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**Supplemental Methods**

***Search Strategy***

We surveyed fifteen leading journals for RCTs recruiting patients admitted to an ICU and published since 1990. The MeSH terms brain injuries/, craniocerebral trauma critical care/, critical illness/, intensive care/, intensive care units/, ventilators, mechanical/, systematic respiratory distress syndrome/ acute respiratory distress syndrome/ and acute lung injury/ were all searched in Medline, and limited these journals: *New England Journal of Medicine*, *JAMA*, *Lancet*, *Annals of Internal Medicine*, *British Medical Journal*, *American Journal of Respiratory and Critical Care Medicine*, *Critical Care Medicine,* *Intensive Care Medicine*, *Chest*, *Critical Care*, *Journal of Critical Care*, *Shock,* *Journal of Trauma, Infection, and Critical Care*, *Pediatric Critical Medicine*, and *Journal of Pediatrics*.

Database: Ovid MEDLINE(R) <1946 to August Week 2 2019>

Search Strategy:

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1 (exp brain injuries/ or exp craniocerebral trauma/ or neurotrauma.mp.) and (icu or critical or intensive).mp. (8143)

2 (critical adj1 (care or ill$)).mp. (84083)

3 exp ventilators, mechanical/ or (non-invasive adj1 ventilat$).mp. or artificial respiration/ (54712)

4 exp systemic inflammatory response syndrome/ or exp sepsis/ (121301)

5 exp shock, septic/ (21665)

6 exp respiratory distress syndrome, adult/ or ARDS.mp. (20946)

7 exp acute lung injury/ (5767)

8 exp critical care/ or exp critical illness/ (75783)

9 exp intensive care/ or exp intensive care unit/ (121858)

10 or/1-9 (319509)

11 \*burns/ or \*coronary care units/ (39073)

12 10 not 11 (313203)

13 "new england journal of medicine".jn. (77747)

14 jama.jn. (71184)

15 lancet.jn. (135297)

16 "annals of internal medicine".jn. (31448)

17 bmj.jn. (70206)

18 "american journal of respiratory & critical care medicine".jn. (14345)

19 critical care medicine.jn. (19970)

20 intensive care medicine.jn. (10292)

21 chest.jn. (33153)

22 critical care london england.jn. (6430)

23 "journal of critical care".jn. (3034)

24 shock.jn. (4481)

25 "journal of trauma injury infection & critical care".jn. (15399)

26 "journal of pediatrics".jn. (30970)

27 pediatric critical care medicine.jn. (3514)

28 12 and (or/13-27) (46012)

29 limit 28 to yr="1990 - 2018" (40733)

30 limit 29 to randomized controlled trial (2592)

***Calculation of Incremental Risk Differences***

For each trial, we calculated incremental risk differences [RD] as the incremental mortality risk between successive time points 1 and 2 in experimental group A (the group with the higher mortality) minus the incremental mortality risk in experimental group B (the group with the lower mortality):

Incremental RD =$ \frac{D\_{2,A}- D\_{1,A}}{N\_{A}- D\_{1,A}}- \frac{D\_{2,B}- D\_{1,B}}{N\_{B}- D\_{1,B}}$

Where D2A and D2B are the cumulative number of deaths at the second time point, D1A and D1B are the cumulative number of deaths at the first time point, and NA and Ni are the total numbers of patients randomized to study groups A and B. The numerators are the number of additional deaths that occurred between the two time points in each randomized group, while the denominators reflect the number of patients alive at the earlier time point (i.e. those still alive at the earlier time point 1).

For example, assume a trial of having 100 subjects randomized to one of two study groups- A and B - at baseline (T0). If by time point 1 (T1) 5 patients in group A and 6 patients in group B had died, and that by the more remote time point 2 (T2) a total of 9 patients in Group A and 8 patients in Group B had died, then the incremental mortality risk between time point 2 and time point 1 would be calculated as (9-5)/(100-5)=4/95 in the first group vs. (8-6)/(100-6)=2/94 in the second group [the denominators of 95 in the intervention group vs. n=94 in the control group representing the living patients at time point 1 who are still at risk between time points 1 and 2], and the incremental risk difference (RD) would be calculated as the difference of these two fractions, 2/94 - 4/95.











