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## Sepsis: Something Old, Something New, and a Systems View

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### Abstract

Sepsis is a clinical syndrome characterized by a multi-system response to a microbial pathogenic insult consisting of a mosaic of interconnected biochemical, cellular, and organ-organ interaction networks. A central thread that connects these responses is inflammation, which, while attempting to defend the body and prevent further harm, causes further damage through the feed-forward, pro-inflammatory effects of damage-associated molecular pattern molecules. In this review, we address the epidemiology and current definitions of sepsis, and focus specifically on the biological cascades that comprise the inflammatory response to sepsis. We suggest that attempts to improve clinical outcomes by targeting specific components of this network have been unsuccessful due to the lack of an integrative, predictive, and individualized systems-based approach to define the time-varying, multi-dimensional state of the patient. We highlight the translational impact of

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### DISCLOSURES

Drs. Vodovotz and Billiar are co-founders of and stakeholders in Immunetrics, Inc., which has licensed from the University of Pittsburgh the rights to commercialize aspects of the mathematical modeling of inflammation. Dr. An is a consultant to Immunetrics, Inc.

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computational modeling and other complex systems approaches as applied to sepsis, including *in silico* clinical trials, patient-specific models, and complexity-based assessments of physiology.

## Keywords

Sepsis; Inflammatory Response; Physiologic Variability; Mathematical Model

## INTRODUCTION

Sepsis is a significant public health concern<sup>1-3</sup>. Though “septicemia” accounts for approximately 1% of overall deaths in the U.S.<sup>4</sup>, the number is much larger (nearly 10%) when factoring in deaths from pneumonia and other causes of severe sepsis. Sepsis affects persons of all ages,<sup>5</sup> is the leading cause of morbidity and mortality for patients admitted to an intensive care unit (ICU), and may be considered the 10<sup>th</sup> leading cause of death overall in the United States. The incidence of sepsis is projected to increase by 1.5% per year, rising to more than 1,110,000 cases or more annually by 2020<sup>2</sup>. Sepsis also reduces the quality of life of many of those who survive.

Despite a large body of scientific literature concerning individual mechanisms of disease in sepsis – implicating organ dysfunction caused by failure of key processes in epithelial cells and involving various biological mechanisms from endothelial defects to dysregulated inflammation and the associated complement and coagulation networks - there are few therapies and relatively imprecise diagnostics for sepsis. In the present review, we suggest that our view of sepsis has evolved from a general concept, to that of rigidly defined (but seldom absolute) diagnoses, to a more fluid perception of sepsis as a dynamic progression of host-pathogen interactions that can be assessed by examining the dynamic, multi-dimensional state of the patient (Fig. 1). By “dynamic” we mean time-varying, and by “state” we mean literally the compendium of all relevant variables that can inform a clinician about the pathophysiology and biological state of a patient at a given instant. Importantly, a characterization of this “dynamic state” could be considered sufficiently complete when the data contained therein are sufficient for prediction of the future course of the patient. Thus, the concept of “dynamic state” encompasses the idea that the data that make up this state are sufficient to predict the progression of a patient for a clinically appropriate future duration, and that these data are of sufficient granularity to reflect all relevant biological and physiological processes and therefore amenable for analysis using predictive computational models and algorithms. Though potentially daunting in scope, we suggest that the concept of the dynamic state underlies a modern, mechanistic view of a very old disease, one that better encompasses the progression of this disease in individual patients rather than focusing on rigid, pre-defined diagnoses.

## SEPSIS: A BRIEF HISTORY

The difficulty in developing mechanistically-based diagnoses has hampered our understanding of the pathophysiology of sepsis, and to a certain degree has impaired the development of successful therapies. In beginning to unravel the mechanistic underpinnings of sepsis with the goals of improved diagnosis and therapy, it is useful to trace the dynamic evolution of our concepts concerning this disease. Starting from the origins of the word “sepsis” approximately 2700 years ago in the Greek word “σηψις” (the “decomposition of animal or vegetable organic matter in the presence of bacteria”<sup>19</sup>), our view of sepsis has progressed through various stages. The initial view of the process was encapsulated in the Germ Theory, in which pathogens were the sole causes of sepsis<sup>20-22</sup>. Subsequent advances led to the development of fairly rigid diagnostic guidelines based on the host’s response to

infection, guidelines developed in part in response to the inability to curb sepsis solely through therapy aimed at the pathogen (see below). The most recent development has been the emergence of a multi-scale, systems perspective of host-pathogen interactions at the organ, tissue, cellular, and molecular levels (Fig. 1)<sup>23-31</sup>. Below, we focus on this most recent development.

