A Complex Systems View of Sepsis: Implications for Nursing

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Sepsis is a complicated syndrome that manifests within the complex adaptive system that is the human body. Complexity theory and the recently emerged applied complexity science illustrate these phenomena and the body’s response in light of understanding these complex systems. Provision of careful observation by the nurse may recognize signs of moving into a nonadaptive or declining status, facilitating detection before complete sepsis or chaos. Systems or tools that aid the bedside nurse in prompt identification of sepsis and facilitate standardized evidence-based interventions are proving to be a valuable means in the care of the septic patient.

Keywords: Complexity theory, Evidence-based practice
Sepsis, Septic shock

Mechanistic Versus Complex Systems View of Physiology

Some biologic organisms are inherently complex systems. A complex system is characterized by a certain functional degree of interaction between structural, organizational, and regulatory elements that define the organism. The understanding of the complex system should be contrasted to the traditional mechanistic understanding of physiology and biological systems as being made up of “parts” that can be “fixed” or “replaced” as distinct elements in a machine, such as an automobile. In other words, in complexity, the whole is greater than the sum of the parts because of the interaction of the structure and function.

One of the key features and distinct properties of complex systems is the ability to adapt to changing environmental, metabolic, and disease states, which facilitates survival. Again, whereas a range of functionality is present in machines, adaptability to the environment is not present. The human body is composed of a myriad of discreet components, such as differentiated cells, organs, organ systems, and, ultimately, a functioning organism. Interactions between a large number of cells (e.g., cardiomyocytes) as they form organs (e.g., heart) and organ systems (e.g., cardiovascular system) are intuitive examples of structural and organizational complexity. If one also considers the hierarchical feedback loops acting on the cardiovascular system (such as autonomous nervous system, circulating catecholamine levels, chemoreflexes and baroreflexes, among others), regulatory complexity also becomes an understandable subject. The above features are not present in relatively simple mechanistic structures such as commonly used machines. Although this holistic view is assumed to be understood and followed in medicine, the traditional view of teaching physiology and medicine, coupled with current partitioned monitoring of organ and system function at the bedside, may lead some providers to follow and treat abnormalities.
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in the body as distinct organ-specific features and also re-
pair them as distinct abnormalities. For example, if blood
pressure is too low, we administer vasopressor agents, or
if the body temperature is too high, we decrease it by using
antipyretic medications or external cooling methods. As
critical-care nurses, we consider the symptoms in the con-
text of interactions within the body and treat the whole
patient. This reductionist examination of individual com-
ponents assuming linear relationships fails to adequately
describe the individual and adaptability in response to
disease.1-3

This does not mean that healthcare providers do not
already use critical-thinking skills or see the patients as a
hole. Nurses are very good at using a holistic approach when
caring for our patients.

Complicated syndromes such as sepsis represent com-
plex biologic processes that affect the organism from the
cellular to organismic level. Every individual will respond
differently to interventions because multiple components of
the system are interrogated at the same time, leading to the
manifestation of complicated interactive changes in a mul-
titude of variables. Symptomatic treatment of such pheno-
mena will only take us so far. It is here that the nonlinear
dynamics of complexity theory aids the understanding of
human biologic processes.2 Nonlinear means that inter-
actions between component variables of a system are not
necessarily simple proportional cause-and-effect relation-
ships leading to expected results, but rather dispropor-
tionate ones. This leads to only partially predictable responses
during disease resulting from nonadditive interactions of
multiple component variables in the system.2 The patient’s
current position or state on the trajectory to recovery or
demise may change rapidly over time. The purpose of this
article was to describe sepsis in light of complexity theory
and applied complexity science, illustrating this compli-
cated phenomenon, the body’s response to sepsis, and nurs-
ing implications in the care of these patients.

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Theory of Complexity Science
Systems can be complicated yet not complex. A mechanical
system may have multiple interacting elements, yet behave
in a linear fashion where a stimulus results in a consistent,
measurable, and predictable response. It is possible to un-
derstand such systems from evaluation of the individual
components.2 All living or biologic systems are in constant
interaction with the components within them and with the
environment (external agents) and do not behave in a simple
linear manner. To better describe complex systems with a
multitude of interacting component variables, nonlinear
dynamics, a science of phenomena that change in a nonlinear
fashion, must be used.1 Components of a nonlinear system
interact via some degree of coupling, causing overall re-
sponses to exceed responses by individual components.2,3