**Supplemental Table 1: RCTs Included in Systematic Review**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author Year | Intervention | EnrolYear | Harm | %US | ICU | Hosp | 7d | 14d | 28/30d | 60d | 90d | 180d | ≥1y | Minp |
| *Non-Sepsis/SIRS, Non-ALI/ARDS* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Gutierrez 1992 | Gastric tonometry | 1990 |  | 0%-Arg | **Y** | Y | Y | Y | Y |  |  |  |  | <0.05  |
| GBS Steroid Trial Group 1990 | Steroids (GBS) | 1989 | Y | 0% |  |  | Y | Y | Y | **Y** | **Y** | **Y** | Y-48 wks | <0.2 |
| Hammond 1992 | Selective Digest.Decontam. | 1990 |  | 0%-SAfr | Y | Y |  |  |  |  |  |  |  |  |
| Korinek 1993 | Selective Digest.Decontam. | 1990 |  | 0% | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Ben-Menachem 1994\* | Sucraflate/cimetidine | 1992 |  | 100% | Y | Y |  |  |  |  |  |  |  |  |
| Hayes 1994 | High oxygen | n/r | Y | 0% | **Y** | **Y** | Y | Y | Y |  |  |  |  | <0.05 |
| Gattionni 1995\* | High oxygen/cardiac index | 1992 |  | 0% | Y |  | Y | Y | Y | Y | Y | Y |  |  |
| Atkinson 1998 | Immunonutrition | 1993 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Corwin 1999 | Erythropoietin | 1995 |  | 100% |  |  | Y | Y | Y |  |  |  |  |  |
| Esteban 1999 | 120 v 30 min SBT0 | 1996 |  | 0% | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Hébert/TRICC 1999 | Restrictive transfusion | 1996 |  | 0% | Y | **Y** | Y | Y | **Y** | Y |  |  |  | <0.2 |
| Holzapfel 1999 | Sinusitis Eval. (Nasal Intub.) | n/r |  | 0% |  |  | Y | **Y** | **Y** | **Y** |  |  |  | <0.05 |
| Takala 1999 | Growth hormone (Finland) | 1995 | Y | 0% | **Y** | **Y** | **Y** | **Y** | **Y** |  |  | **Y** |  | <0.05 |
| Takala 1999 | Growth hormone (Europe) | 1995 | Y | 0% | **Y** | **Y** | **Y** | **Y** | **Y** |  |  | **Y** |  | <0.05 |
| Bauer 2000 | Supp. parenteral nutrition | 1997 |  | 0% |  |  | Y | Y | Y | Y | Y |  | Y-2y |  |
| Fagon 2000 | BAL v ETT sputum culture | 1997 |  | 0% |  |  | Y | **Y** | Y |  |  |  |  | <0.05 |
| Gomersall 2000  | Gastric tonometry | 1996 |  | 0%-HK | Y | Y | Y | Y | Y |  |  |  |  |  |
| Herr 2000 | Propofol±EDTA  | 1995 |  | 100% |  |  | **Y** |  | **Y** |  |  |  |  | <0.05 |
| Higgins 2000 | Propofol+EDTA v other sed. | n/r |  | 100% |  |  | Y |  | Y |  |  |  |  |  |
| Bergmans 2001^ | Selective Digest.Decontam. | 1995 |  | 0% | **Y** | Y |  |  | Y | Y | Y | Y | Y | <0.2 |
| Stiell 2001 | Epi v Vaso (cardiac arrest) | 1998 |  | 0% |  | Y |  |  | Y |  |  |  |  |  |
| Van den Berghe 2001 | Intensive insulin therapy | 2000 |  | 0% | **Y** | **Y** |  |  |  |  |  |  |  | <0.05 |
| Corwin 2002 | Erythropoietin | 2000 |  | 100% |  |  | Y | Y | Y |  |  |  |  |  |
| Krueger 2002 | Select IV&Digest.Decontam | n/r |  | 0% | **Y** |  | Y | Y | Y | Y |  |  | Y | <0.05 |
| Ralph 2002 | Dopexamine | n/r |  | 0% | Y | Y | Y |  |  |  |  |  |  |  |
| de Jonge 2003 | Select IV&Digest.Decontam | 2000 |  | 0% | **Y** | **Y** | Y | Y | Y | **Y** | **Y** |  |  | <0.05 |
| Hall 2003 | Enteral glutamine | 1998 |  | 0% | Y | Y |  |  | Y |  |  | Y |  |  |
| Sandham 2003 | Pulmonary Artery Catheter | 1994 |  | 0% |  | Y | Y | Y | Y | Y | Y | Y | Y |  |
| Krishnan 2004 | Vent Weaning Protocol | 2000 |  | 100% | Y | Y |  |  |  |  |  |  |  |  |
| Rumback 2004 | Early tracheostomy | n/r |  | 100% |  | **Y** | Y | Y | **Y** |  |  |  |  | <0.05 |
| SAFE 2004 | Albumin | 2002 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Harvey 2005 | Pulmonary Artery Catheter | 2003 |  | 0% | Y | Y | Y | Y | Y | Y1 | Y1 |  |  |  |
| Kieft 2005 | Immunonutrition | 1999 |  | 0% | Y | Y |  |  | Y |  |  |  |  |  |
| Pearse 2005 | Early Goal DirectedTherapy | 2003 |  | 0% |  |  |  |  | Y | Y |  |  |  |  |
| Boots 2006 | HME v HW humidification | n/r |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| CCCTG/VAP 2006 | BAL v ETT sputum culture | 2002 |  | <10% | Y | Y |  | Y | Y |  |  |  |  |  |
| Ferrer 2006 | NIV post extubation | 2002 |  | 0% | **Y** | Y | Y | Y | Y | Y | Y |  |  | <0.05 |
| Kollef/POPS-1 2006 | Iseganan-antimicr peptide | 2004 | Y | 10-90% |  |  | **Y** | **Y** |  |  |  |  |  | <0.2 |
| Lellouche 2006 | Computer-driven weaning | 2003 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Sylvester 2006 | Surg v percutaneous trach | 1999 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Thwaites 2006 | Magnesium (for tetanus) | 2003 |  | 0%-Viet |  | Y | Y | Y | Y |  |  |  |  |  |
| Van den Berghe 2006 | Intensive insulin therapy | 2003 |  | 0% | Y | Y |  |  | Y |  | Y |  |  |  |
| Vinsonneau 2006 | Contin v intermit dialysis | 2001 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| von Nieuwenhoven 2006 | Semirecumbent position | 2000 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Chytra 2007 | Esoph Doppler Guided IVF | 2004 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Corwin 2007 | Erythropoietin | 2005 |  | 100% |  |  | Y | Y | **Y** |  |  | **Y**-140d |  | <0.2 |
| Pandharipande/MENDS 2007 | Dexmedetomidine v loraz. | 2005 |  | 100% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Templeton 2007 | Chest physiotherapy | 1998 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Valencia 2007 | Contin. auto. cuff pressure | 2004 | Y | 0% | Y | Y | **Y** | **Y** | Y | Y | Y |  |  | <0.2 |
| Arabi 2008 | Intensive insulin therapy | 2005 |  | 0%-KSA | Y | Y | Y2 | Y2 | **Y** 2 |  |  |  |  | <0.05 |
| Berger 2008 | IV antioxidants | 2003 |  | 0% | Y | Y |  |  |  |  | Y |  |  |  |
| Blot 2008 | Early tracheostomy | 2003 |  | 0% |  |  | Y | Y | Y | Y |  |  |  |  |
| Bucknall 2008 | Protocolized sedation | n/r |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Clec’h 2008 | No daily routine CXR | 2006 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| De La Rosa 2008 | Intensive insulin therapy | 2004 |  | 0%-Col | Y | Y |  |  | Y |  |  |  |  |  |
| Desachy 2008 | Immed. v gradual feeding | n/r |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Girard/ABC 2008 | Sedation+weaning protocol | 2005 |  | 100% |  |  | Y | Y | Y | **Y** | **Y** | **Y** | **Y** | <0.05 |
| Gray 2008 | C/BiPAP (for pulm edema)  | 2005 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Myburgh/CAT 2008 | Epinephrine v Norepi | 2005 |  | 0% |  |  |  |  | Y |  | Y |  |  |  |
