

Landmark studies in Critical Care for 2014

1. Neurology

- (i) A comparison of four treatments for generalized convulsive **status epilepticus**. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998 Sep 17;339(12):792-8
- (ii) Dexamethasone in adults with **bacterial meningitis**. European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. *N Engl J Med*. 2002 Nov 14;347(20):1549-56
- (iii) Thrombolysis with alteplase 3-4.5 h after **acute ischaemic stroke** (SITS-ISTR): an observational study. *Lancet*. 2008 Oct 11;372(9646):1303-9
- (iv) Surgical decompression for space-occupying **cerebral infarction** (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol*, 8 (2009), pp. 326–33
- (v) **Long term cognitive impairment after critical illness**. *N Engl J Med* 2013; 369: 1306-1316

2. Respiratory

- (i) Effect of a **protective-ventilation strategy** on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998 Feb 5;338(6):347-54
- (ii) Ventilation with **lower tidal volumes** as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000 May 4;342(18):1301-8
- (iii) A multicentre randomised controlled trial of the early use of **non-invasive ventilation** in acute exacerbation of chronic obstructive pulmonary disease on general respiratory wards. *Lancet*, 355 (2000), pp. 1931–1935
- (iv) Efficacy and safety of **corticosteroids** for persistent acute respiratory distress syndrome. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. *N Engl J Med*. 2006 Apr 20;354(16):1671-84
- (v) Efficacy and safety of a paired sedation and **ventilator weaning protocol** for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008 Jan 12;371(9607):126-34
- (vi) Efficacy and economic assessment of conventional ventilatory support versus **extracorporeal membrane oxygenation** for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009 Oct 17;374(9698):1351-63
- (vii) **Neuromuscular Blockers** in Early Acute Respiratory Distress Syndrome. ACURASYS Study Investigators. *N Engl J Med* 2010; 363:1107-1116
- (viii) **Functional disability 5 years after acute respiratory distress syndrome**. *N Engl J Med* 2011; 364: 1293-304
- (ix) Effect of intravenous **β-2 agonist treatment** on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet*. 2012 Jan 21;379 (9812):229 – 235
- (x) **Intrapleural use of tissue plasminogen activator and DNase in pleural effusion**. *N Engl J Med* 2011; 365: 518-26
- (xi) **A trial of intraoperative low tidal volume ventilation in abdominal surgery**. *N Engl J Med* 2013; 369:428-37
- (xii) **High frequency oscillation for acute respiratory distress syndrome**. *N Engl J Med* 2013; 806-13
- (xiii) **Prone positioning in severe acute respiratory distress syndrome**. *N Engl J Med* 2013; 368: 2159-68

- (xiv) [Rosuvastatin in sepsis associated acute respiratory distress syndrome. *N Engl J Med* 2014; 370: 2191-2200](#)

3. Cardiovascular

- (i) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and [congestive heart failure](#). The SOLVD Investigators. *N Engl J Med* 1991;325:293-302
- (ii) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for [Cardiogenic Shock](#). *N Engl J Med*. 1999 Aug 26;341(9):625-34
- (iii) The effect of spironolactone on morbidity and mortality in patients with [severe heart failure](#). *N Engl J Med* 1999;341:709-717
- (iv) Mild [therapeutic hypothermia](#) to improve the neurologic outcome after cardiac arrest. The Hypothermia after Cardiac Arrest Study Group. *N Engl J Med* 2002;346:549-556
- (v) Heparin plus alteplase compared with heparin alone in patients with submassive [pulmonary embolism](#). *N Engl J Med* 2002;347:1143-1150
- (vi) Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced [Chronic Heart Failure](#). The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. *N Engl J Med* 2004; 350:2140-2150
- (vii) A Comparison of [Albumin and Saline](#) for Fluid Resuscitation in the Intensive Care Unit. The SAFE Study Investigators. *N Engl J Med* 2004;350:2247-56
- (viii) Amiodarone or an implantable cardioverter-defibrillator for [congestive heart failure](#). *N Engl J Med* 2005;352:225-237
- (ix) Norepinephrine plus dobutamine versus epinephrine alone for management of [septic shock](#): a randomised trial. *Lancet*. 2007 Aug 25;370(9588):676-84
- (x) Vasopressin versus norepinephrine infusion in patients with [septic shock](#). *N Engl J Med* 2008;358:877-887
- (xi) Vasopressin and Epinephrine vs. Epinephrine Alone in [Cardiopulmonary Resuscitation](#). *N Engl J Med* 2008; 359(1):21-30
- (xii) Epidemiologic Study of In-Hospital [Cardiopulmonary Resuscitation](#) in the Elderly. *N Engl J Med* 2009; 361:22-31
- (xiii) B-CONVINCED: Beta-blocker CONTinuation Vs. INTerruption in patients with [Congestive heart failure](#) hospitalizED for a decompensation episode. *Eur Heart J* 2009;30:2186-2192
- (xiv) Compression-Only CPR or Standard CPR in [Out-of-Hospital Cardiac Arrest](#). *Engl J Med* 2010; 363:434-442
- (xv) [Cardiopulmonary resuscitation](#) with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet*. 2008 Aug 16;372(9638):554-61
- (xvi) Comparison of Dopamine and Norepinephrine in the Treatment of [Shock](#). The SOAP II Investigators. *N Engl J Med* 2010; 362:779-789
- (xvii) [Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124-134](#)
- (xviii) [Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367:1901-11](#)
- (xix) [Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370: 1412-1421](#)
- (xx) [High versus low blood pressure target in patients with septic shock. *N Engl J Med* 2014; 370: 1583-1593](#)

