REVIEW

Patient-related determinants of host response and sepsis outcome

M.A. Wiewel[1,2], L.A van Vught[1,2], T. van der Poll[1,2], M.J. Schultz[3]

[1]Center for Experimental and Molecular Medicine, [2]Center for Infection and Immunity Amsterdam, [3]Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence

M.A. Wiewel - m.a.wiewel@amc.uva.nl.

Abstract

Sepsis is an important cause of morbidity and mortality in intensive care unit patients. In this review, the results of studies with specific research questions performed within a large prospective observational study on sepsis in the Netherlands are discussed. The studies investigated various factors that may affect the host response during sepsis, and may have an impact on the outcome, including prior medication (antiplatelet agents, calcium channel blockers, and statins), HIV infection, and hypothermia. Neither prior medication nor HIV infection were associated with large differences in the host response during sepsis, whereas only prior use of calcium channel blockers was associated with an improved outcome. In addition, while hypothermia was not associated with an altered immune response, there was an independent association between hypothermia and mortality.

Introduction

Worldwide, more than 19 million cases of severe sepsis are estimated to occur annually, resulting in more than 5 million deaths.[1]. The incidence rate of sepsis is estimated at 270 per 100,000 person years in high-income countries.[1] The incidence of sepsis has increased over the past decades[2,3] and this trend is expected to continue due to ageing of the population, increased burden of comorbidities, cumulative use of immunosuppressive drugs, chemotherapy, transplantation and invasive procedures.[4] Hence, sepsis is a large burden on human health.

One essence of sepsis pathogenesis lies in the failure of the body to effectively eliminate the invading pathogen, repair tissue and reconstitute homeostasis upon infection. Sepsis is in part the consequence of a dysregulated host response to infection, characterised by disproportionate pro- and anti-inflammatory components, coagulation and complement factors, and disturbed vascular responses, including increased leukocyte adhesion, vasodilation, and loss of endothelial barrier function, leading to tissue and organ damage.[5,6]

This review discusses various studies with specific research questions performed within the 'Molecular Diagnosis and Risk Stratification of Sepsis' (MARS) study, a large prospective observational study of sepsis in two academic intensive care units (ICUs) in the Netherlands. Various factors that may have an effect on the host response during sepsis, and may impact outcome were studied, including cardiovascular medication (antiplatelet agents, calcium channel blockers, and statins), HIV infection, and hypothermia *(figure 1)*. These studies were bundled in an academic thesis.
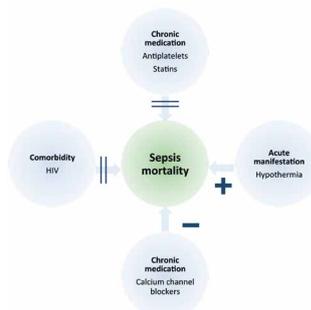

Figure 1. Association between host factors and survival in critically ill patients with sepsis Hypothermia was associated with increased mortality, calcium channel blocker use with reduced mortality. HIV, antiplatelet and statin therapy were not associated with altered mortality. Host response biomarkers were largely similar in patients with and without the particular host factor.

The MARS study

The MARS study was a collaboration of multiple partners and registered at clinicaltrials.gov (identifier NCT01905033). The primary aim of the MARS study was to develop tools that can provide rapid and accurate information on pathogen and host immune response or status. These tools should be easy to use,

available at or close to the bedside, aiding the clinician in the determination of the optimal treatment in an individual patient. From 2011 until 2013, consecutive patients aged 18 years or older and admitted to the mixed medical-surgical ICUs of the Academic Medical Center in Amsterdam and the University Medical Center Utrecht were included if they were expected to have a length of stay of at least 24 hours; the project had no other inclusion and exclusion criteria.[7-11]

Clinical data were prospectively collected from all patients, including demographics, premorbid comorbidities, use of prior (cardiovascular) medication, ICU admission characteristics, daily physiological measurements, disease severity scores, complications such as acute kidney injury and acute respiratory distress syndrome, and microbiology test results and antibiotic prescriptions. For all patients, leftover plasma was stored for protein biomarker analysis, including measurement of cytokines, endothelial activation and coagulation markers; also, whole blood was collected for genome wide RNA expression profiling of leukocytes. During the three-year study period, 6984 unique patients were enrolled in the MARS study, amounting to 8305 ICU admissions.

