# Which multicenter randomized controlled trials in critical care medicine have shown reduced mortality? A systematic review

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**Online Supplement**

**Table S1.** Randomized controlled trials in which decreased mortality was reported

| First author, year (ref) | Number of centers | Study population | Intervention | | Outcome | Outcome rate | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Study group (n) | Control group (n) | | Study group (%) | Control group (%) | |
| **Amendola et al 2018 (8)** | 4 | AKI | Goal-directed therapy (n=48) | Standard practice (n=51) | Hospital mortality[a] | 31% | 51% | 0.048 |
| **Annane 2018 (9)** | 34 | Sepsis | Hydrocortisone + fludrocortisone (n=614) | Placebo (n=627) | 90-day mortality[b] | 43.0% | 49.1% | 0.03 |
| **de Jong 2016 (10)** | 15 | ICU | Procalcitonin-guided therapy (n=761) | Standard practice (n=785) | 28-day mortality[c] | 20% | 25% | 0.001 |
| **Guerin 2013 (11)** | 27 | ARDS | Prone position (n=229) | Supine position (n=237) | 28-day mortality | 16% | 32.8% | <0.001 |
| **Guntupalli 2013 (12)** | 24 | Sepsis | Talactoferrin (n=97) | Placebo (n=93) | 6-month mortality[d] | 21.1% | 35.6% | 0.03 |
| **Nava 2011 (13)** | 3 | AHRF | NIV (n=41) | Standard practice (n=41) | 6-month mortality | 11.7% | 50% | 0.014 |
| **Papazian 2010 (14)** | 20 | ARDS | Cisatracurium besylate (n=178) | Placebo (n=162) | 90-day hospital mortality[e] | 30.8% | 44.6% | 0.04 |
| **Ferrer 2009 (15)** | 3 | AHRF | NIV (54) | Conventional oxygen (n=52) | 90-day mortality[f] | 11% | 31% | 0.02 |
| **de Smet et al 2009 (16)** | 13 | ICU | SDD (n =2045)<br>SOD (n =1904) | Standard practice (n=1990) | 28-day mortality | SDD: 26.9%;<br>SOD 26.6% | 27.5% | 0.22<br>0.045 |
| **Ferrer et al 2006 (17)** | 2 | ICU | NIV (n=79) | Conventional oxygen (n=83) | ICU-mortality | 3% | 14% | 0.015 |
| **Villar et al 2006 (18)** | 8 | ARDS | Pflex/low VT (n=50) | Standard practice (n=45) | ICU mortality | 32% | 53.3% | 0.04 |
| **Panacek 2004 (19)** | 157 | Sepsis | Afelimomab (n=488) | Placebo (n=510) | 28-day mortality | 43.60% | 47.60% | 0.041 |
| **Ferrer 2003 (20)** | 2 | ICU | NIV (n=21) | Conventional weaning (n=22) | ICU survival | 90% | 59% | 0.04 |
| **Ferrer 2003 (21)** | 3 | Acute hypoxemic respiratory failure | NIV (n=51) | High-concentration oxygen therapy (n=54) | ICU mortality | 18% | 39% | 0.028 |
| **Annane 2002 (22)** | 19 | Sepsis | Hydrocortisone + fludrocortisone (n=114) | Placebo (n=115) | 28-day survival[g] | 53% | 63% | 0.02 |

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|---|---|---|---|---|---|---|---|---|
| **Bernard 2001 (23)** | 164 | Sepsis | rh-APC (n=850) | Placebo (n=840) | 28-day mortality | 24.70% | 30.8% | 0.005 |
| **Brower 2000 (24)** | 10 | ARDS | VT 6 ml/kg PBW (n=432) | VT 12 ml/kg PBW (n=429) | Hospital mortality | 31% | 39.8% | 0.007 |
| **Esteban 2000 (25)** | 12 | ARDS | PCV (n=37) | VCV (n=42) | Hospital mortality | 51% | 78% | 0.02 |
| **Fagon 2000 (26)** | 31 | Pneumonia | Invasive management in VAP (n=204) | Clinical management (n=209) | 14-day mortality | 16.2% | 25.8% | 0.022 |
| **Nava 1998 (27)** | 3 | AHRF | Non-invasive pressure support ventilation (n=25) | Invasive pressure support ventilation (n=25) | 60-day survival | 92% | 72% | 0.009 |
| **Amato 1998 (28)** | 2 | ARDS | Protective ventilation (n=29) | Conventional ventilation (n=24) | 28-day mortality | 38% | 71% | <0.001 |
| **Baudo 1998 (29)** | 3 | Sepsis | Antithrombin III (n=60) | Placebo (n=60) | 30-day survival | 30% | 13% | 0.03 |
| **Brochard 1995 (30)** | 5 | AHRF | NIV (n=42) | Standard practice (n=42) | In-hospital mortality | 9% | 29% | 0.02 |
| **Fisher 1994 (31)** | 12 | Sepsis | IL-1ra 17 mg/: n=25; 67 mg/h: n=24; 133 mg/h: n=25 | Placebo (n=25) | 28-day mortality | 17 mg/h, group: 32% 67 mg/h, group: 25% 133 mg/h group: 16% | 44% | 0.015 |
| **Gutierrez 1992 (32)** | 9 | ICU | Gastric intramucosal pH (n=135) | Standard practice (n=125) | Hospital survival | 58% | 42% | < 0.01 |
| **Dominioni 1991 (33)** | 4 | Sepsis | High dose IgG (n=29) | Placebo (n=33) | ICU mortality | 38% | 67% | <0.05 |
| **Ziegler 1991 (34)** | 24 | Sepsis and Gram-negative bacteremia | HA-1A (n=105) | Placebo (n=95) | 28-day mortality | 30% | 49% | 0.014 |

AKI: acute kidney injury; AHRF: acute hypercapnic respiratory failure; ECMO: extracorporeal membrane oxygenation; NIV: non-invasive ventilation; SDD: selective digestive decontamination; SOD: selective oral decontamination; rh-APC: recombinant human activated protein C; VT: tidal volume; PCV: pressure control ventilation; VCV: volume control ventilation; VAP: ventilator-associated pneumonia; IL-1ra : interleukin-1 receptor antagonist; IgG: immunoglobulin G; PBW: predicted body weight; HA-1A: human monoclonal IgM antibody; ARDS: acute respiratory distress síndrome; ICU: intensive care unit.
a ICU mortality 39.4% vs 20.8%, p=0.326
b Mortality at ICU discharge (35.4% vs. 41%, P = 0.04); hospital discharge (39.0% vs. 45.3%, P = 0.02), and day 180 (46.6% vs. 52.5%, P = 0.04);
c Intention to treat group; per protocol 20% vs 27%, p=0.01;

d 28-day and 3-month mortality were not significant (p=0.052; p=0.08, respectively)
e In patients with PaO2/FIO2 ratio < 120.
f ICU mortality 6% vs 8%, p=0.71; Hospital mortality 11% vs 22%, p=0.25.
g In non-responders to the corticotropin test;

**Table S2.** Randomized controlled trials in which increased mortality was reported

| First author, year (ref) | Number of centers | Study population | Intervention | | Outcome | Outcome rate | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Study group (n) | Control group (n) | | Study group (%) | Control group (%) | |
| **Guidet 2017 (35)** | 24 | ICU | Systematic ICU admission (n=1519) | Standard practice (n=1518) | 6-month mortality | 45%[a] | 39% | <0.001 |
| **Cavalcanti 2017 (36)** | 120 | ARDS | Recruitment maneuver and PEEP titration (n=501) | Low PEEP (n=509) | 28-day mortality | 55.3%[b] | 49.3% | 0.04 |
| **Ferguson 2013 (37)** | 39 | ARDS | HFOV (n=275) | PCV (n=273) | In-hospital mortality | 47% | 35% | 0.005 |
| **Heyland 2013 (38)** | 40 | ICU | Glutamine (n=301), antioxidants (n=307) or both (n=310) | Placebo (n=300) | 28-day mortality | 32.4% | 27.2% | 0.05 |
| **Mourvillier 2013 (39)** | 49 | Sepsis | Hypothermia (n=49) | Standard practice (n=49) | 3-month mortality | 51% | 34% | 0.05 |
| **Perner 2012 (40)** | 26 | Sepsis | 6% HES 130/0.42[c] (n=398) | Ringer´s acetate (n=400) | 90-day mortality | 51% | 43% | 0.03 |
| **Gao Smith 2012 (41)** | 46 | ARDS | IV salbutamol (n=162) | Placebo (n=164) | 28-day mortality | 34% | 23% | 0.033 |
| **Elseviers 2010 (42)** | 9 | AKI | RRT (n=650) | Conservative management (n=653) | Hospital mortality | 50.3% | 63.7% | <0.001 |
| **Lopez 2004 (43)** | 124 | Sepsis | Nitric oxide synthase inhibitor 546C88 (n=439) | Placebo (n=358) | 28-day survival | 59% | 49% | 0.001 |
| **Esteban 2004 (44)** | 37 | ARF | NIPPV (n=114) | Standard practice (n=107) | ICU mortality | 25% | 14% | 0.048 |
| **Mehta 2001 (45)** | 4 | ICU | CRRT (n=84) | IHD (n=82) | ICU mortality | 59.5% | 41.5% | <0.02 |
| **Esteban 2000 (25)** | 12 | ARDS | VCV (n=42) | PCV (n=37) | Hospital mortality | 78% | 51% | 0.02 |
| **Sloan 1999 (46)** | 18 | Hemorrhagic shock | DCLHb (n=52) | Placebo (n=46) | 28-day mortality | 46% | 17% | 0.003 |
| **Takala** | 18 (n=6 in | ICU | Growth hormone | Placebo | In-hospital | 39% | 20%[d] | <0.001 |