| ATN 2008 | Intensive v standard RRT | 2005 |  | 100% |  | Y | Y | Y | Y | Y |  |  |  |  |
| Xiao 2008 | Progesterone (for TBI) | 2005 |  | 0%-Chi |  | **Y** |  |  |  |  | **Y** | **Y** |  | <0.05 |
| Xirouchaki 2008 | PAV+ vs PSV | 2007 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Ferrer 2009 | NIV post extubation | 2006 |  | 0% | Y | Y | Y | Y | Y | **Y** | **Y** |  |  | <0.05 |
| Jabre/KETASED 2009 | Etomidate v ketamine (for intub) | 2007 |  | 0% |  |  | **Y** | Y | Y |  |  |  |  | <0.2 |
| Knight 2009 | Syn(pre+pro)biotic | 2004 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| NICE-SUGAR 2009 | Intensive insulin therapy | 2006 | Y | 0% | Y | **Y** | Y | Y | Y | **Y** | **Y** |  |  | <0.05 |
| Oudemans 2009 | Citrate v heparin (for CRRT) | 2005 |  | 0% |  | **Y** | Y | Y | **Y** | **Y** | **Y** |  |  | <0.05 |
| Patman 2009 | Respiratory Physiotherapy | 2002 |  | 0% | **Y** |  |  |  |  |  | **Y** |  |  | <0.2 |
| Preiser/Glucontrol2009 | Intensive insulin therapy | 2005 | Y | 0% | Y | **Y** |  |  | **Y** |  |  |  |  | <0.2 |
| RENAL 2009 | Intensive v standard CRRT | 2007 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Riker/SEDCOM 2009 | Dexmedetomidine v midaz. | 2006 |  | >80% | Y |  |  |  | Y |  |  |  |  |  |
| Timsit/Dressing 2009 | 3 v 7d CVC dressing change | 2007 |  | 0% | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Timsit/Dressing 2009 | Chlorhexidine CVC dressing | 2007 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Treggiari 2009 | Light v deep sedation | 2004 |  | 0% | Y | Y |  |  | Y |  |  |  |  |  |
| Barraud 2010 | Probiotics | 2007 |  | 0% | Y |  | Y | Y | Y | Y | Y |  |  |  |
| Hajjar/TRACS 2010 | Liberal transfus (for card surg) | 2009 |  | 0%-Bra |  |  | Y | Y | **Y** |  |  |  |  | <0.2 |
| Lacherade 2010 | Subglottic secretion drain. | 2005 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Maggiore 2010 | Helium-O2 (for COPD Rx NIV) | 2001 |  | 0% | Y | Y |  |  | **Y** |  |  |  |  | <0.2 |
| Montejo/REGANE 2010 | High v low gastric resid. vol. | 2006 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Staudinger 2010 | Continuous lateral rotation | 2007 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Strøm 2010 | No sedation protocol | 2008 |  | 0% | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Terragni 2010 | Early tracheostomy | 2006 |  | 0% |  | Y |  |  | Y |  |  |  | Y |  |
| van Eijk 2010 | Rivastigmine (for delirium) | 2009 | Y | 0% |  |  | Y | **Y** | **Y** | **Y** | **Y** |  |  | <0.2 |
| Andrews/SIGNET 2011 | IV glutamine | 2006 |  | 0% | Y |  | Y | Y | Y | **Y** | Y | Y |  | <0.2 |
| Andrews/SIGNET 2011 | IV selenium | 2006 |  | 0% | Y |  | Y | Y | Y | Y | Y | Y |  |  |
| PROTECT 2011 | LMW v unfraction. heparin | 2008 |  | <10% | Y | **Y** |  |  |  |  |  |  |  | <0.2 |
| Trouillet 2011 | Early trach. (for card. surg.) | 2007 |  | 0% |  |  | Y | Y | Y | Y | Y |  | Y3 |  |
| Caesar/EPaNIC 2011 | Early v late parental nutr. | 2009 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| David 2011 | Closed v open suctioning | 2007 |  | 0%-Ind | Y | Y |  |  |  |  |  |  |  |  |
| Ducros 2011 | CPAP (for pulm edema) | 2006 |  | 0% |  | Y | Y |  |  |  |  |  |  |  |
| Grau 2011 | IV glutamine | 2006 |  | 0% | Y |  |  |  |  |  |  | Y |  |  |
| Hauser/CONTROL 2011 | Act Fac VII (for trauma) | 2007 |  | 10-90% |  |  |  |  | Y |  | Y |  |  |  |
| Makris 2011 | Pravastatin | 2009 |  | 0% | **Y** |  |  |  | **Y** |  |  | Y |  | <0.05 |
| Rice 2011 | Trophic v full energy feeds | 2006 |  | 100% |  | Y | Y | Y | Y |  |  |  |  |  |
| Singer/TICACOS 2011 | Calorimetric-guided feeds | 2007 |  | 0%-Isr | Y | **Y** |  |  |  | Y |  |  |  | <0.2 |
| Takala 2011 | Non-invasive CO monitor | 2007 | Y | 0% | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Chesnut 2012 | ICP monitor (for severe TBI) | 2010 |  | 0%SAm |  |  | Y | **Y** | **Y** | Y | Y | Y |  | <0.2 |
| Kwakman 2012 | Honey (for CVC infxn prev)  | 2010 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Mehta/SLEAP 2012 | Sed Protocol±Daily Interupt | 2009 |  | <10% | Y | Y |  |  |  |  |  |  |  |  |
| Mekontso Dessap 2012 | BNP fluid mgmt. (for wean) | 2008 |  | 0% | Y | Y |  |  |  | Y |  |  |  |  |
| Myburgh/CHEST 2012 | 6% HES (130/0.4) v saline | 2011 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Schädler 2012 | Automated Vent Weaning | 2007 |  | 0% |  |  |  |  | Y |  | Y |  |  |  |
| Annane/CRISTAL 2013 | Colloid v crystalloid | 2007 |  | 0% | Y | Y | Y | Y | Y | **Y** | **Y** |  |  | <0.05 |
| Denehy 2013 | Exercise rehabilitaton | 2008 |  | 0% | Y | Y |  |  | Y |  | Y | Y | Y |  |
| Doig 2013 | Early parenteral nutrition | 2009 |  | 0% | **Y** | Y |  |  |  | Y |  |  |  | <0.2 |
| Heiddegger 2013 | Supp parenteral nutrition | 2009 |  | 0% | Y | **Y** |  |  |  |  |  |  |  | <0.2 |
| Hernandez 2013 | Cuff deflation (for trach wean) | 2010 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Heyland/REDOX 2013 | IV glutamine | 2008 | Y | ~10% |  | **Y** | Y | **Y** | **Y** | **Y** | **Y** | **Y** |  | <0.05 |
| Heyland/REDOX 2013 | IV antioxidants | 2008 | Y | ~10% |  | Y | Y | Y | Y | Y | Y | Y |  |  |
| Nielsen/TTM 2013 | Hypothermia (card. arrest) | 2011 | Y | 0% | **Y** | Y | Y | **Y** | Y | Y | Y | Y |  | <0.2 |
| Papazian/STATIN-VAP 2013 | Simvistatin (for susp. VAP) | 2011 | Y | 0% | Y | Y | Y | Y | **Y** |  |  |  |  | <0.2 |
| Reignier/NUTRIREA1 2013 | No gastric. resid. vol. monitoring | 2010 |  | 0% | Y |  |  |  | Y |  | Y |  |  |  |
| Vignon/CIREA I 2013 | Pneum. compr. v stockings | 2009 |  | 0% |  |  | Y-6d |  | Y |  | Y |  |  |  |
| Walsh/RELIEVE 2013 | Restrictive transfusion | 2010 |  | 0% | Y | Y | Y | Y | Y | **Y** | **Y** | **Y** |  | <0.2 |
| Young/TracMan 2013 | Early tracheostomy | 2006 |  | 0% | Y | Y | Y | Y | Y | Y | Y | Y |  |  |
| Amrein/VITdAL-ICU 2014 | High dose Vitamin D3 | 2011 |  | 0% | Y | Y | Y | Y | Y | **Y** | **Y** | Y |  | <0.05 |
| Boom 2014 | Continuous glucose monitoring | 2012 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Bove 2014 | Fenoldopam in AKI (for card surg) | 2010 |  | 0% | Y |  |  |  | Y |  |  |  |  |  |
