Commentary

Bugs, genes, and the intensive care unit

Kerina Jane Denny[1,2], Jeffrey Lipman[1,2,3]

[1]Department of Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia; [2]Burns, Trauma & Critical Care Research Centre, The University of Queensland, Brisbane, Australia; [3]Faculty of Health, Queensland University of Technology, Brisbane, Australia

Correspondence to: Dr. Kerina J. Denny. Department of Intensive Care Royal Brisbane and Women's Hospital, Herston, QLD, 4006, Australia. Email: k.denny@uq.edu.au.

Submitted May 15, 2016. Accepted for publication May 27, 2016.
doi: 10.21037/jtd.2016.06.19
View this article at: http://dx.doi.org/10.21037/jtd.2016.06.19

Severe sepsis and septic shock are among the leading causes of mortality in critically ill patients (1). Patients who survive the initial septic insult often still die in the intensive care unit (ICU) despite receiving timely resuscitation and appropriate early antibiotic therapy. What kills these patients? Why do some patients with sepsis succumb whilst others survive? What distinguishes sepsis from other diseases that cause significant systemic inflammation and immunomodulation?

It has been hypothesized that the immune suppression observed in sepsis could predispose to the development of secondary hospital-acquired infection, with the late phase of sepsis associated with a significant re-emergence of positive blood cultures (2). Although this is a biologically plausible supposition, previous research has not convincingly addressed: (I) whether sepsis-associated immunosuppression is a significant risk factor for secondary infection; (II) if secondary nosocomial infections contribute significantly to the mortality of patients admitted with sepsis; and (III) whether it is possible to prospectively differentiate between those patients who go on to develop secondary ICU-acquired infections and those who do not.

In a recent prospective study published in *JAMA*, van Vught and colleagues (3) aimed to determine the incidence, risk factors, and attributable mortality of secondary infection in patients admitted to the ICU with sepsis. In the study period, there were 1,719 admissions for sepsis with 232 admissions (13.5%) being complicated by a secondary ICU-acquired infection. In a subgroup of 461 patients with sepsis on admission, the investigators performed whole-genome expression profiling of blood leukocytes, both at the time of ICU admission and again on the day that ICU-acquired complications occurred. In doing so, the investigators elegantly demonstrated the value of an insight into the transcriptome in sepsis research. We herein discuss three of the ways in which whole gene expression was utilized by van Vught and colleagues to provide insight into the pathophysiology of sepsis. Finally, other potential uses of whole genome profiling in critically ill septic patients are addressed.

Characterizing the host immune response to sepsis

Whole gene expression analysis can be used to characterize the host immune response to sepsis. Analogous to previous studies (4), van Vught *et al.* demonstrated that the genomic response to sepsis was typified by the concurrent upregulation of multiple pro- and anti-inflammatory pathways, with downregulation of adaptive immune system pathways. Intriguingly, very similar patterns of immune response have been demonstrated in patients with burn injuries and after severe blunt trauma (5).

The similarity in the immunogenomic phenotype between patients with infectious and non-infectious conditions may partly explain the finding that there was a comparable incidence of ICU-acquired infection in those patients admitted with non-infectious diagnosis (15.1%) (3). van Vught and colleagues were understandably cautious with direct comparisons between these two populations due to significant differences in antibiotic exposure and ICU length-of-stay between the groups. Nonetheless, it is interesting to note that patients with an admission diagnosis of sepsis had both a higher incidence of acquiring more than one nosocomial infection and more ICU-acquired infections with opportunistic pathogens. The authors hypothesized that this may relate to possible immune suppression in the

sepsis group, however this supposition is inconsistent with previous studies demonstrating similar immunophenotypes in patients with non-infectious conditions (5). We therefore propose differences in antibiotic exposure as an alternative potential explanation.

Prior antibiotic exposure has previously been identified as a significant risk factor for future resistant nosocomial infections (6). Antibiotics are known to significantly alter microbiome composition through the selection of opportunistic pathogens that can cause disease (6). The van Vught *et al.* study was not designed to assess the role of antibiotics as a risk factor for secondary nosocomial infection in patients with sepsis and extrapolations into the role of antibiotics from this dataset is further confounded by the use of selective decontamination of the digestive tract and selective oropharyngeal decontamination in this study population. We thus propose that future studies utilizing gene expression analysis to determine the impact of antibiotics on host immune responses could be of significant interest in delineating the role of primary sepsis versus antibiotic therapy with regards to risk of secondary infection.

Determining whether differences in leukocyte gene expression can predict risk of secondary nosocomial infection

In a relatively novel application of transcriptome research in sepsis, van Vught and colleagues aimed to determine whether differences in the leukocyte gene expression could identify which patients with sepsis go on to develop a secondary nosocomial infection.

Van Vught and colleagues found that the leukocyte genomic response in patients at baseline in patients admitted with sepsis did not differ between those patients who did and did not go on to develop a secondary infection. Thus it is likely that other factors confer greater susceptibility to nosocomial infections in patients admitted with sepsis. Indeed, consistent with previous studies (7), the investigators identified more severe disease, use of central venous lines, and mechanical ventilation as significant risk factors for ICU-acquired infection.