By 1990, after approximately 20 years of intensive care and 40 years of anti-sepsis therapies based on the Germ Theory suggested that many patients could die despite antibiotics and life support, the notion emerged that the host's intertwined inflammatory and physiological responses to the pathogen were at least as much to blame as the pathogen itself<sup>32</sup>. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) agreed on a new definition of sepsis as the development of a systemic inflammatory response syndrome (SIRS) due to infection. The severity of sepsis was graded based on the development of hemodynamic compromise and associated organ dysfunction as follows: severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS)<sup>33</sup>. These definitions served as a more uniform reference point for performing clinical trials, facilitating hypothesis generation, and establishing guidelines for the care of the septic patient (Fig. 1). The 1991 North American Consensus Conference concept of SIRS is now considered outdated, however, and the four SIRS criteria have been expanded to a longer list of possible signs of sepsis in the latest definitions<sup>34</sup>. These were developed in 2001, under the auspices of the SCCM, the European Society of Intensive Care Medicine, the ACCP, and the Surgical Infection Societies. The conferees concluded that the diagnostic criteria for SIRS were overly sensitive and nonspecific, and that a more comprehensive list of signs and symptoms that may accompany sepsis would better reflect the clinical response to infection<sup>34</sup>. In addition, a staging system was proposed for the purpose of incorporating both host factors and response to a particular infectious insult. This concept, termed *PIRO* (*pre disposition, infection, response, organ dysfunction*)<sup>34</sup> represents an attempt to include the patient's response to treatment in the diagnosis.

As important as these advances have been, we suggest that these metrics and criteria remain too imprecise to move beyond identifying population tendencies, and are removed from the increasing mechanistic knowledge being generated. We have progressed in our understanding of sepsis to include high-dimensional genomic and proteomic datasets, signal processing techniques that assist in creating diagnostic sense from chaotic physiological data, and mechanistic mathematical modeling based on pre-clinical and clinical data. This increased resolution of knowledge regarding the pathophysiology of sepsis has offered the promise of more precise characterization of the disease. These advances have also raised the possibility of defining the multi-dimensional "state" of an individual sepsis patient, based on direct measurements of the molecules that orchestrate the interplay among infection, inflammation, and organ dysfunction (Fig. 1)<sup>46</sup>. As we discuss below, these emerging approaches may help define sepsis in a more precise fashion (Fig. 2) that includes detailed, dynamic physiologic and molecular characteristics of patient sub-groups, and, eventually, of individuals.

## SEPSIS: A PROCESS FLOW

Just as the conceptual evolution of sepsis has been dynamic, we now appreciate that the pathogenesis of sepsis involves a dynamic, complex process of cellular activation resulting in the activation of neutrophils, monocytes and microvascular endothelial cells; the triggering of neuroendocrine mechanisms; and activation of the complement, coagulation, and fibrinolytic systems. Acute inflammation is a central mechanism that helps connect these processes across time and space (Fig. 2A). The innate immune response recognizes the presence of invading pathogens, acts towards initial containment, recruits additional cells to

