Trials - 2014
• Single center study
• 263 patients in septic shock
• Randomized controlled trial of the first 6hrs
• Standard care vs. treatment protocol
• Absolute reduction in mortality: 16% (NNT=6)
Early Goal-Directed Therapy: Treatment Protocol

- Supplemental oxygen ± endotracheal intubation and mechanical ventilation
- Central venous and arterial catheterization
- Sedation, paralysis (if intubated), or both
  - CVP ≤ 8 mm Hg
    - Crystalloid
    - Colloid
  - CVP 8-12 mm Hg
  - MAP < 65 mm Hg
    - Vasoactive agents
  - MAP ≥ 90 mm Hg
  - ScvO₂ < 70%
    - Transfusion of red cells until hematocrit ≥ 30%
    - Inotropic agents
  - ScvO₂ ≥ 70%
    - Inotropic agents
- Goals achieved
  - No
  - Yes
- Hospital admission

Potential for RBC and Inotropes

Early insertion of ScvO₂ catheter

Therapy titrated to CVP, MAP and ScvO₂

Early Goal Directed Therapy

- Dramatic mortality benefit
- Trial included expensive ScvO2 monitor
- High mortality rate in standard therapy group
- Multiple measures included in protocol
  - Which was the most helpful?
  - Are they are helpful?
  - Could some elements be harmful?
The 2014 RCT’s of EGDT

• ProCESS (US) – 1341 patients in 31 hospitals assigned to 3 groups
  – No difference in mortality
• ARISE (A/NZ) – 1600 patients in 51 hospitals assigned to 2 groups
  – No difference in mortality
• ProMISe (UK) – 1260 patients in 56 hospitals assigned to 2 groups
  – No difference in mortality
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

### A Primary mortality outcome of each study

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events, EGDT</th>
<th>Events, control</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al. (2001)</td>
<td>0.52 (0.31, 0.86)</td>
<td>38/130</td>
<td>59/133</td>
<td>10.40</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>1.47 (0.82, 2.60)</td>
<td>34/150</td>
<td>25/150</td>
<td>4.87</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>1.17 (0.88, 1.55)</td>
<td>92/439</td>
<td>167/902</td>
<td>21.78</td>
</tr>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
<td>30.71</td>
</tr>
<tr>
<td>ProMISe Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>100.00</td>
</tr>
</tbody>
</table>

DOI 10.1007/s00134-015-3822-1
What is the legacy of EGDT?

• Provided a construct on how to understand resuscitation:
  – Start early
  – Correct hypovolemia
  – Restore perfusion pressure
  – And in some cases a little more may be required!
Figure 1. Mean Annual Mortality in Patients With Severe Sepsis

Sepsis Mortality in the 21st Century
Surviving Sepsis Guidelines

The Keys to Sepsis Care

• Early recognition and source control
• Early antibiotic administration
• Early Initial Resuscitation with Fluid and Vasopressors
Source Control

• Specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis or septic shock

• The required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made.
Antibiotics

• IV antimicrobials should be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.
  (strong recommendation, moderate quality of evidence)

• Use empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.
  (strong recommendation, moderate quality of evidence)
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc
Antibiotic Timing in Major Sepsis Studies

- Rivers EGDT: Majority in 6 hours
- Kumar: Median of 6 hours
- ProCESS: Majority in 3 hours
- ARISE: Median of 70 minutes
- ProMISE: Median of 2.5 hours
Initial Resuscitation

• In the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid should fluid be given within the first 3 hours.

  (Strong recommendation; low quality of evidence)

• Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status.

