

From static to dynamic: a sepsis-specific dynamic model from clinical criteria in polytrauma patients

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Early recognition and diagnosis are the key to improve sepsis outcome

Sepsis is undoubtedly the most clinically challenging disease encountered in critically ill patients. The common consensus defines sepsis as a dysregulated host inflammatory response to an infectious agent (1). Sepsis is associated with mortality rates of around 30%, although these vary according to geographical location (2). There is no specific treatment for patients with sepsis, and management therefore relies on infection control—with source removal and effective antibiotics—along with organ function support (3).

Precision medicine, in which individualized therapies are provided to patients based on the specific genomic, cellular, and inflammatory alterations accompanying their disease process, is revolutionizing the treatment of cancer and other conditions (4). Such targeted treatment has been shown to be associated with enhanced clinical response among patients with cancer, often with diminished toxicity. Precision medicine is grounded in quantitative methods, in a sense replacing diagnosis of a specific disease or syndrome with a digital data stream about the individual patient. There would appear to be substantial potential for a similarly tailored approach to sepsis, given the heterogeneity of cellular responses associated with this condition. However, precision medicine for sepsis is hampered by multiple factors, not least among them being what causes sepsis and how to diagnose impending sepsis (5).

Because extensive pre-clinical data suggested an overwhelming inflammatory response to be responsible for the clinical syndrome of 'sepsis', numerous clinical trials have been conducted over the past three decades with an intent to counteract the inflammatory response. None of these trials showed convincing (if any) beneficial effects, though meta-analyses have suggested that, in aggregate, clinical trials targeting inflammation suggested some benefit (6). Since it has been accepted that 'simply' blocking single pathways such as tumor necrosis factor (TNF)- α does not suffice to treat sepsis (7), the number of clinical trials has dropped significantly. Indeed, a recent perspective article suggested that inflammation was an epiphenomenon, rather than a generative mechanism in sepsis (8). Suffice it to say that it is increasingly appreciated that sepsis is far more complex than initially appreciated, and underlying mechanisms likely involve multiple redundant, often parallel, pathways (9).

The recent Sepsis-3 guidelines attempt to skirt around this difficulty by simplifying the diagnostic criteria for sepsis (10), but this has led to some controversy as well (11,12). Ideally, a diagnostic test of some sort is needed to state definitively and unequivocally that a given patient 'has sepsis' or not. Given the aforementioned complexity, however, it is perhaps not surprising that a sepsis-specific clinical, biochemical, or molecular biomarker continues to elude us (13). The lack of precise diagnostic criteria or

definition also impacts on clinical research development, in particular making the identification of patients, evaluation of the efficacy of treatment, and assessment of patient outcomes more problematic. Without the appropriate and timely diagnosis of sepsis, clinical trials investigating novel therapeutics remain methodologically challenging. Thus, one key question pursued by investigators is: how can we improve our ability to diagnose sepsis?

There is good evidence that early diagnosis of sepsis is paramount to enable rapid treatment, improve outcomes, and reduce unnecessary antibiotic therapy. However, unlike polytrauma, the initial signs of sepsis are subtle and easily missed by clinicians. In addition, the signs that constitute the systemic inflammatory response syndrome (SIRS) criteria were selected to be sensitive, but not necessarily specific for sepsis, making early diagnosis of the syndrome prone to false-positive classifications.

The utility of inflammation biomarkers for sepsis—including various cytokines, cell surface markers, receptors, complement and coagulation factors, and acute phase reactants—has been proposed and assessed clinically (13). However, none of these potential biomarkers has a high specificity for sepsis, and consequently none has reached clinical use. Thus, at present, there is no ideal clinical gold standard for the diagnosis of sepsis, as microbiology is not sensitive enough and laboratory tests are non-specific for use as a reference standard (14).