eliminate the pathogens and, concurrently, involves feedback mechanisms that serve to limit and restrict the pro-inflammatory component such that homeostatic dynamic equilibrium can be re-established<sup>49</sup>. These factors function in a series of interlinked and overlapping networks, suggesting that “inflammation is communication”<sup>50</sup>. Like any situation that involves communication, the content, tone, and context matters a great deal. On the one hand, an appropriately robust inflammatory response is necessary to survive diverse insults both in the very short and long term<sup>51</sup>. It is important to note that though organs obtained from sepsis patients *post mortem* may not exhibit histological damage<sup>52</sup>, these organs are nonetheless dysfunctional as a result of various defects that manifest, at the cellular level, in both epithelial<sup>53</sup> and endothelial cells. We suggest that this dysfunction occurs due to a positive feedback loop in which inflammation induced by pathogen-derived signals leads to the release from epithelial and endothelial cells of Damage-Associated Molecular Pattern (DAMP) molecules, the molecular messengers of tissue damage. In turn, these “danger signals” stimulate nearby inflammatory cells to produce more of the classical inflammatory mediators, leading to further release of DAMP’s and ultimately to self-maintaining inflammation even after the pathogen has been cleared (Fig. 2B). The body is equipped to suppress inflammation and drive cell/tissue/organ healing both through the production of anti-inflammatory mediators as well as through an inherent suppression of pro-inflammatory signaling (referred to as tolerance or desensitization). However, in progressive sepsis, these anti-inflammatory influences are either insufficient to suppress self-maintaining inflammation, or are over-produced and lead to an immunosuppressed state.

In the following sections, we will describe some of these components and place them into an appropriate context. It should be noted that presenting the information requires a linear structure; this should in no way obscure the complex dynamic actuality of the system in reality (Fig. 2). We suggest that the key to developing effective diagnostics and treatments for sepsis requires effective characterization of the architecture and dynamics of the inflammatory system from a mechanistic standpoint.

### Pathogen Recognition

The innate immune system is a highly evolutionarily conserved host defense mechanism against pathogens<sup>57</sup>, though an alternative viewpoint suggests that this system evolved in order to respond to trauma and injury (see below)<sup>58</sup>. Innate immune responses to pathogens are initiated by pattern recognition receptors (PRRs), which recognize specific structures of microorganisms (Fig. 2). At least four families of PRRs are recognized: Toll-like receptors (TLRs); nucleotide oligomerization domain leucine-rich repeat (NOD-LRR) proteins; cytoplasmic caspase activation and recruiting domain helicases such as retinoic-acid-inducible gene I (RIG-I)-like helicases (RLHs); and C-type lectin receptors expressed on dendritic and myeloid cells. Bacteria and viruses have molecular structures that are: generally not shared with their host, common among related pathogens, and invariant. These molecular signatures are also expressed by nonpathogenic and commensal bacteria<sup>59</sup> and are now referred to as pathogen-associated molecular pattern (PAMP) molecules or microbial-associated molecular pattern (MAMP) molecules. Though further studies are necessary to fully elucidate this phenomenon, the degree to which a given sepsis patient responds to a given PAMP may be in part controlled by single nucleotide polymorphisms (SNPs) in PRR’s such as TLR4 and related molecules such as CD14. In general, all sepsis patients manifest robust inflammatory responses to PAMPs, unless they have specific genetic deficiencies in relevant intracellular signaling molecules<sup>66</sup>.

### Inflammatory Signal Transduction

Inflammatory signals are transduced by a series of adaptor molecules that bind to the PRRs and protein kinases and phosphatases that control signal propagation in the cytoplasm,

culminating either in the rapid, post-transcriptional or post-translational modulation of a variety of inflammatory mediators, or in the activation of various transcription factors (Fig. 2B). These factors include nuclear factor- $\kappa$ B (NF- $\kappa$ B), activator protein-1 (AP-1), members of the CCAAT-enhancer-binding protein (C/EBP) family, Early Growth Response Protein 1 (EGR-1), p53 and Signal Transducer and Activator of Transcription 1 (STAT1). These mechanisms have been the subject of considerable study and have been reviewed extensively elsewhere.

### Production of “Classical” Inflammatory Mediators

A wide variety of cytokines and effector molecules such as reactive oxygen and nitrogen species are produced as a consequence of the receptor binding and signaling events described above (Fig. 2B). Many of these mediators and their actions in sepsis have been studied for two decades and have been discussed extensively elsewhere. It is important to note that among the earliest mediators to be tested both experimentally and clinically in sepsis, tumor necrosis factor alpha (TNF- $\alpha$ ) continues to be of interest from a systems perspective, since it is central to a well-studied positive feedback loop that augments both further production of TNF- $\alpha$  as well as numerous other inflammatory mediators. TNF- $\alpha$  also helps drive the production of anti-inflammatory cytokines. In patients with established SIRS, both pro-inflammatory cytokines and anti-inflammatory species co-exist in the circulation in markedly increased amounts, the simultaneous presence of both pro-inflammatory cytokines and their counter-regulators has been associated with adverse outcomes. Though the phenotype of systemic inflammation can be recapitulated by exogenous administration of TNF- $\alpha$ , a series of failed anti-cytokine clinical trials - as well as subsequent studies demonstrating the beneficial and necessary roles of TNF- $\alpha$  in a well-balanced inflammatory response - has led to a retrospective recognition of the individual- and context-specific interplay of pro- and anti-inflammatory mediators.