| Diaz-Prieto 2014 | Early tracheostomy | 2007 |  | 0% |  | Y |  |  | Y |  | Y |  |  |  |
| Harvey/CALORIES 2014 | Early parenteral v enteral feeds | 2012 |  | 0% | **Y** | Y | **Y** | **Y** | Y | Y | Y |  |  | <0.2 |
| Jüttler/DESTINY II 2014 | Hemicraniect. (for MCA CVA) | 2011 |  | 0% |  |  | **Y** | **Y** | **Y** | **Y** | **Y** | **Y** |  | <0.05 |
| Kalfon/CGAO–REA 2014 | Comput. Inten. insulin ther. | 2010 |  | 0% | Y | Y |  |  | Y |  | Y |  |  |  |
| Lellouche 2014 | HME vs HH4 (for NIV) | 2003 |  | 0% | **Y** | Y | Y | Y | Y |  |  |  |  | <0.2 |
| Mazano 2014 | Q2h v Q4h repositioning | 2010 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Meyer/PEITHO 2014 | Fibrinolysis (for intermed. risk PE) | 2010 |  | 0% |  |  | Y |  | Y |  |  |  |  |  |
| Pearse/OPTIMISE 2014 | CO guided therapy peri-op | 2011 |  | 0% |  |  | **Y** | Y | Y | Y | Y | **Y** |  | <0.2 |
| Pérez-Bárcena 2014 | IV glutamine (for trauma) | 2011 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Robertson 2014 | Restrictive transfus. (for TBI) | 2009 |  | 100% |  |  | **Y** | Y | Y | Y | Y | Y |  | <0.2 |
| Robertson 2014\* | Erythropoietin (for TBI) | 2009 |  | 100% |  |  | Y | Y | Y | Y | Y | Y |  |  |
| Schefold/CONVINT 2014 | Contin v intermit dialysis | 2004 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Schindler/CASH 2014 | Citrate v heparin (for CRRT) | 2008 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Seguin 2014 | Oropharyngeal povidone I2 | 2009 |  | 0% | Y |  |  |  |  |  | Y |  |  |  |
| van Zantan/MetaPlus 2014 | Immunonutrition | 2011 |  | 0% | Y | Y | **Y** | **Y** | Y | Y | **Y** | Y |  | <0.2 |
| Zhou 2014 | Combined propofol+midaz. | 2010 |  | 0%-Chi | Y | Y |  |  |  |  |  |  |  |  |
| Andrews/ Eurotherm3235 2015 | Hypothermia(for ICH in TBI) | 2012 | Y | 0% |  |  | Y | **Y** | **Y** | **Y** | **Y** | Y |  | <0.05 |
| Arabi/PermiT 2015 | Permissive underfeeding | 2012 |  | 0%-KSA | Y | Y | Y | Y | Y | Y | Y | Y |  |  |
| Doig 2015 | IV amino acids | 2012 |  | 0% | Y | Y |  |  |  |  | Y |  |  |  |
| Gattas 2015 | Citrate v heparin (for CRRT) | 2011 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Lacroix/ABLE 2015 | Fresh v standard age pRBC  | 2011 |  | 0% | **Y** | Y | Y | Y | Y | Y | Y |  |  | <0.2 |
| Mesejo 2015 | Diabetic feeds (for hyperglyc.) | 2011 |  | 0% |  |  |  |  | Y |  |  | Y |  |  |
| Mimoz/CLEAN 2015 | Chlorhexidine v povidone I2 | 2013 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Mimoz/CLEAN 2015 | Scrubbing for CVC insertion | 2013 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Murphy/TiTRE2 2015 | Liberal transfus (for card surg) | 2011 |  | 0% |  |  | Y | Y | Y | Y | **Y** |  |  | <0.05 |
| Nichol/EPO-TBI 2015 | EPO in TBI | 2012 |  | 0% |  |  | **Y** | **Y** | **Y** | **Y** | **Y** | ***Y****(<.2)* |  | <0.05 |
| Souweine 2015 | EtOH lock (for HD CVC) | 2010 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Stucker 2015 | Citrate v heparin (for CRRT) | 2012 |  | 0% |  |  |  |  | Y |  | Y |  |  |  |
| Whitlock/SIRS 2015 | Steroids (for card surgery) | 2010 |  | 9% |  |  | Y | Y | **Y** | Y | **Y** | Y |  | <0.2 |
| Zarbock/RenalRIPC 2015 | Ischem precond (for card surg) | 2014 |  | 0% |  | Y |  |  | Y |  |  |  |  |  |
| Bandeshe 2016^ | Inhaled heparin | 2012 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Barbosa 2016 | Magnesium | 2013 |  | 0%-Bra | Y | **Y** |  |  |  |  |  |  |  | <0.2 |
| Demoule 2016 | NAVA v PSV weaning | 2012 |  | 0% | Y |  |  |  | Y |  |  |  |  |  |
| Gaudry/AKIKI 2016 | Early RRT | 2014 |  | 0% |  |  | Y | Y | Y | Y |  |  |  |  |
| Girardis/Oxygen-ICU 2016 | SpO2 94-98% v 97-100% | 2011 |  | 0% | **Y** | **Y** | **Y** | **Y** | **Y** |  |  |  |  | <0.05 |
| Gobatto/TRACHUS 2016 | U/S v Bronch guided perc trach | 2014 |  | 0%-Bra | Y | Y |  |  |  |  |  |  |  |  |
| Hernandez 2016 | HFNC v O2 (low risk extub) | 2013 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Hernandez 2016 | NIV v HFNC (high risk extub) | 2013 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| IRONMAN 2016 | IV iron | 2014 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Jaber/NIVAS 2016 | NIV (abdominal surgery) | 2014 |  | 0% |  |  | Y | **Y** | **Y** | **Y** | **Y** |  |  | <0.2 |
| Legriel/HYPERNATUS 2016 | Hypotherm (status epilept.) | 2013 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Morris 2016 | Standardized rehabilitation | 2012 |  | 100% |  | Y |  |  |  |  |  | Y |  |  |
| Moss 2016 | Intensive physiotherapy | 2012 |  | 100% | Y | Y |  |  | Y |  | Y | Y |  |  |
| Panwar 2016 | SpO2 88-92% v ≥96% | 2014 |  | 0% | Y |  |  |  |  |  | Y |  |  |  |
| Schaller 2016 | Early mobilisation | 2014 | Y | 60% |  | **Y** |  |  |  |  | Y |  |  | <0.2 |
| Schmid 2016 | Early Goal Directed Therapy | 2011 |  | 0% |  | Y |  |  |  |  |  |  | Y |  |
| Selvanderan/POP-UP 2016 | Pantoprazole | 2015 | Y | 0% |  |  | **Y** | Y | Y | Y | Y |  |  | <0.2 |
| Swan/CHG-BATH 2016 | Chlorhexidine bath | 2012 |  | 100% | Y | Y |  |  |  |  |  |  |  |  |
| Zeng 2016 | Probiotics | 2012 |  | 0%-Chi | Y | Y |  |  |  |  |  |  |  |  |
| Allingstrup/EAT-ICU 2017 | Early parenteral nutrition | 2015 |  | 0% |  |  |  |  | Y | Y | Y | Y |  |  |
| Cooper/TRANSFUSE 2017 | Fresh v oldest pRBC | 2014 |  | 0% |  |  | Y | Y | Y | Y | Y | Y |  |  |
| Dubois/LOGIC-2 2017 | Automated v nurse IIT | 2014 |  | 0% | Y | Y |  |  |  |  | Y |  |  |  |
| Landoni/CHEETAH 2017 | Levosimendan (card. surg) | 2013 | Y | 0% | Y | Y | **Y** | Y | Y | Y | Y | Y |  | <0.2 |
| Lascarrou 2017 | Video v direct laryngoscopy | 2015 |  | 0% | Y |  |  |  | Y |  |  |  |  |  |
| Li Bassi 2017 | Semirecumb. v lat. Trendel. | 2013 |  | <10% | **Y** | Y | Y | Y | Y |  |  |  |  | <0.2 |
| Mehta/LEVO-CTS 2017 | Levosimendan (card. surg) | 2015 |  | 10-90% |  |  | Y | ***Y*** *( <.05)* | Y | **Y** | **Y** |  |  | <0.2 |
| Vargas/VHYPER 2017 | NIV post extubation | 2010 |  | 0% | **Y** |  | Y | **Y** | **Y** | Y | Y |  |  | <0.2 |
| Wischmeyer/TOP-UP 2017 | Suppl. parenteral nutrition | 2013 |  | 10-90% | Y | Y |  |  |  |  |  | Y |  |  |
| Yasuda 2017\* | Chlorhexidine v povidone I2 | 2013 |  | 0%-Jap | **Y** | Y |  |  |  |  |  |  |  | <0.2 |
| Zhang 2017 | Shenfu post cardiac arrest | 2013 |  | 0%-Chi |  |  | **Y** | **Y** | **Y** | **Y** | **Y** |  |  | <0.05 |