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| **1999 (47)** | Finnish branch; n=12 in European branch) | | (n=258: n=119 in Finnish branch; n=139 in European branch) | (n=264: n=123 in Finnish branch; n=141 in European branch) | mortality | 44% | 18%[e] | <0.001 |
| **Fisher 1996 (48)** | 15 | Sepsis | TNFR:Fc (n=108; n=30 low dose 0.15 mg/kg, n=29 middle dose 0.45 mg/kg, n=49 high dose 1.5 mg/kg) | Placebo (n=33) | 28-day mortality | 53%[f] | 30% | 0.02 |
| **Hayes 1994 (49)** | 2 | ICU | High $DO_2$ and $VO_2$ (n=50) | Standard $DO_2$ and $VO_2$ (n=50) | In-hospital mortality | 54% | 34% | 0.04 |

ARDS: acute respiratory distress syndrome; HFOV: high frequency oscillatory ventilation; PCV: pressure control ventilation; HES: hydroxyethyl starch; NIPPV: non-invasive positive pressure ventilation; (C)RRT: (continuous) renal replacement therapy; IHD: intermittent hemodialysis; DCLHb: diaspirin cross linked hemoglobin; TNFR:Fc: tumor necrosis factor receptor and Fc portion of IgG1; $DO_2$: oxygen delivery; $VO_2$: oxygen consumption; ICU: intensive care unit; AKI: acute kidney injury; ARF: acute respiratory failure; PEEP: positive-end-expiratory pressure; VCV: volume controlled ventilation.

a No difference in mortality when adjusted for baseline characteristics (p=NS). In-hospital mortality significantly higher in intervention group (30% vs. 21%; absolute risk difference p<0.001; adjusted absolute risk difference p=0.03);

b 6-month mortality (65.3%vs 59.9%; HR, 1.18; 95%CI, 1.01 to 1.38; P = .04), no difference in ICU mortality or hospital mortality;

c HES dose of up to 33 ml/kg of ideal body weight.

d in the Finnish study;

e in the European study;

f in high dose group; in all groups combined P=NS.

**Table S3.** Randomized controlled trials in which no change in mortality was reported

| Authors, year (ref) | Number of centers | Study population | Intervention | | Outcome | Outcome rate | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Study group (n) | Control group (n) | | Study group (%) | Control group (%) | |
| **Hernandez et al 2019 (50)** | 28 | Sepsis | Peripheral perfusion–targeted resuscitation (n=212) | Lactate level–targeted resuscitation (n = 212) | 28-day mortality | 34.9 | 43.4 | 0.06 |
| **Mahmoodpoor et al 2019 (51)** | 2 | ICU | Probiotics (n=48) | Placebo (n=54) | ICU-mortality | 10.4% | 11.1% | 0.58 |
| **Arabi et al 2019 (52)** | 20 | ICU | Intermittent pneumatic compression (n=991) | Control group (n=1012) | 90-day mortality | 26.1% | 26.7% | NR |
| **Jones et al 2018 (53)** | 16 | Sepsis | Low-dose levocarnitine, 6 g (n=35); medium-dose levocarnitine, 12 g (n=34); high-dose levocarnitine, 18 g (n=106) | Placebo (n=75) | 28-day mortality | Levocarnitine 18 g: 43.3% | 49.5% | 0.4 |
| **Krag et al 2018 (54)** | 33 | ICU (risk of GI bleeding) | Pantoprazole (n=1642) | Placebo (n=1640) | 90-day mortality | 31.1% | 30.4% | 0.76 |
| **Wittekamp et al 2018 (55)** | 13 | ICU | CHX (n=2107), SOD (n=2224), SSD (n=2082) | Standard practice (n=2251) | ICU-mortality | CHX: 31.5%; SOD:30.8%; SSD:31% | 30.7 | NR |
| **Pickkers et al 2018 (56)** | 53 | AKI | Recombinant alkaline phosphatase 0.4 mg/kg (n=31); 0.8 mg/kg (n=32); 1.6 mg/kg (n=111). | Placebo group (n=116) | 28-day mortality | 0.4 mg/kg: 25.8% 0.8 mg/kg: 12.5% 1.6 mg/kg: 14.4% | 26.7 | NR |
| **Perkins et al 2018 (57)** | 41 | ICU | Invasive weaning (n=182) | Non-invasive weaning (n=182) | 30-day survival | 86.3% | 86.8% | 0.83 |
| **Azoulay et al 2018 (58)** | 32 | AHRF | High-flow oxygen therapy (n=388) | Standard oxygen therapy (n = 388) | 28-day mortality | 35.6% | 36.1% | 0.94 |
| **Nardi et al 2018 (59)** | 5 | Sepsis | Target StO2>80% (n=54) | Control (n=49) | 7-day mortality | 33.3% | 28.6% | 0.67 |
| **Itenov et al 2018 (60)** | 10 | Sepsis | Hypothermia (n=217) | Standard practice (n=215) | 30-day mortality | 44.2% | 35.8% | 0.07 |

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| **Girard et al 2018 (61)** | 16 | ICU | Haloperidol (n=192); Ziprasidone (n=190) | Placebo (N = 184) | 30-day mortality | Haloperidol: 26% Ziprasidone: 28% | 27% | NR |
| **Target Investigators 2018 (62)** | 46 | ICU | Daily nutrition 1.5-kcal (n=1971) | Daily nutrition 1.0-kcal (N = 1985) | 90-day mortality | 26.8% | 25.7% | NR |
| **Prevent Investigators 2018 (63)** | 6 | ICU | Low tidal volume (n=477) | Intermediate tidal volume (n = 484) | 28-day mortality | 34.9% | 32.1% | 0.3 |
| **Pinder et al 2018 (64)** | 5 | Sepsis | GM-CSF (n=17) | Placebo (n=21) | 30-day mortality | 7.7% | 30% | NR |
| **Dellinger et al 2018 (65)** | 55 | Sepsis | Polymyxin B hemoperfusion (n=224) | Sham hemoperfusion (n=226) | 28-day mortality | 37.7%^ | 34.5% | 0.49 |
| **Barbar et al 2018 (66)** | 29 | AKI | Early renal-replacement (n=246) | Delayed renal-replacement (n=242) | 90-day mortality | 58%ç | 54% | 0.39 |
| **van Meenen et al 2018 (67)** | 7 | ICU | On–demand nebulization (n=455) | Routine nebulization (n=467) | 28-day mortality | 31.0%$ | 31.9% | 0.78 |
| **Reignier et al 2018 (68)** | 44 | ICU | Parenteral (n=1202) | Enteral (n=1208) | 28-day mortality | 37%@ | 35% | 0.33 |
| **Combes et al 2018 (69)** | 64 | ARDS | ECMO (n=124) | Conventional treatment (n=125) | 60-day mortality | 35% | 46% | 0.09 |
| **van den Boogaard et al 2018 (70)** | 21 | ICU | Haloperidol 1 mg (n=350) Haloperidol 2 mg (n=732) | Placebo (n=707) | 28-day survival | Haloperidol 1 mg: 81.7% haloperidol 2 mg: 83.3%& | 82.7% | NR |
| **Venkatesh et al 2018 (71)** | 69 | Sepsis | Hydrocortisone continuous infusion (n=1853) | Placebo (n=1860) | 90-day mortality | 27.9%* | 28.8% | 0.5 |
| **Khanna et al 2017 (72)** | 75 | Vasodilatory shock (80% sepsis) | Angiotensin II (n=163) | Placebo (n=158) | 28-day mortality | 46%a | 54% | 0.22 |
| **Cooper et al 2017 (73)** | 59 | ICU | Freshest blood available (n=2457) | Oldest blood available (n=2462) | 90-day mortality | 24.8%b | 24.1% | 0.57 |
| **Futier et al 2017 (74)** | 9 | Major surgery | IV norepinephrine to targeted systolic blood pressure to 10% of reference value (n=147) | IV ephedrine if SBP<80 mmHg or 40% lower than reference value (n=145) | 30-day mortality | 6.1 | 5.5 | 0.82 |
| **Landoni et al 2017 (75)** | 14 | Post-cardiac surgery on ICU | Levosimendan (n=248) | Placebo (n=258) | 30-day mortality | 12.9% | 12.8% | 0.9 |

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| **Wischmeyer et al 2017 (76)** | 11 | ICU | SPN + EN (n=73) | EN (n=52) | ICU mortality | 13.5% | 17.8% | 0.71 |
| **Valette et al 2017 (77)** | 3 | ICU | Sodium bicarbonate (n=151) | Sodium saline 0.9% (n=156) | ICU mortality | 15.9% | 16% | >0.99 |
| **Van der Geest et al 2017 (78)** | 2 | ICU | Procalcitonin-guided therapy (n=276) | Control group (n=276) | 28-day mortality | 29%[c] | 32% | 0.36 |
| **Qiu et al 2017 (79)** | 7 | ICU | Fat-modified enteral formula (n=71) | Standard enteral formula (n=73) | In-hospital mortality | 24.1% | 28.2% | 0.71 |
| **Keh et al 2016 (80)** | 34 | Sepsis | Hydrocortisone (n=190) | Placebo (n=190) | 28-day mortality | 8.8% | 8.2% | 0.86 |
| **Park et al 2016 (81)** | 2 | AKI | High dose CVVHDF (n=105) | Conventional dose CVVHDF (n=107) | 28-day mortality | 65.7% | 64.5% | 0.5 |
| **Bloos et al 2016 (82)** | 33 | Sepsis | Sodium selenite (n=543) | Placebo (n=546) | 28-day mortality | 28.3% | 25.5% | 0.3 |
| **Donnino et al 2016 (83)** | 3 | Post-cardiac arrest | Hydrocortisone (n=25) | Placebo (n=25) | Survival to hospital discharge | 50% | 0% | 0.46 |
| **Faisy et al 2016 (84)** | 15 | Acute respiratory failure (COPD) | Acetazolamide (n=147) | Placebo (n=194) | ICU mortality | 11.7% | 13.4% | 0.61 |
| **Legriel et al 2016 (85)** | 16 | Convulsive status epilepticus | Hypothermia (n=138) | Standard practice (n=130) | 90-day mortality | 13%[d] | 15% | 0.67 |
| **Wiberg et al 2016 (86)** | 2 | Post-cardiac arrest refractory shock | Exenatide (glucagon-like peptide-1 analog) (n=60) | Placebo (n=58) | 30-day mortality | 25% | 36% | 0.19 |
| **Kacmarek et al 2016 (87)** | 20 | ARDS | Open lung approach (n=28) | Standard ventilation (n=34) | 60-day mortality | 29%[e] | 33% | 0.18 |
| **Ziegler et al 2016 (88)** | 5 | Surgical ICU | Glutamine supplemented TPN (n=75) | Standard TPN (n=75) | 6-month mortality | 31.4%[f] | 29.7% | 0.88 |
| **Cavalcanti et al 2016 (89)** | 118 | ICU | Quality improvement interventions (n=59) | Standard practice (n=59) | 60-day in-hospital mortality | 32.9% | 34.8% | 0.88 |
| **Gaudry et al 2016 (90)** | 31 | ICU | Early renal replacement strategy (n=311) | Delayed renal replacement strategy (n=308) | 60-day survival | 48.5% | 49.7% | 0.79 |
| **Torres et al 2015 (91)** | 3 | Severe CAP | Methylprednisolone (n=61) | Placebo (n=59) | In-hospital mortality | 10%[g] | 15% | 0.37 |
| **Payen et al 2015 (92)** | 18 | Sepsis | PMX (n=119) | Standard (n=113) | 28-day mortality | 27.7% | 19.5% | 0.14 |
| **Deye et al 2015 (93)** | 18 | Cardiac Arrest | Endovascular cooling method | External cooling method | 28-day survival | 41.9% | 38.1% | 0.07 |