### DAMP's and “late mediators” of sepsis

As has been recently appreciated, intracellular molecules (e.g. intracellular proteins or fragments thereof, DNA, and even inorganic crystals) that are expressed or released following host tissue injury are endogenous equivalents of PAMPs. These molecules are known as alarmins or Damage-associated Molecular Patterns (DAMPs). DAMPs, like PAMPs, also bind to PRRs either expressed on the surface of immune cells or present intracellularly (Fig. 2). In the setting of sepsis, high mobility group protein B1 (HMGB1), a nuclear protein that stabilize nucleosome formation in almost all eukaryotic cells, is a key DAMP<sup>85–87</sup> and a therapeutic target. HMGB1 is but one member of a growing list of DAMP's<sup>89</sup>. For example, mitochondrial DNA and other products were recently reported to be DAMPs in the setting of trauma.<sup>90</sup>

While extensive, reductionist studies have yielded a tremendous amount of data and the potential for sepsis therapies directed against inflammatory cytokines<sup>74</sup>, TLR's<sup>91–93</sup> DAMP's such as HMGB1<sup>94–96</sup>, and mediators of inflammatory signal transduction<sup>97–99</sup>, we suggest that the development and implementation of such therapies will require an understanding of the complexity of the myriad actions and interactions of these ligands and receptors (Fig. 3)<sup>100–102</sup>.

## CHANGES IN PHYSIOLOGY DURING SEPSIS: INSIGHTS FROM COMPLEX SYSTEMS

Inflammation-induced organ dysfunction is a hallmark of sepsis. From a systems perspective, it has been hypothesized for over 15 years that these oscillatory systems are coupled, and that the disruption of this coupling is a hallmark of sepsis<sup>38</sup>. Both experimental

and clinical studies have suggested that one measure of this disrupted oscillatory coupling is reduced variability (or increased regularity) in various physiologic signals, chief among them being heart rate (Fig. 3)<sup>103–105</sup>. Time-domain analysis of heart rate variability (HRV) has subsequently evolved as a potential non-invasive diagnostic modality for sepsis<sup>106</sup>. These data can also be used indirectly to detect variability attributed to sympathetic and parasympathetic branches of the autonomic nervous system as well as other physiological processes that affect heart rate, including respiration, blood pressure, and temperature<sup>106</sup>. Using these sophisticated signal processing techniques, various studies have reported that a decrease in HRV indices may be potentially diagnostic of higher morbidity and mortality in critically ill patients. In addition to HRV, examination of other physiologic parameters from a complex systems approach has also yielded valuable insights into the physiology of sepsis. For example, changes in ventilation and breath-to-breath variability occur with sepsis, particularly in the setting of respiratory failure. Multiple mechanisms have been implicated including increased central drive and increased metabolic requirements<sup>115</sup>, as well the cyclooxygenase pathway<sup>116</sup>. Furthermore, these changes in breathing and heart rate variability have implications for heart-lung interactions in sepsis. However, we are still far from a complete understanding of the iterative, recursive interactions between inflammation and HRV. Based on prior work in animal models of sepsis (F.J. Jacono and T.E. Dick, unpublished observations), we hypothesize that pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$  act to decrease HRV and breathing pattern variability by affecting the central nervous system in septic patients, and that in turn reduced physiological variability further stimulates inflammation. If this hypothesis is correct, a systems understanding may allow us to unify the pattern-based, diagnostically relevant use of physiological waveforms with the increasingly detailed, mechanistic understanding of acute inflammation in order to improve therapy for sepsis (Fig. 3).