A key aspect of biology that is typically overlooked in the clinical setting is that of dynamics: biological processes change, often dramatically, as a function of time. This is especially true in the setting of sepsis and trauma, in which massive changes in biology and physiology occur over a period of minutes to hours to days. These dynamics are often caused by, and also drive, positive and negative feedbacks on multiple systems in the body. The nonlinearity of these dynamic changes may be one key reason that the mystery of sepsis continues to elude us. Thus, dynamics are a key place to look for improvement of clinical sepsis diagnosis (15-17). Over the past decade, we and others have attempted to decipher the bio-complexity of inflammation in the settings of sepsis and trauma, using computational models to ultimately improve clinical translation. We and others have suggested *in silico* modeling as a computationally-based framework for integrating data derived from basic biology experiments as well as preclinical and clinical studies (9,18). Other studies have demonstrated that computational modeling methods can harness real-time data incorporated into electronic health records to predict

clinically relevant outcomes in patients with sepsis (19,20). Data-driven models such as dynamic Bayesian and neural networks have been employed to predict the progression of organ failure based on the Sequential Organ Failure Assessment (SOFA) score and mortality in the intensive care unit (ICU) (21). Although the aforementioned studies demonstrate the feasibility of extracting clinically relevant information pertaining to patients with sepsis, they do not specifically deal with the early identification of sepsis. Thus, computer-based integrated systems deployed early during the clinical course are needed for continuous data collection and analysis to identify and triage patients who might be septic.

Dynamic inference of sepsis clinical criteria

One elegant approach to overcome this issue was conducted recently by Lindner and colleagues (22). In this study, the investigators developed a sepsis-specific algorithm in a polytrauma cohort admitted to the ICU. They focused on polytrauma patients because these patients are susceptible to nosocomial infections and sepsis, and, as touched upon above, the time =0 for initiating the cascade of intertwined physiologic derangements can be determined fairly precisely (unlike sepsis).

The algorithm described by Lindner *et al.* advances the conventional concept of the clinical assessment of SIRS, from a static dichotomous classification of patients towards a dynamic, real-time, quantitative characterization of the inflammatory process. This study demonstrates the feasibility of defining the complex dynamics of inflammation using correlative, data-driven modeling approaches, which include regression techniques that build models predictive within the conditions of the data upon which they were trained. Although these methods do not provide detailed mechanistic insight, they can be used to understand abstract features of the response, such as the presence of nonlinearities and the order of the response. The main drawback of this class of models is that they are often lack mechanistic insight, and can be over-fit to the data on which they were trained (19,23).

Several strengths of this innovative study are worthy of mention. The study is based on a retrospective analysis of a clinically well-characterized, carefully selected, adult ICU patient population which complements the contemporary German polytrauma patients. The authors were thoughtful with regard to their use of dynamic data-driven models, and their specificity analyses were reassuring in suggesting

that their findings were robust. The key novelty of the work presented concerns the derivation of three numerical constructs: (I) a metric the authors call λ , which is based on the minute-to-minute SIRS data and which accounts for the overall trend in number of SIRS criteria; (II) the count of changes in λ (which the authors call “ Δ ”); and (III) a quantification of fluctuations in SIRS criteria (which the authors call “C”). The authors further strengthened their findings by using logistic regression analysis to identify factors independently associated with the diagnosis of sepsis. Collectively, these analyses allowed for increased specificity of the model to predict sepsis in the 24 h period prior to actual sepsis diagnosis. Their primary findings focused on differences within the sepsis cohort, but there is an added value in including a non-sepsis comparator group, and here the investigators chose a well-matched, contemporary patient population of ICU patients without sepsis.

Conclusions and future perspective

The study by Lindner and colleagues demonstrate the importance of implementing timely and accurate recording systems in hospital ICUs for the objective collection of patient data which could facilitate early sepsis diagnosis. Rather than simply collecting more static data, a focused collection of measurements over time can preserve important events and features of a patient's state. This may at least flag these patients to healthcare professionals, so that appropriate investigations and further management can be implemented in a timely fashion. A dynamic decision support system that accurately predicts sepsis could focus limited resources, avoid ‘alert fatigue’ that may accompany decision support systems, and decrease procedural complications for patients. Indeed, work from multiple groups, key among them Moorman and collaborators, has focused on the clinical prognostic value of dynamic assessment of physiologic waveforms (e.g., heart rate variability) in the setting of pediatric sepsis (24,25).

