

Reducing Mortality in Critically Ill Patients

Giovanni Landoni
Martina Baiardo Redaelli
Chiara Sartini
Alberto Zangrillo
Rinaldo Bellomo
Editors

Second Edition

 Springer

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Preface

Critically ill patients are at high risk of mortality, and each effort is made by clinicians to improve survival. This fragile patient population requires multiple invasive and noninvasive life support interventions that may range from cardiopulmonary resuscitation to the most accurate nutritional support.

Working with such a fragile population is challenging, no critically ill patient is like the other and the vastness of knowledge required in critical care makes this discipline one of the most demanding medical specialties. In this context, evidence-based medicine together with international guidelines is the cornerstone to drive therapeutic choices.

Unfortunately, guidelines cannot cover all the variables met in clinical practice and performing high-quality clinical research is challenging in this specific setting.

However, systematically searching in the scientific literature, we have found more than 300 randomized controlled trials (RCTs) investigating interventions (drug, strategies, or techniques) with a proven statistically significant effect on mortality. The majority of these interventions were found to improve survival, while few of them were found to be detrimental in critically ill patients.

In this textbook, we summarize the available evidence-based interventions, with a significant mortality effect, in critical care medicine. The volume has been crafted to systematically combine the RCTs in dedicated chapters according to the specific topic. Most of them enclose interventions increasing survival, while in three separate chapters the reader will find the summary of the interventions increasing mortality, the interventions with still unclear conflicting evidences, and a last chapter collecting the latest evidences, not matching with the previously treated topics. Although the chapters are arranged in a progressive manner, in order to empower each other, the reader can even choose a single chapter to deepen his specific field of interest.

This volume encloses a fundamental piece of evidence-based medicine. It is addressed to critical care physicians who daily deal with challenging therapeutic choices, to residents and medical students as a base to build their critical care knowledge, and to researcher who wants to understand where the state of the art in critical care evidence is, in order to properly address future studies.

As editors, we are profoundly grateful to all the authors of this book for their excellent contribution and their motivation to help spreading the available knowledge in evidence-based critical care medicine. We must also acknowledge that

hundreds of colleagues from all over the world, despite not mentioned as authors of this textbook, gave a significant contribution to this work, spending their time to help us in the consensus building and systematic review process that is beneath this volume and give strength to each chapter.

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Decision-Making in the Democracy Medicine Era: The Consensus Conference Process

1

Massimiliano Greco, Maria Luisa Azzolini,
and Giacomo Monti

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Randomized controlled trials (RCTs) are the gold standard of evidence-based medicine.

However, their application on the population of critically ill patients acted as a conundrum for researchers in the last decades [1]. A significant number of well-designed, robust, multicenter RCTs failed to find significant effects in this population [2]. This is due to the characteristics of critically ill patients, which have wide variation in mortality risk, according to difference in baseline conditions, ICU admission reason, and previous comorbidities. Lack of external validity, contrasting results between similar trials, and difficulties in interpretation of results led to a blurred picture on the evidence available in critical care.

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Likewise, this condition worsens due to several low-quality non-randomized or observational studies, which should be considered by clinicians as exploratory hypotheses only.

Given these premises, the modern clinicians try to achieve an updated and clear picture of the best evidence available in medical literature. While consensus conferences and guidelines were designed to simplify this task, their approach has been criticized, due to the preeminent role of experts and the possibility of introducing expert-related bias [3, 4].

To overcome these limitations, a third way has been proposed and has already been employed in different medical fields: the democracy-based medicine [5–8].

In this book, we present the result of both an updated democratic consensus conference and the last available randomized evidence influencing mortality in critically ill setting.

The process of consensus building has been described elsewhere [5] and is summarized in this chapter.

1.1 Systematic Review

Authors performed a systematic review on the major scientific databases (MEDLINE/PubMed, Scopus and Embase) to identify all RCTs on any type of intervention influencing mortality in critically ill and perioperative patients, with a statistically significant effect on mortality.

Inclusion criteria were:

- RCT published in a peer-reviewed journal reporting a statistical significant difference in mortality without adjustment for baseline characteristics.
- Involving adult patients in critically ill setting.
- Assessing non-surgical interventions (drugs, strategy, or techniques).

The literature research identified more than 52,255 papers that were screened at title/abstract level, of these 262 were discussed in an in-person meeting, and analyzed by 32 experts. Several papers were excluded because of methodological flaws or exclusion criteria.