Complex systems also display sensitivity to initial con-
ditions, where a small change earlier in the history of the
system may lead to large changes in the state of the system
later in time, sometimes leading to nonpredictable out-
comes.4 Components of a complex system often display
features of structural or organizational self-similarity or
fractal patterns. A structural example of this in the hu-
man body includes the pattern of the bronchial tree and
similarly to the vascular system. Dynamic examples are
behavioral response patterns. Emergence is another char-
acteristic that describes the combination of more than 1
component into a new entity and cannot be reduced to its
constituent parts, or easily predictable.1,5 The immune
system represents this feature.1,5 Emerging behaviors are
common in nature and usually result from complex inter-
actions between component variables. Adaptability is an
emergent behavior because it encompasses a new response
to something previously not seen. Emergence allows for a
specific function or response in the body to develop with-
out central control. This is an example of autonomy of the
complex system, which increases its robustness and ability
to withstand stress. The immune system is the most evident
example of emergence and adaptability, such as mounting
an aggressive response to an invading organism, develop-
ing antibodies, or mitigating future system degradation.
This process is achieved with the complementary interac-
tion of innate and adaptive immunity. Self-organization, an
important characteristic of complex systems such as the
human body, represents the ability to maintain homeosta-
sis or dynamic equilibrium in the presence of changing con-
ditions caused by environmental, disease, or genetic factors.
Such a feature is characterized by robustness, an essential
property of biologic systems, which comprises adaptation
to external forces (ability to withstand or adapt to environ-
mental changes), and graceful degradation (slow aging pro-
cess).6 Connectivity describes the interrelationships of the
system, a process manifested by the overall health or ill-
ness of the individual such as the interrelationship between
the circulatory, respiratory, and immune systems.1 The no-
tion of systems is foundational in nursing because human
beings are considered complex adaptive systems.7

Sepsis
Sepsis is not a discreet disease state but is rather a continuum
of multifactorial illnesses that threaten the adaptive process
of the human system (Figure 1). Generalized infection coupled
with some degree of metabolic change (e.g., temperature, heart rate, respiratory rate, or white blood cell count) is traditionally defined as sepsis.8 Severe sepsis occurs when organ dysfunction results from the infectious process or the body’s inadequate response to infection.8 Septic shock is defined as significant hypotension refractory to adequate fluid resuscitation resulting from disease progression and requiring vasopressor therapy.8 Ultimately, the onset of multiple organ failure is the result of loss of compensatory mechanisms and without aggressive intervention will progress to death of the patient.8

Accurate diagnosis of sepsis is complicated by the lack of a criterion-standard diagnostic tool. Reliance on detection of pathogenic organisms in blood, pulmonary, urinary, or tissue cultures and clinical suspicion of sepsis remain the current diagnostic paradigm. However, a negative culture may not eliminate the possibility of sepsis. A large multicenter European study found that 40% of 1177 patients treated for sepsis lacked positive cultures.9 Furthermore, the host response to systemic infection is poorly understood, and many promising treatments have failed validation in large, multicenter trials.10-12 Targeted compartmentalized therapy such as activated protein C, corticosteroids, or immunoglobulins may affect one part of the complex system that controls the body’s response to sepsis. Yet, ultimately, this may prove inadequate because of the many biologic processes involved because they do not address the systemic manifestation of the entire syndrome.10-12

Intrapatient variability based on age, gender, race, genetic profile, or comorbidity further confounds the ability to describe the multifaceted disease process of sepsis. Better described as a syndrome, sepsis may manifest differently because of variability within patients.14

Sepsis is a complex syndrome, occurring at every level of biologic organization: (1) gene, (2) protein, (3) cell, (4) tissue, (5) organ, (6) system, and (7) organism (Figure 2).14 As noted by Ahn and colleagues,3 the application of clinical practice should be systems-oriented. Therapy targeted to a single level fails to address the multiple areas of dysfunction. Thus, effective treatment for sepsis tends to be multifaceted and comprehensive.15 Multiple systems are involved in the body’s response to infection and sepsis. Multiple organ support is provided to sustain the body during recovery (Table). The immune system serves as the primary line of defense, inciting a generalized inflammatory response that is not inherently detrimental.16 This response manifests systemwide at the cellular level and is mediated by the nervous system, primarily through vagus nerve stimulation.17,18 However, the systemic inflammatory response syndrome (SIRS) that may facilitate destruction of invading microorganisms is counteracted by the compensatory anti-inflammatory response syndrome, an interaction that may negatively affect individual organ function.19 Often, the multiple organ failure associated with poor outcomes from septic events is attributed to the body’s overreaction to infection. The acute response may be counterproductive and even fatal.4

Panels of biomarkers have been found to be more effective than individual assays in the detection of sepsis.20 Bundles of interventions are required to address the multisystem dysfunction initiated upon the host response to overwhelming infection.21 The principles of the Surviving Sepsis Campaign22 and early goal-directed therapy of severe sepsis and septic shock23 highlight the requirement for a multifaceted approach to the management of sepsis. Rapid provision of broad-spectrum antibiotic coverage is coupled with aggressive organ support such as improving cardiovascular function, maintaining renal function, and optimizing cellular oxygen delivery. Care delivery “bundles” are used to ensure essential elements of complex comprehensive therapy are promptly provided.
Sepsis as It Affects a Complex System