Prior cardiovascular medication

Cardiovascular disease is among the most common premorbid diseases in sepsis patients.[12,13] Preclinical studies using animals and observational studies in humans suggest that several cardiovascular drugs possess anti-inflammatory, antioxidant and other immune-modulatory effects, which, when used during infection, may modify the host response to sepsis.[14-17]

Antiplatelet therapy

Besides their role in primary haemostasis, platelets also exert important immune functions.[16,18] While platelets have been implicated in multiple inflammatory and procoagulant reactions, knowledge on effects of antiplatelet therapy on host response in sepsis patients is very limited. In the MARS study it was hypothesised that antiplatelet therapy modifies the host response during sepsis. In the MARS cohort, severity of illness upon ICU admission was similar in antiplatelet users compared with non-users and there was no association with an altered risk of mortality.[19] There was also no association between prior antiplatelet therapy and plasma concentrations of biomarkers indicative of key host responses to severe infection. Specifically, antiplatelet therapy was not associated with alterations in systemic inflammation, coagulation, endothelial activation, or renal injury during sepsis.

Previous observational studies investigating associations between antiplatelet therapy and outcomes in patients admitted to an ICU with sepsis have reported variable results.[20-23] Two of these studies used propensity matching to correct for baseline differences between antiplatelet users and non-users.[21,23] One of them entailed patients admitted to a medical ICU with severe

sepsis or septic shock, and observed no influence of antiplatelet therapy after adjusting for the propensity to receive antiplatelet therapy and severity of illness, calculated using the APACHE III score.[21] The other one encompassed patients admitted to the ICU with systemic inflammatory response syndrome (SIRS), a subgroup of which was classified as sepsis; propensity analysis revealed a mortality reduction in acetylsalicylic acid users in both the overall SIRS population and the sepsis subgroup.[23] While both studies adjusted for concurrent statin use, other prior medication use, such as beta-blockers, calcium channel blockers, and ACE inhibitors, was not taken into account.[21,23] The third study consisted of a regression analysis to establish the impact of prior antiplatelet therapy on sepsis outcome showing an association between low-dose acetylsalicylic acid therapy with decreased hospital or ICU mortality.[22] Another study concerning the continuous use of acetylsalicylic acid during ICU stay reported similar findings.[24] Lastly, an investigation reported an association between prior antiplatelet treatment and reduced sepsis mortality using a medical claims database.[20] The analysis of the MARS data was different from these previous reports in several aspects. First, in the MARS study patients were prospectively enrolled and classified based on strict diagnostic criteria and post-hoc assessment of trained research physicians, taking into account all available clinical and microbiological information. Second, propensity matching allowed us to compose comparable patients cohorts with respect to multiple relevant patient characteristics. Sepsis patients are heterogeneous in terms of age, comorbidity, genetic background, severity, site and microbiology, and plasma biomarker levels demonstrated variability between patients, which may explain the lack of effect by prior antiplatelet therapy. Nonetheless, these data argue against a beneficial effect of prior antiplatelet therapy on sepsis severity and outcome. To our knowledge no randomised controlled trials of antiplatelet therapy have been performed in critically ill sepsis patients.

Statins

Several investigators have looked at the association between prior statin use and outcome in hospitalised patients with infections. Considering the abundant literature on pleiotropic non-lipid-lowering properties of statins, the MARS study was used to explore associations between prior statin use and host response characteristics in critically ill patients with sepsis. For this, plasma biomarkers were measured to provide insight into systemic inflammatory reactions, activation of the endothelium and the coagulation system, and studied whole genome expression profiles in blood leukocytes. Sepsis patients who were on prior statin therapy prior to admission were compared with those who were not on prior statin therapy, in both the complete and in a propensity score matched cohort. The results of this analysis suggest that prior statin therapy does not affect any of the host response pathways in ICU patients with sepsis

(as yet unpublished data). In the MARS cohort, prior statin use was not associated with altered mortality either.