1.2 Reaching Consensus in Democracy Medicine

The process of Democracy Medicine was based on an international meeting held at an academic center and on an online surveys/vote. After the systematic review and the experts meeting, interventions reducing and increasing mortality were identified and position statements for the next step generated. Subsequently, an online platform hosted a survey where colleagues could express their agreement on the proposed statements. This second step collected and validated the original statements

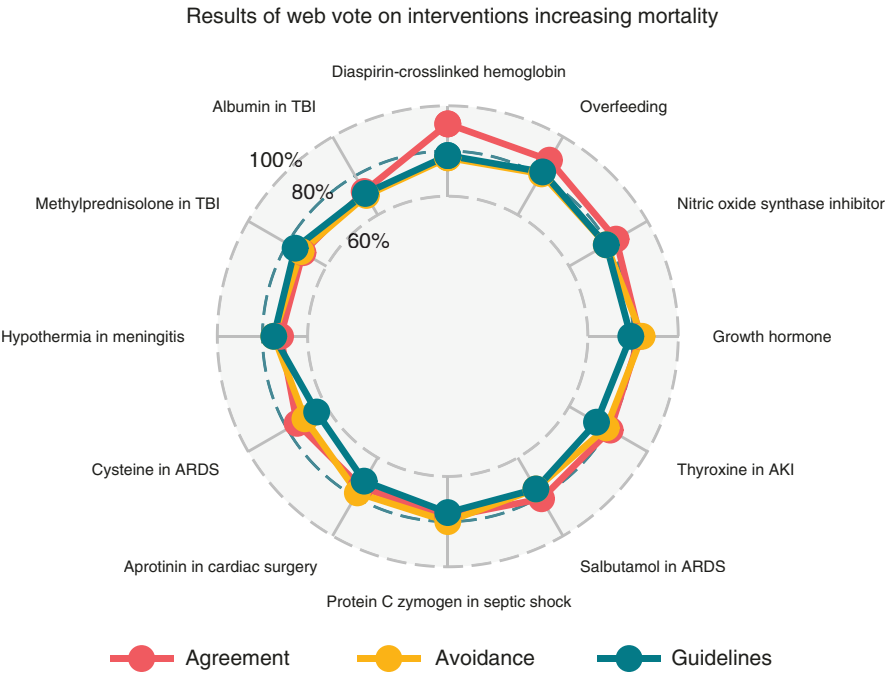


Fig. 1.1 Results of the web-vote on interventions increasing mortality. Abbreviations: AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; TBI = traumatic brain injury

according to the opinions of hundreds of colleagues from 46 countries. Interventions not reaching 67% agreement on their efficacy or on their detrimental effect were excluded.

The results of the web survey for interventions increasing mortality are reported in Fig. 1.1, while results for interventions reducing mortality are reported in Fig. 1.2.

1.3 The Identified Topics, the Book, and the Diffusion of the Evidence to the International Community of Colleagues

Topics reducing mortality [6–71] and increasing mortality [72–83] were thus finally identified and are reported in Table 1.1.

Given the international relevance and the amount of information collected, generated, and organized through the whole process, the authors disseminated consensus results to reach the widest audience of peers. Two main article regarding the consensus were published in the Journal of Cardiothoracic and Vascular Anesthesia [84, 85].