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| | | | (n=203) | (n=197) | | | | |
| **Lacroix et al 2015 (94)** | 64 | ICU | Fresh blood (n=1207) | Standard blood (n=1206) | 90-day mortality | 37.0%[h] | 35.3% | NR |
| **Combes et al 2015 (95)** | 4 | Post-cardiac surgery shock | Early HVHF (n=112) | CVVHDF (n=112) | 30-day mortality | 36%[i] | 36% | 1 |
| **Lemiale et al 2015 (96)** | 28 | Acute hypoxemic respiratory failure | NIV (n=191) | Oxygen alone (n=183) | 28-day mortality | 24.1% | 27.3% | 0.47 |
| **Vincent et al 2015 (97)** | 77 | Sepsis | Talactoferrin (n=153) | Placebo (n=152) | 28-day mortality | 24.8% | 17.8% | 0.11 |
| **Mouncey et al 2015 (98)** | 56 | Sepsis | EGDT (n=630) | Standard practice (n=630) | 90-day mortality | 29.5% | 29.2% | 0.9 |
| **Peake et al 2014 (99)** | 51 | Sepsis | EGDT (n=796) | Standard practice (n=804) | 90-day mortality | 18.6% | 18.8% | 0.9 |
| **Yealy et al 2014 (100)** | 31 | Sepsis | EGDT (n=439) | Standard practice (N=456) | 60-day in-hospital mortality | 21% | Usual care:18.9%; protocol-based standard-therapy group:18.2% | 0.83; 0.31 |
| **Van Zanten et al 2014 (101)** | 14 | ICU | IMHP (n=152) | HP (n=149) | 28-day mortality | 20% | 17% | 0.42 |
| **Abroug F et al 2014 (102)** | 2 | AHRF (COPD) | Prednisone (n=111) | Placebo (n=106) | ICU mortality | 15.3% | 14.2% | 0.81 |
| **Giamarellos-Bourboulis et al 2014 (103)** | 3 | Sepsis | Clarithromycin (n=302) | Placebo (n=298) | 28-day mortality | 18.5% | 17.1% | 0.67 |
| **Asfar et al 2014 (104)** | 29 | Sepsis | High blood pressure target group (n=388) | Low blood pressure target group (n=388) | 28-day mortality | 36.6% | 34% | 0.57 |
| **Caironi et al 2014 (105)** | 100 | Sepsis | 20% albumin and crystalloid solution (n=903) | crystalloid solution alone (n=907) | 28 day mortality | 31.8% | 32% | 0.94 |
| **Leaf et al 2014 (106)** | 44 | ARDS | Rosuvastatin (n=379) | Placebo (n=366) | Hospital mortality | 28.5% | 24.9% | 0.21 |
| **Holst et al 2014 (107)** | 32 | Sepsis | Higher Hb level (n=496) | Lower Hb level (n=502) | 90-day mortality | 45% | 43% | 0.44 |
| **Harvey et al 2014 (108)** | 33 | ICU | Parenteral group (n=1191) | Enteral group (n=1197) | 30-day mortality | 33,1% | 34.2% | 0.57 |
| **Young et al 2013 (109)** | 72 | Prolonged mechanical ventilation | Early tracheostomy (n=455) | Late tracheostomy (n=454) | 30-day mortality | 30.8% | 31.5% | 0.81 |
| **Opal et al 2013 (110)** | 197 | Sepsis | TLR4 antagonist (n=1304) | Placebo (n=657) | 28-day mortality | 28.1% | 26.9% | 0.59 |
| **Papazian et** | 26 | VAP | Simvastatin | Placebo | 28-day mortality | 21% | 15% | 0.1 |

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| **al 2013 (111)** | | | (n=146) | (n=138) | | | | |
| **Annane et al 2013 (112)** | 24 | Sepsis | Drotrecogin alfa (activated) (n=208) | Placebo (n=203) | 90-day mortality | 47.6% | 46.3% | 0.79 |
| **Young et al 2013 (113)** | 29 | ARDS | HFOV (n=398) | Conventional ventilation (n=397) | 30-day mortality | 41.7% | 41.1% | 0.85 |
| **Hung et al 2013 (114)** | 5 | Severe HIAI influenza | High dose IVIgG (n=17) | Normal IVIgG (n=17) | Mortality | 29.4% | 23.5% | NR |
| **Vincent et al 2013 (115)** | 33 | Sepsis + DIC | ART-123 (n=370) | Placebo (n=371) | 28-day mortality | 17.8% | 21.6% | 0.27 |
| **Annane et al 2013 (116)** | 57 | Hypovolemic shock | Colloids (n=1414) | Crystalloids (n=1443) | 28-day mortality | 25.4% | 27% | 0.26 |
| **Doig et al 2013 (117)** | 31 | ICU | Early parenteral nutrition (n=681) | Standard practice (n=682) | 60-day mortality | 21.5% | 22.8% | 0.6 |
| **Durante-Mangoni et al 2013 (118)** | 5 | Drug-resistant *Acinetobacter baumannii* | Colistin + rifampicin (n=104) | Colistin (n=105) | 30-day mortality | 43.3% | 42.9% | 0.95 |
| **Vignon et al 2013 (119)** | 9 | High risk of bleeding | IPC+graduated compression stockings (n=204) | graduated compression stockings (n=202) | 30-day mortality | 29.9% | 28.7% | NR |
| **Myburgh et al 2012 (120)** | 32 | ICU | Voluven (HES 130/0.4) (n=3358) | 0.9% saline (n=3384) | 90-day mortality | 18% | 17% | 0.26 |
| **Ranieri et al 2012 (121)** | 208 | Sepsis | Drotrecogin alfa (activated) (n=846) | Placebo (n=834) | 28-day mortality | 26.4%[l] | 24.2% | 0.31 |
| **Thiele et al 2012 (122)** | 37 | Cardiogenic shock | IABP (n=301) | Standard practice (n=299) | 30-day mortality | 39.7% | 41.3% | 0.69 |
| **Jensen et al 2011 (123)** | 9 | ICU | Procalcitonin-guided interventions (n=604) | Standard practice (n=596) | 28-day mortality | 31.5% | 32% | 0.83 |
| **Wunderink et al 2011 (124)** | 188 | Severe CAP | rTFP inhibitor (n=946) | Placebo (n=918) | 28-day mortality | 18% | 17.9% | 0.61 |
| **Spragg et al 2010 (125)** | 161 | ALI | Protein C-based surfactant (n=419) | Standard practice (n=424) | 28-day survival | 77.3% | 76.2% | 0.26 |
| **Jansen et al 2010 (126)** | 348 | ICU | Lactate guided treatment (n=171) | Standard therapy (n=177) | Hospital mortality | 33.9%[k] | 43.5% | 0.067 |
| **Peek et al 2010 (127)** | 148 | ARDS | ECMO (n=90) | Conventional management (n=90) | 6-month mortality | 33% | 53% | NR |
| **Jones et al** | 3 | Sepsis | $ScvO_2$ | Lactate clearance | In-hospital | 23%[l] | 17% | NR |

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|---|---|---|---|---|---|---|---|---|
| **2010 (128)** | | | (n=150) | (n=150) | mortality | | | |
| **Rice et al 2010 (129)** | 93 | Sepsis | TAK-242 (n=183) | Placebo (n=91) | 28-day mortality | 22% low dose group 17% high dose group | 24% | 0.26 |
| **Annane et al 2010 (130)** | 11 | Sepsis | Intensive insulin (n=255) | Conventional glucose control (n=254) | 90-day mortality | 45.9% | 42.9% | 0.5 |
| | | | Hydrocortisone+fludrocortisone (n=245) | Hydrocortisone (n=264) | | 42.9% | 45.8% | 0.5 |
| **Bouadma et al 2010 (131)** | 8 | ICU | Procalcitonin (n=311) | Control (n=319) | 28-day mortality | 21.2% | 20.4% | NR |
| **Tidswell et al 2010 (132)** | 99 | Sepsis | IV eritoran tetrasodium (45 mg, n=103; 105 mg, n=94) | Placebo (n=96) | 28-day mortality | 105 mg: 26.6%; 45 mg: 32% | 33.3% | 0.335 |
| **Hauser et al 2010 (133)** | 150 | Refractory traumatic hemorrhage | rFVIIa (n=221) | Placebo (n=247) | 30-day mortality | 11%[n] | 10.7% | 0.93 |
| **Taccone et al 2009 (134)** | 25 | ARDS | Prone position (n=168) | Supine position (n=174) | 28-day mortality | 31%[o] | 32.8% | 0.74 |
| **Palizas et al 2009 (135)** | 6 | Sepsis | pHi (n=64) | Cardiac index (n=66) | 28-day mortality | 28.1% | 30.3% | 0.98 |
| **Bellomo et al 2009 (136)** | 35 | ICU | High intensity CVVHDF (n=722) | Low intensity CVVHDF (n=743) | 90-day mortality | 44.7%[p] | 44.7% | 0.99 |
| **Dellinger et al 2009 (137)** | 235 | Gram-negative sepsis | GR270773 lipid emulsion (n=780) | Placebo (n=599) | 28-day mortality | Low dose group: 25.8% High dose: 31.3% | 26.9% | Low dose vs placebo: p=0.329 High dose vs placebo: p=0.879 |
| **Kesecioglu et al 2009 (138)** | 67 | ARDS | Exogenous natural surfactant (n=208) | Standard practice (n=210) | 28-day mortality | 28.8% | 24.5% | 0.22 |
| **Lins et al 2009 (139)** | 9 | AKI | CRRT (n=172) | IRRT (n=144) | Hospital mortality | 58.1% | 62.5% | 0.43 |
| **Preiser et al 2009 (140)** | 21 | ICU | Tight glucose control (n=536) | Standard glucose control (n=542) | ICU mortality | 17.2%[q] | 15.3% | 0.41 |
| **Schuetz et al 2009 (141)** | 6 | LRTI | Procalcitonin algorithm (n=103) | Standard therapy (n=130) | 30-day mortality | 5.1%[r] | 4.8% | NR |
| **Doig et al 2008 (142)** | 27 | ICU | Evidence-based feeding guideline | Standard feeding (n=557) | Hospital mortality | 28.9% | 27.4% | 0.75 |

