10. Peake SL, Delaney A, Bailey M, et al; The ARISE investigators and the ANZICS Clinical Trials Group: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506
11. Rowan KM, Angus DC, Bailey M, et al; PRISM Investigators: Early, goal-directed therapy for septic shock – a patient-level meta-analysis. *N Engl J Med* 2017; 376:2223–2234
12. Brower RG, Matthay MA, Morris A, et al; The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
13. Okonkwo DO, Shutter LA, Moore C, et al: Brain tissue oxygen monitoring and management in severe traumatic brain injury (BOOST-II): A phase II randomized trial. *Crit Care Med* 2017; 45:1907–1914
14. Le Roux P, Menon DM, Citerio G, et al: Consensus summary statement of the international multidisciplinary consensus conference on multimodality monitoring in neurocritical care. *Neurocrit Care* 2014; 21:S1–S26
15. Saugel B, Michard F, Scheeren TWL: Goal-directed therapy: Hit early and personalize! *J Clin Monit Comput* 2018; 32: 375–377

Saved From Sepsis: Can Immunotherapy Improve Acute and Postacute Outcomes?*

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Sepsis causes millions of deaths per year with mortality still ranging from 25% in the developed world up to 50% in developing countries (1). Sepsis-induced lymphocytopenia is common, affecting approximately 25–60% of patients with septic shock (2). Secondary immunosuppression has been in part attributed to lymphocyte cell death secondary to apoptosis (2). Apoptosis in sepsis affects multiple different cell lines including both circulatory cells such as lymphocytes and solid organ cells such as splenocytes and intestinal epithelial cells (2, 3). Lymphocyte apoptosis is reported to be two times higher than other critically ill patients and five times higher than controls (2). Of interest, neutrophils do not appear to be subject to sepsis-induced apoptosis and in fact, many patients with sepsis demonstrate neutrophilia (2). Unfortunately, the neutrophils become functionally deficient, thus still rendering them a component of the overall level of immunosuppression in sepsis.

Sepsis-induced lymphocytopenia is associated with poor outcomes among patients in the ICU, including mortality at both 28 days and 1-year survival; however, there are many other confounding factors that can also cause lymphocytopenia other than sepsis in the ICU (2, 4). Current literature suggests that the longer the persistence of the lymphocytopenia, the worse the outcome (2, 5). Sepsis-induced immunosuppressive states occur within the first few days of hospitalization and often persists beyond hospital discharge (5). Among survivors, there may be an increased risk for development of secondary infections, including healthcare-associated infections (2, 6). Further, the state of immunosuppression due to sepsis also predisposes patients to the risk of reactivation of latent viruses such as cytomegalovirus (7). The development of immunosuppression negatively impacts the prognosis of patients to survive the acute phase of sepsis resuscitation, but may also increase the risk for secondary infections both in-hospital and post-discharge, prompting hospital readmission (5, 6, 8, 9).

With increasing rates of index sepsis survivorship, there is concurrently an increased patient population at risk for hospital readmissions and secondary infections (10). Hospital readmissions after an index hospitalization for sepsis are common, with approximately 25% being readmitted within 30 days and 48% within 180 days (11, 12). Those with medical comorbidities had a higher risk of readmissions, and the majority of readmissions were secondary to infections deemed either recurrent or unresolved (11, 12). Over time, there has been a small decrease in hospital readmission for sepsis; however, this comes at the cost of increased post-sepsis Emergency Department visits (10).

Given the association with worse outcomes and potential risk of secondary infections, targeting restoration of lymphocytes is an attractive treatment strategy for sepsis. In animal models, antiprogrammed cell death ligand-1 (anti–PD-L1) antibody has been shown to inhibit lymphocyte apoptosis with overall improvement in survival (2, 13).

PD1 receptors play an integral negative role in immunoregulation and have been studied in both cancer therapy for multiple malignancies and in relation to HIV latency (13–17). Unlike cancers where PD1 up-regulation varies and thereby limits potential efficacy of therapeutic targets, PD1 is upregulated in sepsis (16). Further, among patients with sepsis due to multidrug-resistant infections, anti–PD-L1 may be associated with improvement in lymphocytopenia and increase in interferon-gamma production (3). Anti–PD-L1 has also been used for other infections, such as JC virus, hepatitis C, HIV, and mucormycosis, with promising results, but this is based on very limited evidence (3). Therapeutically, these antibodies function as immune checkpoint inhibitors to the PD-L1 and PD-L2 ligands, thereby minimizing the lymphocyte apoptosis

*See also p. 632.

Key Words: antiprogrammed cell death ligand-1; immunomodulation; lymphocytopenia; sepsis

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and resultant immunosuppression (13). In sepsis models, PD1 receptors appear to be upregulated, and antibody blockade of these receptors may reduce sepsis-induced immunosuppression, therefore making this a potential therapy in patients with sepsis induced-lymphocytopenia (13).