Future prospective studies, such as those from Lindner *et al.*, which incorporate additional information on patient history, laboratory data, and established biomarkers to the algorithm are warranted to improve the sensitivity and specificity of the model. In particular, the evolving organ dysfunction central to the pathogenesis of sepsis appears to be a pivotal confounder and an important outcome measure in any trial of therapies for sepsis. Thus, adding a composite metric score of organ dysfunction such as the Marshall multiple organ dysfunction score or SOFA score to the model would

potentially enhance the predictive accuracy. Overall, the analyses presented in this study demonstrate the promise of predicting and particularly diagnosis of sepsis, which may facilitate sepsis risk assessment and improve compliance with therapeutic guidelines, and ultimately significantly decrease the risk of sepsis mortality.

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Footnote

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References

1. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250-6.
2. Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014;2:380-6.
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
4. Jameson JL, Longo DL. Precision medicine—personalized, problematic, and promising. *N Engl J Med* 2015;372:2229-34.
5. Buchman TG, Billiar TR, Elster E, et al. Precision Medicine for Critical Illness and Injury. *Crit Care Med* 2016;44:1635-8.
6. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med* 2014;20:195-203.
7. Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet* 1998;351:929-33.
8. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. *Immunity* 2014;40:463-75.
9. Namas R, Zamora R, Namas R, et al. Sepsis: Something old, something new, and a systems view. *J Crit Care* 2012;27:314.e1-11.
10. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria

- for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:775-87.
11. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest* 2016;149:1117-8.
 12. Abraham E. New Definitions for Sepsis and Septic Shock: Continuing Evolution but With Much Still to Be Done. *JAMA* 2016;315:757-9.
 13. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care* 2010;14:R15.
 14. De La Rosa GD, Valencia ML, Arango CM, et al. Toward an operative diagnosis in sepsis: a latent class approach. *BMC Infect Dis* 2008;8:18.
 15. Jopling J, Buchman TG. Sepsis through the eyes of an engineer -- why treatments have succeeded and failed. *Crit Rev Biomed Eng* 2012;40:353-61.
 16. Buchman TG. The digital patient: predicting physiologic dynamics with mathematical models. *Crit Care Med* 2009;37:1167-8.
 17. Buchman TG. Nonlinear dynamics, complex systems, and the pathobiology of critical illness. *Curr Opin Crit Care* 2004;10:378-82.
 18. Vodovotz Y, Billiar TR. In silico modeling: methods and applications to trauma and sepsis. *Crit Care Med* 2013;41:2008-14.
 19. Peelen L, de Keizer NF, Jonge Ed, et al. Using hierarchical dynamic Bayesian networks to investigate dynamics of organ failure in patients in the Intensive Care Unit. *J Biomed Inform* 2010;43:273-86.
 20. Hanisch E, Büssow M, Brause R, et al. Individual prognosis of critically ill patients with septic shock by neural network? *Chirurg* 1998;69:77-81.
 21. Pittet D, Thiévent B, Wenzel RP, et al. Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients. *Am J Respir Crit Care Med* 1996;153:684-93.
 22. Lindner HA, Balaban Ü, Sturm T, et al. An Algorithm for Systemic Inflammatory Response Syndrome Criteria-Based Prediction of Sepsis in a Polytrauma Cohort. *Crit Care Med* 2016;44:2199-207.
 23. Namas RA, Mi Q, Namas R, et al. Insights into the Role of Chemokines, Damage-Associated Molecular Patterns, and Lymphocyte-Derived Mediators from Computational Models of Trauma-Induced Inflammation. *Antioxid Redox Signal* 2015;23:1370-87.
 24. 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;159:900-6.e1.
 25. Moss TJ, Lake DE, Calland JF, et al. Signatures of Subacute Potentially Catastrophic Illness in the ICU: Model Development and Validation. *Crit Care Med* 2016;44:1639-48.

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