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The current understanding of sepsis and research priorities for the future

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This special issue of *Virulence* is entirely devoted to the topic of sepsis and septic shock. Septic shock continues to pose formidable challenges for emergency room physicians, critical care specialists, surgeons, and infectious disease clinicians alike in caring for these critically ill patients. Early recognition of sepsis and improved therapies to manage the multi-organ dysfunction that frequently follows sepsis pathophysiology remain major unmet medical needs. The interplay between virulence factors of the pathogen and the antimicrobial defenses of the host are critical determinants of outcome in sepsis and septic shock.[1] This issue of *Virulence* will specifically focus on both the pathogen-related factors and the host defense mechanisms that lead to septic shock and contribute to its resolution or fatal outcome. We have assembled a stellar group of international experts in the field of sepsis research and compiled their ideas and collective wisdom in this special issue. We hope to provide a detailed review of the state of the art and science of septic shock research as it currently exists, extending from the molecular level to the population level.

This issue begins with a description of current secular trends into the epidemiology of sepsis and septic shock worldwide. The paper by Mayr, Yende, and Angus[2] provides an overview of the clinical parameters and consequences of sepsis across different populations of "at risk" patients worldwide. The complex interactions between pre-existing, chronic diseases, and host response capabilities against invasive microbial pathogens are considered in this epidemiologic review. The impact of gender and sex sterol effects on the host response in sepsis is reviewed by Angele and colleagues.[3] Females throughout the mammalian class are less susceptible to infection and death from infection compared with their male counterparts. This appears to be true in humans as well and insights into the explanation for these gender differences might provide some new therapeutic approaches to sepsis.

The history behind the current classification of sepsis and the systemic inflammatory response is provided by Robert Balk,[4] a long standing colleague and frequent co-author of Roger Bone. John Marshall provides an alternative way of looking at, and better characterizing, the acute systemic inflammatory process in sepsis using the PIRO model (predisposition, insult/infection, response, organ dysfunction) that he helped to develop.[5] The terminology of sepsis and our lack of ability to specifically identify important subgroups within a large and heterogeneous group of patients defined by term "sepsis" remain imprecise and an area of much-needed additional research.[6]

Our current understanding about the interaction between pathogen and host immune defenses is considered in a series of three manuscripts in this issue of *Virulence*. The first paper is by Drs Wiersinga, Leopold, Cranendonk, and van der Poll.[7] The host immune response and the pattern recognition receptors that orchestrate the host response to infection are reviewed in detail in this paper. An in-depth discussion of the relative importance of the hyper-inflammatory process vs. the prolonged, sepsis-induced, immunosuppressive phase is provided by Drs Boomer, Green, and Hotchkiss.[8] The weight of evidence now supports the view that the immune-suppressive phase is the predominant immunologic response in most patients with sepsis.[9] This changes the paradigm for treatment interventions when trying to establish immune reconstitution in septic patients. The next paper by Giamarellos and Christaki focuses on those special virulence characteristics possessed by bacterial pathogens that can evade host defenses and disseminate into the systemic circulation of the host.[10]

The fundamental role of mitochondrial dysfunction in sepsis is expertly reviewed by Mervyn Singer.[11] Cellular energetics and the loss of mitochondrial function play a major role in the pathophysiology of sepsis at the cellular and tissue level. Insights into new treatment strategies are being illustrated through the investigation of mitochondrial function and dysfunction during sepsis. The critically important, underlying pathophysiology of the microcirculatory dysfunction of sepsis is reviewed in detail by Drs DeBacker, Cortes, Donadello, and Vincent.[12] Ultimately, the presence or absence of reacquisition of adequate tissue perfusion to vital organs largely determines the outcome in septic shock and remains a major target for improved therapeutic interventions.

The role of specific pathogens and related host responses directed against these pathogens are considered in a series of papers in this issue of *Virulence*. Anand Kumar presents compelling evidence of an alternative way of looking at sepsis focused on pathogen load and the need to bring the microbial burden to a rapid resolution is essential in treating septic shock.[13] The unique role of meningococcal disease and its complex interactions with various components of the complement system is considered by Lewis and Ram.[14] A similarly distinct and highly specialized host response to group A streptococci in the

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pathogenesis of toxic shock syndrome is detailed by Reglinski and Sriskandan.[15] The immunology of superantigens and the myriad of exotoxins produced by group A streptococci are reviewed in this paper. Finally, the complex interactions between influenza and bacterial pathogens in severe sepsis are described by Florescu and Kalil.[16] Although many viral pathogens predispose to secondary bacterial infections, influenza is likely the most common and potentially most lethal virus that contributes to bacterial sepsis.