| Daubin 2018 | Procalcitonin guided abx in COPD | 2013 | Y | 0% | Y |  |  |  | Y |  | **Y** |  |  | <0.2 |
| Fossat 2018 | In-bed cycling | 2015 | Y | 0% | Y | Y |  |  | **Y** |  |  | Y |  | <0.2 |
| Girard/MIND-USA 2018\* | Anti-psychotics | 2014 |  | 100% |  |  | Y | Y | Y | Y |  |  |  |  |
| Klarin 2018 | Oral lactobacill. v chlorhex. | 2009 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Krag/SUP-ICU 2018 | Pantoprazole | 2016 | Y | 0% |  |  | Y | **Y** | Y | Y | Y |  |  | <0.2 |
| McWilliams 2018 | Enhanced rehabilitation | 2017 |  | 0% | Y | Y |  |  |  |  | Y |  |  |  |
| Perkins/BREATHE 2018 | NIV weaning | 2015 |  | 0% | Y | Y |  |  | Y |  | Y | Y |  |  |
| PReVENT 2018 | Lung protect. vent. (no ALI) | 2016 | Y | 0% | ***Y*** *(<.2)* | Y | **Y** | Y | Y | Y | Y |  |  | <0.05 |
| Reignier/NUTRIREA2 2018 | Parenteral v enteral feeds | 2014 |  | 0% | Y | Y |  |  | Y |  | Y |  |  |  |
| Ridley 2018 | Suppl. parenteral nutrition | 2015 |  | 0% | Y | Y |  |  |  |  | Y | Y |  |  |
| Sarfati 2018 | Rehabil. with passive tilting | 2014 |  | 0% | **Y** | **Y** |  |  |  |  |  |  |  | <0.05 |
| TARGET 2018 | Concentrated enteral feeds | 2017 |  | 0% |  | Y | Y | Y | Y | Y | Y |  |  |  |
| van den Boorgaard/ REDUCE 2018\* | Haldoperidol | 2015 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| van Meenan 2018 | Prn v sched NAC & ventolin | 2015 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Zhu 2018 | Post pyloric feeding | 2016 |  | 0%-Chi | Y | Y |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Sepsis** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Greenman 1991 | E5 murine endotoxin Ab | 1988 |  | 100% |  |  | Y | Y | Y |  |  |  |  |  |
| Dhainaut 1994 | Platelet-act factor antagon. | 1991 |  | 0% |  |  | Y | Y | **Y** |  |  |  |  | <0.2 |
| Fisher 1994\* | IL-1 receptor antagonist | n/r |  | 10-90% |  |  | **Y** | **Y** | Y |  |  |  |  | <0.2 |
| Abraham/NORSEPT I 1995\* | TNFα Ab | 1991 |  | 90% |  |  | **Y** | **Y** | Y |  |  |  |  | <0.2 |
| Bone 1995 | E5 murine endotoxin Ab | 1990 | Y | 100% |  |  | **Y** | Y | Y |  |  |  |  | <0.05 |
| Willatts 1995 | Taurolidine(anti-endotoxin) | n/r |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Cohen/INTERSEPT 1996\* | TNFα Ab | 1992 |  | <10% |  |  | Y | Y | Y |  |  |  |  |  |
| Fisher 1996\* | TNFreceptor:Fc fusion prot | n/r | Y | 100% |  |  | **Y** | Y | **Y** |  |  |  |  | <0.2 |
| Opal 1997 | IL-1 receptor antagonist | n/r |  | 10-90% |  |  | Y | Y | Y |  |  |  |  |  |
| Abraham 1997\* | p55 TNF recept fusion prot | n/r |  | 10-90% |  |  | **Y** | **Y** | Y |  |  |  |  | <0.2 |
| Abraham/NORSEPTII 1998 | TNFα Ab | n/r |  | 99% |  |  | Y | Y | Y |  |  |  |  |  |
| Baudo 1998 | Antithrombin III | 1992 |  | 0% | Y |  | Y | Y | Y |  |  |  |  |  |
| Dhainaut 1998 | Platelet-act factor antagon. | 1993 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Angus 2000 | E5 murine endotoxin Ab | 1995 |  | 100% |  |  |  | Y | Y |  |  |  |  |  |
| Abraham 2001 | TissueFactor Pathway Inhib | 1999 |  | 10-90% |  |  | Y | Y | Y |  |  |  |  |  |
| Bernard/PROWESS 2001 | Activated Protein C | 2000 |  | 10-90% |  | **Y**5 | Y | **Y** | **Y** | **Y**5 | Y5 | Y5 | Y5 | <0.05 |
| Reinhart/RAMSES 2001 | TNFα Ab fragment | 1996 |  | 0% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Rivers 2001 | Early Goal DirectedTherapy | 1998 |  | 100% |  | **Y** |  |  | **Y** | **Y** |  |  |  | <0.05 |
| Schortgen 2001 | 6% HES (200/0.6) v gelatin | 1999 |  | 0% | Y |  | Y | Y |  |  |  |  |  |  |
| Warren/KyberSept 2001 | Antithrombin III | 1999 |  | 10-90% |  |  | Y | Y | Y | Y-56d | Y |  |  |  |
| Annane 2002 | Steroids | 1997 |  | 0% | Y | Y | **Y** | Y | Y |  |  |  | Y | <0.05 |
| Busund 2002 | Plasmapheresis | 1996 |  | 0% |  |  | Y | Y | **Y** |  |  |  |  | <0.05 |
| Abraham 2003\* | Phospholipase A2 inhibitor | 1999 | Y | 100% |  |  | **Y** | Y | Y |  |  |  |  | <0.2 |
| Abraham/OPTIMIST 2003 | Tiss Fact Path Inhib INR≥1.2 | 2001 |  | 10-90% |  |  | Y | Y | Y |  |  |  |  |  |
| Abraham/OPTIMIST 2003 | Tiss Fact Path Inhib INR<1.2 | 2001 |  | 10-90% |  |  | Y | Y | **Y** |  |  |  |  | <0.05 |
| Albertson 2003 | Enterobacteriaceae Ag Ab | n/r |  | 100% |  |  | Y | Y | Y |  |  |  |  |  |
| Chastre 2003 | 8d v 15d antibiotics(for VAP) | 2000 |  | 0% |  | Y | Y | Y | Y | Y |  |  |  |  |
| Richard 2003 | Pulmonary artery catheter | 2000 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Root 2003 | G-CSF | 1997 | Y | 10-90% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Shuster 2003 | Platelet-activating factor | 1999 |  | 100% |  |  | Y | **Y** | **Y** |  |  |  |  | <0.05 |
| Opal/COMPASS 2004 | Platelet-activating factor | 2002 |  | 10-90% |  |  | Y | Y | Y |  |  |  |  |  |
| Bakker 2004 | NO synthase inhibitor | n/r |  | 26% |  |  | Y | Y | Y |  |  |  |  |  |
| López 2004 | NO synthase inhibitor | 1997 | Y | 10-90% |  |  | **Y** | **Y** | **Y** | **Y** | **Y** |  |  | <0.05 |
| Panacek/MONARCS 2004 | TNFα Ab F(ab’)2 fragment | 1997 |  | >80% |  |  | **Y** | Y | **Y** |  |  |  |  | <0.05 |
| Reinhart 2004 | Extracorp endotox absorb | n/r |  | 0% |  |  | Y |  | Y |  |  |  |  |  |
| Abraham/ADDRESS 2005 | Activated Protein C | 2003 |  | ~40% |  | Y | Y | Y | Y | Y6 | Y6 | Y6 | Y6 |  |
| Lin 2006 | Early Goal DirectedTherapy | 2003 |  | 0%-Tai | **Y** | **Y** |  |  |  |  |  |  |  | <0.05 |
| Hentrich 2006 | IgMA-enrich IVIg (for neutropen.) | 1996 |  | 0% |  |  |  |  | Y | Y |  |  |  |  |
| Pontes-Arruda 2006 | Immunonutrition | n/r |  | 0%-Bra |  |  | Y | **Y** | **Y** |  |  |  |  | <0.05 |
| Angstwurm 2007 | Selenium | 2002 |  | 0% |  |  | Y | **Y** | Y |  |  |  |  | <0.05 |
| Annane/CATS 2007 | Norepi+Dobut v Epi | 2002 |  | 0% | Y | Y | Y | **Y** | Y | Y | Y |  |  | <0.2 |
| Levi/XPRESS 2007 | Heparin (in act prot C) | 2004 |  | ~45% |  |  | Y | **Y** | **Y** |  |  |  |  | <0.2 |
| Werdan/SBITS 2007 | IVIg v albumin | 1993 |  | 0% | Y |  | Y | Y | Y | Y | **Y** |  |  | <0.05 |
| Brunkhorst 2008 | Intensive insulin therapy | 2004 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Brunkhorst 2008 | 10% HES (200/0.5) v Ringers | 2004 | Y | 0% |  |  | Y | Y | Y | **Y** | **Y** |  |  | <0.2 |