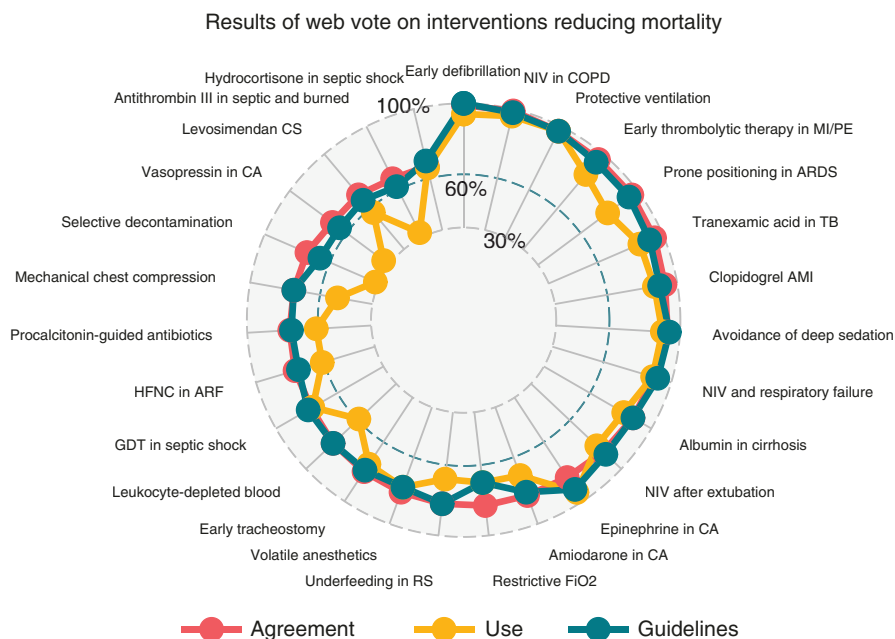


Fig. 1.2 Results of the web-vote on interventions reducing mortality. Abbreviations: *NIV* = non-invasive ventilation; *COPD* = chronic obstructive pulmonary disease; *MI* = myocardial infarction; *PE* = pulmonary embolism; *ARDS* = acute distress respiratory syndrome; *AMI* = acute myocardial infarction; *CA* = cardiac arrest; *FiO₂* = inspiratory fraction of oxygen; *RS* = refeeding syndrome; *GDT* = goal-directed therapy; *HFNC* = high flow nasal cannula; *ARF* = acute respiratory failure; *CS* = cardiogenic shock

Interventions reducing mortality, with the evidence supporting them, are extensively described in this book. Indeed, the reader will find them along the chapters, included in the appropriate topic. Conversely, the reader will find interventions increasing mortality and those with conflicting evidences (having at the same time RCTs both in favor or against mortality reduction), summarized in two separate chapters.

The last chapter reviews the latest randomized evidences on mortality, published after the consensus conference and dealing with topics not discussed in previous chapters.

1.4 A Common Shell for a Flexible Process

The democratic process has been in place among all the previous consensus conferences [86–92]. They focused on critically ill patients [90, 91], on interventions in cardiac anesthesia [88, 92], on the perioperative period of any surgery [86, 87], and on patients with or at risk for acute kidney injury [89].

Table 1.1 The interventions influencing mortality identified by the Consensus Conference

Increasing survival		Increasing mortality
Early defibrillation [26, 27]	Volatile anesthetics in cardiac surgery [8, 65]	Diaspirin cross-linked hemoglobin [82]
NIV in COPD [6, 46]	Early tracheostomy [59, 60]	Overfeeding [76]
Protective ventilation [10, 49, 52]	Leukocyte-depleted blood [32, 33]	NOS inhibitor in septic shock [73]
Early thrombolytic therapy in MI/PE [56–58, 66]	GDT in septic shock [28, 30]	Human growth hormone [78]
Prone positioning in ARDS [9, 12, 50]	HFNC in Respiratory Failure [7]	Thyroxine in AKI [72]
Tranexamic acid in trauma [61]	Procalcitonin-guided antibiotics [70]	IV Salbutamol in ARDS [81]
Clopidogrel in MI [21]	Mechanical chest compression [36–39]	Protein C zymogen [80]
Avoidance of deep sedation [51, 55, 67]	Selective decontamination [11, 22–25]	Aprotinin in noncardiac surgery [79]
NIV and respiratory failure [41–45, 68]	Vasopressin in cardiac arrest [63, 64]	Cysteine prodrug [74]
Albumin in cirrhosis [14]	Levosimendan in cardiogenic shock [34, 35]	Hypothermia in meningitis [77]
Epinephrine in cardiac arrest [71]	Antithrombin III in septic and burned [17, 19, 93]	Methylprednisolone in TBI [75]
Amiodarone in cardiac arrest [15, 16, 62]	Hydrocortisone in septic shock [31]	Albumin in TBI [83]
Restrictive FiO ₂ [53, 54]	NIV after extubation [18, 29, 40, 47, 48]	
Underfeeding in refeeding syndrome [69]		

NIV Non-invasive ventilation, *MI* myocardial infarction, *PE* pulmonary embolism, *ARDS* Acute respiratory distress syndrome, *TBI* Traumatic brain injury, *HFNC* High Flow Nasal Cannula, *GDT* Goal Directed Therapy, *NOS* nitric oxide synthase, *COPD* Chronic obstructive pulmonary disease (COPD)

Each time a manuscript with the consensus results was published on an international journal. There were only small differences related to the systematic review (according to the broadness and complexity of the subject), and some variance in the questions posed by the web survey.

The Democratic Consensus process, to our knowledge, is the only method employed to share the evaluation of best medical evidence with a global audience of clinicians and to allow to reach agreement among a large population of colleagues.

This book is a compendium of our last Democracy-Based Medicine process involving critically ill and perioperative patients and comprises RCT-based evidence on highly selected specific topics.