Renewed interest in the diagnostic utility of metrics such as HRV in the setting of trauma and sepsis suggests that these methods may reach clinical utility in the near future (see the recent 9<sup>th</sup> International Conference on Complexity in Acute Illness; [http://www.iccai.org/sci\\_info\\_2010.php](http://www.iccai.org/sci_info_2010.php)). We suggest that in order for the analyses of physiologic variability to progress beyond pattern analysis, a mechanistic understanding of how sepsis results in reduced physiologic variability is required. We further suggest that the inflammatory mechanisms described above will affect physiologic function (and will therefore manifest as changes in indices of physiologic variability); in turn, these changes in physiology will impact the inflammatory response (Fig. 3).

## DECIPHERING THE NONLINEAR PROCESS FLOW OF SEPSIS VIA COMPUTATIONAL SIMULATIONS

Despite promising results at the basic science and pre-clinical level, large-scale trials of therapies targeted at inhibiting specific inflammatory mediators have generally failed to improve survival<sup>118</sup>. Above, we have discussed the growing recognition that inflammation and the physiology to which it is coupled demonstrates complex, nonlinear behavior. This property significantly limits the intuitive extrapolation to system/patient level effects of mechanistic knowledge derived from basic science. Reductionism has been successful when applied to systems whose behavior can be reduced to a “linear” (i.e. single direct relationship) representation such that the results of various independent experiments can be aggregated additively to obtain and predict the behavior of the system as a whole<sup>28</sup>. However, systems such as the acute inflammatory response, that have multiple feedback loops and saturating dose response kinetics, are inherently nonlinear. The nonlinear interactions among pathogen recognition elements, signal transduction pathways, inflammatory mediators, DAMP’s, and the physiologic processes that they collectively

impact (Fig. 2A) require more sophisticated mathematical representation for their characterization<sup>23–31</sup>.

Systems biology approaches may offer a solution to understanding these interactions. For addressing complex biological processes such as the acute inflammatory response in sepsis<sup>28</sup>, both the NIH in its Roadmap Initiative (<http://nihroadmap.nih.gov/>) and the FDA in its “Critical Path” document have called for the use of *in silico* (computer) models to augment preclinical animal studies in order to develop novel therapies<sup>120</sup>. *In silico* studies use the growing power of digital computers to mine large databases in search of patterns that either elucidate mechanisms or that are diagnostically useful<sup>121</sup>. Mathematical models of physiology characterize the evolution of observables over time, and are therefore dynamic. Their purpose is predictive description—to provide entailment and insight into what the future state of the system might be, given knowledge of the current state of the system. This dynamic property suggests that mathematical models can be considered as testable hypotheses. When a mathematical model predicts measurable behavior that emulates the physiology under study, one can reasonably infer that the mathematical model has, in fact, captured potentially useful interrelations<sup>28</sup>. Conversely, when model and experiment disagree, the assumptions encapsulated in the model must be reassessed (it should be noted that this process is not limited to mathematical models). Therefore, transparency in model construction is critical, such that the assumptions underlying the model can be examined in detail. Since behavioral nonlinearities and high-dimensional parameter spaces represent challenges in the calibration of such models to experimental data, and since such data fitting is further impaired by uncertainty and variability of sparse observations (especially in settings of preclinical and clinical studies)<sup>122</sup>, the formalisms associated with mathematical models may provide a framework in which underlying hypotheses can be more effectively examined and modified.

There have been notable successes in the translational applications of mechanistic mathematical models of acute inflammation as applied to sepsis, trauma, and wound healing. On a purely theoretical level, simple models of acute inflammation have suggested that morbidity and mortality in sepsis may arise from diverse insult- and patient-specific circumstances such as pathogen number and virulence (i.e. degree to which pathogens stimulate a pro-inflammatory response), as well as the degree to which DAMPs are produced in response to both the pathogen and pro-inflammatory mediators<sup>123</sup>. Mathematical models of some of the inflammatory signal-transduction cascades described above may help drive mechanism-based drug discovery and device development, namely for the demonstration of likely efficacy throughout the development process; augmentation of and integration with existing experimental data sets directed towards drug/device development; and the execution of simulated clinical trials, both to facilitate the planning of future clinical trials.<sup>124–126</sup> (Fig. 3). Other mathematical models were used to yield insights into the acute inflammatory response in diverse shock states (most importantly the suggestion that a common “wiring framework” but different initial conditions could account for diverse manifestations of endotoxemic vs. hemorrhagic shock)<sup>127–132</sup>, as well as the responses to anthrax<sup>133</sup> and necrotizing enterocolitis<sup>134</sup>. At the pre-clinical level, mathematical modeling has helped define and predict the acute inflammatory responses of experimental animals and humans<sup>138</sup>, all crucial advances if we are to bridge the gap from imperfect pre-clinical animal models to the setting of human sepsis.