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| | | | (n=561) | | | | | |
| **Blot et al 2008 (143)** | 25 | Mechanical ventilation | Early tracheostomy (n=61) | Prolonged intubation (n=62) | 28-day mortality | 20% | 24% | NR |
| **Palevsky et al 2008 (144)** | 27 | AKI | Intensive renal replacement therapy (n=563) | Less intensive renal replacement therapy (n=561) | 60-day mortality | 53.6% | 51.5% | 0.47 |
| **Russell et al 2008 (145)** | 27 | Sepsis | Vasopressin (n=396) | Norepinephrine (n=382) | 28-day mortality | 35.4%[s] | 39.3% | 0.26 |
| **Mercat et al 2008 (146)** | 37 | ARDS | Increased recruitment strategy (n=385) | Minimal distension strategy (n=382) | 28-day mortality | 27.8% | 31.2% | 0.31 |
| **Meade et al 2008 (147)** | 30 | ARDS | Open-lung ventilation (n=475) | Control ventilation (508) | Hospital mortality | 36.4%[t] | 40.4% | 0.19 |
| **Brunkhorst et al 2008 (148)** | 18 | Sepsis | Intensive insulin (n=247) | Conventional Insulin (n=290) therapy | 28-day mortality | 24.7%[u] | 26% | 0.74 |
| | | | 10% pentastarch (HES 200/0.5) (n=262) | Ringer´s lactate (n=275) | | 26.7% | 24.1% | 0.48 |
| **Sprung et al 2008 (149)** | 52 | Sepsis | Hydrocortisone (n=251) | Placebo (n=248) | 28-day mortality | Not responsive to corticotropin: 39.2% Responsive to corticotropin: 28.8% | Not responsive to corticotropin: 36.1% Responsive to corticotropin: 28.7% | Not responsive p=0.69 Responsive p=1.00 |
| **Giamarellos et al 2008 (150)** | 3 | Sepsis and VAP | Clarithromycin (n=100) | Placebo (n=100) | 28-day mortality | 23.3%[x] | 25.5% | 0.86 |
| **Tumlin et al 2008 (151)** | 12 | AKI | CVVH + RAD (n=40) | CRRT (n=18) | 28-day mortality | 33.3% | 61.1% | 0.08 |
| **Fernandez et al 2008 (152)** | 17 | ARDS | Prone position (n=21) | Supine position (n=19) | 60-day mortality | 38% | 53% | 0.3 |
| **Heyland et al 2008 (153)** | 28 | VAP | Meropenem and ciprofloxacin (n=369) | Meropenem (n=370) | 28-day mortality | 25.6% | 29.4% | 0.74 |
| **Kinasewitz et al 2008 (154)** | 15 | Distributive shock (94% sepsis) | Pyridoxalated hemoglobin polyoxyethylene (n=33) | Placebo (n=29) | 28-day mortality | 57.6% | 58.6% | NR |
| **Werdan et al 2008 (155)** | 11 | Cardiac surgery | IV IgG (n=110) | Placebo (n=108) | 28-day mortality | 39.1% | 31.5% | NR |
| **Manzano et** | 3 | Mechanical | PEEP 5-8 cm $H_2O$ | No PEEP | Hospital mortality | 29.7% | 25.4% | 0.58 |

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| **al 2008 (156)** | | ventilation | (n=66) | (n=65) | | | | |
| **Werdan et al 2007 (157)** | 23 | Sepsis | IVIgG (n=321) | Placebo (n=303) | 28-day mortality | 39.3% | 37.3% | 0.66 |
| **Moritz et al 2007 (158)** | 3 | Cardiogenic pulmonary edema | Bilevel PAP (n=50) | B-CPAP (n=59) | Hospital mortality | 8% | 14% | NR |
| **Annane et al 2007 (159)** | 19 | Sepsis | Norepinephrine + dobutamine (n=169) | Epinephrine (n=161) | 28-day mortality | 34% | 40% | 0.31 |
| **Levi et al 2007 (160)** | 224 | Sepsis | DrotAA + low molecular weight/unfractionated heparin (n=976) | DrotAA + placebo (n=959) | 28-day mortality | 28.3% | 31.9% | 0.08 |
| **Stoutenbeek et al 2007 (161)** | 17 | Multiple trauma | SDD (n=201) | Control (n=200) | Late mortality | 13.4% | 17.2% | 0.35 |
| **Angstwurm et al 2007 (162)** | 11 | Sepsis | Sodium-selenite (n=92) | Placebo (n=97) | 28-day mortality | 39.7% | 50% | 0.109 |
| **van Ruler et al 2007 (163)** | 7 | Severe peritonitis | On-demand re-laparotomy (n=114) | Planned re-laparotomy (n=115) | 12-month mortality | 36% | 29% | 0.22 |
| **Hentrich et al 2006 (1645)** | 6 | Sepsis | ivIGMA (n=103) | Control (n=103) | 28-day mortality | 26.2% | 28.2% | 0.93 |
| **Heyland et al 2006 (165)** | 28 | VAP | BAL (n=365) | Endotracheal aspiration (n=374) | 28-day mortality | 18.9% | 18.4% | 0.94 |
| **Radrizzani et al 2006 (166)** | 33 | Sepsis | Early parenteral nutrition (n=145) | Enteral immunonutrition (n=142) | 28-day mortality | 15.1% | 15.6% | 0.89 |
| **Wheeler et al 2006 (167)** | 20 | ARDS | PAC (n=513) | Central venous catheter (n=487) | 60-day mortality | 27.4% | 26.3% | 0.69 |
| **Wiedemann et al 2006 (168)** | 20 | ARDS | Conservative fluid strategy (n=503) | Liberal fluid strategy (n=497) | 60-day mortality | 25.5% | 28.4% | 0.3 |
| **Steinberg et al 2006 (169)** | 25 | ARDS | Methylprednisolone (n=89) | Placebo (n=91) | 60-day mortality | 29.2% | 28.6% | 1.0 |
| **Mancebo et al 2006 (170)** | 13 | ARDS | Prone position (n=76) | Supine position (n=60) | ICU mortality | 43% | 58% | 0.12 |
| **Vinsonneau et al 2006 (171)** | 21 | AKI | CVVHF (n=175) | IHD (n=184) | 60-day survival | 33% | 32% | 0.98 |
| **Rodriguez et al 2005 (172)** | 5 | Sepsis | High-dose IV immunoglobulin (n=29) | Placebo (n=27) | 30-day mortality | 27.5% | 48.1% | 0.06 |
| **Harvey et al** | 65 | ICU | PAC | No PAC | Hospital mortality | 68% | 66% | 0.39 |

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| **2005 (173)** | | | (n=506) | (n=507) | | | | |
| **Abraham et al 2005 (174)** | 516 | Sepsis | DrotAA (n=1316) | Placebo (n=1297) | 28-day mortality | 18.5% | 17% | 0.34 |
| **Tumlin et al 2005 (175)** | 3 | AKI | Fenoldopam mesylate (n=80) | Placebo (n=75) | 21-day mortality | 13.8% | 25.3% | 0.06 |
| **Zeiher et al 2005 (176)** | 75 | Sepsis | LY315920Na/S-5920 (n=188) | Placebo (n=185) | 28-day mortality | 39.4% | 31.9% | 0.09 |
| **Guerin et al 2004 (177)** | 21 | Acute hypoxemic respiratory failure | Prone position (n=413) | Supine position (n=378) | 28-day mortality | 32.4% | 31.5% | 0.77 |
| **Spragg et al 2004 (178)** | 109 | ARDS | Protein C-based surfactant (n=224) | Control (n=224) | 28-day survival | 68% | 64% | 0.54 |
| **Brower et al 2004 (179)** | 23 | ARDS | Higher PEEP (n=276) | Lower PEEP (n=273) | Hospital mortality | 27.5% | 24.9% | 0.48 |
| **Albrecht et al 2004 (180)** | 13 | Sepsis | BN 52021 (ginkgolide B) (n=44) | Placebo (n=44) | 28-day mortality | 42% | 51% | 0.17 |
| **Finfer et al 2004 (181)** | 16 | ICU | 4% albumin (n=3473) | Saline (n=3460) | 28-day mortality | 20.9% | 21.1% | 0.87 |
| **Opal et al 2004 (182)** | 146 | Sepsis | rPAF-AH (n=460) | Placebo (n=457) | 28-day mortality | 25% | 24% | 0.8 |
| **Abraham et al 2003 (183)** | 72 | Sepsis | High-dose LY315920Na/S-5920 (n=194) Low dose LY315920Na/S-5920 (n=196) | Placebo (n=196) | 28-day mortality | High dose group: 36.1% Low-dose group:37.2% | 33.2% | 0.525 |
| **Abraham et al 2003 (184)** | 245 | Sepsis | Tifacogin (n=880) | Placebo (n=874) | 28-day mortality | 34.2% | 33.9% | 0.88 |
| **Albertson et al 2003 (185)** | 33 | Gram-negative sepsis | MAB-T88 (n=411) | Placebo (n=415) | 28-day mortality | 37% | 34% | 0.36 |
| **Chastre et al 2003 (186)** | 51 | VAP | 8-day antibiotic regimen for VAP (n=197) | 15-day antibiotic regimen for VAP (n=204) | 28-day mortality | 18.8% | 17.2% | NR |
| **Richard et al 2003 (187)** | 36 | Shock or ARDS | PAC (n=335) | No PAC (n=341) | 28-day mortality | 59.4% | 61% | 0.67 |
| **Root et al 2003 (188)** | 96 | Pneumonia + severe sepsis | Filgrastim (n=348) | Placebo (n=353) | 29-day mortality | 29% | 25.5% | 0.383 |
| **Sandham et al 2003 (189)** | 19 | High risk surgical | PAC (n=997) | No PAC (n=997) | In-hospital mortality | 7.7% | 7.8% | 0.93 |
| **Bouman et al 2002 (190)** | 2 | AKI | Early high-volume hemofiltration (n=35) | Late low-volume hemofiltration (n=36) | 28-day survival | Early high-volume group: | Late low-volume: 75% | 0.8 |

