

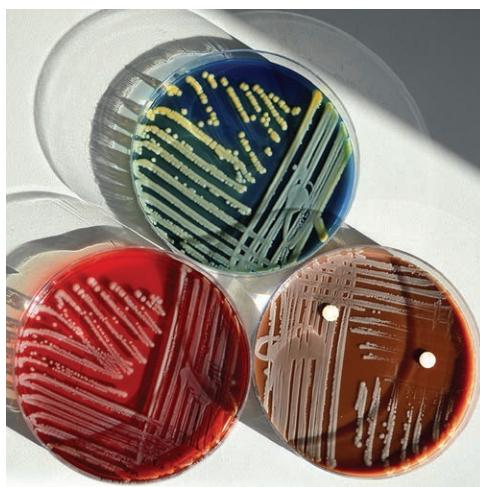
Immunotherapy for Sepsis

A Good Idea or Another Dead End?

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THE treatment of sepsis remains an intractable problem in critical care. It has been called the “graveyard”¹ for pharmaceutical companies in recognition of dozens of negative clinical trials; this reflects multiple distinct approaches that appeared promising based on *in vitro* experiments and animal models but that failed to improve survival in patients with sepsis. To date, the only therapies for sepsis remain supportive care, including prompt administration of antibiotics, adequate source control of the underlying infection (if known), and vigilance to prevent iatrogenicity and the other complications of being critically ill. The lack of a specific therapy for sepsis reflects our inadequate understanding of its pathogenesis. While it was initially believed that an “excessive” inflammatory response accounted for the manifestations of sepsis, antiinflammatory therapy was persistently unsuccessful in human clinical trials.² Now, a dominant theory for what causes death in sepsis is that the immune system becomes anergic, making patients vulnerable to nosocomial infection.³ It has been suggested that patients with sepsis therefore be treated with immunostimulants.⁴

In this issue, Kusakabe *et al.*⁵ report that administration of interferon- β 12 h after cecal ligation and perforation improved survival in a mouse model of severe sepsis. While only 25% of control mice survived, the survival rate was more than 50% in the interferon- β -treated group. Animals treated with interferon- β after the onset of sepsis displayed enhanced leukocyte function, including increased phagocytosis and cytokine expression. A strength of this study is that the cecal ligation and perforation model of sepsis is the gold standard in the field, mimicking what clinicians might see after an intraabdominal perforation and resultant fecal soiling. This study adds to a substantial body of preclinical literature, largely in mouse models of sepsis, suggesting that modulation of the immune system can improve survival.^{6,7} However, it is important to note that Kusakabe *et al.* also observed that prophylactic administration of



“...[W]hat causes mortality from sepsis?”

interferon- β —3 h prior to cecal ligation and perforation—was associated with *worsened* survival (only 4% of animals survived) and with impaired immune function. While the detrimental effect on survival may have been unexpected, the potentially immunosuppressive actions of interferon- β are well known.^{8,9}

What can clinicians take away from this study? While the trial was well conducted, it is uncertain how the findings might ultimately be translated to the bedside. From a practical standpoint, the observation that prophylactic administration of interferon- β is harmful is clearly problematic. The sequence of events in sepsis can be complex, and it is not uncommon for

patients to develop a second episode of sepsis. For example, a patient with septic shock from bowel ischemia often develops a second ischemic episode hours to days later. The study by Kusakabe *et al.* highlights the risk of immunomodulation during acute infection.

More fundamentally, it is unclear whether immunosuppression accounts for death from sepsis in patients. There is no doubt that alterations in the immune system occur during sepsis; these include lymphocyte apoptosis, reduced cytokine production, and decreased functioning of antigen-presenting cells.⁴ It is less clear whether these alterations cause pathology or are instead markers of severity of illness (“epiphenomena”). Epidemiologic data suggest that intensive care unit–acquired infections occur more frequently in the sickest sepsis patients, but that they do *not* substantially contribute to overall mortality. In a large prospective cohort study of intensive care unit patients (more than 3,600 admissions, almost half for sepsis), van Vught *et al.*¹⁰ reported the incidence and attributable mortality of intensive care unit–acquired infection. The hypothesis was that if sepsis-induced immunosuppression was a major cause of death, septic patients who developed intensive care unit–acquired infections should have a higher mortality rate than those who did not. Instead, the absolute difference in mortality in patients with sepsis and patients with sepsis who did not develop an intensive care

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unit-acquired infection was only 2% higher in the group with intensive care unit-acquired infection at 60 days after intensive care unit admission. The percentage of intensive care unit mortality caused by intensive care unit-acquired infection was only 5.5% at 30 days and 10.9% at 60 days after admission. This modest effect of intensive care unit-acquired infection on mortality rates was observed despite a genomic response in blood leukocytes of sepsis patients consistent with immunosuppression. An earlier but smaller retrospective cohort study of patients dying with septic shock reported similar findings.¹¹ Thus, nosocomial infection is not a major contributor to mortality in septic patients.