Initial translational successes of mathematical models involved the ability to reproduce (and suggest improvements to) clinical trials in sepsis (Fig. 3); these successes have been extended to the design of prospective clinical trials. One *in silico* clinical trial platform (Immunetrics, Inc.) was recently augmented to include a multi-scale, equation-based mechanistic simulation that encompasses dynamic interactions among multiple tissues,

immune cells, and inflammatory mediators, along with a “virtual clinician” (an automated system to examine simulated patients’ status at clinically relevant intervals and administer standard of care interventions as necessary). This mathematical model was fit to time course data consisting of various biomarkers and clinical markers, both inflammatory and physiologic variables from published human endotoxemia studies<sup>141</sup> as well and community-acquired severe sepsis patients in the Genetic and Inflammatory Markers of Sepsis (GenIMS)<sup>77</sup> study. This model was capable of reproducing the entire spectrum of patients in the GenIMS study by altering only a handful of parameters related to pathogen, antibiotic efficacy and baseline patient status. The model simulations provided evidence of changes in disease progression and likelihood of survival as a function of various treatments, patient stratification on the basis of outcome and time of death, and predictive ability for patient outcome beyond hospital discharge. Model training and optimization led to the identification of a minimum set of temporal analyte data required to predict future trajectories and outcomes of patients (S. Chang, Y. Vodovotz, J.A. Kellum, and D.C. Angus, unpublished observations). We suggest that computational platforms such as this one could usher in a new era of rationally-designed drugs, as well as informing the design of future clinical trials (Fig. 3).

From a potentially diagnostic standpoint (and in accord with clinical findings described above), studies involving mechanistic mathematical models of sepsis suggest that detrimental outcomes are accompanied by the simultaneous elevation of both pro- and anti-inflammatory mediators. Moreover, recent mathematical modeling studies have begun to lay the foundation for a similar mechanistic underpinning for the interactions between inflammation and HRV. Furthermore, insights provided by data-driven modeling approaches such as Principal Component Analysis (PCA) in individual trauma/sepsis patients suggest that characteristic profiles of pro- and anti-inflammatory cytokines are both central drivers of the pathology of severely ill patients, and that Principal Cytokine “barcodes” may be of diagnostic potential even though raw cytokine data may not. These advances in the use of mathematical modeling and related systems approaches hold the potential to change the way drugs and diagnostics are developed and clinical trials are designed and carried out, all based on rational, mechanistic, and, in a sense “predictable” underpinnings.

## CONCLUSIONS AND FUTURE PROSPECTS

We have come quite a long way since the early attempts at mathematical modeling in sepsis were met with both hope<sup>145</sup> and skepticism<sup>121</sup>. The septic response, a complex chain of events involving pro- and anti-inflammatory processes, humoral and cellular reactions, and microcirculatory alterations, requires that we move away from a biomarker search (whether biological or physiological<sup>158–161</sup>). Although many of these individual markers have shown merit in defined cohorts, we suggest that merely sorting through an ever-growing array of biomarkers and metrics of physiological signals will not solve the problem of accurate diagnosis or prediction of treatment efficacy. Rather, mechanistically-oriented computational simulation and modeling may be a means for reconciling the diverse attempts at diagnosis of sepsis, as well as providing a rational framework for the design of new, personalized therapies (Fig. 3). Though substantial additional work is needed, we suggest that computational modeling can facilitate the transition from static diagnosis towards a dynamic definition of the state of the individual septic patient.