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| | | | Early low-volume hemofiltration (n=35) | | | 74.3% Early low-volume: 68.8% | | |
| **Reinhart et al 2001 (191)** | 84 | Sepsis | Afelimomab (n=224) | Placebo (n=222) | 28-day mortality | 54% | 57.7% | 0.36 |
| **Abraham et al 2001 (192)** | 108 | Sepsis | Lenercept (n=662) | Placebo (n=680) | 28-day mortality | 27% | 28% | 0.141 |
| **Gattinoni et al 2001 (193)** | 30 | ARDS | Prone position (n=152) | Supine position (n=152) | 10-day mortality | 21.1% | 25% | NR |
| **Vincent et al 2001 (194)** | 31 | ARDS | Liposomal PGE1 (TLC C-53) (n=70) | Placebo (n=32) | 28-day mortality | 30% | 28% | 0.78 |
| **Warren et al 2001 (195)** | 211 | Sepsis | High-dose antithrombin III (n=1157) | Placebo (n=1157) | Over-all 28-day mortality | 38.9% | 38.7% | 0.94 |
| **Angus et al 2000 (196)** | 136 | Gram-negative sepsis | Murine monoclonal antibody E5 (n=550) | Placebo (n=552) | 14-day mortality | 29.7% | 31.1% | 0.67 |
| **ARDS network 2000 (197)** | 24 | ARDS | Ketoconazole (n=117) | Placebo (n=117) | In-hospital mortality | 35.2% | 34.1% | 0.85 |
| **Poeze et al 2000 (198)** | 9 | Sepsis | PAF-antagonist TCV-309 (n=49) | Placebo (n=48) | 56-day mortality | 51% | 41.7% | 0.47 |
| **Takala et al 2000 (199)** | 13 | Major abdominal surgery | Dopexamine (n=272) | Placebo (n=140) | 28-day mortality | Dopexamine 0.5 mcg/kg/min: 7% Dopexamine 2 mcg/kg/min: 15% | 13% | 0.13 |
| **Demetriades et al 1999 (200)** | 19 | Acute hemorrhagic trauma | rBPI21 (n=202) | Placebo (n=199) | 15-day mortality | 6% | 5% | NR |
| **Hebert et al 1999 (201)** | 25 | ICU | Restrictive transfusion strategy (n=418) | Liberal transfusion strategy (n=420) | 30-day mortality | 18.7% | 23.3% | 0.11 |
| **Abraham et al 1998 (202)** | 105 | Sepsis | TNF-alpha Mab (n=949) | Placebo (n=930) | 28-day mortality | 40.3% | 42.8% | 0.27 |
| **Brochard et al 1998 (203)** | 25 | ARDS | Plateau pressure limitation (n= 58) | Standard practice (n=58) | 60-day mortality | 46.6% | 37.9% | 0.38 |
| **Dhainaut et al 1998 (204)** | 59 | Gram-negative sepsis | PAFra BN52021 (n=300) | Placebo (n=308) | 28-day mortality | 47% | 49% | 0.5 |
| **Wasserman** | 23 | Severe burns | Interferon-gamma | Placebo | 90-day mortality | 20.1% | 21.4% | 0.675 |

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| **et al 1998 (205)** | | | (n=109) | (n=107) | | | | |
| **Opal et al 1997 (206)** | 91 | Sepsis | rhIL-1ra (n=350) | Placebo (n=346) | 28-day mortality | 33.6% | 35.7% | 0.49 |
| **Anzueto et al 1996 (207)** | 63 | ARDS | Aerosolized surfactant (n=364) | Placebo (n=361) | 30-day mortality | 40% | 40% | NR |
| **Cohen et al 1996 (208)** | 40 | Sepsis | BAY x 1351 (n=287) | Placebo (n=133) | 28-day mortality | 3 mg/kg group: 31.5% 15 mg/kg group: 42.4% | 39.5% | NR |
| **Abraham et al 1995 (209)** | 31 | Sepsis | TNF-alpha MAb (n=664) | Placebo (n=330) | 28-day mortality | 7.5 mg/kg group: 29.5% 15 mg/kg group: 31.3% | 33.1% | 7.5 mg/kg group: 0.33 15 mg/kg group: 0.61 |
| **Bone et al 1995 (210)** | 53 | Sepsis | E5 (n=264) | Placebo (n=266) | 30-day mortality | 30% | 26% | 0.21 |
| **Gattinoni et al 1995 (211)** | 56 | ICU | Goal-directed therapy (n=510) | Control (n=252) | ICU-mortality | Cardiac index group: 48.6% Oxygen index group: 52.1% | 48.4% | 0.638 |
| **Fisher et al 1994 (212)** | 63 | Sepsis | IL-1ra (n=591) | Placebo (n=302) | 28-day mortality | 1 mg/kg/h group: 31% 2 mg/kg/h group: 29% | 34% | 0.22 |
| **McCloskey et al 1994 (213)** | 513 | Sepsis | HA-1A (n=1228) | Placebo (n=1199) | 14-day mortality | 33% | 32% | 0.864 |
| **Suter et al 1994 (214)** | 4 | Acute lung injury | NAC (n=32) | Placebo (n=29) | 1-month mortality | 22% | 35% | NR |
| **Gastinne et al 1992 (215)** | 15 | ICU | Prophylactic non-absorbable antibioticsz5 (n=220) | Placebo (n=225) | ICU mortality | 34% | 30% | 0.37 |
| **Bone et al 1989 (216)** | 13 | ARDS | Prostaglandin E1 (n=100) | Placebo (n=50) | 30-day mortality | 60% | 48% | NR |
| **Calandra et al 1988 (217)** | 10 | Sepsis | Human IgG antibody to *Escherichia coli* J5 (n=100) | Standard IgG (n=100) | 14-day mortality | 50% | 49% | NR |
| **Bone et al 1987 (218)** | 19 | Sepsis | High-dose methylprednisolone (n=191) | Placebo (n=191) | 14-day mortality | 34% | 25% | 0.06 |
| **Veterans** | 10 | Sepsis | High dose | Placebo | 14-day mortality | 21% | 22% | 0.97 |

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| **administration 1987 (219)** | | | glucocorticoid (n=112) | (n=111) | | | | |

ARDS: acute respiratory distress syndrome; CAP: community acquired pneumonia. COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; EGDT: early goal-directed therapy; ICU: intensive care unit; TPN: total parenteral nutrition; MODS: multiple organ dysfunction syndrome; PMX: polymyxin hemoperfusion; Hb: hemoglobin; SPN: supplemental parenteral nutrition; EN: enteral nutrition; HVHF: high volume hemofiltration; IMHP: r high-protein enteral nutrition enriched with immune-modulating nutrients; NIV: non-invasive ventilation; TTM: targeted temperature management; TLR4: Toll-like receptor 4; HES: Hydroxyethyl starch; HFOV: high frequency oscillatory ventilation; H-IVIG: high dose immunoglobulin G; (ART-123) recombinant thrombomodulin; Peep: positive end-expiratory pressure; PAP: positive airway pressure; IPC: intermittent pneumatic compression; DrotAA: Drotecogin alfa activated; IABP: intra-aortic balloon pump; NIPSV: non-invasive pressure support ventilation; CPAP: continuous positive airway ventilation; rTFP: recombinant tissue factor pathway inhibitor; ScvO2: central venous oxygen saturation; rFVIIa: recombinant tissue factor VIIa; TAK-242: Toll like receptor-4 inhibitor; pHi: intra-mucosal pH; CVVHDF: continuous veno-venous hemofiltration; CRRT: continuous renal replacement therapy; IRRT: intermittent renal replacement therapy; CVVH: continuous venovenous hemofiltration; PEEP: positive end expiratory pressure; SDD: selective digestive decontamination; BAL: bronchoalveolar lavage; rPAF-AH: recombinant human platelet-activating factor; VAP: ventilator associated pneumonia; PAC: pulmonary artery catheter; PGE1: prostaglandin E1; rhIL-1ra: recombinant human interleukin-1 receptor antagonist; HA-1A: human monoclonal IgM antibody; TNF-alpha: tumor necrosis factor alpha; NAC: N-acetylcysteine; AKI: acute kidney injury.; AHRF: acute hypercapnic respiratory failure; SBP: systolic blood pressure; GM-CSF: granulocyte-macrophage colony stimulating factor; HVHF: high-volume hemofiltration; RAD: renal assist device

