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| **Table E3. Summary of all analyzed trials** |
| **Year** | **Journal** | **Title** | **Mortality Outcome** | **Loss to f/u** | **Fragility Index** |
| **1977** | Lancet | Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards. | Primary | 0 | 3 |
| **1994** | Crit Care Med | Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. | Primary | 0 | 0 |
| **1994** | NEJM | Elevation of systemic oxygen delivery in the treatment of critically ill patients. | Secondary | 0 | 0 |
| **1995** | NEJM | Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. | Secondary | 0 | 1 |
| **1997** | Crit Care Med | Parenteral administration of different amounts of branch-chain amino acids in septic patients: clinical and metabolic aspects. | Secondary | 0 | 2 |
| **1998** | NEJM | Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. | Primary | 0 | 1 |
| **1998** | AIM | Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. | Secondary | 0 | 0 |
| **1999** | NEJM | Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis | Primary | 0 | 3 |
| **1999** | JAMA | Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. | Primary | 0 | 4 |
| **1999** | Crit Care Med | Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group. | Secondary | 0 | 3 |
| **1999** | NEJM | Increased mortality associated with growth hormone treatment in critically ill adults. | Secondary | 0 | 20 |
| **2000** | Crit Care Med | An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. | Primary | 0 | 0 |
| **2000** | AIM | Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. | Primary | 0 | 3 |
| **2000** | NEJM | 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. | Primary | 9 | 11 |
| **2000** | Chest | Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. | Primary | 0 | 2 |
| **2000** | Lancet | Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. | Secondary | 0 | 1 |
| **2000** | Intensive Care Med | Safety and efficacy of propofol with EDTA when used for sedation of surgical intensive care unit patients. | Secondary | 0 | 3 |
| **2001** | NEJM | Efficacy and safety of recombinant human activated protein C for severe sepsis. | Primary | 0 | 15 |
| **2001** | Kidney International | A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure | Primary | 0 | 2 |
| **2001** | Lancet | Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. | Primary | 0 | 2 |
| **2002** | JAMA | Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. | Primary | 1 | 0 |
| **2002** | NEJM | Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. | Secondary | 0 | 3 |
| **2003** | Crit Care Med | Recombinant platelet-activating factor acetylhydrolase to prevent acute respiratory distress syndrome and mortality in severe sepsis: Phase IIb, multicenter, randomized, placebo-controlled, clinical trial. | Secondary | 3 | 1 |
| **2003** | AJRCCM | Noninvasive ventilation during persistent weaning failure: a randomized controlled trial.  | Secondary | 0 | 1 |
| **2003** | AJRCCM | Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. | Secondary | 0 | 2 |
| **2004** | Crit Care Med | Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. | Primary | 0 | 12 |
| **2004** | NEJM | Noninvasive positive-pressure ventilation for respiratory failure after extubation. | Primary | 0 | 1 |
| **2004** | Intensive Care Med | Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. | Secondary | 0 | 1 |
| **2004** | Crit Care Med | A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. | Secondary | 0 | 7 |
| **2004** | Anaes Analg | The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial | Secondary | 0 | 9 |
| **2005** | J Am Coll Cardiol | High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study | Primary | 0 | 0 |
| **2005** | JAMA | Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. | Primary | 2 | 12 |
| **2005** | AJRCCM | Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study | Secondary | 0 | 2 |
| **2005** | Chinese Med J | Pulmonary infection control window in treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centred study. | Secondary | 0 | 1 |
| **2006** | Crit Care Med | A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial | Primary | 0 | 3 |
| **2006** | AJRCCM | Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. | Secondary | 0 | 2 |
| **2008** | Lancet | 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. | Secondary | 1 | 5 |
| **2008** | Critical Care | Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. | Secondary | 0 | 1 |
| **2009** | NEJM | Intensive versus conventional glucose control in critically ill patients. | Primary | 82 | 11 |
| **2009** | JAMA | Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. | Secondary | 0 | 0 |
| **2009** | Lancet | Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. | Secondary | 0 | 2 |
| **2010** | Lancet | 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. | Primary | 84 | 48 |
| **2010** | Chinese Med J | Clinical efficacy and safety of recruitment maneuver in patients with acute respiratory distress syndrome using low tidal volume ventilation: a multicenter randomized controlled clinical trial | Primary | 0 | 0 |
| **2011** | Age Ageing | Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial | Secondary | 0 | 0 |
| **2011** | Crit Care Med | Effect of pravastatin on the frequency of ventilator-associated pneumonia and on intensive care unit mortality: open-label, randomized study. | Secondary | 0 | 1 |
| **2012** | Lancet | Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. | Primary | 2 | 1 |
| **2012** | NEJM | Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. | Primary | 6 | 2 |
| **2012** | Crit Care Med | C1-esterase inhibitor infusion increases survival rates for patients with sepsis. | Secondary | 0 | 3 |
| **2012** | AJRCCM | Fever control using external cooling in septic shock: a randomized controlled trial. | Secondary | 0 | 3 |
| **2013** | NEJM | High-frequency oscillation in early acute respiratory distress syndrome. | Primary | 0 | 10 |
| **2013** | Crit Care Med | A phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of talactoferrin in patients with severe sepsis | Primary | 0 | 1 |
| **2013** | NEJM | A randomized trial of glutamine and antioxidants in critically ill patients. | Primary | 5 | 5 |
| **2013** | NEJM | Prone positioning in severe acute respiratory distress syndrome. | Primary | 8 | 20 |
| **2013** | Health Technol Assess | Beta-Agonist Lung injury TrIal-2 (BALTI-2): a multicentre, randomised, double-blind, placebo-controlled trial and economic evaluation of intravenous infusion of salbutamol versus placebo in patients with acute respiratory distress syndrome | Primary | 2 | 1 |
| **2013** | JAMA | Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. | Primary | 0 | 0 |
| **2013** | JAMA | Induced hypothermia in severe bacterial meningitis: a randomized clinical trial | Secondary | 0 | 0 |