Metabolic Response in Sepsis and its Management

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Disclosure of Interest

- Advisory Board Fresenius Kabi
- Advisory Board Shire
History of critical care

Evolution over the millenniums developed a metabolic response to injury that **did not** involve:

- Ambulance
- Operating theatre
- ICU support
- Rehabilitation
So what has changed?

Retrieval  Resuscitation  Imaging  Ventilator & metabolic support
Survival of the fittest

- The metabolic response to severe injury by the host focuses on survival for the critical hours (days)
- The shock phase of the response where the body ‘shuts down’
  - Vasoconstriction to reduce fluid losses
  - ↓ Reduced metabolic rate
  - ↑ Gluconeogenesis

- In modern ICUs
  - Aggressive fluid resuscitation, vasopressor therapy, mechanical ventilation and early antibiotic therapy
Sepsis

• ‘Sepsis is a clinical syndrome that results from a dysregulated inflammatory response to infection that leads to organ dysfunction’ Taeb 2017 Nutr Clin Prac

• Sepsis has a high mortality,
  • Global Burden of Disease, more that 10 million people die of infection, higher than cancer!

• Sepsis is amongst the most common reason for admission to ICU
  • In Europe 37% sepsis and 30% for severe sepsis Vincent 2006, Crit care Med
  • Even with optimal care mortality >10% from sepsis and >40% septic shock
Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.

Sepsis is a syndrome shaped by pathogen factors and host factors (e.g., sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
Key Concepts of Sepsis cont.

- The clinical and biological phenotype of sepsis can be modified by pre-existing acute illness, long-standing comorbidities, medication, and interventions.
- Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.
Sepsis-3 Definitions

• **Sepsis**: Life-threatening organ dysfunction caused by dysregulated host response to infection

• **Septic Shock**: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

doi:10.1001/jama.2016.0287
Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.

Best Practice Statement
Recognising Sepsis

- Relies on assessing variety of non specific signs, symptoms, examination and laboratory values
  - Advanced age,
  - Immunodeficiency,
  - Chronic disease (diabetes, renal failure etc.)
  - Recent acute illness

Systemic Inflammatory Response syndrome SIRS

<table>
<thead>
<tr>
<th>SIRS Criteria (any 2 of the following)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/ min</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>&gt;38 or &lt;36</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>12,000/mm³ or &lt;4000/mm³</td>
</tr>
</tbody>
</table>
### 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>
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</tr>
<tr>
<td>Pao&lt;sub&gt;2&lt;/sub&gt;/FiO&lt;sub&gt;2&lt;/sub&gt;, mm Hg (kPa)</td>
<td>≥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>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Platelets, ×10&lt;sup&gt;3&lt;/sup&gt;/µL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
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<tr>
<td><strong>Liver</strong></td>
<td></td>
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<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><strong>Cardiovascular</strong></td>
<td></td>
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<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)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score&lt;sup&gt;c&lt;/sup&gt;</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>
<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:** FiO<sub>2</sub>, fraction of inspired oxygen; MAP, mean arterial pressure; Pao<sub>2</sub>, partial pressure of oxygen.  
<sup>a</sup> Adapted from Vincent et al.<sup>27</sup>  
<sup>b</sup> Catecholamine doses are given as µg/kg/min for at least 1 hour.  
<sup>c</sup> Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
Management of Sepsis

• Controversial, but:
  • Antibiotics
  • Early identification of the source of infection (if possible control it)
  • Prompt resuscitation
  • Multidisciplinary team

No level 1 evidence for single intervention that reduces mortality

Taeb et al 2017
Rivers Protocol

Potential for RBC and Inotropes Therapy

titrated to CVP, MAP and ScvO2

Early insertion of ScvO2 catheter

Potential for RBC and Inotropes
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

Intravenous Fluids

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGDT</td>
<td>2.8 L</td>
<td>2.3 L</td>
</tr>
</tbody>
</table>

Intravenous Antibiotics

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGDT</td>
<td>97.5%</td>
<td>96.9%</td>
</tr>
</tbody>
</table>
The River’s work was useful....

- As it provided us a construct on how to understand resuscitation:
  - Start early- (give antibiotics)
  - Correct hypovolaemia
  - Restore perfusion pressure
  - And in some cases a little more may be required..

- These concepts are as important today as they ever were.

Source Control

• We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.

