EMERGENCY MEDICINE REPORTS

An Update on Sepsis Clinical Research: Impact on ED Management

Adjunctive Therapies Under Investigation

Investigational Therapy	Conclusions	Study
The TLR-4 antagonist, TAK 242 (Resatorvid)	TLR-4 antagonist TAK-242 did not suppress cytokine levels in patients with septic shock or respiratory failure, nor did it improve mortality rates in septic shock and respiratory failure patients.[20]	Rice TW, Wheeler AP, Bernard GR, et al. A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Crit Care Med* 2010;38:1685.
The human anti-endotoxin monoclonal antibody, HA-1A	Human monoclonal antibody HA-1A was not effective in reducing 14-day mortality rates in patients with gram-negative bacteremia and septic shock.[21]	McCloskey RV, Straube RC, Sanders C, et al. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group. *Ann Intern Med* 1994;121:1.
	Treatment with E5 murine monoclonal antiendotoxin antibody in patients with gram-negative sepsis did not improve short-term survival.[22]	Angus DC, Birmingham MC, Balk RA, et al. E5 murine monoclonal anti-endotoxin antibody in gram-negative sepsis: A randomized controlled trial. E5 Study Investigators. *JAMA* 2000;283:1723.
The human anti-Enterobacteriaceae common antigen (ECA) monoclonal antibody	Treatment with the human monoclonal antibody to Enterobacteriaceae, MAB-T88, did not improve the mortality in patients with presumed Gram-negative sepsis or in those patients with proven enterobacterial common antigen infections.[23]	Albertson TE, Panacek EA, MacArthur RD, et al. Multicenter evaluation of a human monoclonal antibody to Enterobacteriaceae common antigen in patients with Gram-negative sepsis. *Crit Care Med* 2003;31:419.
Granulocyte colony-stimulating factor (filgrastim, G-CSF)	The addition of filgrastim to the antibiotic and supportive care treatment of patients with severe sepsis secondary to pneumonia was safe, but was not effective at reducing mortality rates or complications from this infection.[24]	Root RK, Lodato RF, Patrick W, et al. Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003;31:367.
Anti-tumor necrosis factor monoclonal antibody	There was a significant reduction in mortality at 3 days in septic shock patients treated with TNF-alpha MAb. However, there was no significant long-term survival advantage at 28 days following treatment with TNF-alpha MAb among shock patients treated with placebo or TNF-alpha MAb.[25]	Abraham E, Wunderink R, Silverman H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* 1995;273:934.
	There was no improvement in survival in septic shock patients treated with monoclonal antibody to human tumour necrosis factor , TNF alpha MAb.[26]	Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet* 1998;351:929.
Tumor necrosis factor receptor antagonist	Lenercept (p55 tumor necrosis factor receptor fusion protein) had no significant effect on mortality or on the incidence or resolution of organ dysfunction in severe sepsis and septic shock patients.[27]	Abraham E, Laterre PF, Garbino J, et al. Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: A randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. *Crit Care Med* 2001;29:503.
Interleukin-1 receptor antagonist	A 72-hr continuous intravenous infusion of interleukin-1 receptor antagonist, rhIL-1ra, did not result in a statistically significant reduction in mortality.[28]	Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 1997;25:1115
Antithrombin (formerly known as antithrombin III)	High-dose antithrombin III therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic. Additionally, high-dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin.[29]	Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869.
	Replacement therapy with ATIII reduces mortality in septic shock patients.[30]	Baudo F, Caimi TM, de Cataldo F, et al. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: A controlled double-blind, randomized, multicenter study. *Intensive Care Med* 1998;24:336.
	Treatment with high-dose antithrombin III may increase survival time up to 90 days in patients with severe sepsis and high risk of death. This benefit may be even stronger when concomitant heparin is avoided.[31]	Wiedermann CJ, Hoffmann JN, Juers M, et al. High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: Efficacy and safety. *Crit Care Med* 2006;34:285.
Ibuprofen	In patients with sepsis, treatment with ibuprofen reduces levels of prostacyclin and thromboxane, and decreases fever, tachycardia, oxygen consumption, and lactic acidosis. However, it does not prevent the development of shock or ARDS and it does not improve survival.[32]	Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997;336:912.

Adjunctive Therapies Under Investigation (continued)

Investigational Therapy	Conclusions	Study
N-acetylcysteine	Early NAC treatment aggravated sepsis-induced organ failure, in particular cardiovascular failure.[33]	Spapen HD, Diltoer MW, Nguyen DN, et al. Effects of N-acetylcysteine on microalbuminuria and organ failure in acute severe sepsis: Results of a pilot study. *Chest* 2005;127:1413.
	NAC can cause cardiovascular depression in septic patients when administered 24 hours after the onset of sepsis. Therefore, clinicians should avoid intravenous N-acetylcysteine use in SIRS and sepsis patients.[34]	Szakmany T, Hauser B, Radermacher P. N-acetylcysteine for sepsis and systemic inflammatory response in adults. *Cochrane Database Syst Rev* 2012;9:CD006616.
Nitric oxide inhibitors	Low doses of a nitric oxide synthase inhibitor, L-NMMA, causes a widespread increase in vascular tone and raises blood pressure in patients with septic shock, with a subsequent fall in cardiac output.[35]	Petros A, Lamb G, Leone A, et al. Effects of a nitric oxide synthase inhibitor in humans with septic shock. *Cardiovasc Res* 1994;28:34.
	The nonselective nitric oxide synthase inhibitor, 546C88, increased mortality in patients with septic shock.[36]	López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. *Crit Care Med* 2004;32:21.
The bradykinin antagonist, deltibant	The bradykinin antagonist, deltibant (CP-0127) may have some effect on survival in patients with SIRS and gram-negative sepsis.[37]	Fein AM, Bernard GR, Criner GJ, et al. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127). Results of a randomized, double-blind, placebo-controlled trial. CP-0127 SIRS and Sepsis Study Group. *JAMA* 1997;277:482.
Growth hormone	In patients with prolonged critical illness, high doses of growth hormone resulted in increased morbidity and mortality.[38]	Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999;341:785.
Intravenous selenium supplementation	The adjuvant treatment of severe sepsis and septic shock patients with high-dose sodium-selenite reduced mortality rates.[39]	Angstwurm MW, Engelmann L, Zimmermann T, et al. Selenium in Intensive Care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007;35:118.

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