^ MODS >9: all participants: 44.5% vs. 43.9%, p=0.94; Per protocol all participants: 28.9% vs. 29.2%, p=0.94; Per protocol MODS >9: 33% vs 36.4%, p=0.58.
Ç 28-day mortality: 45% vs 42%, p=0.48; 180-day mortality: 61% vs 57%, p=0.37.
$ 90-day mortality: 45% vs 43%, p= 0.28; ICU mortality: 33% vs 31%, p=0.17; hospital mortality: 36% vs 34%, p=0.25.
@ ICU mortality: 29.7% vs. 29.3%, p=0.94; 90-day mortality: 38.5% vs.36.7%, p=0.94; hospital mortality: 38.7% vs. 37.7%, p=0.78.
& 90-day mortality haloperidol 1 mg: 78.6%, haloperidol 2 mg: 79.1% vs control 79.1%, p= NS
*28-day mortality 22.3% vs 24.3%; p=0.13
a 7-day mortality 28.8% vs 34.8%; p=0.22.
b No difference in 28-day (p=0.61) or 180-day mortality (p=0.75); in the subgroup analysis (APACHE score >21.5%, 90 day mortality significantly greater in the short-term storage group (37.7% vs 34%, OR 1.18 (95% CI, 1.00-1.39, p = 0.05)
c 90-day mortality rates 38% vs 40%, p=0.53
d ICU mortality 9% vs 12%, p=0.64; hospital mortality (including ICU) 12% vs 15%, p=0.55;
e Main outcome measures were 60-day and ICU mortality and ventilator free days, ICU mortality was 25% in the OLA group vs 30% ARDS network protocol; p=0,53),
f Total hospital mortality was 13/75 (17.3%) with STD-PN compared with 11/75 (14,7%) with GLN-PN (p=0.66); Mortality at 28 days after entry was STD-PN, 12/75 (16.0%) vs GLN-PN, 11/75 (14.7%); p=0.82.
g; 5% in the methylprednisolone vs 12% in the placebo group (p=0.21) (PP population).
h ICU mortality: 26.7% vs, 24.2%, p=NS; In hospital mortality 33.3% vs 31.9%, p=NS; 28-day mortality 30.6% vs 28.8%, p=NS.
i 60-day mortality: 43% vs 38%, p=0.82; 90-day mortality 46% vs 38%, p=0.28; ICU mortality: 44% vs 39%, p=0.5; In-hospital mortality 45% vs 39%,p=0.42. l 90-day mortality 30.7% vs 34.2%, p=0.03.
j 90-day mortality was DrotAA 34.1% vs placebo 32.7%, p=0.56.
k In the sub-group analysis adjusted for predictive risk factors, hospital mortality was lower in the lactate-guided group (p=0.006).
l Per protocol 17% vs 22%, p=NS, respectively.
n For penetrating trauma rFVIIa 18.2% vs placebo 13.2%, p=0.4).

o For patients with moderate hypoxemia (n=192) 25.5% vs 22.5%, p=0.62; severe hypoxemia (n=150) 37.8% vs 46.1%, p=0.31; ICU mortality for the entire population 38.1% vs 42%, p=0.47; moderate hypoxemia 31.9% vs 31.6%, p= 0.97; severe hypoxemia 45.9% vs 55.3%, p=0.25); 6-month mortality for the entire population 47% vs 52.3%, p=0.33; moderate hypoxemia 42.6% vs 43.9%, p= 0.33; severe hypoxemia 52.7% vs 63.2%, p= 0.19).
p 28-day mortality high intensity group 38.5% vs low intensity group 36.9%, p= 0.52.
q Hospital mortality 23.3% vs 19.4%, p=0.11; 28-day mortality: 18.7% vs 15.3%, p=0.51.
r In the per protocol population 4.6% vs 4.8%, p=NS.
s 90-day outcome 43.9% vs 49.6%, p=0.11;
t ICU mortality 30.5% vs 35%, p=0.13; Death during mechanical ventilation 28.6% vs 33.1%, p=0.13; 28-day mortality 28.4% vs 32.3%, p=0.13.
u 90-day mortality insulin therapy: 39.7% vs 35.4%, p=0.31; fluid resuscitation 41% vs 33.9%, p=0.09.
x Crude mortality 31/100 vs 28/100, p=0.76; 7-day mortality 6/100 vs 8/100, p=0.78

Table S4. Quality of reporting and methodological quality of multicenter randomized controlled trials showing decreased mortality

| First Author | Allocation concealment | Stopped early/adequacy for stopping | Type of analysis | Sample size calculated | % reduction wanted | % mortality assumed in controlled group | α |
|---|---|---|---|---|---|---|---|
| **Amendola et al 2018 (8)** | Yes | No | NR | 96 | NR | NR | 0.05 |
| **Annane et al 2018 (9)** | Yes | No | ITT | 1280 | 10% | 45% | 0.05 |
| **de Jong et al 2016 (10)** | Yes | No | MITT | 1262 | 15% | 28% | 0.02 |
| **Guerin et al 2013 (11)** | Yes | No | ITT | 456 | 15% | 60% | 0.05 |
| **Guntupalli et al 2013 (12)** | Yes | No | MITT | 190 | 13% | 30% | <0.2 |
| **Nava et al (13)** | Yes | No | ITT | 80 | 25% | NR | 0.05 |
| **Papazian et al 2010 (14)** | Yes | No | ITT | 340 | 15% | 50% | 0.05 |
| **Ferrer et al 2009 (15)** | Yes | No | ITT | 106 | 41% | NR | 0.05 |
| **de Smet et al 2009 (16)** | Yes | No | ITT | 2300 | 4% | 20% | 0.05 |
| **Ferrer et al 2006 (17)** | Yes | No | ITT | 162 | 35% | NR | 0.05 |
| **Villar et al 2006 (18)** | Yes | Yes/Yes | ITT | 148 | 20% | 50% | 0.05 |
| **Panacek et al 2004 (19)** | Yes | Yes/Yes | ITT | 1000 | 10% | NR | 0.04 |
| **Ferrer et al (2003) (20)** | No | No | PP | 84 | NR | NR | 0.05 |
| **Ferrer et al (2003) (21)** | No | No | PP | 102 | NR | NR | 0.05 |
| **Annane et al 2002 (22)** | Yes | No | ITT | 270 | 20% | 95% (non-responders) | 0.05 |
| **Bernard et al 2001 (23)** | Yes | Yes/Yes | ITT | 2280 | NR | NR | 0.05 |
| **Brower et al 2000 (24)** | Yes | Yes/Yes | ITT | 1000 | 10% | 50% | 0.05 |
| **Esteban et al 2000 (25)** | Yes | No | ITT | NR | NR | NR | 0.05 |
| **Fagon et al 2000 (26)** | Yes | No | ITT | 400 | 10% | 30% | 0.05 |
| **Nava et al (27)** | Yes | No | NR | NR | NR | NR | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Amato et al 1998 (28)** | Yes | Yes/Yes | ITT | 58 | x 2.4 | NR | 0.05 |
| **Baudo et al 1998 (29)** | Yes | No | ITT | 120 | 50% | 60% | 0.05 |
| **Brouchard et al 1995 (30)** | Yes | No | NR | NR | NR | NR | 0.05 |
| **Fisher et al 1994 (31)** | Yes | No | ITT | NR | NR | NR | NR |
| **Gutierrez et al 1992 (32)** | Yes | No | ITT | 260 | NR | NR | 0.02 |
| **Dominioni et al 1991 (33)** | Yes | No | ITT | 60 | 30% | 50% | 0.05 |
| **Ziegler et al 1991 (34)** | Yes | No | ITT | NR | 15% | 30% | 0.05 |

Abbreviations: ITT: intention to treat: MITT: modified intention to treat; NR: not reported

Table S5. Quality of reporting and methodologic quality of multicenter randomized controlled trials showing increased mortality

| First Author | Allocation concealment | Stopped early/adequacy for stopping | Type of analysis | Sample size calculated | % reduction wanted | % mortality assumed in controlled group | α |
|---|---|---|---|---|---|---|---|
| **Guidet et al 2017 (35)** | No | No | ITT | 3000 | 6% | 32% | 0.05 |
| **Cavalcanti et al 2017 (36)** | No | No | ITT | 520 | NR | 25% | 0.05 |
| **Ferguson et al 2013 (37)** | Yes | Yes/No | ITT | 1200 | 20% | 45% | 0.05 |
| **Heyland et al 2013 (38)** | Yes | No | ITT | 1200 | 7.5% | 30% | 0.04 |
| **Mourvillier et al 2013 (39)** | Yes | Yes | ITT | 276 | NR | NR | 0.05 |
| **Perner et al 2012 (40)** | Yes | No | MITT | 800 | 10% | 45% | 0.05 |
| **Gao Smith et al 2012 (41)** | Yes | Yes/Yes | ITT | 1334 | 8.8% | 44% | 0.05 |
| **Elseviers et al 2010 (42)** | No | No | PP | NR | NR | NR | NR |
| **Lopez et al 2004 (43)** | Yes | Yes/Yes | ITT | 4400 | 5% | 50% | 0.05 |
| **Esteban et al 2004 (44)** | Yes | Yes/Yes | ITT | 388 | 13% | 33% | 0.05 |
| **Mehta et al 2001 (45)** | Yes | No | ITT | NR | NR | NR | 0.05 |
| **Esteban et al 2000 (25)** | Yes | No | ITT | NR | NR | NR | 0.05 |
| **Sloan et al 1999 (46)** | Yes | Yes/Yes | ITT | 850 | 10% | 40% | 0.05 |
| **Takala et al 1999 (47)** | No | No | PP | 360 | NR | NR | 0.05 |
| **Fisher et al 1996 (48)** | No | No | ITT | NR | NR | NR | 0.05 |
| **Hayes et al 1994 (49)** | Yes | Yes/Yes | PP | 260 | 15% | 33% | 0.05 |

Abbreviations: ITT: intention to treat. MITT: modified intention to treat. PP: per protocol. NR: not reported

