

A Complex Systems View of Sepsis: Implications for Nursing

LTC Elizabeth A. Mann-Salinas, PhD, RN; Joan Engebretson, DrPH, RN; Andriy I. Batchinsky, MD

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

[DIMENS CRIT CARE NURS. 2013;32(1):12-17]

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 (eg, cardiomyocytes) as they form organs (eg, heart) and organ systems (eg, 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.¹ 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

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 JAN 2013		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE A Complex Systems View of Sepsis: Implications for Nursing.				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Mann-Salinas E. A., Engebretson J., Batchinsky A. I.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 6	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

in the body as distinct organ-specific features and also repair 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 context of interactions within the body and treat the whole patient. This reductionist examination of individual components 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 whole. Nurses are very good at using a holistic approach when caring for our patients.

Complicated syndromes such as sepsis represent complex 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 multitude of variables. Symptomatic treatment of such phenomena 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 interactions between component variables of a system are not necessarily simple proportional cause-and-effect relationships leading to expected results, but rather disproportionate 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 complicated phenomenon, the body's response to sepsis, and nursing implications in the care of these patients.

The patient's current position or state on the trajectory to recovery or demise may change rapidly over time.

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 understand 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 responses to exceed responses by individual components.^{2,3}

Complex systems also display sensitivity to initial conditions, 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 outcomes.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 human body includes the pattern of the bronchial tree and similarly to the vascular system. Dynamic examples are behavioral response patterns. Emergence is another characteristic 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 interactions 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 without 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, developing antibodies, or mitigating future system degradation. This process is achieved with the complementary interaction of innate and adaptive immunity. Self-organization, an important characteristic of complex systems such as the human body, represents the ability to maintain homeostasis or dynamic equilibrium in the presence of changing conditions 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 environmental changes), and graceful degradation (slow aging process).⁶ Connectivity describes the interrelationships of the system, a process manifested by the overall health or illness of the individual such as the interrelationship between the circulatory, respiratory, and immune systems.¹ The notion 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

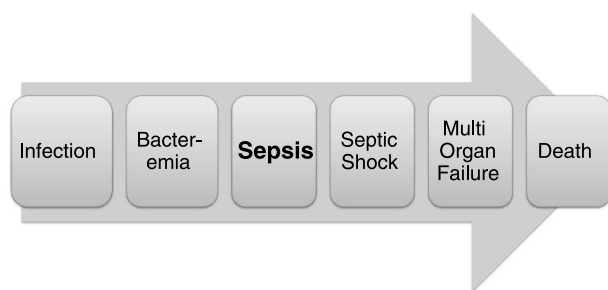


Figure 1. The sepsis syndrome. Adapted from Bone.¹⁹

with some degree of metabolic change (eg, 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

Inpatient 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 and even more so based on that individual's state of wellness or illness prior to disease as well as their current state. Further complicating the management of sepsis is the pathogen-host response

characterized by the adaptation of bacteria to the host response, modifying resistance and toxin production.¹³

Better described as a syndrome, sepsis may manifest differently because of variability within patients.

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 system-wide 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.

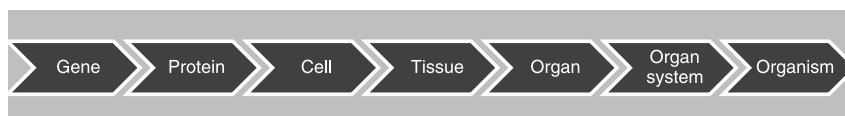


Figure 2. Model of the hierarchy of complex biological systems.

TABLE **Components of a Basic Sepsis Bundle (Based on Surviving Sepsis Campaign Recommendations²²)**

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

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.¹ 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 interconnectivity 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.¹⁹

Understanding Complex Adaptive Systems

The dynamic interplay of the components of the system is an adaptive behavior, facilitating robustness and resulting in an active state of response.³ However, loss of complexity or responsiveness of biologic systems has been identified as

a bad omen, indicating the loss of homeostasis and adaptability.^{2,24,25} 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 1996.²⁶ 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 colleagues²⁷⁻³⁰ 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.²⁷⁻³⁰ The loss of regulatory feedback (complexity) is reflected in measurably lower structural complexity of the signal.²⁷⁻³⁰ Conceptually, this monitoring approach is a continuation of the traditional heart rate variability analysis capability^{31,32} but with newer, more robust tools and based on complex systems principles.³³ Furthermore, the group extended this monitoring approach to evaluation of critically injured patients with respect to their injury severity²⁹ and status of receiving lifesaving interventions.³⁴ Recently, using similar monitoring approaches based on complex systems understanding of physiology, Moorman and colleagues³⁵ 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.^{14,16} An and colleagues¹⁴ 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 Vodovotz and colleagues.¹⁶ In silico, or purely computerized, experimental models have demonstrated success in the attempt to describe the innate

immune response and determine effective treatments for sepsis and multiple organ failure. Such computer simulation is known as agent-based modeling, where analysis of nonlinear patterns allows for better understanding of complex interconnected processes.³⁶ This agent-based modeling approach was used to evaluate the dynamic interplay within the innate immune system and for development of treatments for complications associated with SIRS and multiple organ failure. Coupling engineering principles with complex clinical scenarios offers great promise for identifying effective treatment for a complicated disease such as sepsis.