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## ABBREVIATIONS

|              |  |
|--------------|--|
| <b>ICU</b>   | Intensive care unit                                    |
| <b>HIV</b>   | Human immunodeficiency virus                           |
| <b>ACCP</b>  | American College of Chest Physicians                   |
| <b>SCCM</b>  | Society of Critical Care Medicine                      |
| <b>MODS</b>  | Multiple Organ Dysfunction Syndrome                    |
| <b>SIRS</b>  | Systemic Inflammatory Response Syndrome                |
| <b>PIRO</b>  | predisposition; infection; response; organ dysfunction |
| <b>PRRs</b>  | Pattern recognition receptors                          |
| <b>PAMPs</b> | Pathogen-associated molecular patterns                 |
| <b>MAMPs</b> | Microbial-associated molecular patterns                |
| <b>DAMPs</b> | Damage-associated molecular patterns                   |
| <b>AIR</b>   | Acute inflammatory response                            |
| <b>HRV</b>   | Heart rate variability                                 |

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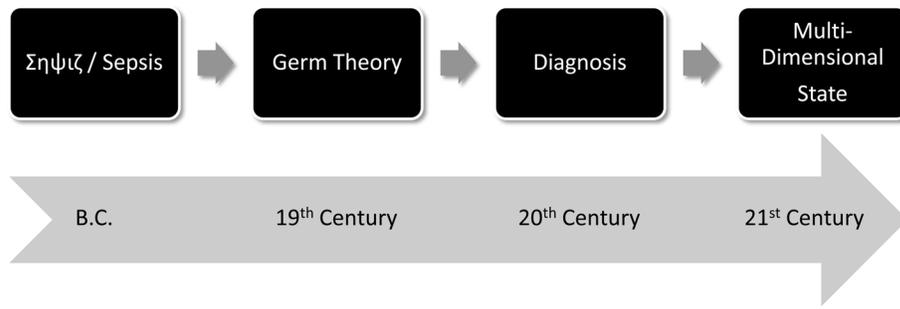
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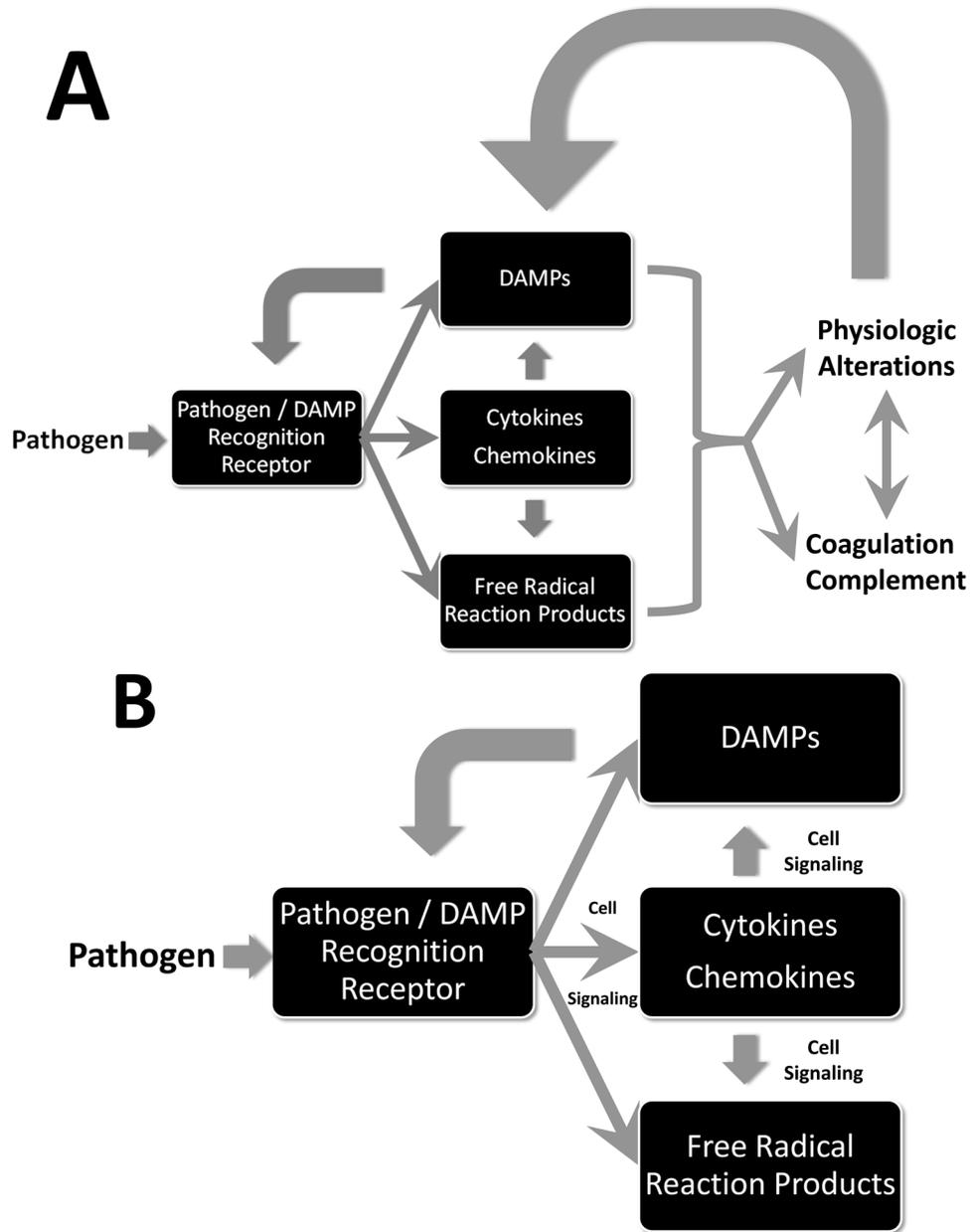
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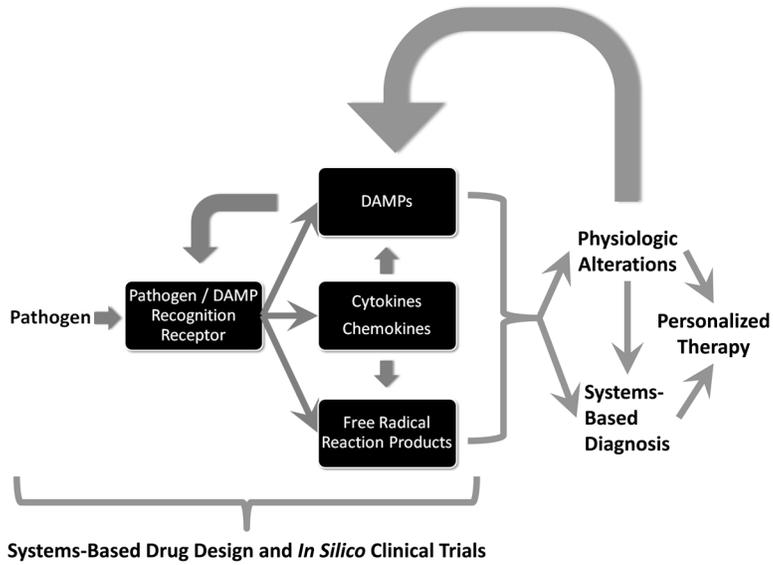