**Table S6**. Quality of reporting and methodologic quality of multicenter randomized controlled trials showing no effect on mortality

| First Author | Allocation concealment | Stopped early/adequacy for stopping | Type of analysis | Sample size calculated | % reduction wanted | % mortality assumed in control group | α |
|---|---|---|---|---|---|---|---|
| **Hernandez et al 2019 (50)** | Yes | No | ITT | 420 | 15% | 45% | 0.05 |
| **Mahmoodpoor et al 2019 (51)** | Yes | No | NR | 90 | NR | NR | 0.05 |
| **Arabi et al 2019 (52)** | Yes | No | MIT | 2000 | NR | NR | 0.05 |
| **Jones et al 2018 (53)** | Yes | No | MITT/PP | 250 | NR | NR | 0.05 |
| **Krag et al 2018 (54)** | Yes | No | ITT/PP | 3350 | 5% | 25% | 0.05 |
| **Wittekamp et al 2018 (55)** | Yes | No | ITT | 10800 | 10% | 27.5% | 0.05 |
| **Pickkers et al 2018 (56)** | Yes | No | ITT | 245 | NR | NR | 0.05 |
| **Perkins et al 2018 (57)** | Yes | No | ITT | 280 | NR | NR | 0.05 |
| **Azoulay et al 2018 (58)** | Yes | No | ITT | 779 | 10% | 30% | 0.05 |
| **Nardi et al 2018 (59)** | Yes | Yes | ITT | NR | 20% | 50% | 0.05 |
| **Itenov et al 2018 (60)** | Yes | Yes | MITT | 560 | 21% | 48% | 0.05 |
| **Girard et al 2018 (61)** | Yes | No | ITT | 561 | NR | NR | 0.025 |
| **Target Investigators 2018 (62)** | Yes | No | MITT | 3774 | 5.9% | 25% | 0.05 |
| **Prevent Investigators 2018 (63)** | Yes | No | ITT | 952 | NR | NR | 0.05 |
| **Pinder et al 2018 (64)** | Yes | No | MITT | 150 | 40% | 20% | 0.05 |
| **Dellinger et al 2018 (65)** | Yes | No | ITT/PP | 360 | 15% | 35% | 0.05 |
| **Barbar et al 2018 (66)** | Yes | Yes/Yes | ITT | 864 | 10% | 55% | 0.05 |
| **van Meenen et al 2018 (67)** | Yes | No | ITT | 890 | NR | NR | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reignier et al 2018 (68)** | Yes | Yes/Yes | ITT | 2854 | 5% | 37% | 0.049 |
| **Combes et al 2018 (69)** | Yes | Yes/Yes | ITT | 331 | 20% | 60% | 0.05 |
| **van den Boogaard et al 2018 (70)** | Yes | Yes/Yes | ITT | 1430 | 15% | 20% | 0.05 |
| **Venkatesh et al 2018 (71)** | Yes | No | ITT | 3800 | 5% | 33% | 0.05 |
| **Khanna et al 2017 (72)** | Yes | No | ITT | 38 | NR | NR | 0.05 |
| **Cooper et al 2017 (73)** | Yes | No | ITT | 4664 | 15% | 28% | 0.05 |
| **Futier et al 2017 (74)** | Yes | No | ITT | 300 | NR | NR | 0.05 |
| **Landoni et al 2017 (75)** | Yes | Yes | ITT | 870 | 8% | 12.7% | 0.05 |
| **Wischmeyer et al 2017 (76)** | Yes | No | ITT | 120 | NR | NR | 0.05 |
| **Valette et al 2017 (77)** | Yes | No | MITT | 282 | 10% | NR | 0.05 |
| **Van der Geest et al 2017 (78)** | Yes | No | ITT | 550 | 10% | 20% | 0.05 |
| **Qiu et al 2017 (79)** | Yes | No | ITT | 122 | NR | NR | 0.05 |
| **Keh et al 2016 (80)** | Yes | No | ITT | 338 | 15% | NR | 0.05 |
| **Park et al 2016 (81)** | Yes | No | ITT | 172 | 20% | 60% | 0.05 |
| **Bloos et al 2016 (82)** | Yes | No | ITT | 496 | 10% | 48% | 0.05 |
| **Donnino et al 2016 (83)** | NR | No | NR | 50 | NR | NR | 0.05 |
| **Faisy et al. 2016 (84)** | Yes | No | ITT | 380 | NR | NR | 0.05 |
| **Legriel et al 2016 (85)** | Yes | No | ITT | 270 | 20% | NR | 0.05 |
| **Wiberg et al 2016 (86)** | Yes | No | ITT | 120 | NR | NR | 0.05 |
| **Kacmarek et al 2016 (87)** | No | No | ITT | 600 | 12.5% | 45% | 0.05 |
| **Ziegler et al 2016 (88)** | Yes | No | ITT | 150 | 25% | 22% | 0.05 |
| **Cavalcanti et al 2016 (89)** | Yes | No | ITT | 102 | 5% | 0% | 0.05 |
| **Gaudry et al 2016 (90)** | Yes | No | ITT | 546 | 15% | 55% | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Torres et al 2015 (91)** | Yes | No | ITT and PP | 120 | NR | NR | 0.05 |
| **Payen et al 2015 (92)** | Yes | No | ITT and PP | 240 | 20% | 37% | 0.05 |
| **Deye et al 2015 (93)** | Yes | No | ITT | 400 | NR | NR | 0.05 |
| **Lacroix et al 2015 (94)** | Yes | No | ITT | 2510 | 5% | 25% | 0.05 |
| **Combes et al 2015 (95)** | Yes | Yes/Yes | ITT | 360 | 12% | 25% | 0.05 |
| **Lemiale et al 2015 (96)** | Yes | Yes/Yes | ITT | 350 | 11.9% | 30% | 0.05 |
| **Vincent et al 2015 (97)** | Yes | No | ITT | 1260 | 20,0% | 40% | 0.05 |
| **Mouncey et al 2015 (98)** | Yes | No | ITT | 1600 | 7.6% | 28% | 0.05 |
| **Peake et al 2014 (99)** | Yes | No | ITT | 1350 | 6-7% | 30-46% | 0.05 |
| **Yealy et al 2014 (100)** | Yes | Yes/No (low recruitment) | ITT | 300 | 12% | 22% | 0.05 |
| **Van Zanten et al 2014 (101)** | Yes | No | ITT | 300 | NR | NR | 0.05 |
| **Abroug et al 2014 (102)** | Yes | No | PP | 600 | >10% | 25% | 0.05 |
| **Giamarellos-Bourboulis et al 2014 (103)** | Yes | No | ITT | 800 | 10% | 45% | 0.05 |
| **Asfar et al 2014 (104)** | No | No | ITT | 1350 | 7.5% | 45% | 0.05 |
| **Caironi et al 2014 (105)** | Yes | No | ITT | 10000 | 25% | 61% | 0.05 |
| **Leaf et al 2014 (106)** | Yes | No | ITT | 690 | 12.5% | 50% | 0.05 |
| **Holst et al 2014 (107)** | No | No | ITT | 2400 | 6.4% | 32% | 0.05 |
| **Harvey et al 2014 (108)** | Yes | No | MITT | 900 | 11% | 55% | 0.05 |
| **Young et al 2013 (109)** | Yes | No | MITT | 2000 | 7.5% | 40% | 0.05 |
| **Opal et al 2013 (110)** | Yes | Yes/Yes | ITT | 1002 | 8% | 30% | 0.025 |
| **Papazian et al 2013 (111)** | Yes | Yes/No | ITT | 1280 | 10% | 45% | 0.05 |
| **Annane et al 2013 (112)** | Yes | No | ITT | 1006 | 9% | 45% | 0.05 |

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|---|---|---|---|---|---|---|---|
| **Young et al 2013 (113)** | Yes | No | ITT | NR | NR | NR | NR |
| **Hung et al 2013 (114)** | Yes | No | ITT | 750 | 11% | 32% | 0.05 |
| **Vincent et al 2013 (115)** | Yes | No | ITT | 3010 | 5% | 20% | 0.05 |
| **Annane et al 2013 (116)** | Yes | No | ITT | 1470 | 7.7% | 29.7% | 0.05 |
| **Doig et al 2013 (117)** | Yes | No | ITT | 207 | 20% | 60% | 0.05 |
| **Durante-Mangoni et al 2013 (118)** | Yes | No | ITT | 356 | 60% | 15% | 0.05 |
| **Vignon et al 2013 (119)** | Yes | No | ITT | 7000 | 3.5% | 26% | 0.05 |
| **Myburgh et al 2012 (120)** | Yes | No | ITT | 1500 | 7% | 35% | 0.05 |
| **Ranieri et al 2012 (121)** | Yes | No | ITT | 588 | 12% | 56% | 0.05 |
| **Thiele et al 2012 (122)** | Yes | No | ITT | 1200 | 7.5% | 31% | 0.05 |
| **Jensen et al 2011 (123)** | Yes | No | ITT | 200 | 15% | 30% | 0.05 |
| **Wunderink et al 2011 (124)** | Yes | Yes/Yes | MITT | 1200 | 7.6% | 33.4% | 0.025 |
| **Spragg et al 2010 (125)** | Yes | No | ITT | 350 | 15% | 42% | 0.05 |
| **Jansen et al 2010 (126)** | Yes | No | ITT and PP | 300 | 10% | 25% | 0.05 |
| **Peek et al 2010 (127)** | Yes | No | ITT | 240 | 18% | 70% | 0.05 |
| **Jones et al 2010 (128)** | Yes | Yes/Yes (futility) | ITT | 1440 | 6% | 40% | 0.05 |
| **Rice et al 2010 (129)** | No | No | ITT | 508 | 12.5% | 50% | 0.05 |
| **Annane et al 2010 (130)** | Yes | No | ITT | 600 | 10% | 35% | 0.05 |
| **Bouadma et al 2010 (131)** | Yes | No | MITT | 300 | 15% | APACHE-stratified | 0.05 |
| **Tidswell et al 2010 (132)** | Yes | Yes/No | ITT | 1276 | 16.7% | 30% | 0.05 |
| **Hauser et al 2010 (133)** | No | No | ITT | 340 | 15% | 50% | 0.05 |
| **Taccone et al 2009 (134)** | Yes | No | ITT | 128 | 20% | 40% | 0.05 |
| **Palizas et al 2009 (135)** | Yes | No | ITT | 1500 | 8.5% | 60% | <0.05 |