To date, there are little clinical trial data on immunomodulatory therapy for sepsis. A small (n = 38 patients) placebo-controlled study of granulocyte-macrophage colony-stimulating factor in patients with severe sepsis or septic shock and low levels of monocyte human leukocyte antigen-antigen D related (a cell surface receptor required for antigen presentation) reported improvements in monocyte function in the treatment group; however, granulocyte-macrophage colony-stimulating factor had no significant effect on clinical parameters except a shorter duration of mechanical ventilation.¹² Similarly, a meta-analysis of placebo-controlled studies of granulocyte-colony stimulating factor or granulocyte-macrophage colony-stimulating factor for sepsis observed no difference in 28-day mortality.¹³ Thus, while immunosuppression is a characteristic feature of human sepsis, clinical trials of immunostimulation are unlikely to show benefit in most patients with sepsis.

If not immunosuppression, what causes mortality from sepsis? Fortunately there are numerous alternative hypotheses to explain organ failure from sepsis. The loss of endothelial barrier integrity leads to vascular leakage in both acute respiratory distress syndrome and sepsis.^{14–16} Tissue edema, both subcutaneous and visceral, while long recognized as a typical feature of human sepsis, is absent from most animal models. Edema can itself impair organ function either by disrupting diffusion of oxygen or by directly affecting the tissue parenchyma. There is therefore great interest in determining whether the enhancement of vascular integrity can alter the outcome of human sepsis,^{17–19} and I anticipate clinical trials of this approach in the next few years.

In addition to vascular leakage, other theories exist (as reviewed by van der Poll *et al.*²⁰). For instance, the autonomic nervous system has been shown to regulate inflammation,²¹ and stimulation of the vagus nerve improved survival in a mouse model of sepsis.²² Impaired mitochondrial function during sepsis has long been observed²³ and is postulated to contribute to sepsis-induced organ dysfunction.^{24,25}

In conclusion, progress in the treatment of sepsis is likely to come only when we understand its underlying mechanisms. Sepsis is a highly heterogeneous clinical entity, defined as a syndrome of organ dysfunction in response to infection. For a given patient, it is challenging to know whether any specific organ dysfunction (*e.g.*, immunosuppression, vascular leakage) represents the cause or the effect of the overall clinical picture. Indeed, it is

possible that sepsis represents a constellation of different disorders manifesting as organ dysfunction, rather than a specific disease. However, despite the accumulated negative clinical trials, there are grounds for optimism. There have been advances in our ability to interrogate large clinical datasets, which enable the generation of clinically relevant hypotheses.²⁶ When these advances are combined with novel tools to manipulate the genome²⁷ and perform definitive preclinical experiments, it seems only a matter of time before we understand the causes and mechanisms of sepsis. Whether sepsis turns out to be one disease or many, this will be good news for clinicians and most importantly for patients suffering from this devastating syndrome.

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Competing Interests

Dr. Lee is a coinventor on a patent for a Tie2 agonist (Vasculotide) in the treatment of influenza and serves on the scientific advisory board for Vasomune (Toronto, Canada).

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References

1. Riedemann NC, Guo RF, Ward PA: The enigma of sepsis. *J Clin Invest* 2003; 112:460–7
2. Zeni F, Freeman B, Natanson C: Anti-inflammatory therapies to treat sepsis and septic shock: A reassessment. *Crit Care Med* 1997; 25:1095–100
3. Hotchkiss RS, Nicholson DW: Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol* 2006; 6:813–22
4. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD 2nd, Kreisel D, Krupnick AS, Srivastava A, Swanson PE, Green JM, Hotchkiss RS: Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011; 306:2594–605
5. Kusakabe Y, Uchida K, Yamamura Y, Hiruma T, Totsu T, Tamai Y, Tsuyuzaki H, Hasegawa K, Chang K, Yamada Y: Early-phase innate immune suppression in murine severe sepsis is restored with systemic interferon- β . *ANESTHESIOLOGY* 2018; 129:131–42
6. Scumpia PO, Delano MJ, Kelly-Scumpia KM, Weinstein JS, Wynn JL, Winfield RD, Xia C, Chung CS, Ayala A, Atkinson MA, Reeves WH, Clare-Salzler MJ, Moldawer LL: Treatment with GITR agonistic antibody corrects adaptive immune dysfunction in sepsis. *Blood* 2007; 110:3673–81
7. Wesche-Soldato DE, Chung CS, Lomas-Neira J, Doughty LA, Gregory SH, Ayala A: *In vivo* delivery of caspase-8 or Fas siRNA improves the survival of septic mice. *Blood* 2005; 106:2295–301
8. Pace JL, MacKay RJ, Hayes MP: Suppressive effect of interferon-beta on development of tumoricidal activity in mouse macrophages. *J Leukoc Biol* 1987; 41:257–63
9. Ling PD, Warren MK, Vogel SN: Antagonistic effect of interferon-beta on the interferon-gamma-induced expression of Ia antigen in murine macrophages. *J Immunol* 1985; 135:1857–63