Nursing Implications

The first line of defense in recognizing and managing a patient with sepsis is the bedside critical-care nurse. The nurse through careful observation of the patient will recognize the signs and symptoms of any deterioration in the patient's status. This will facilitate detection well before complete chaos or sepsis. Changes in vital signs and signs of decreased perfusion may be noted, such as diminished heart rate variability. The loss of interbreath complexity may be used to detect a patient's declining status.³⁴⁻³⁷ Nurses providing care in the critical-care environment may be overwhelmed with multiple patients to manage, short staffing, and a dizzying array of data to interpret. Identifying the meaningful patterns among various physiologic systems indicative of worsening infection may be difficult for even the most experienced caregiver. Novice nurses may lack comprehensive understanding of the presentation of sepsis and fail to recognize onset in a timely manner. Experienced critical-care nurses must mentor novice nurses to recognize the signs and symptoms of sepsis and its subsequent consequences. Nursing has traditionally offered a holistic focus on patient care and systems orientation, so bringing this concept to the identification and management of sepsis is a natural step. Use of monitoring technology may alleviate information overload and help nurses focus on clinically meaningful information. Introducing evidence-based bundles of multiple therapeutic interventions can streamline and standardize response to the onset of sepsis by nursing staff through addressing all facets of the body's response to the infectious process (Table). Standardized methods of displaying complex information and use of computerized checklists and treatment algorithms may facilitate care delivery.

Use of monitoring technology may alleviate information overload and help nurses focus on clinically meaningful information.

Computer decision support systems provide the opportunity to introduce detailed and complicated algorithms for

detection and management of sepsis in the clinical environment and may lead to improved patient outcomes.³⁸ The concept of a "sniffer" to data mine electronic medical records for patterns associated with worsening infection has been effective, as demonstrated by researchers at the Mayo Clinic.^{39,40} Computer technology brings evidence-based practice to the bedside, providing alerts to caregivers that curtail the impact of varying levels of providers' understanding of sepsis.

Finally, it is important for nurses to differentiate between complexity theory (ideas) and the science (application) in support of scientific inquiry. Nurses can use complexity theory concepts to gain an understanding of the functioning of a complex adaptive system and then apply that knowledge to clinical issues. Use of computers to accommodate large amounts of data allows for the application to evaluate 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 unique and novel adaptation. Sepsis is also a complex process that interacts with the body's systems. An important feature of these complex systems is distributed, rather than centralized, control. Generally distributed control allows for much more efficient and effective response but makes understanding the dynamics of sepsis challenging. A major component of complexity is the existence of patterns, which follow a few simple rules. This feature may differentiate a healthy complex system from one that has lost complexity or fallen into random chaos, thus making the loss of complexity or the loss of patterning a major characteristic of severe sepsis. Engineering modeling promises advancement of our knowledge of the disease by defining intrinsic patterns, and clinical computer 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

1. Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. *Crit Care Med*. 2000;28(7):2193-2200.
2. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet*. 1996; 347(9011):1312-1314.
3. Ahn AC, Tewari M, Poon CS, Phillips RS. The limits of reductionism in medicine: could systems biology offer an alternative? *PLoS Med*. 2006;3(6):e208.