The lack of success with translating discoveries in the animal laboratory to successful treatments for patients in the intensive care unit with sepsis is a stark reminder of how inadequate our animal models are when it comes to understanding sepsis. The various issues related to animal models of sepsis are considered in an objective and critical manner by Mitchell Fink.[17] Recent evidence of the poor to completely absent predictive correlations between the genomics of mice and humans following systemic infection bespeaks of the need to improve our preclinical models in septic shock.[18]

The critical need for improved biomarkers for the rapid diagnosis of sepsis is detailed by Bloos and Reinhart.[19] Our current inability to detect important subpopulations within the septic patient population by clinical criteria alone is evidenced by the simple lack of value of SIRS criteria to distinguish between hyperinflammatory or hypoinflammatory host responses in sepsis.[1,9] Efforts to develop better biomarkers to assist the clinician in the rapid and accurate diagnosis of sepsis are considered in this review.

Special populations with unique yet overlapping characteristics are considered in a series of papers in this issue. The first manuscript relates to the problem of invasive candidiasis in the critically ill patient. Drs Delaloye and Calandra discuss the current diagnostic algorithms available to make a rapid diagnosis of candidiasis in the ICU patient.[20] This is a major challenge from both a clinical and laboratory perspective. The poor outcomes associated with delayed or inadequate treatment for disseminated candidiasis is a stark reminder of the importance of making this diagnosis with skill and alacrity. Improvements in molecular diagnostic methods and treatment strategies are now underway in the management of candidiasis in the ICU.

The unique characteristics of sepsis in neonates (expertly reviewed by Shah and Padbury[21]) and the post-neonatal, pediatric sepsis patients are highlighted by Randolph and McCulloh.[22] These special patient populations require individualized treatment that may differ substantially from the management of adult sepsis. A brief review of the new surviving sepsis campaign guidelines for the treatment of adult sepsis is provided by Schorr, Zanotti, and Dellinger.[23] The 2012 guidelines are practical, informative, and quite helpful in organizing the appropriate treatment approach to a septic patient.[24] Optimal fluid management and glucose control is described in detail in the following article by Simon Finfer.[25]

The final section of this sepsis issue relates to complexities of treatment of systemic infections in an age of progressively increasing, antibiotic resistance. The emerging issues of extreme drug resistance in gram-negative bacteria are discussed in a timely review by Pop-Vicas.[26] We are running out of antimicrobial agents to treat common gram-negative infections and the future looks rather bleak with respect to the development of new chemotherapeutic agents. Because of this shortcoming, therapies other than antimicrobial chemotherapy are now under consideration. One option is to approach the intrinsic virulence of the organism based upon the toxins produced by the invasive bacterial pathogen. The current status of the role of bacterial toxins in sepsis pathogenesis is discussed by Dr Ramachandran.[27]

One of the most attractive targets for management of septic shock from an immunologic perspective is vaccines or immunotherapy directed against bacterial endotoxin. This topic is discussed at length by Alan Cross in his paper on anti-endotoxin vaccines.[28] The last manuscript in this issue rekindles an old idea that is making a distinct comeback as a potential therapeutic option. Instead of using chemotherapy, the idea of using phage therapy with a specific bacteriophage or phages against specific bacterial pathogens is witnessing a rebirth in interest by clinical investigators. The promise and problems of phage therapy as an alternative to antibiotics is discussed by Xavier Wittebole.[29] Some combination of non-antibiotic therapy with standard antibiotic strategies might become a common management approach for septic shock therapy in the future.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-51; PMID:23984731; http://dx.doi.org/10.1056/NEJMra1208623
2. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014; 5:4-11; PMID:24335434; http://dx.doi.org/10.4161/viru.27372
3. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: Cardiovascular and immunological aspects. Virulence 2014; 5:12-9; PMID:24193307; http://dx.doi.org/10.4161/viru.26982
4. Balk RA. Systemic inflammatory response syndrome (SIRS): Where did it come from and is it still relevant today? Virulence 2014; 5:20-6; PMID:24280933; http://dx.doi.org/10.4161/viru.27135
5. Marshall JC. The PIRO (Predisposition, Insult, Response, Organ Dysfunction) model: Towards a staging system for acute illness. Virulence 2014; 5:27-35; PMID:24184604; http://dx.doi.org/10.4161/viru.26908
6. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet 2013; 381:774-5; PMID:23472921; http://dx.doi.org/10.1016/S0140-6736(12)61815-7
7. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence 2014; 5:36-44; PMID:23774844; http://dx.doi.org/10.4161/viru.25436
8. Boomer JS, Green JM, Hotchkiss S. The changing immune system in sepsis: Is individualized immune-modulatory therapy the answer? Virulence 2014; 5:45-56; PMID: 24067565; http://dx.doi.org/10.4161/viru.26516
9. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 2013; 13:260-8; PMID:23427891; http://dx.doi.org/10.1016/S1473-3099(13)70001-X
10. Christaki E, Giamarellos-Bourboulis EJ. The complex pathogenesis of bacteremia: From antimicrobial clearance mechanisms to the genetic background of the host. Virulence 2014; 5:57-65; PMID:24067507; http://dx.doi.org/10.4161/viru.26514
11. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence 2014; 5:66-72; PMID:24185508; http://dx.doi.org/10.4161/viru.26907