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|---|---|---|---|---|---|---|---|
| **Bellomo et al 2009 (136)** | Yes | No | ITT | 1260 | 5% | 25% | 0.05 |
| **Dellinger et al 2009 (137)** | No | Yes/Yes | NR | 1000 | 10% | 40% | 0.05 |
| **Kesecioglu et al 2009 (138)** | No | Yes/Yes | MITT | 1260 | 5% | 25% | ≤ 0.05 |
| **Lins et al 2009 (139)** | Yes | No | ITT | 814 | 10% | 50% | 0.05 |
| **Preiser et al 2009 (140)** | Yes | Yes/No (low recruitment) | ITT | 1750 | 4% | 16% | 0.05 |
| **Schuetz et al 2009 (141)** | Yes | No | ITT | 1002 | 7.5% | 20% | 0.05 |
| **Doig et al 2008 (142)** | Yes | No | ITT | 1386 | 5.2% | 28.9% | 0.05 |
| **Blot et al 2008 (143)** | Yes | No | ITT | 234 | 13% | 45% | 0.05 |
| **Palevsky et al 2008 (144)** | Yes | No | ITT | 1164 | 10% | 55% | 0.05 |
| **Russell et al 2008 (145)** | Yes | No | ITT | 776 | 10% | 60% | 0.05 |
| **Mercat et al 2008 (146)** | Yes | No | ITT | 800 | 10% | 40% | 0.05 |
| **Meade et al 2008 (147)** | Yes | No | ITT | 980 | 9% | 45% | 0.05 |
| **Brunkhorst et al 2008 (148)** | No | Yes/Yes (for the intensive insulin arm) | ITT | 600 | 10% | 40% | 0.05 |
| **Sprung et al 2008 (149)** | Yes | Yes/Yes | ITT | 800 | 10% | 50% | 0.05 |
| **Giamarellos et al 2008 (150)** | Yes | No | ITT | 200 | 5% | NS | 0.05 |
| **Tumlin et al 2008 (151)** | Yes | No | ITT | NR | NR | NR | NR |
| **Fernandez et al 2008 (152)** | Yes | Yes/No | NR | 250 | 15% | 60% | 0.05 |
| **Heyland et al 2008 (153)** | Yes | Yes/Yes | ITT | 740 | 10% | 40% | 0.49 |
| **Kinasewitz et al 2008 (154)** | Yes | Yes/No | NR | 1000 | 10% | 40% | 0.05 |
| **Werdan et al 2008 (155)** | Yes | No | ITT | 280 | 20% | 60% | 0.05 |
| **Manzano et al 2008 (156)** | Yes | Yes/No (low recruitment) | ITT | 434 | 15% | 42% | 0.05 |
| **Werdan et al 2007 (157)** | Yes | No | PP | 800 | 10% | 30% | 0.05 |
| **Moritz et al** | No | No | ITT | 120 | 20% | 9% in the CPAP | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2007 (158)** | | | | | | group versus 29% in the bilevel PAP | |
| **Annane et al 2007 (159)** | Yes | No | ITT | 340 | 20% | 60% | 0.05 |
| **Levi et al 2007 (160)** | No | No | ITT | 2000 | <2.8% | 31% | 0.05 |
| **Stoutenbeek et al 2007 (161)** | Yes | Yes/Yes | ITT | NR | 12.5% | 25% | 0.05 |
| **Angstwurm et al 2007 (162)** | Yes | No | ITT | 196 | 20% | 40% | 0.05 |
| **van Ruler et al 2007 (163)** | Yes | No | ITT | 222 | 10% | 44% | 0.05 |
| **Hentrich et al 2006 (164)** | Yes | No | ITT | 164 | 20% | 50% | 0.05 |
| **Heyland et al 2006 (165)** | No | No | ITT | 740 | 10% | 40% | 0.049 |
| **Radrizzani et al 2006 (166)** | Yes | No | ITT | 1500 | 9% | 35% | 0.05 |
| **Wheeler et al 2006 (168)** | Yes | No | ITT | 1000 | 10% | 31% | 0.05 |
| **Wiedemann et al 2006 (168)** | No | No | ITT | 1000 | 10% | 31% | 0.05 |
| **Steinberg et al 2006 (169)** | No | No | ITT | 180 | 20% | 40% | 0.05 |
| **Mancebo et al, 2006 (170)** | Yes | No | ITT | 200 | 20% | 50% | 0.05 |
| **Vinsonneau et al 2006 (171)** | Yes | No | ITT | 440 | 15% | 45% | 0.05 |
| **Rodriguez et al 2005 (172)** | Yes | No | ITT | 90 | 30% | 50% | 0.05 |
| **Harvey et al 2005 (173)** | Yes | No | ITT | 1281 | 10% | 69% | 0.05 |
| **Abraham et al 2005 (174)** | Yes | Yes/Yes | ITT | 11444 | 4% | 16% | 0.05 |
| **Tumlin et al 2005 (175)** | Yes | No | ITT | NR | NR | NR | NR |
| **Zeiher et al 2005 (176)** | Yes | Yes/Yes (futility) | ITT | 466 | 30% | 30% | 0.1 |
| **Guerin et al 2004 (177)** | Yes | No | ITT | 752 | 10% | 40% | 0.05 |
| **Spragg et al 2004 (178)** | Yes | No | ITT | 220 | NR | NR | 0.05 |
| **Brower et al 2004 (179)** | Yes | Yes/Yes | ITT | 750 | 10% | 28% | 0.05 |
| **Albrecht et al 2004 (180)** | Yes | Yes/Yes | ITT | 400 | 20% | 55% | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Finfer et al 2004 (181)** | Yes | No | ITT | 7000 | 3% | 15% | 0.05 |
| **Opal et al 2004 (182)** | Yes | Yes/Yes (futility) | ITT | 2522 | 4.8% | 24% | 0.05 |
| **Abraham et al 2003 (183)** | Yes | Yes/Yes | ITT | 750 | 2.5-5% | 30% | 0.05 |
| **Abraham et al 2003 (184)** | Yes | No | ITT | 1550 | 25% | NR | 0.05 |
| **Albertson et al 2003 (185)** | Yes | No | ITT | 850 | 15% | 40% | 0.05 |
| **Chastre et al 2003 (186)** | Yes | No | ITT | 400 | 10% | 40% | 0.1 |
| **Richard et al 2003 (187)** | Yes | No | ITT | 1100 | 10% | 40% | 0.05 |
| **Root et al 2003 (188)** | Yes | No | MITT | 700 | 10% | 35% | 0.05 |
| **Sandham et al 2003 (189)** | Yes | No | ITT | 2000 | 5% | 15% | 0.05 |
| **Bouman et al 2002 (190)** | No | No | ITT | 105 | 40% | 80% | 0.05 |
| **Reinhart et al 2001 (191)** | No | No | ITT | 500 | 12.5% | 65% | 0.05 |
| **Abraham et al 2001 (192)** | Yes | No | ITT | 1340 | 30% | 30% | 0.025 |
| **Gattinoni et al 2001 (193)** | Yes | Yes/No | ITT and PP | 150 | 20% | 95 deaths in prone position group at 10 days | 0.05 |
| **Vincent et al 2001 (194)** | No | Yes/Yes (futility) | ITT | 180 | NR | NR | NR |
| **Warren et al 2001 (195)** | Yes | No | PP | 2300 | 7% | 45% | 0.05 |
| **Angus et al 2000 (196)** | Yes | No | ITT | 1700 | 7% | 28% | 0.045 |
| **ARDS network 2000 (197)** | Yes | Yes/Yes | ITT | NR | 10% | NR | 0.05 |
| **Poeze et al 2000 (198)** | No | No | ITT | NR | NR | NR | NR |
| **Takala et al 2000 (199)** | Yes | No | ITT | 405 | 10.5% | 17.5% | 0.05 |
| **Demetriades et al 1999 (200)** | NR | No | ITT | 400 | 15% | 50% | 0.05 |
| **Hebert et al 1999 (201)** | Yes | No | ITT | 1620 | 5.5% | 27.5% | 0.05 |
| **Abraham et al 1998 (202)** | Yes | No | ITT | 1900 | 17% | 46% | 0.048 |
| **Brochard et al** | Yes | Yes/Yes | ITT | 240 | 20% | 50% | 0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **1998 (203)** | | | | | | | |
| **Dhainaut et al 1998 (204)** | No | No | ITT | 1260 | 5% | 25% | 0.05 |
| **Wasserman et al 1998 (205)** | Yes | No | ITT | NR | 20% | 40% | 0.05 |
| **Opal et al 1997 (206)** | No | Yes/Yes | NR | 1300 | NR | NR | 0.05 |
| **Anzueto et al 1996 (207)** | Yes | Yes/Yes | ITT | 700 | 10% | 50% | 0.05 |
| **Cohen et al 1996 (208)** | Yes | No | ITT | 960 | 10.4% | 26% | 0.023 |
| **Abraham et al 1995 (209)** | Yes | No | ITT | 640 | 40% | 26% | 0.046 |
| **Bone et al 1995 (210)** | No | No | PP | 640 | 10% | 20% | 0.05 |
| **Gattinoni et al 1995 (211)** | Yes | No | ITT | NR | NR | NR | 0.05 |
| **Fisher et al 1994 (212)** | Yes | No | ITT | 900 | 7.6% | 40% | 0.05 |
| **McCloskey et al 1994 (213)** | Yes | Yes/Yes | ITT | 1500 | 9% | 49% | 0.05 |
| **Suter et al 1994 (214)** | Yes | No | NR | NR | NR | NR | NR |
| **Gastinne et al 1992 (215)** | Yes | Yes/Yes | ITT | 600 | 10% | 40% | 0.05 |
| **Bone et al 1989 (216)** | Yes | No | ITT | 160 | NR | NR | NR |
| **Calandra et al 1988 (217)** | Yes | No | PP | 102 | 50% | 70% | 0.05 |
| **Bone et al 1987 (218)** | Yes | No | ITT | 400 | NR | NR | NR |
| **Veterans administration 1987 (219)** | Yes | No | ITT | 276 | 66% | 36% | 0.05 |

Abbreviations: ITT: intention to treat. MITT: modified intention to treat. PP: per protocol. NR: not reported