| Russell/VASST 2008 | Vasopressin v NorEpi | 2003 |  | <10% |  |  | Y | Y | Y | **Y** | **Y** |  |  | <0.2 |
| Sprung/CORTICUS 2008 | Steroids | 2004 |  | 0% | Y | Y | **Y** | Y | Y |  |  |  | Y | <0.2 |
| Werdan/ESSICS 2008 | IVIg (for card surg w/ SIRS) | 1998 |  | 0% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Dellinger/LIPOS 2009\* | Phospholipid emulsion | 2005 |  | 13% |  |  | Y | Y | Y |  |  |  |  |  |
| Dhainaut 2009 | Activated Protein C 7 v 4d | 2006 | Y | 10-90% |  | **Y** |  |  | Y |  |  |  |  | <0.2 |
| Dupont 2009 | Lipo Ampho B v micafungin | 2003 |  | <10% |  |  | Y-8d | Y | Y | Y | Y |  |  |  |
| Jaimes/HETRASE 2009 | Heparin | 2006 |  | 0%-Col |  | Y | Y | Y | Y |  |  |  |  |  |
| Palizas 2009 | Gastric tonometry | 1999 |  | 0%SAm |  |  | Y | Y | Y |  |  |  |  |  |
| Bouadma/PRORATA 2010 | Procalcitonin guided abx | 2007 |  | 0% |  |  | Y | Y | Y | Y |  |  |  |  |
| De Backer/SOAP II 2010 | NorEpi v dopamine (all shock) | 2005 |  | 0% | Y | Y | **Y** | Y | Y |  |  | Y | Y | <0.05 |
| Jansen/LACTATE 2010 | Lactate-guided resuscitation | 2007 |  | 0% | Y | Y | Y | Y | Y | Y | **Y** | Y |  | <0.05 |
| Patel 2010 | NorEpi v dopamine | 2006 |  | 100% |  |  | **Y** | Y | Y |  |  |  |  | <0.2 |
| Rice 2010\* | Toll-like receptor 4 inhibitor | 2008 |  | 10-90% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Tidswell 2010\* | Toll-like receptor 4 inhibitor | 2003 |  | 90% |  |  | Y | Y | Y |  |  |  |  |  |
| Jensen/PASS 2011 | Procalcitonin guided abx | 2007 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Pontes-Arruda/ INTERCEPT 2011 | Immunonutrition (Oxepa) | 2008 |  | 0%-Bra |  |  | Y | **Y** | Y |  |  |  |  | <0.05 |
| Brunkhorst 2012 | Dual v single antibiotics | 2009 |  | 0% |  |  | Y | Y | Y | Y-56d | Y |  |  |  |
| Chytra 2012 | Continuous v intermittent abx | 2009 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Guidet/CHRYSTMAS 2012 | 6% HES (130/0.4) v 0.9% NS | 2009 |  | 0% |  |  |  |  | Y |  | Y |  |  |  |
| Kim 2012 | Broad spectrum abx(for HAP) | 2005 | Y | 0%-Kor |  | Y |  | Y | **Y** |  |  |  |  | <0.2 |
| Perner/6S 2012 | 6% HES (130/0.42) v Ringers | 2010 | Y | 0% |  |  | Y | Y | Y | **Y** | **Y** | Y7 | Y7 | <0.05 |
| Ranieri/PROWESS SHOCK 2012 | Activated Protein C | 2009 | Y | 10-90% |  |  | Y | **Y** | Y | Y | Y |  |  | <0.2 |
| Schortgen/Sepsiscool2012 | External cooling (for fever) | 2008 |  | 0% | Y | Y | **Y** | **Y** |  |  |  |  |  | <0.05 |
| Trof 2012 | Pressure v Volume Hemodyn.8 | 2008 |  | 0% | Y | Y | **Y** | Y | Y |  |  |  |  | <0.2 |
| Annane/APROCCHSS 2013 | Activated Protein C | 2010 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Guntupalli 2013 | Talactoferrin | 2008 |  | 100% |  |  | Y | Y | **Y** | Y | Y | **Y** |  | <0.05 |
| Joannes-Boyau/IVOIRE 2013 | High-volume hemofiltration | 2008 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Kruger/ANZ-STATInS 2013  | Atorvastatin | 2009 |  | 0% | Y | Y |  |  | **Y** |  | Y |  |  | <0.2 |
| Morelli 2013 | Esmolol | 2011 |  | 0% | **Y** | **Y** | **Y** | **Y** | **Y** |  |  |  |  | <0.05 |
| Opal/ACCESS 2013 | Toll-like receptor 4 inhibitor | 2008 |  |  |  |  | Y | Y | Y | Y | Y | Y | Y |  |
| Vincent 2013  | Thrombomodulin (for DIC) | 2008 |  | 16% |  |  | Y | Y | **Y** |  |  |  |  | <0.2 |
| Wu/ETASS 2013 | Thymosin alpha 1 | 2009 |  | 0%-Chi | Y | **Y** | Y | Y | Y |  |  |  |  | <0.05 |
| ARISE 2014 | Early Goal DirectedTherapy | 2011 |  | 0% | Y | Y | Y | **Y** | Y | Y | Y |  |  | <0.2 |
| Asfar/SEPISPAM 2014 | Mean BP 80 v 65 mm Hg | 2011 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Bernard 2014 | TNFα Ab fragment | 2011 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Caironi/ALBIOS 2014 | Albumin (for level <30 g/L) | 2010 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Holst/TRISS 2014 | Restrictive transfusion | 2012 |  | 0% |  |  | Y-5d | Y | Y | Y | Y | Y16 | Y16 |  |
| Karnard 2014 | Ulinastatin (trypsin inhibitor) | 2010 |  | 0%-Ind |  |  | Y | Y | **Y** |  |  |  |  | <0.2 |
| Leone/AZUREA 2014 | Deescal v contin empir abx | 2012 |  | 0% |  | Y | Y | Y | Y | Y | Y |  |  |  |
| ProCESS 2014^ | Early Goal DirectedTherapy | 2010 |  | 100% |  |  | Y | Y | Y | Y | Y | Y | Y |  |
| Shehabi/ProGUARD 2014 | Procalcitonin guided abx | 2012 |  | 0% | Y | Y |  |  |  |  | Y |  |  |  |
| Dulhunty/BLING II 2015 | Continuous v intermittent abx | 2013 |  | 0% | Y | Y | Y | Y | Y | Y | Y |  |  |  |
| Mouncey/ProMISe2015 | Early Goal DirectedTherapy | 2012 |  | 0% |  | Y | Y | Y | Y | Y | Y |  |  |  |
| Payen/ABDOMIX 2015 | Polymyxin B hemoperfusion | 2012 | Y | 0% |  |  | Y | Y | **Y** | **Y** | **Y** |  |  | <0.2 |
| Vincent/OASIS 2015 | Talactoferrin | 2012 | Y | 10-90% |  | **Y** | Y | Y | Y |  | **Y** |  |  | <0.05 |
| Young/HEAT 2015 | Acetominophen (for fever) | 2013 |  | 0% |  |  | **Y** | Y | Y | Y | Y |  |  | <0.05 |
| Zhang 2015 | Volume v Pressure Hemodyn.9 | 2013 |  | 0%-Chi |  |  |  | Y | Y |  |  |  |  |  |
| Abdul-Aziz/BLISS 2016 | Continuous v intermittent abx | 2013 |  | 0%-Mal | Y |  | **Y** | Y | **Y** |  |  |  |  | <0.2 |
| Gordon/VANISH 2016 | Vasopressin v norepineph. | 2014 |  | 0% | Y | Y | Y | **Y** | Y |  |  |  |  | <0.2 |
| Gordon/VANISH 2016 | Steroids | 2014 |  | 0% | Y | Y | Y | Y | Y |  |  |  |  |  |
| Hjortrup/CLASSIC 2016 | Fluid restriction | 2015 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Hyvernet 2016 | Contin. v intermit. Steroids | 2009 |  | 0% | Y | Y | **Y** | ***Y*** *(<.2)* | Y |  | Y |  |  | <0.05 |
| Keh/HYPRESS 2016 | Steroids | 2011 |  | 0% | Y | Y | Y | Y | Y | Y | Y | Y |  |  |
| Timsit/EMPIRICUS 2016 | Micafungin | 2013 | Y | 0% |  |  | **Y** | Y | Y | Y | Y |  |  | <0.2 |
| Tongyoo 2016 | Steroids | 2012 |  | 0%-Thai |  |  | Y | Y | Y | Y |  |  |  |  |
| Bergamin/TRICOP 2017 | Liberal v restrictive transfxn | 2013 |  | 0%-Bra | ***Y*** *(<.2)* |  | Y | ***Y*** *(<.2)* | ***Y****(<.2)* | ***Y****(<.2)* | **Y** |  |  | <0.05 |
| Kawazoe/DESIRE 2017 | Dexmedetomidine | 2014 |  | 0%-Jap |  |  | Y | **Y** | **Y** |  |  |  |  | <0.2 |
| Limaye 2017 | Gancyclovir | 2013 |  | 100% |  |  | Y | Y | Y | Y | Y | Y |  |  |
| Madsen/INSTINCT 2017 | IVIg | 2015 |  | 0% |  |  | Y | Y | Y | Y | Y | Y |  |  |