  (Best Practice Statement)
Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate ≥ 4 mmol/L
(Based on SSC bundle and CMS threshold)

- **No high flow oxygen and No ESRD on dialysis or CHF**
  - Rapid infusion of 30 ml/kg crystalloid

- Pneumonia or ALI with high flow oxygen requirements
  - Not intubated/mechanically ventilated
    - Consider intubation/mechanical ventilation to facilitate 30 ml/kg crystalloid infusion
  - Intubated/mechanically ventilated
    - Rapid infusion of 30 ml/kg crystalloid

- ESRD on hemodialysis or CHF
  - Total of 30 ml/kg crystalloid with frequent reassessment of oxygenation

Considerations post 30ml/kg crystalloid infusion

1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
   - blood pressure/heart rate response
   - urine output
   - cardiothoracic ultrasound
   - CVP, ScvO2
   - pulse pressure variation
   - lactate clearance/normalization
   - dynamic measurement such as response of flow to fluid bolus or passive leg raising
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

All=acute lung injury; CHF=congestive heart failure; CMS=US Centers for Medicare and Medicaid Services; CVP=central venous pressure; ESRD=end stage renal disease; kg=kilograms; ml=millilitres; oxyhemoglobin; ScvO2=superior vena cava oxygen saturation

Dynamic Reassessment

• Static measurements, such as CVP, are unproven as markers of fluid responsiveness

• Dynamic measurements
  – Passive leg raise
  – Fluid challenges
  – Variations in pulse pressure relative to changes in intrathoracic pressure
Fluid Therapy

• Crystalloids are the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock

(Strong recommendation, moderate quality of evidence).

• Albumin in addition to crystalloids may be given when patients require substantial amounts of crystalloids

(weak recommendation, low quality of evidence)
Crystalloids and Colloids

• Balanced Fluids vs. Normal Saline
  – Chloride-rich fluid associated with renal failure
  – Effect not yet proven to be clinically meaningful

• Comparative benefits of albumin still not clear despite numerous trials

• Starch is dangerous and should be avoided
Initial target mean arterial pressure should be 65 mmHg in patients with septic shock requiring vasopressors.

(Strong recommendation; moderate quality of evidence)
Vasoactive agents

- **Norepinephrine** is the first choice vasopressor (strong recommendation, moderate quality of evidence)

- Add either **vasopressin** (up to 0.03 U/min) or **epinephrine** to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage (weak recommendation, low quality of evidence)
If shock is not resolving quickly.....

- Further hemodynamic assessment (such as assessing cardiac function) should be used to determine the type of shock if the clinical examination does not lead to a clear diagnosis.  
  (Best Practice Statement)

- Use dynamic over static variables be used to predict fluid responsiveness, where available.  
  (Weak recommendation; low quality of evidence)
Lactate can help guide resuscitation

- We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion

(Weak recommendation; low quality of evidence)
## Proposed Medicare Guidelines

<table>
<thead>
<tr>
<th>Performed by Hour 3</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Initial lactate level</strong></td>
<td>1. <strong>Initial lactate level</strong>&lt;br&gt;2. <strong>Broad spectrum antibiotics</strong> administered intravenously&lt;br&gt;3. <strong>Blood cultures prior to antibiotics</strong></td>
<td>1. Resuscitation with 30 cc/kg of crystalloid fluid&lt;br&gt;2. Vaspressors if the shock is refractory to resuscitation&lt;br&gt;3. If hypotension is refractory to the fluids or initial lactate is ≥4 the following must be documented:&lt;br&gt; a. Repeat volume status and tissue perfusion assessment consisting of:&lt;br&gt;   i. A focused physical exam performed by the provider including vital signs, cardiopulmonary exam, capillary refill evaluation, peripheral pulse evaluation, and skin exam&lt;br&gt;   ii. Any two of the following:&lt;br&gt;      1. Central venous pressure measurement&lt;br&gt;      2. Central venous oxygen saturation&lt;br&gt;      3. Bedside cardiovascular ultrasound&lt;br&gt;      4. Passive leg raise exam by provider or fluid challenge exam</td>
</tr>
</tbody>
</table>
### Proposed Medicare Guidelines