The study Immune checkpoint inhibition in sepsis by Hotchkiss et al (18), in this issue of *Critical Care Medicine*, is a Phase Ib, prospective randomized double-blind placebo controlled multicenter trial of adult patients admitted to the ICU with sepsis or septic shock who had sepsis-associated immunosuppression as defined by an absolute lymphocyte count of less than or equal to 1,100 cells/μL. Patients were randomized to receive either an infusion of anti–PD-L1 (BMS-936559) at staged doses or placebo. Primary objectives were to assess the safety and tolerability of the anti–PD-L1 treatment over a total of 90 days with secondary objectives assessing the pharmacokinetics, the receptor uptake and the effect of a single dose of the drug on overall immune function via assessment of monocyte human leukocyte antigen-DR levels as a marker for immunoparalysis. Twenty-five patients were randomized and 14 completed the 90-day follow-up. The control and treatment groups were statistically different at baseline, with the treated group being older and sicker based on organ dysfunction. Adverse events recorded were not uncommon among critically ill patients and the only events reported to be believed secondary to the study treatment were an increase of amylase, lipase, and blood lactate dehydrogenase. Based on the dose given, the half-life ranged from 29 hours to 189 hours, an apparent faster elimination as compared with those with cancer. Along those receiving the single highest dose at 900 mg, the measured receptor occupancy lasted for 28 days; for the lowest dose, it lasted 8 days. There was no evidence of secondary cytokine storm secondary to therapy.

With any immune modulating therapy, the risks must be evaluated. In preventing apoptosis, there is concern for a possible cytokine storm, subsequent end-organ damage, and overall worsened survival (2, 13, 15). Although the authors cite the potential treatments adverse events including pancreatitis and pneumonitis, which are clearly of particular concern among the critically ill patients, there are other described adverse events including fatigue, varying dermatologic manifestations, hypothyroidism, hepatitis, renal failure, and neurologic toxicities (15). In fact, in the study by Hotchkiss et al (18), compared with placebo, the anti–PD-L1 treatment arm had a numerically higher number of deaths (30% vs 0%), higher grade 3–4 adverse events (35% vs 0%), higher rate of hypotension (55% vs 0%), and higher rate of respiratory disorders (25% vs 0%); even though the small sample size of the study precludes a precise interpretation, all of these safety issues had zero rate in the placebo arm. Two other limitations of this new study include the fact that a dose-effect on cytokines and human leukocyte antigen (HLA)-DR, as well as a faster immune restoration could not be detected by the use of anti–PD-L1.

The anti–PD-L1 approach has the potential to impact sepsis in two phases: 1) during the acute index sepsis episode via decrease in end-organ damage by reducing apoptosis and improving the overall immune function, assuming that a cytokine storm is not induced and 2) in the post-sepsis immunosuppression state via decrease in the subsequent risk of secondary infections while the immune system is recovering. Among major remaining questions, the critical ones are regarding the generalizability of these new study findings. At what specific stage of sepsis would immunomodulation therapy be used? Bedside cytometry following decreasing expression of HLA-DR among monocytes? Lymphocytopenia? Both? What if the patient already has pneumonitis, acute respiratory distress syndrome, hepatitis, or pancreatitis? If this only affects T cells, how would this impact the epidemiology and outcome of secondary bacterial infections? Is there any risk of an immune reconstitution syndrome and its subsequent harmful effects?

We congratulate Hotchkiss et al (18) for their important work which moves the field forward regarding the understanding of the immunotherapy effects on sepsis. Although the approach is initially appealing, the short- and long-term clinical consequences of this immunotherapy remain unknown in patients with sepsis. Larger randomized studies are needed to assess anti–PD-L1 clinical safety and efficacy, combined with a comprehensive evaluation of index sepsis and secondary infections, readmissions, and survival outcomes.

REFERENCES

1. Machado FR, Cavalcanti AB, Bozza FA, et al: The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): An observational study. *Lancet Infect Dis* 2017; 17:1180–1189
2. Girardot T, Rimmelé T, Venet F, et al: Apoptosis-induced lymphopenia in sepsis and other severe injuries. *Apoptosis* 2017; 22:295–305
3. Thampy LK, Remy KE, Walton AH, et al: Restoration of T cell function in multi-drug resistant bacterial sepsis after interleukin-7, anti-PD-L1, and OX-40 administration. *PLoS One* 2018; 13:e0199497
4. Drewry AM, Samra N, Skrupky LP, et al: Persistent lymphopenia after diagnosis of sepsis predicts mortality. *Shock* 2014; 42:383–391
5. Zorio V, Venet F, Delwarde B, et al: Assessment of sepsis-induced immunosuppression at ICU discharge and 6 months after ICU discharge. *Ann Intensive Care* 2017; 7:80
6. van Vught LA, Klouwenberg PMK, Spitoni C, et al: Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. *JAMA* 2016; 315:1469–1479
7. Kalil AC, Florescu DF: Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. *Crit Care Med* 2009; 37:2350–2358
8. Delano MJ, Thayer T, Gabrilovich S, et al: Sepsis induces early alterations in innate immunity that impact mortality to secondary infection. *J Immunol* 2011; 186:195–202
9. Kumar V: T cells and their immunometabolism: A novel way to understanding sepsis immunopathogenesis and future therapeutics. *Eur J Cell Biol* 2018; 97:379–392
10. Meyer N, Harhay MO, Small DS, et al: Temporal trends in incidence, sepsis-related mortality, and hospital-based acute care after sepsis. *Crit Care Med* 2018; 46:354–360
11. Goodwin AJ, Rice DA, Simpson KN, et al: Frequency, cost and risk factors of readmissions among severe sepsis survivors. *Crit Care Med* 2015; 43:738
12. Sun A, Netzer G, Small DS, et al: Association between index hospitalization and hospital readmission in sepsis survivors. *Crit Care Med* 2016; 44:478–487
13. Venet F, Rimmele T, Monneret G: Management of sepsis-induced immunosuppression. *Crit Care Clin* 2018; 34:97–106
14. Evans VA, van der Sluis RM, Solomon A, et al: PD-1 contributes to the establishment and maintenance of HIV-1 latency. *AIDS* 2018; 32:1491–1497