| Rouzé/S-TAFE 2017 | Biomarker guided anti-fungal | 2015 |  | 0% | Y |  |  |  | Y |  |  |  |  |  |
| Zhou 2017 | Lactate v ScvO2 resuscitation | 2014 |  | 0%-Chi |  |  | Y | ***Y*** *(<.2)* | **Y** | **Y** |  |  |  | <0.05 |
| Annane/APROCCHSS 2018 | Steroids | 2012 |  | 0% | **Y** | **Y** | **Y** | ***Y*** *(<.2)* | ***Y****(<.2)* | **Y** | **Y** | **Y** |  | <0.05 |
| Barbar/IDEAL-ICU 2018 | Early RRT | 2014 |  | 0% | Y | Y | Y | Y | Y | Y | Y | Y |  |  |
| Dellinger/EUPHRATES 2018 | Polymyxin B hemoperfusion | 2013 | Y | 10-90% |  |  | Y | Y | Y |  | Y | **Y** |  | <0.2 |
| Montravers/ DURAPOP 2018 | 8d v 15d abx (for abdo infxn) | 2013 |  | 0% |  |  | Y | **Y** | Y |  |  |  |  | <0.2 |
| Venkatesh/ADRENAL 2018 | Steroids | 2015 |  | 0% |  |  | ***Y****(<.2)* | **Y** | ***Y****(<.2)* | Y | Y |  |  | <0.05 |
| Welte/CIGMA 2018 | IVIg (ventilated CAP) | 2012 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **ARDS** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Anzueto 1996 | Surfactant | 1992 | Y | 10-90% |  |  | **Y** | Y | Y |  |  |  |  | <0.2 |
| Brochard 1998 | Lung Protective Ventilation | 1995 |  | 10-90% |  |  | Y | Y | Y | Y |  |  |  |  |
| Stewart 1998 | Lung Protective Ventilation | 1996 |  | 0% | Y | Y | Y | Y | Y |  |  |  |  |  |
| Lundin 1999 | Inhaled NO | 1995 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| ARDS Net 200010 | Ketoconazole | 1996 |  | 100% |  | Y | Y | Y | Y | Y | Y | Y |  |  |
| ARDS Net 200010 | Lung Protective Ventilation | 1997 |  | 100% |  | **Y** | Y | **Y** | **Y** | **Y** | **Y** | **Y** |  | <0.05 |
| Delclaux 2000 | CPAP v oxygen | 1998 |  | 0% | Y | Y |  |  |  |  |  |  |  |  |
| Gattinoni/PS I 2001 | Prone ventilation | 1998 |  | 0% | Y |  | **Y**-10d | Y | Y | Y | Y | Y |  | <0.2 |
| ARDS Net 200210 | Lisofylline | 1998 | Y | 100% |  |  | Y | Y | **Y** |  |  |  |  | <0.2 |
| Derdak/MOAT 2002 | High frequency oscillation | 1999 |  | ~70% |  |  | Y | **Y** | **Y** | **Y** | **Y** | **Y** |  | <0.2 |
| Fernández-Vivas 2003 | (Non-invasive) PAV v PSV | 2001 |  | 0% | Y | Y | Y | Y | Y |  |  |  |  |  |
| Ferrer 2003 | BiPAP v oxygen | n/r |  | 0% | **Y** |  | Y | Y | **Y** | **Y** | **Y** |  |  | <0.05 |
| ARDS Net/ALVEOLI 2004 | High v low PEEP | 2000 |  | 100% |  |  | Y | Y | Y | Y |  |  |  |  |
| Guerin 2004 | Prone ventilation | 2000 |  | 0% |  |  | Y | Y | Y | Y | Y |  |  |  |
| Zeiher/STRIVE 2004 | Neutrophil elastase inhib | 2002 | Y | 10-90% |  |  | Y | Y | Y | Y | Y | **Y** |  | <0.05 |
| ARDS Net/FACCT 2006 | Conservative fluid mgmt.11 | 2003 |  | >90% |  |  | Y | Y | **Y** | Y |  |  |  | <0.2 |
| ARDS Net/FACCT 2006 | Pulmonary artery catheter11 | 2003 |  | >90% |  |  | Y | Y | Y | Y |  |  |  |  |
| ARDS Net/LaSRS 2006 | Late steroids12 | 2000 |  | 100% |  |  | Y | Y | Y | Y | Y | Y |  |  |
| Kacmarek 2006\* | Partial liquid ventilation | 1999 | Y | 10-90% |  |  | Y | **Y** | **Y** |  |  |  |  | <0.2 |
| Mancebo 2006 | Prone ventilation | 2000 |  | 0% | **Y** | **Y** | Y | Y | **Y** | **Y** |  |  |  | <0.2 |
| Villar/ARIES 2006 | Low Vt and high PEEP | 2000 |  | 0% | **Y** | **Y** |  | Y |  |  |  |  |  | <0.05 |
| Meade/LOVS 2008 | High v low PEEP | 2003 |  | 0% | **Y** | Y | Y | Y | **Y** |  |  |  |  | <0.2 |
| Mercat/EXPRESS 2008 | High v low PEEP | 2004 |  | 0% |  | Y | **Y** | Y | Y | Y |  |  |  | <0.05 |
| Morris 2008 | Oxothiazolidine | 1997 | Y | >90% |  |  | Y | Y | **Y** |  |  |  |  | <0.05 |
| Kesecioglu 2009 | Surfactant | 2003 | Y | 0% |  |  | Y | Y | **Y** | **Y** | **Y** | **Y** |  | <0.2 |
| Peek/CESAR 2009 | ECMO | 2004 |  | 0% |  |  | Y | **Y** | **Y** | **Y** | **Y** | Y |  | <0.05 |
| Taccone/PS II 2009 | Prone ventilation | 2006 |  | 0% | Y |  | Y | Y | Y | **Y** | Y | Y |  | <0.2 |
| Vincent 2009\* | Act Fac VII | n/r |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Azoulay 2010 | BAL v sput cx (non-intub heme-onc) | 2006 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Determann 2010 | Lung Protective Ventilation | 2006 |  | 0% |  |  | Y | Y | Y |  |  |  |  |  |
| Papazian/ACURASYS 2010 | Paralysis | 2007 |  | 0% | Y | Y | Y | Y | **Y** | Y | Y |  |  | <0.05 |
| Spragg 2011 | Surfactant | 2006 |  | 17% |  |  | Y | **Y** | Y |  | Y | Y |  | <0.2 |
| ARDS Net/ALTA 2011 | Inhaled β2-agonist (albuterol)13 | 2008 | Y | 100% |  |  | **Y** | **Y** | **Y** | Y | Y |  |  | <0.2 |
| Rice/OMEGA 2011 | Omega-3 enteral feeding14 | 2008 | Y | 100% |  |  | Y | Y | Y | **Y** |  |  |  | <0.05 |
| ARDS Net/EDEN 2012 | Permissive underfeeding14 | 2010 |  | 100% |  | Y | Y | Y | Y | Y | Y | Y | Y |  |
| Gao Smith/BALTI-2 2012 | IV β2-agonist (salbutamol) | 2008 | Y | 0% | Y | Y | Y | Y | **Y** |  |  |  |  | <0.05 |
| Paine 2012 | GM-CSF | 2006 |  | 100% |  |  | **Y** | **Y** | Y |  |  | Y |  | <0.2 |
| Ferguson/OSCILLATE 2013 | High frequency oscillation | 2010 | Y | 10-90% | **Y** | **Y** | **Y** | **Y** | **Y** |  |  |  |  | <0.05 |
| Guérin/PROSEVA 2013 | Prone ventilation | 2009 |  | 0% |  |  | **Y** | **Y** | **Y** | **Y** | **Y** |  |  | <0.05 |
| Young/OSCAR 2013 | High frequency oscillation | 2010 |  | 0% | Y | Y | Y | Y | Y |  |  |  |  |  |
| ARDS Net/SAILS 2014 | Rosuvastatin15 | 2011 |  | 100% |  |  | Y | Y | Y | Y | Y |  |  |  |
| McAuley/HARP-2 2014 | Simvistatin | 2012 |  | 0% | Y | **Y** | Y | Y | **Y** | **Y**17 | **Y**17 | **Y**17 | **Y**17 | <0.2 |
| Lemiale/GRRR-OH 2015 | BiPAP v oxygen (immunocomp) | 2014 |  | 0% | Y | Y | Y | Y | Y |  |  | Y |  |  |
| Willson/CARDS 2015 | Surfactant | 2009 |  | 10-90% |  | Y |  |  |  |  | Y |  |  |  |
| Kacmarek 2016 | Decremental PEEP & recruit | 2011 |  | <10% | Y | Y |  |  | Y | Y |  |  |  |  |
| ART 2017 | Recruit. & titrated PEEP | 2014 | Y | 0% | ***Y*** *(<.2)* | ***Y****(<.2)* | **Y** | **Y** | ***Y****(<.2)* |  |  |  |  |  |
| Azoulay/HIGH 2018 | HFNC v face mask oxygen | 2017 |  | 0% | Y | Y | Y | Y | Y |  |  |  |  |  |
| Coombes/EOLIA 2018 | ECMO | 2014 |  | <10% | ***Y*** *(<.2)* | ***Y****(<.2)* | ***Y****(<.2)* | **Y** | ***Y****(<.2)* | ***Y****(<.2)* | ***Y*** *(<.2)* |  |  | <0.05 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Description of Column Headings and Abbreviations within the Table

