Sepsis

What is the Definition of a Definition?

John Marshall MD
October 31, 2016

St. Michael’s
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American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis

Special Articles

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Emery, MD; For the International Sepsis Definitions Conference

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djlil Alnane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH
"A definition is a statement of the meaning of a term"

"a statement that describes what something is"

"An exact statement or description of the nature, scope, or meaning of something."
Construct

How we perceive the problem

Syndrome

Specific clinical phenotype

Disease

Pathologic basis
The Medical Paradigm

Construct

Acute wasting disease

Syndrome

Phthisis, consumption

Disease

Tuberculosis, lung cancer
### Why do we want to define sepsis?

**Patient**
- To diagnose
- To treat

**Population**
- To classify
- To count

To understand
Σηψις

Putrefaction, rot, decay

Hippocrates
460 – 370 BCE
“Moreover the infection is seen to be the same for him who has received or has given the infection; also we speak of infection when the same virus has touched one or the other. Also to those who die from having imbibed poison, we say perhaps that they are infected but not that they have suffered from contagion.”

- *Opera Omnia*, Venice, Junta 1584 pp 77-78
Germ Theory of Disease

Ignaz Semmelweis
1818 - 1865

Robert Koch
1843 - 1910

Louis Pasteur
1822 - 1895
The Medical Paradigm

Construct

Viable microorganisms

Syndrome

Variable

Disease

TB, Puerperal fever, smallpox
The Impact of Understanding Infection

Use of the Words ‘Sepsis’ and ‘Septicemia’
"Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms."

Hugo Schottmüller
1867 - 1936
"Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms."

"... therapy should not be directed against bacteria in the blood but against the released bacterial toxins ...."
“The presence of pus-forming organisms in the bloodstream.”
Who might benefit from treatment with therapies that target the host response?
Sepsis: The systemic host response to infection

- Beneficial vs harmful
- The response to non-infectious threats
Sepsis: The clinical syndrome defined by the presence of both infection and a systemic inflammatory response.

- Expanded clinical criteria
- Stratification – The PIRO model
## The PIRO Model

<table>
<thead>
<tr>
<th>Domain</th>
<th>Present</th>
<th>Future</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition</td>
<td>Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.</td>
<td>Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.</td>
<td>In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future). Specific therapies directed against inciting insult require demonstration and characterization of that insult.</td>
</tr>
<tr>
<td>Insult infection</td>
<td>Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.</td>
<td>Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.</td>
<td>Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator. Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.</td>
</tr>
<tr>
<td>Response</td>
<td>SIRS, other signs of sepsis, shock, CRP.</td>
<td>Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).</td>
<td>Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator. Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).</td>
<td>Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.</td>
<td>Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator. Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.</td>
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- Crit Care Med 31:1250, 2003
Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection

- Emphasis on clinical consequence
- Data-driven
Respiratory rate $\geq 22$ bpm

Altered mentation

Systolic blood pressure $\leq 100$ mmHg
Sepsis: The Medical Paradigm

**Construct**
Host response causes disease

**Syndrome**
Acute organ dysfunction

**Disease**
??????
Why do we want to define sepsis?

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<th>Patient</th>
<th>Population</th>
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<tr>
<td>• To diagnose</td>
<td>• To classify</td>
</tr>
<tr>
<td><em>Early recognition of risk</em></td>
<td><em>Not yet</em></td>
</tr>
<tr>
<td>• To treat</td>
<td>• To count</td>
</tr>
<tr>
<td><em>Early treatment of infection but not response</em></td>
<td><em>Perhaps</em></td>
</tr>
</tbody>
</table>
How Do the Definitions Help Us?

- Facilitate recognition of the patient at risk
- Underline the importance of organ dysfunction to the clinical phenotype
- Establish a role for data in definition
- Recognize that definition is a process
If sepsis is the response, and organ dysfunction the phenotype, then should organ dysfunction evoked by a response to non-infectious stimuli also be considered sepsis? Can we speak of infectious and non-infectious causes of sepsis?
A genomic storm in critically injured humans


If we limit the definition of sepsis to the response to an invading microorganism, then is a response triggered by products of that organism also sepsis?
Endotoxemia occurs in trauma, congestive heart failure, pancreatitis, ischemia-reperfusion injury, heat stroke.
Ongoing Questions

How do we transform a complex concept into specific treatments that can help critically ill patients?
## Cytokine Levels in Human Sepsis

<table>
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<tr>
<th>Cytokine</th>
<th>Median (pg/ml)</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>TNF</td>
<td>83</td>
<td>7 – 57,151</td>
</tr>
<tr>
<td>IL-6</td>
<td>965</td>
<td>8 – 1,553,435</td>
</tr>
<tr>
<td>IL-8</td>
<td>2130</td>
<td>16 – 651,338</td>
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</tbody>
</table>
“Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level.”

Do they help us?

Enrico Fermi