12. DeBacker D, Cortes O, Donadello K, Vincent J-L. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5:73-9; PMID: 24067428; http://dx.doi.org/10.4161/viru.26482
13. Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock: Implications for optimizing antimicrobial therapy. Virulence 2014; 5:80-97; PMID:24184742; http://dx.doi.org/10.4161/viru.26913
14. Lewis LA, Ram S. Meningococcal disease and the complement system. Virulence 2014; 5:98-126; PMID:24104403; http://dx.doi.org/10.4161/viru.26515
15. Reglinski M, Sriskandan S. The contribution of group A streptococcal virulence determinants to the pathogenesis of toxic shock syndrome. Virulence 2014; 5:127-38; PMID:24157731; http://dx.doi.org/10.4161/viru.26400
16. Florescu DF, Kalil AC. The complex link between influenza and severe sepsis. Virulence 2014; 5:137-42; PMID:24253109; http://dx.doi.org/10.4161/viru.27103
17. Fink MP. Animal models of sepsis. Virulence 2014; 5:143-53; PMID:24022070; http://dx.doi.org/10.4161/viru.26083
18. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 2013; 110:3507-12; PMID:23401516; http://dx.doi.org/10.1073/pnas.1222878110
19. Bloos F, Reinhart K. Rapid diagnosis of sepsis. Virulence 2014; 5:154-60; PMID:24335467; http://dx.doi.org/10.4161/viru.27393
20. Delaloye J, Calandra T. Invasive candidiasis as a cause of sepsis in the critically ill patient. Virulence 2014; 5:161-9; PMID:24157707; http:/dx.doi.org/10.4161/viru.26187
21. Shah BA, Padbury JF. Neonatal sepsis: An old problem with new insights. Virulence 2014; 5:170-8; PMID:24185532; http://dx.doi.org/10.4161/viru.26906
22. Randolph AG, McCulloh RJ. Pediatric sepsis: Important considerations for diagnosing and managing severe infections in infants, children and adolescents. Virulence 2014; 5:179-89; PMID:24225404; http://dx.doi.org/10.4161/viru.27045
23. Schorr CA, Zanotti S, Dellinger RP. Management of severe sepsis and septic shock. Virulence 2014; 5:190-9; PMID:24335487; http://dx.doi.org/10.4161/viru.27409
24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al.; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580-637; PMID:23353941; http://dx.doi.org/10.1097/CCM.0b013e31827e83af
25. Finfer S. Clinical controversies in the management of critically ill patients with severe sepsis: Resuscitation fluids and glucose control. Virulence 2014; 5:200-5; PMID:23921249; http://dx.doi.org/10.4161/viru.25855
26. Pop-Vicas A, Opal SM. The clinical impact of multidrug-resistant gram-negative bacilli in the management of septic shock. Virulence 2014; 5:206-12; http://dx.doi.org/10.4161/viru.26210
27. Ramachandran G. Gram-positive and gram-negative toxins in the context of sepsis. Virulence 2014; 5:213-8; PMID:24193365; http://dx.doi.org/10.4161/viru.27024
28. Cross AS. Anti-endotoxin vaccines: Back to the future. Virulence 2014; 5:219-24; PMID:23974910; http://dx.doi.org/10.4161/viru.25965
29. Wittebole X, De Roock S, Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence 2014; 5:225-35; PMID:23973944; http://dx.doi.org/10.4161/viru.25991