Previous investigations in patients with infection and/or sepsis studying the association between statin use and host response biomarkers were small or limited in the number of biomarkers studied. Only one study focused on sepsis patients admitted to the ICU, which showed that atorvastatin treatment was neither associated with altered plasma IL-6 levels nor survival.[25] Prior statin therapy, however, was associated with low baseline plasma IL-6 levels and continuation of atorvastatin in this cohort was linked to improved survival.[25]

Most observational studies have shown a survival benefit for patients with sepsis on prior statin therapy, with recent meta-analyses reporting an overall lower risk of sepsis and infection-associated death in prior statin users.[26,27] Several trials were undertaken, demonstrating no therapeutic effect of statins on sepsis outcome.[27,28] Heterogeneity of the study groups was an important limitation of the meta-analysed observational studies. Therefore, in the MARS study the analyses were adjusted for important co-variables, including many comorbidities and prior (cardiovascular) medication. Also, 'healthy user' effects cannot be ruled out, which may have influenced the protective effect of statins in some studies, and publication bias may have occurred. Altogether, these data suggest that statin therapy does not influence the host response to sepsis in patients requiring ICU admission.

Calcium channel blockers

Studies in animals have suggested that calcium channel blockers (CCBs) can lower mortality induced by endotoxaemia or sepsis by restoring intracellular calcium homeostasis;[29-33] however, knowledge on the association between prior CCB use and outcome in humans with sepsis is limited. Therefore, this association was studied in the MARS cohort of critically ill patients with sepsis. Prior use of CCBs was associated with improved survival in multivariable analysis of the complete cohort as well as in analysis of a cohort in which CCB users were matched to controls by demographics, comorbidities and prior medication.[34] The influence of CCBs on three key host response systems implicated in sepsis pathogenesis was studied (i.e., activation of the cytokine network, the vascular endothelium and the coagulation system) by measuring biomarkers indicative of these responses during the first four days after ICU admission. Biomarkers were similar in propensity-matched CCB users and non-users except for less reduction in antithrombin levels relative to normal values in CCB users. In the unmatched cohort, CCB use was associated with reduced cytokine release and blunted reductions in the anticoagulant proteins antithrombin and protein C, which suggests some effect of CCBs in patients who also receive other cardioprotective and/or vasoactive drugs. Since the finding on the potential beneficial effect of prior CCB use in patients

with sepsis was the first report on this association, these data should be confirmed in another sepsis cohort. One earlier study reported on the link between CCB use and outcome of severe infection. This retrospective analysis of the clinical records of 388 bacteraemic patients caused by aerobic Gram-negative bacilli and Staphylococcus aureus, prior CCB use was not associated with altered mortality in multivariate analysis. [35] This study differed from the MARS study in various ways, i.e., its retrospective nature, and patient inclusion criteria (only bacteraemic patients and the absence of information about the type of care).[35]

In multivariate analyses the relation between prior use of other cardioprotective medication and sepsis mortality was investigated. In particular the role of beta-blocker therapy in sepsis is currently under debate; a randomised controlled trial demonstrated a significant difference in 28-day mortality between septic shock patients treated with esmolol (49.4%), compared with the placebo group (80.5%).[36] In the MARS cohort, prior use of beta-blockers was not associated with altered 30-day mortality. One earlier observational study reported on prior beta-blocker use and sepsis outcome.[37] Patients previously prescribed beta-blockers had a lower frequency of death at 28 days than those previously untreated. Of importance, patients in this study were included based on hospital discharge records versus prospective inclusion by dedicated research physicians in the MARS study, and the fact that all hospitalised patients were enrolled versus ICU patients. [37] In a cohort of patients with pneumonia, prior beta-blocker use was not associated with mortality.[38] This study is different to the MARS study in that only pneumonia patients requiring hospital admission were included, whereas the MARS study was conducted in sepsis patients requiring intensive care and with different sources of infection.

