

Sepsis Definitions

A Work in Progress

John C. Marshall, MD, FRCSC

KEYWORDS

- Sepsis • Systemic inflammatory response syndrome • Stratification
- Organ dysfunction • Shock • Epidemiology

KEY POINTS

- The concept of sepsis is ancient and predates by millennia the understanding of the role of infection.
- Inherent in this concept is the notion that the resultant disease is effected through the innate response of the host, and manifested as physiologic organ dysfunction.
- A focus on improved definition serves to support early recognition of the at-risk patient to expedite appropriate anti-infectious and supportive care.
- Improved definitions also facilitate an understanding of epidemiology and of the global burden of disease.
- Existing definitions have not empowered the development of specific biologic therapies, and the process of definition is inherently a work in progress.

The recognition that infection is a transmissible disease caused by the invasion of healthy tissues by pathogenic microorganisms was a product of multiple scientific advances in the nineteenth century. Over evolutionary history, however, the dynamic interactions between microbes and their multicellular hosts have shaped the immune system and become imprinted in the genome. The consequence is an enormously complex process, at once fundamental to survival and one of the leading causes of death on the planet.¹ It follows that the description and understanding of this process has been a continuing challenge, rooted in the history of human sentience and continuing imperfectly to this day.

WHAT IS A DEFINITION, AND WHY IS IT IMPORTANT?

A definition, according to the Merriam-Webster dictionary, is "... an explanation of the meaning of a word ..." (<https://www.merriam-webster.com/dictionary/definition>).

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Departments of Surgery and Critical Care Medicine, St. Michael's Hospital, 4th Floor Bond Wing, Room 4-007, 30 Bond Street, Toronto, ON M5B 1W8, Canada

E-mail address: marshallj@smh.ca

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A word may have meaning because people create that meaning and agree on the criteria that define it—an inning in baseball is defined as 3 outs by each team, a kilogram is defined as the weight of a bar of platinum, and marriage is defined as the legal union between 2 individuals. Equally, a word may have meaning because data derived from the scientific process establish a plausible constraint: a year is the time required for the earth to revolve around the sun, sandstone is that form of rock resulting from the compression of sand, and cancer is a disease characterized by the abnormal proliferation of transformed cells. A definition delimits what something is and, as importantly, what it is not. A crow is a bird because of an implicit consensus on what makes a living organism a bird; it is not a flying insect for precisely the same reason. Definitions enable ordering the world—to describe it and so to modify it.

By defining sepsis, the parameters of a disease process are established—what it is as well as what it is not—and by implication, a range of interventions that might modify its course is established. A process is characterized from multiple perspectives—pathophysiology, clinical phenotype, prognosis, and potential to respond to therapeutic intervention. A definition may subserve some, but not all, these goals. The definition of cancer as an abnormal proliferation of biologically transformed cells provides a foundation for considering acute myelogenous leukemia and peritoneal liposarcoma as examples of a common pathologic process but provides no insight into common mechanisms of modifying the clinical course of disease.

The ongoing challenge of defining sepsis underlines this complexity. Sepsis is the clinical syndrome resulting from an acute host response to a threat. That response is clinically heterogeneous and not amenable to simple diagnostic criteria; conversely, it is evoked by a highly diverse group of threats. Efforts to define sepsis predate by millennia the contemporary understanding of the role of microbial infection. Conversely, contemporary definitions ignore the fact that the underlying biological process is not unique to infection but rather reflects a conserved response to danger in a variety of forms. The process of definition requires that arbitrary, human-imposed limitations be applied.

Medical definitions describe populations of patients whose clinical trajectory is shaped by a common process and who might, therefore, benefit from interventions that target that process. The validation of a medical definition, however, requires more than consensus: it requires that the definition reliably inform one or more treatment approaches that can be shown to alter clinical outcomes, that it converts a syndrome to a disease.

The evolving construct of sepsis reflects this process, a process that remains unfinished.

ANCIENT PERSPECTIVES

The Egyptians were the first to articulate a medical construct of sepsis. As outlined in the Ebers Papyrus (1500 BCE), they believed that a disease-producing force designated as *whdw*, pronounced “*ukhedu*,” originated in the intestine and could, under some circumstances, pass into the body and produce disease, whose manifestations included suppuration and fever.²

The word, *sepsis*, is of Greek origin, first appearing in the epics of Homer, and denoting the rotting of flesh.³ Hippocrates (460–370 BCE) is generally credited with the first definition of sepsis. He postulated that living things die and decay through 1 of 2 processes. Sepsis was the process of death and decay associated with illness, putrefaction, and a foul smell; *pepsis*, on the other hand, was decay that resulted in well-being, exemplified as the digestion of food or the fermentation of grapes to produce wine.²

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