4. Papanthanasoglou ED, Bozas E, Giannakopoulou MD. Multiple organ dysfunction syndrome pathogenesis and care: a complex systems' theory perspective. *Nurs Crit Care*. 2008;13(5):249-259.
5. Buchman TG, Cobb JP, Lapedes AS, Kepler TB. Complex systems analysis: a tool for shock research. *Shock*. 2001;16(4):248-251.
6. Kitano H. Systems biology: a brief overview. *Science*. 2002;295(5560):1662-1664.
7. Engebretson J, Hickey JV. Complexity science and complex adaptive systems. In: Butts JB, Rich KL, eds. *Philosophies and Theories for Advanced Nursing Practice*. Burlington, MA: Jones & Bartlett Learning; 2011.
8. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
9. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34(2):344-353.
10. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301(22):2362-2375.
11. Turgeon AF, Hutton B, Fergusson DA, et al. Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med*. 2007;146(3):193-203.
12. Wiedermann CJ, Kaneider NC. A meta-analysis of controlled trials of recombinant human activated protein C therapy in patients with sepsis. *BMC Emerg Med*. 2005;5:7.
13. Shankar R, Melstrom KA Jr, Gamelli RL. Inflammation and sepsis: past, present, and the future. *J Burn Care Res*. 2007;28(4):566-571.
14. An G, Faeder J, Vodovotz Y. Translational systems biology: introduction of an engineering approach to the pathophysiology of the burn patient. *J Burn Care Res*. 2008;29(2):277-285.
15. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med*. 2010;36(2):222-231.
16. Vodovotz Y, Csete M, Bartels J, Chang S, An G. Translational systems biology of inflammation. *PLoS Comput Biol*. 2008;4(4):e1000014.
17. Rosas-Ballina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. *Neuron*. 2009;64(1):28-32.
18. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458-462.
19. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med*. 1996;24(7):1125-1128.
20. Casserly B, Read R, Levy MM. Multimarker panels in sepsis. *Crit Care Clin*. 2011;27(2):391-405.
21. Rivers EP, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. *Crit Care Clin*. 2008;24(3 suppl):S1-S47.
22. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
23. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
24. Buchman TG. Nonlinear dynamics, complex systems, and the pathobiology of critical illness. *Curr Opin Crit Care*. 2004;10(5):378-382.
25. Lundelin K, Vigil L, Bua S, Gomez-Mestre I, Honrubia T, Varela M. Differences in complexity of glycemic profile in survivors and nonsurvivors in an intensive care unit: a pilot study. *Crit Care Med*. 2010;38(3):849-854.
26. Godin PJ, Buchman TG. Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med*. 1996;24(7):1107-1116.
27. Batchinsky AI, Cooke WH, Kuusela T, Cancio LC. Loss of complexity characterizes the heart rate response to experimental hemorrhagic shock in swine. *Crit Care Med*. 2007;35(2):519-525.
28. Batchinsky AI, Cooke WH, Kuusela TA, Jordan BS, Wang JJ, Cancio LC. Sympathetic nerve activity and heart rate variability during severe hemorrhagic shock in sheep. *Auton Neurosci*. 2007;136(1-2):43-51.
29. Batchinsky AI, Cancio LC, Salinas J, et al. Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients. *J Trauma*. 2007;63(3):512-518.
30. Batchinsky AI, Skinner JE, Necsoiu C, Jordan BS, Weiss D, Cancio LC. New measures of heart-rate complexity: effect of chest trauma and hemorrhage. *J Trauma*. 2010;68(5):1178-1185.
31. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981;213(4504):220-222.
32. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol*. 1985;248(1 pt 2):H151-153.
33. Goldberger AL, Giles F. Filley lecture. Complex systems. *Proc Am Thorac Soc*. 2006;3(6):467-471.
34. Cancio LC, Batchinsky AI, Salinas J, et al. Heart-rate complexity for prediction of prehospital lifesaving interventions in trauma patients. *J Trauma*. 2008;65(4):813-819.
35. Moorman JR, Carlo WA, Kattwinkel J, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. *J Pediatr*. 2011;159(6):900-906.
36. An G. In silico experiments of existing and hypothetical cytokine-directed clinical trials using agent-based modeling. *Crit Care Med*. 2004;32(10):2050-2060.
37. White CE, Batchinsky AI, Necsoiu C, et al. Lower interbreath interval complexity is associated with extubation failure in mechanically ventilated patients during spontaneous breathing trials. *J Trauma*. 2010;68(6):1310-1316.
38. McKinley BA, Moore LJ, Sucher JF, et al. Computer protocol facilitates evidence-based care of sepsis in the surgical intensive care unit. *J Trauma*. 2011;70(5):1153-1166; discussion 1157-1166.
39. Herasevich V, Afessa B, Chute CG, Gajic O. Designing and testing computer based screening engine for severe sepsis/septic shock. *AMIA Annu Symp Proc*. 2008;6:966.
40. Herasevich V, Pieper MS, Pulido J, Gajic O. Enrollment into a time sensitive clinical study in the critical care setting: results from computerized septic shock sniffer implementation. *J Am Med Inform Assoc*. 2011;18(5):639-644.

ABOUT THE AUTHORS

LTC Elizabeth A. Mann-Salinas, PhD, RN, is a nurse scientist at the US Army Institute of Surgical Research, Fort Sam Houston, Texas. She has particular research interest in sepsis and improvement in deliver of care systems.

Joan Engebretson, DrPH, RN, is a professor at the University of Texas Health Science Center, Houston. She is interested in the application of complexity and complex systems to health care.

Andriy I. Batchinsky, MD, is a surgeon and research scientist at the US Army Institute of Surgical Research, Fort Sam Houston, Texas. He is interested in the application of medical informatics and complex systems science to management of critically injured patients as well as use of extracorporeal life support for treatment of single-organ and multiorgan failure.

The authors have disclosed that they have no significant relationship with, or financial interest in, any commercial companies pertaining to this article.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Address correspondence and reprint requests to: LTC Elizabeth A. Mann-Salinas, PhD, RN, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Ave, Fort Sam Houston, TX 78234 (Elizabeth.Mann@us.army.mil).