HIV infection

The epidemiology of sepsis in patients infected with the human immunodeficiency virus (HIV) has changed dramatically upon the introduction of combination antiretroviral therapy.[39] The incidence of opportunistic infections has decreased and long-term survival improved; however, invasive bacterial infections and sepsis remain an important cause of morbidity and mortality in HIV patients.[40,41] The MARS investigators studied the impact of chronic HIV infection on the presentation, outcome and host response of sepsis patients.[42] ICU admissions of HIV-positive patients for sepsis more often involved pneumonia compared with admissions of HIV-negative patients. There were no significant differences in mortality up to one year after admission between HIV-positive and HIV-negative patients in the total sepsis cohort, as well as in the pneumosepsis subgroup. In ICU patients with sepsis, HIV/AIDS was independently associated with in-hospital mortality in other studies.[43-45] However, these differed from the MARS investigation in patient

selection[43,44] and setting,[45] resulting in a cohort of patients with more severe disease [43-45]. Over time, standards of care for HIV patients have improved considerably and studies suggest that survival of critically ill HIV-infected patients has improved in the era of widespread cART availability.[46,47] These findings indicate that in a setting with excellent access to care and HIV treatment, the prognosis of sepsis patients with HIV infection admitted to the ICU has become similar to that of patients without HIV infection.

As there were large demographic differences between HIV-positive and -negative patients, a control cohort of 90 admissions of HIV-negative pneumonia patients matched for age, sex and race was composed to study the host response. The levels of most host response biomarkers were similar in admissions of HIV-positive and HIV-negative patients, with the exception of interferon-γ and soluble ICAM-1, which were higher in HIV-positive patients at day 0 and 2.

Two earlier studies on the host response in adult HIV patients with sepsis have been published, reporting plasma cytokine levels.[48,49] HIV status had little impact; one of these studies reported elevated plasma IL-10 levels in the presence of unaltered plasma IL-6 levels in HIV-positive patients with sepsis.[49].However, these only included patients with advanced AIDS defining disease and high mortality rates (around 50%).[48,49] Chronic HIV infection seems to induce endothelial cell activation and disturbances,[50] responses that are also observed in patients with sepsis.[51] In Malawian children with severe bacterial infection, plasma angiopoietin-2, an angiogenic peptide that increases endothelial activation and vascular permeability, was more elevated in patients with HIV co-infection compared with controls.[52] In the adult ICU patients with pneumosepsis from the MARS cohort, HIV status did not influence plasma levels of specific endothelial cell activation markers (angiopoietin-1 and -2, and soluble E-selectin). Interestingly, HIV-positive patients displayed higher circulating levels of soluble ICAM-1, which can be shed by both endothelial cells and leukocytes. HIV infection can enhance the release of exosomes containing ADAM17 (ADAM metallopeptidase domain 17), the cleaving protease for ICAM-1, which promotes ICAM-1 shedding.[53] Increased levels of IFN-γ, as observed in the MARS study, may also contribute to the release of sICAM-1.[54]

Hypothermia

Patients with sepsis can display profound hypothermia, being observed in 9-35% of septic patients,[55,56] the underlying mechanism of which is poorly understood. Immune suppression, due to an excessive anti-inflammatory response, has been proposed as a mechanism for hypothermia.[59]. Also, a recent study showed that hypothermia was associated with lymphopenia following diagnosis of sepsis,[60] thereby potentially accounting for the association with adverse outcome.[55,56,61,62] The MARS study aimed to determine risk factors of the occurrence of hypothermia during the first 24 hours of ICU admission and to characterise the host response in patients with hypothermic sepsis.[57] Lower body mass index, hypertension and chronic cardiovascular insufficiency were associated with hypothermic sepsis. Hypothermia was independently associated with mortality in multivariate analysis, confirming previous studies.[55,58]

