

REFERENCES

- Gaieski D, Edwards J, Kallan M, Carr B: Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 41: 1167, 2013. [PMID: 23442987]
- Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303, 2001. [PMID: 11445675]
- 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* 311: 1308, 2014. [PMID: 24638143]
- Jones AE, Shapiro N, Trzeciak S, Arnold H, Claremont H, Kline JA: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 303: 739, 2010. [PMID: 20179283]
- Vincent JL, Ramesh MK, Ernest D, et al: A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. *Crit Care Med* 41: 2069, 2013. [PMID: 23979365]
- Pavon A, Binquet C, Kara F, et al: Profile of the risk of death after septic shock in the present era: an epidemiologic study. *Crit Care Med* 41: 2600, 2013. [PMID: 23963127]
- Roe MT, Messenger JC, Weintraub WS, et al: Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 56: 254, 2010. [PMID: 20633817]
- Kucher N, Rossi E, De Rosa M, Goldhaber SZ: Massive pulmonary embolism. *Circulation* 113: 577, 2006. [PMID: 16432055]
- Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB: 30-Day risk-standardized mortality and readmission rates after ischemic stroke in critical access hospitals. *Stroke* 43: 2741, 2012. [PMID: 22935397]
- Hofhuys JG, Spronk PE, van Stel HF, Schrijvers AJ, Rommes J, Bakker J: The impact of severe sepsis on health-related quality of life: a long-term follow-up study. *Anesth Analg* 107: 1957, 2008. [PMID: 19020144]
- Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348: 1546, 2003. [PMID: 12700374]
- Filbin MR, Arias SA, Camargo CA Jr, Barche A, Pallin DJ: Sepsis visits and antibiotic utilization in U.S. emergency departments. *Crit Care Med* 42: 528, 2014. [PMID: 24201179]
- Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31: 1250, 2003. [PMID: 12682500]
- Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 273: 117, 1995. [PMID: 7799491]
- Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315: 801, 2016. [PMID: 26903338]
- Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE: The impact of the Sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med* 45: 1436, 2017. [PMID: 28542029]
- http://www.hret-hen.org/topics/sepsis/HRETHEN_ChangePackage_Sepsis.pdf (Health Research and Educational Trust: Severe Sepsis and Septic Shock Change Package: 2016. Chicago, IL.) Accessed November 2, 2016.
- Levy MM, Evans LE, Rhodes A: The Surviving Sepsis Campaign bundle: 2018 update. *Crit Care Med* 46: 997, 2018. [PMID: 29767636]
- Churpek MM, Snyder A, Han X, et al: qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU. *Am J Respir Crit Care Med* 195: 906, 2017. [PMID: 27649072]
- Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AF, Lipman J: SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection. *Chest* 151: 586, 2017. [PMID: 27876592]
- Zimmerman JE, Kramer A: Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 34: 1297, 2006. [PMID: 16540951]
- Shapiro N, Wolfe R, Moore R, Smith E, Burdick E, Bates D: Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 31: 670, 2003. [PMID: 12626967]
- Puskarich M, Kline JA, Summers RL, Jones AE: Prognostic value of incremental lactate elevations in emergency department patients with suspected infection. *Acad Emerg Med* 19: 983, 2012. [PMID: 22905962]
- Levy B: Lactate and shock state: the metabolic review. *Curr Opin Crit Care* 12: 315, 2006. [PMID: 16810041]
- Trzeciak S, Dellinger R, Chansky ME, et al: Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med* 33: 970, 2007. [PMID: 17431582]
- Shapiro NI, Howell MD, Talmor D, et al: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 45: 524, 2005. [PMID: 15855951]
- Puskarich MA, Illich BM, Jones AE: Prognosis of emergency department patients with suspected infection and intermediate lactate levels: a systematic review. *J Crit Care* 14: S0883, 2014. [PMID: 24559577]
- Jones AE, Leonard MM, Hernandez-Nino J, Kline JA: Determination of the effect of in vitro time, temperature, and tourniquet use on whole blood venous point-of-care lactate concentrations. *Acad Emerg Med* 14: 587, 2007. [PMID: 17513689]
- Nguyen H, Rivers E, Knoblich B, et al: Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 32: 1637, 2004. [PMID: 15286537]
- Arnold RC, Shapiro NI, Jones AE, et al: Multi-center study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock* 32: 36, 2009. [PMID: 19533847]
- Angus DC, van der Poll T: Severe sepsis and septic shock. *N Engl J Med* 369: 840, 2013. [PMID: 23984731]
- Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 348: 138, 2003. [PMID: 12519925]
- Trzeciak S, McCoy JV, Dellinger RP, et al: Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 hours in patients with sepsis. *Intensive Care Med* 34: 2210, 2008. [PMID: 18594793]
- Zhang Q, Raoof M, Chen Y, et al: Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464: 104, 2010. [PMID: 20203610]
- Jones A, Tayal V, Sullivan D, Kline J: Randomized controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. *Crit Care Med* 32: 1703, 2004. [PMID: 15286547]
- Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, Huertos-Randchal MJ: Sepsis-induced cardiomyopathy. *Curr Cardiol Rev* 7: 163, 2011. [PMID: 22758615]
- The ARDS Definition Task Force: Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 307: 2526, 2012. [PMID: 22797452]
- Sharma B, Sharma M, Majumder M, Steier W, Sangal A, Kalawar M: Thrombocytopenia in septic shock patients: a prospective observational study of incidence, risk factors and correlation with clinical outcome. *Anaesth Intensive Care* 35: 874, 2007. [PMID: 18084977]
- Vincent JL, Yagushi A, Pradier O: Platelet function in sepsis. *Crit Care Med* 30: S313, 2002. [PMID: 12004253]
- Schuetz P, Kennedy M, Lucas JM, et al: Initial management and outcomes of patients with hyperglycemia and suspected sepsis in the non-critical care inpatient setting. *Am J Med* 125: 670, 2012. [PMID: 22608986]
- Annan D, Bellissant E, Bollaert PE, et al: Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 301: 2362, 2009. [PMID: 19509383]
- Dellinger R, Levy M, Rhodes A, et al: Surviving Sepsis Campaign: international guidelines for the management of severe sepsis and septic shock 2012. *Crit Care Med* 41: 580, 2013. [PMID: 23353941]
- Wacker C, Prkno A, Brunkhorst FM, Schlattmann P: Procalcitonin as a diagnostic marker for sepsis: a systematic review and metaanalysis. *Lancet Infect Dis* 13: 426, 2013. [PMID: 23375419]
- Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A: Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med* 31: 1737, 2003. [PMID: 12794413]
- Prkno A, Wacker C, Brunkhorst FM, Schlattmann P: Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock: a systematic review and meta-analysis. *Crit Care* 17: R291, 2013. [PMID: 24330744]
- Rixen D, Siegel JH: Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. *Crit Care* 9: 441, 2005. [PMID: 16277731]
- Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345: 1368, 2001. [PMID: 11794169]
- Trzeciak S, Dellinger RP, Abata NL, et al: Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 129: 225, 2006. [PMID: 16478835]
- Shapiro NI, Howell MD, Talmor D, et al: Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 34: 1025, 2006. [PMID: 16484890]
- Jones AE, Focht A, Horton JM, Kline JA: Prospective external validation of the clinical effectiveness of an emergency department-based early goal directed therapy protocol for severe sepsis and septic shock. *Chest* 132: 425, 2007. [PMID: 17573521]
- Micek ST, Roubinian N, Heuring T, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 34: 2707, 2006. [PMID: 16943733]
- Nguyen HB, Corbett SW, Steele R, et al: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 35: 1105, 2007. [PMID: 17334251]
- Puskarich M, Trzeciak S, Shapiro N, et al: Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. *Chest* 143: 1548, 2013. [PMID: 23740148]
- Pope J, Jones AE, Gaieski D, et al: Multicenter study of central venous oxygen saturation (ScvO₂) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 55: 40, 2010. [PMID: 19854541]
- The ProCESS Investigators: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 370: 1683, 2014. [PMID: 24635773]
- ARISE Investigators; ANZICS Clinical Trial Group: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 371: 1496, 2014. [PMID: 25272316]