#### Severe Sepsis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>All three must be met within 6 hours:</td>
<td></td>
</tr>
<tr>
<td>1. <strong>Documentation of a suspected source</strong> of infection</td>
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<tr>
<td>2. Two or more manifestations of SIRS criteria:</td>
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</tr>
<tr>
<td>a. Temperature &gt;38.3°C/101°F or &lt;36°C/96.8°F</td>
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</tr>
<tr>
<td>b. Heart rate &gt;90</td>
<td></td>
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<tr>
<td>c. Respiratory rate &gt;20</td>
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<tr>
<td>d. WBC &gt;12 or &lt;4 or &gt;10% bands</td>
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<tr>
<td>3. <strong>Organ Dysfunction</strong>, evidenced by any one of the following:</td>
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</tr>
<tr>
<td>a. SBP &lt; 90 or MAP &lt; 65, or a SBP decrease of more than 40 pts</td>
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<tr>
<td>b. Cr &gt; 2.0 or urine output &lt; 0.5 cc/kg/hour for 2 hours</td>
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<tr>
<td>c. Bilirubin &gt;2 mg/dL (32.4 mol/L)</td>
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<tr>
<td>d. Platelet count &lt; 100</td>
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<tr>
<td>e. INR &gt; 1.5 or PTT &gt; 60</td>
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<tr>
<td>f. Lactate &gt; 2 mmol/L</td>
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</table>

#### Septic Shock

1. There must be documentation of septic shock present and
2. **Tissue hypoperfusion** persisting in the hour after crystalloid fluid administration, evidenced by:
   a. SBP < 90
   b. MAP < 65
   c. Decrease in SBP by >40 points from the patient’s baseline
   d. Lactate ≥4
3. Or if the criteria are not met, but there is provider documentation of septic shock or suspected septic shock
Steroids

- Corticosteroids should NOT be given to patients who meet resuscitation goals

- For patients who cannot reach resuscitation goals despite fluid therapy and vasopressors, steroids may be beneficial
  - Give Hydrocortisone 200mg IV per day
Failed Sepsis Therapies

**Treatment with anti-endotoxins**
- Anti-endotoxin antibodies
- LPS analogs
- LPS elimination
- Bactericidal/permeability-increasing protein

**Treatment with antagonists to specific mediators**
- TNF
  - Anti-TNF antibodies
  - TNF receptors
- IL-1 or IL-1RA
- Coagulants
  - Antithrombin
  - Activated protein C
  - Tissue factor pathway inhibitor
- PAF
  - PAF antagonists
  - PAF-acetylhydrolase
  - PLA2: PLA2 inhibitor

<table>
<thead>
<tr>
<th>Arachidonic acid metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E1</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Thromboxane inhibitors</td>
</tr>
<tr>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Reactive oxygen species</td>
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<tr>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Selenium</td>
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<tr>
<td>Bradykinin: bradykinin agonist</td>
</tr>
<tr>
<td>Nitric oxide: L-NMMA</td>
</tr>
<tr>
<td>Immunostimulation therapy</td>
</tr>
<tr>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor, IFN-γ</td>
</tr>
<tr>
<td>Immunonutrition</td>
</tr>
<tr>
<td>Nonspecific interventions</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
</tr>
<tr>
<td>Pentoxifylline therapy</td>
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<tr>
<td>High-output hemofiltration</td>
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</tbody>
</table>
Old Therapies with New Life

Vitamin C + Thiamine + Hydrocortisone in Sepsis

- Vitamin C and thiamine levels low in sepsis
- Deficiencies may be part of the pathology of sepsis
- Five prior RCTs have suggested benefit from Vitamin C or thiamine in critically ill patients, with no evidence of toxicity
- Before-and-After study of 150 septic patients
  - IV Vitamin C 1.5g q6h
  - IV Hydrocortisone 50mg q6h
  - IV Thiamine 200mg q12h
Vitamin C + Thiamine: Sepsis cure?

Figure 1. Predicted and actual mortality in the treatment and control group. Predicted mortality was derived from the APACHE IV scoring system. p < 0.001 for comparison of treatment vs control group.

Figure 2. Time course of vasopressor dosage (in norepinephrine equivalents) in the treatment group and in the control group survivors and non-survivors. p < 0.001 for comparison of treatment vs control group.

Summary

• Start resuscitation early with source control, intravenous fluids and antibiotics.
• Frequent assessment of the patients’ volume status is crucial throughout the resuscitation period.
• Resuscitation should be guided to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.