“Enrol Year”-median year of trial enrolment.

“Y”-mortality reported at prespecified time point by the trial.

“Harm”- trials Yhere intervention group mortality was higher than control group mortality with p<0.2 at any of the prespecified time points (indicated by “R” in this column).

“Min p”-identifies trials where p<0.05 or p<0.2 at time points indicated with a bold underlined “**Y**”.

Trials not conducted in North America, Europe, or Australia/New Zealand have countries identified (Arg-Argentina, Bra-Brazil, Chi-China, Col-Columbia, HK-Hong Kong, Ind-India, Isr-Israel, Jap-Japan, Kor-Korea, KSA-Kingdom of Saudi Arabia, Mal-Malaysia, SAfr-South Africa, SAm-South America, Tai-Taiwan, Thai-Thailand, Viet-Vietnam)

Footnotes

\*Combined two intervention groups, or two or more dose groups.

^Combined two control groups.

0Published trial designed as 30 v 120 min T-piece spontaneous breathing trial (SBT).

1Followed to 28d; patients discharged alive from hospital before 90 days assumed in publication to still be alive at 90 days.

2Followed to hospital discharge with mean hospital length of stay >50 days. 7d, 14d, and 28d mortality estimated from published survival curve.

3Mortality at median follow up of 873d (2.4y, IQR 1.5-3.3y).

4Published trial designed as heated humidifier (HH) v heat and moisture exchanger (HME).

5Mortality beyond 28 days reported separately in Angus et al, Crit Care Med 2004; 32(11): 2199-206.

6Mortality beyond 28 days reported separately in Laterre et al, Crit Care Med 2007; 35(6): 1457-63.

7Mortality beyond 90 days reported separately in Perner et al, Inten Care Med 2014; 40: 1457-63.

8Published trial designed as volume-guided management using transpulmonary thermodilution (PiCCO system) v pressure-guided management using a pulmonary artery catheter.

9Volume-guided management using transpulmonary thermodilution (PiCCO system) v pressure-guided management using central venous pressure.

102×2 factorial (initially lung protective ventilation with ketoconazole, then with lisofylline after ketoconazole arm stopped early for futility, and finally lisofylline alone after lung protective ventilation arm stopped early for efficacy). For lung protection ventilation and ketoconazole interventions, patients were followed until day 180 or until they were discharged home without the use of assisted ventilation. (Patients who went home before day 180 without the use of assisted ventilation were assumed to be alive at 180 days.) For lisofylline, all patients were followed for 30 days after hospital discharge as per FDA request with only one additional death occurring after hospital discharge (Schoenfeld D. Crit Care 2006; 10: 103).

112×2 factorial. Patients were followed until day 60 (the primary outcome) or until they were discharged home without the use of assisted ventilation. (Patients who went home before day 60 without the use of assisted ventilation were assumed to be alive at 60 days.)

12All patients had complete 180-day follow-up for survival status.

13ALTA had partial co-enrolment with OMEGA/EDEN and followed patients until day 90 or until discharge home (from hospital, rehabilitation, or chronic ventilator facilities) without the use of assisted ventilation.

142×2 factorial until OMEGA arm stopped early for futility. For OMEGA, patients were followed until day 60 or until discharge home (from hospital, rehabilitation, or chronic ventilator facilities) without the use of assisted ventilation. For EDEN, patients were followed to 12 months in a separate report (Needham et al, BMJ 2013; 346: f1532).

1581 patients were co-enrolled with EDEN. SAILS followed patients until day 60 or until discharge home (from hospital, rehabilitation, or chronic ventilator facilities) without the use of assisted ventilation.

16Mortality beyond 90 days reported separately in Rygård et al, Inten Care Med 2016; 42: 1685-94.

17Mortality beyond 28 days reported separately in Agus et al, Crit Care 2017; 21: 108.

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**Sepsis**

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**Supplemental Table 2 Interventions Shown to Improve Survival in ICU-based Clinical Trials**

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| --- | --- |
| **Study Population** | **Intervention** |
| **Sepsis****ARDS/Acute Lung Injury****Other** | ***Pharmacologic agents***  Acetaminophen, activated protein C, antibody to tumor necrosis factor, corticosteroidsa, esmolol,intravenous immunoglobulin, platelet-activating factor acetylhydrolase, selenium, talactoferrin, thymosin-α, tissue factor pathway inhibitor***Resuscitation and Support***Early goal-directed therapy a,f, external cooling, immunonutrition, lactate-guided resuscitationa, norepinephrine vs dopaminea, plasmapheresis, transfusion in septic shock***Ventilatory Support***Extracorporeal membrane oxygenation, non-invasive ventilation b, neuromuscular blockade a, prone positioninga, reduced tidal volume, PEEPa Addition of EDTA to propofol c Citrate anticoagulation for CVVH e Colloid resuscitation Early tracheostomy Erythropoietin for traumatic brain injury  Gastric tonometry Hemicraniectomy for MCA stroke d Immunonutrition Intensive insulin therapy a,f Invasive diagnosis of pneumonia Passive tilting Pravastatin Progesterone for traumatic brain injury Reduced oxygen threshold target Sedation interruption a Selective digestive tract decontamination Shenfu for cardiac arrest Surveillance for sinusitis Vitamin D3  |

1. Recommended or suggested in the 2017 guidelines of the Surviving Sepsis Campaign (1)
2. Recommended in the European Respiratory Society guidelines for non-invasive ventilation (2)
3. Incorporated into formulation of propofol <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019627s066lbl.pdf>
4. Recommended in the American Heart Association/American Stroke Association guidelines for the management of cerebral infarction (3)
5. Recommended in the KDIGO Clinical Practice Guidelines for Acute Kidney Injury (4)
6. Initial results contradicted by findings of subsequent multicenter RCT (1)