Notably, the investigators demonstrated a modest 2% (95% CI, 0.2–3.8%) difference in mortality at day 60 in all patients with a sepsis admission diagnosis compared to patients admitted with sepsis who did not develop an ICU-acquired infection. Nevertheless, nosocomial infections have tremendous costs to the healthcare system (8). Thus, there is value in continuing to identify other factors that contribute to the risk of nosocomial infection with the aim of developing innovative strategies and tools to decrease their incidence.

Whole gene expression analysis as a tool for hypothesis generation

Whole gene expression analysis can also enable for the generation of novel hypotheses. By employing repeated measurement of the transcriptome in each subject, van Vught and colleagues found that those patients with an ICU-acquired infection had a diminished expression of genes involved in leukocyte glucose metabolism at the onset of secondary infection. Glycolysis plays a key role in the capacity of immune cells to mount an inflammatory response (the Warburg effect) (9). The investigators thus hypothesized a role for impaired glycolysis in sepsis that may increase susceptibility to ICU-acquired infections. We await prospective studies to test this hypothesis.

Future directions for whole gene expression analysis in sepsis research

Aside from the above applications, others have proposed that gene expression analysis has additional applications in furthering sepsis research. Of particular interest is the use of transcriptome research in helping guide antibiotic therapy.

Diagnosis of sepsis has been shown to be extremely subjective and variable (10). Clinicians face the dilemma of either potentially withholding a life-saving treatment with the threat of rapid patient deterioration or, conversely, inappropriately administering antibiotics in the absence of infection with the associated harms of antibiotic resistance. Assays that aim to identify the presence of microbes faster than conventional microbiological cultures are in various stages of development (11). These tests, however, remain susceptible to the problems of contamination, colonization, and the possibility of false positives in that small amounts of dead bacteria may be measured leading to the identification of microorganisms that are not necessarily responsible for host disease. We therefore hypothesize that the ideal biomarker for sepsis will come from identification of the host response to sepsis.

Although several host biomarkers for sepsis have been proposed, including C-reactive protein and pro-calcitonin, they have failed to demonstrate the diagnostic accuracy required to guide initiation of antibiotic therapy (12). Given the biological complexity of sepsis, it has been stated

that a stratification strategy based on a panel of multiple biomarkers such as gene expression has more potential to meet the needs of an ideal tool for diagnosis of sepsis and consequently guide antibiotic use (13). Studies that have utilized transcriptome analysis to identify a subset of genes that can predict the presence of sepsis are emerging (14). Others have utilised transcriptome analysis for the purpose of defining subgroups of septic patients with different immune response states and prognoses (15). We await the results of future studies in this area and, in particular, the development of a novel point-of-care test that guides clinicians as to when to commence antibiotics.

Conclusions

By embracing whole genome profiling, van Vught and colleagues have furthered our knowledge of the host immune response to sepsis and secondary infection. We eagerly anticipate future advances in gene-expression technology that have the potential to significantly alter our understanding and management of sepsis.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Zhongheng Zhang (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: van Vught LA, Klein Klouwenberg PM, Spitoni C, *et al.* Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA 2016;315:1469-79.

References

1. Danai P, Martin GS. Epidemiology of sepsis: recent advances. Curr Infect Dis Rep 2005;7:329-34.
2. Otto GP, Sossdorf M, Claus RA, et al. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Crit Care 2011;15:R183.
3. van Vught LA, Klein Klouwenberg PM, Spitoni C, et al. Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA 2016;315:1469-79.
4. 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.
5. Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. J Exp Med 2011;208:2581-90.
6. Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. Front Microbiol 2016;6:1543.
7. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274:639-44.
8. Marchetti A, Rossiter R. Economic burden of healthcare-associated infection in US acute care hospitals: societal perspective. J Med Econ 2013;16:1399-404.
9. Palsson-McDermott EM, O'Neill LA. The Warburg effect then and now: from cancer to inflammatory diseases. Bioessays 2013;35:965-73.
10. Rhee C, Kadri SS, Danner RL, et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. Crit Care 2016;20:89.
11. Tissari P, Zumla A, Tarkka E, et al. Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. Lancet 2010;375:224-30.
12. Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. J Hosp Med 2013;8:530-40.
13. Cornell TT, Wynn J, Shanley TP, et al. Mechanisms and regulation of the gene-expression response to sepsis. Pediatrics 2010;125:1248-58.
14. Sutherland A, Thomas M, Brandon RA, et al. Development and validation of a novel molecular biomarker diagnostic test for the early detection of sepsis. Crit Care 2011;15:R149.
15. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med 2016;4:259-71.

Cite this article as: Denny KJ, Lipman J. Bugs, genes, and the intensive care unit. J Thorac Dis 2016;8(8):E788-E790. doi: 10.21037/jtd.2016.06.19