4. Gastroenterology

- (i) A comparison of sucralfate and ranitidine for the prevention of **upper gastrointestinal bleeding** in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998 Mar 19;338(12):791-7
- 5. Hepatology**
- (i) Terlipressin and albumin vs albumin in patients with cirrhosis and **hepatorenal syndrome**: a randomized study. *Gastroenterology* 2008;134:1352-1359
 - (ii) Early Use of TIPS in Patients with Cirrhosis and **Variceal Bleeding**. The Early TIPS Cooperative Study Group. *N Engl J Med* 2010; 362:2370-2379
- 6. Renal**
- (i) **Low-dose dopamine** in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. 2000 Dec 23-30;356(9248):2139-43
 - (ii) Effects of different doses in **continuous veno-venous haemofiltration** on outcomes of acute renal failure: a prospective randomized trial. *Lancet* 2000;355:26-30
 - (iii) **Intensity of renal support** in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7-20
 - (iv) **Intensity of Renal Support** in Critically Ill Patients with Acute Kidney Injury. The VANIH Acute Renal Failure Trial Network. *N Engl J Med* 2008; 359(1):7-20
 - (v) Intensity of **Continuous Renal-Replacement Therapy** in Critically Ill Patients. The RENAL Replacement Therapy Study Investigators. *N Engl J Med* 2009; 361:1627-163
- 7. Endocrine**
- (i) **Intensive Insulin Therapy** in Critically Ill Patients. *N Engl J Med* 2001;345:1359-1367
 - (ii) Effect of treatment with **low doses of hydrocortisone** and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002 Aug 21;288(7):862-71
 - (iii) **Intensive insulin therapy** in the medical ICU. *N Engl J Med* 2006;354:449-461
 - (iv) **Hydrocortisone therapy** for patients with septic shock. CORTICUS Study Group. *N Engl J Med* 2008;358:111-124
 - (v) **Intensive versus conventional glucose control** in critically ill patients. The NICE-SUGAR Study Investigators. *N Engl J Med* 2009;360:1283-1297
 - (vi) **Hypoglycemia and risk of death in critically ill patients**. *N Engl J Med* 2012; 367: 1108-18
 - (vii) **Reduced cortisol metabolism during critical illness**. *N Engl J Med* 2013; 368: 1477-88
- 8. Haematology**
- (i) A multicenter, randomized, controlled clinical trial of **transfusion requirements** in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999 Feb 11;340(6):409-17
 - (ii) Safety of **Recombinant Activated Factor VII** in Randomized Clinical Trials. *N Engl J Med* 2010; 363:1791-1800
- 9. Rheumatology**
- (i) Rituximab versus Cyclophosphamide for **ANCA-Associated Vasculitis**. RAVE-ITN Research Group. *N Engl J Med* 2010; 363:221-232
- 10. Nutrition**

- (i) Does enteral nutrition compared to **parenteral nutrition** result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004;20:843–848
- (ii) **Immunonutrition** in critically ill patients: a systematic review and analysis of the literature. *Intensive Care Med* (2008) 34:1980–1990
- (iii) Early versus Late **Parenteral Nutrition** in Critically Ill Adults. *N Engl J Med* 2011;365:506–17
- (iv) A randomized trial of **glutamine and antioxidants** in critically ill patients. *N Engl J Med* 2013; 1489-1497