**Figure 1. Sepsis: A brief history**

Our concept of sepsis has progressed from phenomenological description (antiquity) to rigid diagnostic criteria (20<sup>th</sup> century). The future holds the potential for individualized, predictive, and multi-dimensional description of the patient’s state.



**Figure 2. Sepsis: A process flow**  
Upon stimulation by pathogens, a multifaceted inflammatory response ensues, driven by cytokines, free radical reaction products, and damage-associated molecular patterns (DAMPs). *Panel A:* The inflammatory response affects, and is affected by, interactions with physiological systems (manifest as reduced physiological variability) and the coagulation and complement cascades. *Panel B:* The acute inflammatory response is sensed via defined receptors for both pathogen-derived products and DAMPs, and modulated via intracellular signaling pathways.



**Figure 3. Towards multi-dimensional, individualized description of patient state**

The future of sepsis diagnosis and therapy will depend on a growing understanding of the cellular and molecular mechanisms of inflammation by which pathogens are sensed and eliminated, along with the effects of inflammation on physiology and *vice versa*. These interactions will form the basis of computational models used for rational design of drugs and the clinical trials by which those drugs are tested. Multi-dimensional analysis of inflammation biomarkers and physiologic waveforms, along with mechanistic mathematical modeling, may aid in discerning individual patient states for the purposes of diagnosis and therapy.