(Best Practice Statement).
High Quality supportive Care

<table>
<thead>
<tr>
<th>CORNER STONE of TREATMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Cause</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Dysregulated immune system</td>
<td>steroids</td>
</tr>
<tr>
<td>Shock state</td>
<td>Vasopressors, fluids</td>
</tr>
</tbody>
</table>

To be successful, evidence shows that supportive team is needed

- Nursing
- Nutrition support
- Physiotherapy
- Pharmacy
Role of Nutrition support in Sepsis (and other stressors)

- Metabolic Stress response can be triggered by:
  - Trauma
  - Surgery
  - Infection

Stressors release pro-inflammatory mediators in response to infection, trauma that exceeds local environment to a generalised response.

? Results from production of uncontrolled pro-inflammatory mediators

"Cytokine Storm"
Timeline - Injury/Sepsis to Recovery

- Ebb/Shock
  - Phase 1
- Catabolic
  - Phase 2
- Anabolic
  - Phase 3
- Functional recovery
  - Phase 4
Timing and response

1. Neuroendocrine response
   • Activation of postganglionic neuron ➔ norepinephrine ➔ adrenergic receptors
   • Activation of adrenal medulla ➔ noradrenalin and adrenalin

2. Inflammatory response
   • Activation of innate immune cells as response to pathogen
A. Proposed New SIRS-CARS, PICS Model

- Sepsis/Trauma
- Early MOF
- Fulminant death
- Early innate immune response
- Protein Catabolism/Cachexia
- Persistent Inflammation
- SIRS
- CARS
- Defects in Adaptive Immunity
- Indolent Death
A. Proposed New SIRS-CARS, PICS Model

- **Sepsis/Trauma → Early MOF**
- **Pro-Inflammation**
- **Early innate immune response**
- **SIRS**
- **CARS**
- **Protein Catabolism/Cachexia**
- **Persistent Inflammation**
- **Defects in Adaptive Immunity**
- **Anti-Inflammation**
- **Indolent Death**

B. Conceptualized Individual Cell Response

- **Macrophage Activation**
- **TReg**
- **MDSCs**
- **Dendritic Cells**
- **Macrophage Paralysis**
- **T Effector Cell Number and Function**
Clinical consequences

• Energy expenditure
  • Acute phase ➔ moderate elevation of REE
  • As a result of treatment of fever, sedatives, muscle paralysers, assisted ventilation
  • Post injury increased production of reactive oxidative species (ROS)
    • Prevent harm need micronutrients such as Vit E, C, trace elements
    • Gluconeogenesis
Body Can Generate 50%–75% of Pts Glucose Requirements Early!

Hyperglycemia

Is Significant Exogenous Glucose kcal Delivery Needed?

Protein Delivery Essential Due to Catabolism! (How Much?)

Whole body protein catabolism

Acute phase proteins

Glycogenolysis

Gluconeogenesis

Lactate

Glycerol

Amino acids

Glycolysis

Proteolysis

Lipolysis

Glucose

insulin resistance
How much energy to provide

Recommendations change at rapidly!
Indirect calorimetry

- Gold standard?
- Likely to be needed in complex long stay patients
  - Burns
  - Complex surgical patients
The *J* curves show the association between the administered calories related to resting energy expenditure (REE) measured by indirect calorimetry. The yellow arrow shows the energy administered in the control group while the red arrow shows the calories administered in the study group, in relation to REE derived from EAT-ICU study [1]. The *solid line* includes measurements from admission, the *dashed line* excluding the first 2 days and the *dotted line* the patients staying more than 10 days.
Protein metabolism

- Rate of breakdown due to hormonal and inflammatory mediators AND
- Exceeds protein synthesis capacity

To increase lean body mass adequate nutrition is required (but is not sufficient !)
Proposal for targeted nutrition delivery in critical illness

Kcal/kg/day vs. Protein (g/kg/d)

- Protein delivery
- Sepsis trauma
- Severely malnourished?
- Total kcal delivery in well nourished Pt
- Activity/rehab increases

Acute phase (0-5 d post ICU-admit)
Chronic phase (5+ days post ICU-admit)
Recovery phase (post-ICU discharge)
How do you know how you are doing?
Are we creating survivors or victims in critical care? Delivering targeted nutrition to improve outcomes.

Wischmeyer, Paul

Conclusion

• Sepsis is a serious condition with high mortality and morbidity
• It generates a sequence of metabolic activity that alters host responses
• Nutrition support is part of the supportive care program
• Monitoring nutritional goals is as essential as monitoring other aspect of the septic patient.