15. Naidoo J, Page D, Li B, et al: Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015; 26:2375–2391
16. Teng F, Meng X, Kong L, et al: Progress and challenges of predictive biomarkers of anti PD-1/PD-L1 immunotherapy: A systematic review. *Cancer Lett* 2018; 414:166–173
17. Chen L, Han X: Anti–PD-1/PD-L1 therapy of human cancer: Past, present, and future. *J Clin Invest* 2015; 125:3384–3391
18. Hotchkiss RS, Colston E, Yende S, et al: Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 Antibody (BMS-936559). *Crit Care Med* 2019; 47:632–642

What Is the Skinny on Obesity During Sepsis?*

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Sepsis is a leading cause of death in the hospital setting and the prevalence of sepsis is increasing in developing countries (1). Researchers have previously speculated that the aging population (2) and other factors such as unhealthy lifestyle trends, as reflected by higher rates of obesity and complications of the metabolic syndrome (e.g., diabetes mellitus), were contributing factors. The latter seemed to be supported by observations linking certain diets to higher sepsis risk (3), and morbid obesity to increased sepsis mortality (4, 5). However, several studies reported that obesity is associated with lower sepsis mortality risk (6, 7). Despite recent meta-analyses that seem to support the "obesity paradox," the controversy persists because many of the studies included in these analyses failed to adjust for confounding patient factors (inaccurate body mass index [BMI], smoking history, treatment bias) and/or selection bias (e.g., inclusion of subjects with less severe sepsis, analysis restricted to elderly populations) (8).

In this issue of *Critical Care Medicine*, Pepper et al (9) report the results of a large retrospective cohort analysis designed to confirm if obesity confers protection against sepsis mortality. The study by Pepper et al (9) was conducted using the CERNER Healthfacts electronic health record database (Cerner, North Kansas City, MO) derived from 139 U.S. hospitals from 2009 to 2015, which included 55,038 sepsis cases. This dataset includes specific clinical data that is routinely recorded, such as BMI, and the participating hospitals are representative of academic and nonacademic, large and small, urban and rural status. Although retrospective, the study by Pepper et al (9) is the largest study conducted to date to determine the relationship between obesity and sepsis mortality. The BMI data were collected just before or at the time of initial sepsis diagnosis prior to fluid resuscitation, which tends to inflate the BMI, and statistical adjustments were made for known confounders such as comorbidities, site of infection, and geographical location. After adjusting for potential confounding factors (e.g., chronic obstructive pulmonary disease, cancer, heart failure), lower the short-term (in-hospital or discharge to hospice) sepsis mortality correlated with higher BMI, with the highest mortality observed in underweight (31%) and lowest mortality (14%) in obese class-III (BMI > 40 kg/m^2). Overall the relative risk of sepsis mortality among obese patients was 0.73 (0.70–0.77; $p < 0.0001$).

As with any retrospective study, there were study limitations. Historically, the diagnosis of sepsis based upon coding criteria is inconsistent among healthcare providers. Thus, the investigators did not rely solely on diagnosis codes and instead relied upon objective documentation of sepsis-related orders (blood cultures, antibiotics prescribed for at least 4 d) and documentation of organ failures based on the Sequential Organ Failure Assessment score, which is in keeping with the Sepsis-3 definition. However, data were often missing, resulting in the exclusion of greater than 75,000 sepsis encounters due to inadequate data. Another limitation was the reliance solely on sepsis mortality, without knowing the sepsis denominator within the obese and nonobese cohorts. As such, the prevalence of sepsis among obese patients compared with nonobese patients was unknown. Thus, it remains possible that sepsis may be more common in the obese population but is less severe, as reflected by a lower mortality rate.

Assuming that the findings of the study by Pepper et al (9) are valid, what explains the protective effects of obesity during sepsis? Are obese patients more likely to receive optimal care, as per established bundles of sepsis care? A study by O'Brien et al (10) indicates otherwise, showing that obese critically ill patients, many of which were septic, were less likely to receive recommended low tidal volume ventilation (i.e., 6 mL/kg based on ideal body weight), had higher plateau

***See also p. 643.**

Key Words: body mass index; hospital; leptin; mortality; sepsis

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