In a septic patient, inciting the immune system at the cellular level results in a cascade of responses such as (1) global inflammation, (2) cellular death, (3) organ derangement, and (4) ultimately multiple organ failure. This dynamic and nonlinear disease process progresses differently, depending on initial disease conditions present within each individual patient and the unique host response. This makes prediction of the response to infection difficult over time. Significant initial conditions in the setting of sepsis may include (1) exposure to infectious agents, (2) immunocompromise, (3) injury or illness, (4) genetic abnormalities, or (5) underlying comorbidities. Because multiple systems are involved, particularly when organ failure begins, the interconnectedness among constituent systems results in the emergence of unpredictable responses. Cardiac failure may precipitate renal compromise, resulting in metabolite toxicity, causing cell damage in multiple tissues. Such a response may constitute a “negative” emergence as it is not adaptive in the case of sepsis. This further complicates the use of linear approaches. Furthermore, chronic comorbidities such as diabetes or immune dysfunction may influence initial conditions, thus affecting an individual’s response to severe infection and may make detection even more difficult.

When the septic patient is unable to regulate organ function and metabolic processes such as oxygenation, perfusion, and resistance to microbial invasion, the system collapses, and death results. The body’s exaggerated inflammatory response to overwhelming infection causes the most damage to end organs and precipitates death. A bad omen, indicating the loss of homeostasis and adaptability. Several novel approaches for understanding complex systems have recently been introduced to the study of sepsis and multiple organ failure. A complex systems view of uncoupling of biological oscillators as a manifestation of multiorgan failure has been presented by Godin and Buchman in 1996. According to their theory, multiple organ failure is described as the erosion of the interconnections among organ systems as a result of SIRS. The authors suggest future studies to examine the precursors of SIRS as modulators of organ interconnectedness. Following these concepts, several researchers proposed various signal and organ-system-level monitoring tools based on complexity science. For example, Batchinsky and colleagues used various metrics from nonlinear statistics and signal pattern analysis tools to elucidate the effects of hemorrhagic shock, trauma, and resuscitation on cardiovascular regulatory complexity both in animal models and humans. The principle used in these studies is that the irregularity measured from a time series of certain biosignals, such as the electrocardiogram (ECG), is a surrogate for the systems-level response to injury. Specifically, the irregularity of the R-to-R interval of the ECG is believed to be caused by beat-to-beat changes in regulatory feedback. The loss of regulatory feedback (complexity) is reflected in measurably lower structural complexity of the signal.

Conceptually, this monitoring approach is a continuation of the traditional heart rate variability analysis capability but with newer, more robust tools and based on complex systems principles. Furthermore, the group extended this monitoring approach to evaluation of critically injured patients with respect to their injury severity and status of receiving lifesaving interventions. Recently, using similar monitoring approaches based on complex systems understanding of physiology, Moorman and colleagues in 2011 demonstrated in a multicenter randomized study with almost 3000 infants that use of a monitoring system that tracks ECG signal irregularity reduced mortality. This latter study is the best example to date demonstrating that the use of a complex systems principle for monitoring of patient status during sepsis may change outcomes at the bedside.

Translational systems biology is another promising means that may elucidate the complex systems response to sepsis. One approach is applying mathematical modeling to the interpretation of biologic process from the cellular to organism level. An and colleagues in 2008 proposed the use of dynamic mathematical modeling and application of engineering principles to understanding the pathophysiology of burn injury. This concept has been proposed as a means to describe the complex response to the inflammatory response to sepsis by Vodovozt and colleagues. In silico, or purely computerized, experimental models have demonstrated success in the attempt to describe the innate

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**TABLE Components of a Basic Sepsis Bundle (Based on Surviving Sepsis Campaign Recommendations)**

1. Obtain biomarker assays
2. Obtain culture panel (blood, respiratory, urine, wound)
3. Prompt administration of broad-spectrum antibiotics
4. Manage organ dysfunction/septic shock
   - Hemodynamic support
   - Respiratory support
   - Renal support
5. Provide adjunct therapy as required
   - Corticosteroid administration
   - Glucose control

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complex systems. Interconnected systems, coupled with the principle of emergence, allow for the understanding of complex behavior and to facilitate the understanding and development of possible interventions for dynamic biologic conditions such as sepsis. Computer agent modeling may help in developing better predictive understanding of the process of sepsis, which has important clinical application.

CONCLUSION
Humans, as living biologic organisms, should be viewed as complex systems. Interconnected systems, coupled with the principle of emergence, allows for the understanding of complex behavior and to facilitate the understanding and development of possible interventions for dynamic biologic conditions such as sepsis. Engineering modeling promises advancement of our knowledge of the disease by defining intrinsic patterns, and clinical computing decision support systems offer the ability to monitor patient progress in real time. These approaches facilitate understanding the interaction of complex systems by describing the larger-scale view of what is happening. Understanding systems and application of computer modeling tools that aid the nurse in the prompt identification of sepsis and facilitate standardized evidence-based interventions are proving to be valuable in the care of the septic patient.

References


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