11. Infection

- (i) Invasive and noninvasive strategies for management of suspected **ventilator-associated pneumonia**: a randomized trial. *Ann Intern Med* 2000;132:621-630
- (ii) Efficacy and safety of **recombinant human activated protein C** for severe sepsis. Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study. *N Engl J Med* 2001;344:699-709
- (iii) **Early goal-directed therapy** in the treatment of severe sepsis and septic shock. Early Goal-Directed Therapy Collaborative Group. *N Engl J Med*. 2001 Nov 8;345(19):1368-77.
- (iv) **Drotrecogin alfa (activated)** administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003;31:12-19
- (v) Comparison of 8 versus 15 days of antibiotic therapy for **ventilator-associated pneumonia** in adults: a randomized trial. *AMA* 2003;290:2588-2598
- (vi) **Drotrecogin alfa (activated)** for adult patients with severe sepsis and a low risk of death. *N Engl J Med* 2005;353:1332-1341
- (vii) Prevention of nosocomial infection in cardiac surgery by **decontamination** of the nasopharynx and oropharynx with chlorhexidine gluconate. A Randomized Controlled Trial. *JAMA*. 2006;296:2460-2466
- (viii) A randomized trial of diagnostic techniques for **ventilator-associated pneumonia**. the Canadian Critical Care Trials Group. *N Engl J Med* 2006;355:2619-2630
- (ix) An intervention to decrease **catheter-related bloodstream infections** in the ICU. *N Engl J Med* 2006;355:2725-2732
- (x) Predictors of 30-day mortality and hospital costs in patients with **ventilator-associated pneumonia** attributed to potentially antibiotic-resistant gram-negative bacteria. *Chest* 2008;134:281-287
- (xi) Randomized trial of combination versus monotherapy for the empiric treatment of suspected **ventilator-associated pneumonia**. *Crit Care Med* 2008;36:737-744
- (xii) **Decontamination** of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009 Jan 1;360(1):20-31
- (xiii) Hospitalized Patients with 2009 **H1N1 Influenza** in the United States, April–June 2009. The 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. *N Engl J Med* 2009; 361:1935-194
- (xiv) Clinical Aspects of Pandemic 2009 Influenza A (**H1N1**) **Virus Infection**. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. *Engl J Med* 2010; 362:1708-1719
- (xv) Severe 2009 **H1N1 Influenza in Pregnant** and Postpartum Women in California. The California Pandemic (H1N1) Working Group. *N Engl J Med* 2010; 362:27-35
- (xvi) Use of **procalcitonin** to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. PRORATA trial group. *Lancet*. 2010 Feb 6;375(9713):463-74
- (xvii) **Intervention to reduce transmission of resistant bacteria in intensive care**. *N Engl J Med* 2011; 364:1407-18

- (xviii) [Drotretrogin Alfa \(Activated\)](#) in adults with septic shock. *N Engl J Med* 2012; 366: 2055-64
- (xix) [Effect of daily chlorhexidine bathing](#) on hospital acquired infection. *N Engl J Med* 2013; 368: 533-42
- (xx) [Targeted versus universal decolonization](#) to prevent ICU infection. *N Engl J Med* 2013; 368: 2255-65

12. Trauma

- (i) A randomized, controlled trial of methylprednisolone or naloxone in the treatment of [acute spinal-cord injury](#). Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med*. 1990 May 17;322(20):1405-11
- (ii) Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of [acute spinal cord injury](#). Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. *JAMA*. 1997 May 28;277(20):1597-60
- (iii) Effects of [tranexamic acid](#) on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010 Jul 3;376(9734):23-32
- (iv) Very early hypothermia induction in patients with [severe brain injury](#) (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol*. 2011 Feb;10(2):131-9
- (v) Decompressive Craniectomy in Diffuse [Traumatic Brain Injury](#). DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. *N Engl J Med* 2011; 364:1493-1502

13. Surgery

- (i) [Endovascular Repair](#) of Aortic Aneurysm in Patients Physically Ineligible for Open Repair. The United Kingdom EVAR Trial Investigators. *N Engl J Med* 2010; 362:1872-1880

14. General

- (i) [Hyperbaric Oxygen](#) for Acute Carbon Monoxide Poisoning. *N Engl J Med* 2002; 347:1057-1067
- (ii) Assessment of the clinical effectiveness of [pulmonary artery catheters](#) in management of patients in intensive care (PAC-Man): a randomised controlled trial. PAC-Man study collaboration. *Lancet*. 2005 Aug 6-12;366(9484):472-7
- (iii) Introduction of the [medical emergency team](#) (MET) system: a cluster-randomised controlled trial. *Lancet*. 2005 Jun 18-24;365(9477):2091-7
- (iv) [A randomized trial night time physician staffing in an intensive care unit](#). *N Engl J Med* 2013; 368: 2201-2209