In order to obtain insight into the pathophysiological mechanisms, pro- and anti-inflammatory cytokines and endothelial activation markers were measured.. Pro- or anti-inflammatory cytokine levels were not different between hypothermic and non-hypothermic patients in the MARS study, even after correction for disease severity, which is in line with a study in hypothermic patients reporting no difference in circulating levels of proinflammatory cytokines.[62] The host response biomarkers were similar in groups of patients with and without hypothermia, except for plasma fractalkine, which was higher in patients with hypothermia, and this difference remained after correction for disease severity. Fractalkine is a chemokine that has been implicated as a mediator in a diverse spectrum of inflammatory conditions and is associated with adverse outcome in critically ill patients with sepsis.[63] Endothelial cells have been described as an important source of fractalkine.[64] Considering the presence of mainly cardiovascular risk factors in patients with hypothermia, the MARS data may suggest that the endothelium is implicated in hypothermia. The association between hypothermia and enhanced circulating levels of fractalkine in a population with significantly increased disease severity requires further evaluation.

Discussion

Within the MARS consortium a large prospective cohort of critically ill patients was studied, in which patients were methodically categorised and followed by committed research physicians. Besides information on demographics, comorbidities, and other patient-related factors, the MARS database also included extensive data on the septic episodes, i.e., timing of the infection, sepsis-induced organ failure and causative pathogens. In addition, a large set of host response biomarkers were measured, which provided further insight into the immune response of sepsis patients admitted to the intensive care unit. Although the studies on the association between prior medication, disease severity, host response and outcome were performed in an extensive cohort of patients, the observational nature of MARS studies does not allow for assessment of causal relationships. Propensity score matching was implemented to enable estimation of the independent effect of individual factors. The size of the MARS study population allowed it to perform matching by many important covariates; however, bias can remain as a result of unmeasured confounders. Another limitation involves the fact that this study was performed in two centres in the Netherlands, limiting generalisability of the results.

Conclusion

In the future, the number of patients who will present with sepsis is likely to increase due to ageing of the population, aggressive therapies for chronic diseases (most notably cancer) and the emergence of multidrug resistant pathogens. As a consequence, the management of sepsis will remain an important issue in the years to come. In the MARS study several 'external' and host factors that might influence sepsis outcome and the accompanying host response were studied, particularly prior medication (antiplatelet agents, CCBs, statins) and comorbidity (HIV infection). None of these factors had a major impact on the host response to sepsis, while only the use of CCBs was associated with an altered (improved) outcome. In addition, the influence of an acute manifestation of severe infection (i.e., hypothermia) on sepsis outcome and the host response was examined, revealing an independent association between hypothermia and mortality without evidence for an altered immune response. Sepsis patients are heterogeneous in terms of comorbidity, age and host response, therefore adjuvant therapies for sepsis may differ from patient to patient. Great advances have been made in terms of understanding the pathogenesis of sepsis in recent years, and implementation of this increased knowledge in clinical practice will likely facilitate individualised treatment of patients with sepsis.