10. van Vught LA, Klein Klouwenberg PM, Spitoni C, Scicluna BP, Wiewel MA, Horn J, Schultz MJ, Nürnberg P, Bonten MJ, Cremer OL, van der Poll T; MARS Consortium: Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. *JAMA* 2016; 315:1469–79
11. Goldenberg NM, Leligowicz A, Slutsky AS, Friedrich JO, Lee WL: Is nosocomial infection really the major cause of death in sepsis? *Crit Care* 2014; 18:540
12. Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, Weber-Carstens S, Hasper D, Keh D, Zuckermann H, Reinke P, Volk HD: Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: A double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med* 2009; 180:640–8
13. Bo L, Wang F, Zhu J, Li J, Deng X: Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: A meta-analysis. *Crit Care* 2011; 15:R58
14. Ghosh CC, David S, Zhang R, Berghelli A, Milam K, Higgins SJ, Hunter J, Mukherjee A, Wei Y, Tran M, Suber F, Kobzik L, Kain KC, Lu S, Santel A, Yano K, Guha P, Dumont DJ, Christiani DC, Parikh SM: Gene control of tyrosine kinase TIE2 and vascular manifestations of infections. *Proc Natl Acad Sci USA* 2016; 113:2472–7
15. Goldenberg NM, Steinberg BE, Slutsky AS, Lee WL: Broken barriers: A new take on sepsis pathogenesis. *Sci Transl Med* 2011; 3:88ps25
16. Sugiyama MG, Armstrong SM, Wang C, Hwang D, Leong-Poi H, Advani A, Advani S, Zhang H, Szaszi K, Tabuchi A, Kuebler WM, Van Slyke P, Dumont DJ, Lee WL: The Tie2-agonist Vasculotide rescues mice from influenza virus infection. *Sci Rep* 2015; 5:11030
17. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J: Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; 151:1229–38
18. Han S, Lee SJ, Kim KE, Lee HS, Oh N, Park I, Ko E, Oh SJ, Lee YS, Kim D, Lee S, Lee DH, Lee KH, Chae SY, Lee JH, Kim SJ, Kim HC, Kim S, Kim SH, Kim C, Nakaoka Y, He Y, Augustin HG, Hu J, Song PH, Kim YI, Kim P, Kim I, Koh GY: Amelioration of sepsis by TIE2 activation-induced vascular protection. *Sci Transl Med* 2016; 8:335ra55
19. Kumpers P, Gueler F, David S, Slyke PV, Dumont DJ, Park JK, Bockmeyer CL, Parikh SM, Pavenstadt H, Haller H, Shushakova N: The synthetic tie2 agonist peptide vasculotide protects against vascular leakage and reduces mortality in murine abdominal sepsis. *Crit Care* 2011; 15:R261
20. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG: The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol* 2017; 17:407–20
21. Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, Al-Abed Y, Wang H, Metz C, Miller EJ, Tracey KJ, Ulloa L: Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med* 2004; 10:1216–21
22. Huston JM, Gallowitsch-Puerta M, Ochani M, Ochani K, Yuan R, Rosas-Ballina M, Ashok M, Goldstein RS, Chavan S, Pavlov VA, Metz CN, Yang H, Czura CJ, Wang H, Tracey KJ: Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis. *Crit Care Med* 2007; 35:2762–8
23. Singer M, Brealey D: Mitochondrial dysfunction in sepsis. *Biochem Soc Symp* 1999; 66:149–66
24. Larche J, Lancel S, Hassoun SM, Favory R, Decoster B, Marchetti P, Chopin C, Neviere R: Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. *J Am Coll Cardiol* 2006; 48:377–85
25. Arulkumaran N, Pollen S, Greco E, Courtneidge H, Hall AM, Duchon MR, Tam FWK, Unwin RJ, Singer M: Renal tubular cell mitochondrial dysfunction occurs despite preserved renal oxygen delivery in experimental septic acute kidney injury. *Crit Care Med* 2018; 46:e318–25
26. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network: Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014; 2:611–20
27. Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, Hsu PD, Wu X, Jiang W, Marraffini LA, Zhang F: Multiplex genome engineering using CRISPR/Cas systems. *Science* 2013; 339:819–23