57. Mouncey PR, Osborn TM, Power GS, et al: Protocolised Management in Sepsis (ProMiSe): a multicenter randomized controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock. *Health Technol Assess* 19: 1, 2015. [PMID: 26597979]
58. PRISM Investigators, Rowan KM, Angus DC, et al: Early, goal-directed therapy for septic shock: a patient-level meta-analysis. *N Engl J Med* 376: 2223, 2017. [PMID: 28320242]
59. Self WH, Semler MW, Wanderer JP, et al: Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 378: 819, 2018. [PMID: 29485926]
60. Semler MW, Self WH, Wanderer JP, et al: Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 378: 829, 2018. [PMID: 29485925]
61. Asfar P, Meziani F, Hamel J-F, et al: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 370: 1583, 2014. [PMID: 24635770]
62. De Backer D, Aldecoa C, Njimi H, Vincent JL: Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med* 40: 725, 2012. [PMID: 22036860]
63. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 358: 877, 2008. [PMID: 18305265]
64. Annane D, Vignon P, Renault A, et al: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomized trial. *Lancet* 370: 676, 2007. [PMID: 17720019]
65. Zelenitsky S, Rubenstein E, Ariano R, et al: Vancomycin pharmacodynamics and survival in patients with methicillin-resistant *Staphylococcus aureus*-associated septic shock. *Int J Antimicrob Agents* 41: 255, 2013. [PMID: 23312606]
66. Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-Systems Pharmacists, the Infectious Disease Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 66: 82, 2009. [PMID: 19106348]
67. Levy MM, Dellinger RP, Townsend S, et al: The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 36: 222, 2010. [PMID: 20069275]
68. Alam N, Oskam E, Stassen PM, et al: Prehospital antibiotics in the ambulance for sepsis: a multicenter, open label, randomised control trial. *Lancet Respir Med* 6: 40, 2018. [PMID: 29196046]
69. Acute Respiratory Distress 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* 342: 1301, 2000. [PMID: 10793162]
70. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360: 1283, 2009. [PMID: 19318384]
71. Ranieri V, Thompson BT, Barie P, et al: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 366: 2055, 2012. [PMID: 22616830]
72. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288: 862, 2002. [PMID: 12186604]
73. Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 358: 1111, 2008. [PMID: 18184957]
74. Venkatesh B, Finfer S, Cohen J, et al: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 378: 797, 2018. [PMID: 29347874]
75. Annane D, Renault A, Brun-Buisson C, et al: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 378: 809, 2018. [PMID: 29490185]
76. Mohammad Z, Afessa B, Finkielman JD: The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate. *Crit Care* 10: R105, 2006. [PMID: 16859529]
77. Marik PE, Khangoora V, Rivera R, et al: Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-and-after study. *Chest* 151: 1229, 2017. [PMID: 27940189]
78. Laupland K, Church DL, Gregson DB: Blood cultures in ambulatory outpatients. *BMC Infect Dis* 17: 35, 2005. [PMID: 15904503]