Disclosures

References

1. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193:259-72.
2. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311:1308-16.
3. Kumar G, Kumar N, Taneja A, et al. Nationwide trends of severe sepsis in the 21st century (2000-2007). Chest. 2011;140:1223-31.
4. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5:4-11.
5. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353:i1585.
6. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840-51.
7. Scicluna BP, Klein Klouwenberg PM, van Vught LA, et al. A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. Am J Respir Crit Care Med. 2015;192:826-35.
8. Klein Klouwenberg PM, Ong DS, Bos LD, et al. Interobserver agreement of Centers for Disease Control and Prevention criteria for classifying infections in critically ill patients. Crit Care Med. 2013;41:2373-8.
9. 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.
10. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, Management, and Risk-Adjusted Mortality of ICU-Acquired Enterococcal Bacteremia. Clin Infect Dis. 2015:civ560.
11. Geboers DG, de Beer FM, Tuip-de Boer AM, et al. Plasma suPAR as a prognostic biological marker for ICU mortality in ARDS patients. Intensive Care Med. 2015;41:1281-90.
12. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546-54.
13. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323-9.
14. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins: panacea for sepsis? Lancet Infect Dis. 2006;6:242-8.
15. Akinosoglou K, Alexopoulos D. Use of antiplatelet agents in sepsis: a glimpse into the future. Thromb Res. 2014;133:131-8.
16. de Stoppelaar SF, van 't Veer C, van der Poll T. The role of platelets in sepsis. Thromb Haemost. 2014;112:666-77.
17. Mekontso-Dessap A, Brun-Buisson C. Statins: the next step in adjuvant therapy for sepsis? Intensive Care Med. 2006;32:11-4.
18. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. Blood. 2014;123:2759-67.
19. Wiewel MA, de Stoppelaar SF, van Vught LA, et al. Chronic antiplatelet therapy is not associated with alterations in the presentation, outcome, or host response biomarkers during sepsis: a propensity-matched analysis. Intensive Care Med. 2016;42:352-60.
20. Tsai MJ, Ou SM, Shih CJ, et al. Association of prior antiplatelet agents with mortality in sepsis patients: a nationwide population-based cohort study. Intensive Care Med. 2015;41:806-13.
21. Valerio-Rojas JC, Jaffer IJ, Kor DJ, Gajic O, Cartin-Ceba R. Outcomes of severe sepsis and septic shock patients on chronic antiplatelet treatment: a historical cohort study. Crit Care Res Pract. 2013;2013:782573.
22. Otto GP, Sossdorf M, Boettel J, et al. Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock. Platelets. 2013;24:480-5.
23. Eisen DP, Reid D, McBryde ES. Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis. Crit Care Med. 2012;40:1761-7.
24. Sossdorf M, Otto GP, Boettel J, Winning J, Losche W. Benefit of low-dose aspirin and non-steroidal anti-inflammatory drugs in septic patients. Crit Care. 2013;17:402.
25. Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med. 2013;187:743-50.
26. Ma Y, Wen X, Peng J, Lu Y, Guo Z, Lu J. Systematic review and meta-analysis on the association between outpatient statins use and infectious disease-related mortality. PLoS One. 2012;7:e51548.
27. Wan YD, Sun TW, Kan QC, Guan FX, Zhang SG. Effect of statin therapy on mortality from infection and sepsis: a meta-analysis of randomized and observational studies. Crit Care. 2014;18:R71.
28. National Heart L, Blood Institute ACTN, Truwit JD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med. 2014;370:2191-200.
29. Hotchkiss RS, Karl IE. Calcium: a regulator of the inflammatory response in endotoxemia and sepsis. New Horiz. 1996;4:58-71.
30. Bosson S, Kuenzig M, Schwartz SI. Verapamil improves cardiac function and increases survival in canine E. coli endotoxin shock. Circ Shock. 1985;16:307-16.
31. Wyska E. Pretreatment with R(+)-verapamil significantly reduces mortality and cytokine expression in murine model of septic shock. Int Immunopharmacol. 2009;9:478-90.
32. Song SK, Karl IE, Ackerman JJ, Hotchkiss RS. Increased intracellular Ca2+: a critical link in the pathophysiology of sepsis? Proc Natl Acad Sci U S A. 1993;90:3933-7.
33. Bosson S, Kuenzig M, Schwartz SI. Increased survival with calcium antagonists in antibiotic-treated bacteremia. Circ Shock. 1986;19:69-74.
34. Wiewel MA, van Vught LA, Scicluna BP, et al. Prior Use of Calcium Channel Blockers Is Associated With Decreased Mortality in Critically Ill Patients With Sepsis; a Prospective Observational Study. Crit Care Med. 2017;45:454-463.
35. Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. Clin Infect Dis. 2001;33:1352-7.
36. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA. 2013;310:1683-91.
37. Macchia A, Romero M, Comignani PD, et al. Previous prescription of beta-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. Crit Care Med. 2012;40:2768-72.
38. Wu A, Good C, Downs JR, et al. The association of cardioprotective medications with pneumonia-related outcomes. PLoS One. 2014;9:e85797.
39. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis. 2000;30 Suppl 1:S5-14.
40. Huson MA, Stolp SM, van der Poll T, Grobusch MP. Community-acquired bacterial bloodstream infections in HIV-infected patients: a systematic review. Clin Infect Dis. 2014;58:79-92.

41. Japiassu AM, Amancio RT, Mesquita EC, et al. Sepsis is a major determinant of outcome in critically ill HIV/AIDS patients. Crit Care. 2010;14:R152.
42. Wiewel MA, Huson MA, van Vught LA, et al. Impact of HIV infection on the presentation, outcome and host response in patients admitted to the intensive care unit with sepsis; a case control study. Crit Care. 2016;20:322.
43. Mrus JM, Braun L, Yi MS, Linde-Zwirble WT, Johnston JA. Impact of HIV/AIDS on care and outcomes of severe sepsis. Crit Care. 2005;9:R623-30.
44. Tolsma V, Schwebel C, Azoulay E, et al. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. Chest. 2014;146:1205-13.
45. Cribbs SK, Tse C, Andrews J, Shenvi N, Martin GS. Characteristics and Outcomes of HIV-Infected Patients With Severe Sepsis: Continued Risk in the Post-Highly Active Antiretroviral Therapy Era. Crit Care Med. 2015;43:1638-45.
46. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients With HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. Chest. 2009;135:11-7.
47. Huson MA, Bakhshi-Raiez F, Grobusch MP, de Jonge E, de Keizer NF, van der Poll T. Characteristics and Outcome of Patients With AIDS in Dutch ICUs Between 1997 and 2014. Crit Care Med. 2016;44:291-9.
48. Amancio RT, Japiassu AM, Gomes RN, et al. The innate immune response in HIV/AIDS septic shock patients: a comparative study. PLoS One. 2013;8:e68730.
49. Silva JM, Jr., De Sousa dos Santos S. Sepsis in AIDS patients: clinical, etiological and inflammatory characteristics. J Int AIDS Soc. 2013;16:17344.
50. Huson MA, Grobusch MP, van der Poll T. The effect of HIV infection on the host response to bacterial sepsis. Lancet Infect Dis. 2015;15:95-108.
51. Opal SM, van der Poll T. Endothelial barrier dysfunction in septic shock. J Intern Med. 2015;277:277-93.
52. Mankhambo LA, Banda DL, Group IPDS, et al. The role of angiogenic factors in predicting clinical outcome in severe bacterial infection in Malawian children. Crit Care. 2010;14:R91.
53. Lee JH, Wittki S, Brau T, et al. HIV Nef, paxillin, and Pak1/2 regulate activation and secretion of TACE/ADAM10 proteases. Mol Cell. 2013;49:668-79.
54. Witkowska AM, Borawska MH. Soluble intercellular adhesion molecule-1 (sICAM-1): an overview. Eur Cytokine Netw. 2004;15:91-8.
55. Kushimoto S, Gando S, Saitoh D, et al. The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. Crit Care. 2013;17:R271.
56. Clemmer TP, Fisher CJ, Jr., Bone RC, Slotman GJ, Metz CA, Thomas FO. Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group. Crit Care Med. 1992;20:1395-401.
57. Wiewel MA, Harmon MB, van Vught LA, et al. Risk factors, host response and outcome of hypothermic sepsis. Crit Care. 2016;20:328.
58. Tiruvoipati R, Ong K, Gangopadhyay H, Arora S, Carney I, Botha J. Hypothermia predicts mortality in critically ill elderly patients with sepsis. BMC Geriatr. 2010;10:70.
59. Leon LR. Hypothermia in systemic inflammation: role of cytokines. Front Biosci. 2004;9:1877-88.
60. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. Shock. 2014;42:383-91.
61. Drewry AM, Fuller BM, Skrupky LP, Hotchkiss RS. The presence of hypothermia within 24 hours of sepsis diagnosis predicts persistent lymphopenia. Crit Care Med. 2015;43:1165-9.
62. Marik PE, Zaloga GP. Hypothermia and cytokines in septic shock. Intensive Care Med. 2000;26:716-21.
63. Hoogendijk AJ, Wiewel MA, van Vught LA, et al. Plasma fractalkine is a sustained marker of disease severity and outcome in sepsis patients. Crit Care. 2015;19:412.
64. Sung MJ, Kim W, Ahn SY, et al. Protective effect of alpha-lipoic acid in lipopolysaccharide-induced endothelial fractalkine expression. Circ Res. 2005;97:880-90.