References

1. Vincent JL. We should abandon randomized controlled trials in the intensive care unit. In: *Critical care medicine*, vol. 38. Baltimore: Lippincott Williams and Wilkins; 2010. <https://doi.org/10.1097/CCM.0b013e3181f208ac>.
2. Ospina-Tascón GA, Büchele GL, Vincent J-L. Multicenter, randomized, controlled trials evaluating mortality in intensive care: doomed to fail? *Crit Care Med*. 2008;36(4):1311–22. <https://doi.org/10.1097/CCM.0b013e318168ea3e>.
3. Bellomo R. The risks and benefits of the consensus process. In: *Reducing mortality in the peri-operative period*. Cham: Springer; 2014. p. 1–7. https://doi.org/10.1007/978-3-319-02186-7_1.
4. Rotondi AJ, Kvetan V, Carlet J, Sibbald WJ. Consensus conferences in critical care medicine. *Crit Care Clin*. 1997;13(2):417–40. [https://doi.org/10.1016/S0749-0704\(05\)70319-5](https://doi.org/10.1016/S0749-0704(05)70319-5).
5. Greco M, Zangrillo A, Mucchetti M, et al. Democracy-based consensus in medicine. *J Cardiothorac Vasc Anesth*. 2015;29(2):506–9. <https://doi.org/10.1053/j.jvca.2014.11.005>.
6. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355(9219):1931–5. [https://doi.org/10.1016/S0140-6736\(00\)02323-0](https://doi.org/10.1016/S0140-6736(00)02323-0).
7. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxic respiratory failure. *N Engl J Med*. 2015;372(23):2185–96. <https://doi.org/10.1056/NEJMoa1503326>.
8. Likhvantsev VV, Landoni G, Levikov DI, Grebenchikov OA, Skripkin YV, Cherpakov RA. Sevoflurane versus Total intravenous anesthesia for isolated coronary artery bypass surgery with cardiopulmonary bypass: a randomized trial. *J Cardiothorac Vasc Anesth*. 2016;30(5):1221–7. <https://doi.org/10.1053/j.jvca.2016.02.030>.
9. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159–68. <https://doi.org/10.1056/NEJMoa1214103>.
10. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–8. <https://doi.org/10.1056/NEJM200005043421801>.
11. De Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*. 2003;362(9389):1011–6. [https://doi.org/10.1016/S0140-6736\(03\)14409-1](https://doi.org/10.1016/S0140-6736(03)14409-1).
12. Mancebo J, Fernández R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2006;173(11):1233–9. <https://doi.org/10.1164/rccm.200503-353OC>.
13. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet*. 1997;349(9051):535–7. [https://doi.org/10.1016/S0140-6736\(97\)80087-6](https://doi.org/10.1016/S0140-6736(97)80087-6).
14. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341(6):403–9. <https://doi.org/10.1056/nejm199908053410603>.
15. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2002;346(12):884–90. <https://doi.org/10.1056/nejm013029>.
16. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341(12):871–8. <https://doi.org/10.1056/nejm199909163411203>.
17. Baudo F, Caimi TM, de Cataldo F, et al. Antithrombin III (ATILL) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study. *Intensive Care Med*. 1998;24(4):336–42. <https://doi.org/10.1007/s001340050576>.

18. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med*. 2006;173(2):164–70. <https://doi.org/10.1164/rccm.200505-718OC>.
19. Lavrentieva A, Bitzani M, Parlapani A, et al. The efficacy of antithrombin administration in the acute phase of burn injury. *Thromb Haemost*. 2008;100(08):286–90. <https://doi.org/10.1160/th07-11-0684>.
20. Warren BL, Eid A, Singer P, et al. High-dose Antithrombin III in severe Sepsis. *JAMA*. 2001;286(15):1869. <https://doi.org/10.1001/jama.286.15.1869>.
21. Chen ZM, et al. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607–21. [https://doi.org/10.1016/s0140-6736\(05\)67660-x](https://doi.org/10.1016/s0140-6736(05)67660-x).
22. de La Cal MA, Cerdá E, García-Hierro P, et al. Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract. *Ann Surg*. 2005;241(3):424–30. <https://doi.org/10.1097/01.sla.0000154148.58154.d5>.
23. Krueger WA, Lenhart F-P, Neeser G, et al. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients. *Am J Respir Crit Care Med*. 2002;166(8):1029–37. <https://doi.org/10.1164/rccm.2105141>.
24. Rocha LA, Martín MJ, Pita S, et al. Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. *Intensive Care Med*. 1992;18(7):398–404. <https://doi.org/10.1007/bf01694341>.
25. Ulrich C, Harinck-de Weerd JE, Bakker NC, Jacz K, Doornbos L, de Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. *Intensive Care Med*. 1989;15(7):424–31. <https://doi.org/10.1007/bf00255597>.
26. Eisenberg MS. Treatment of ventricular fibrillation. *JAMA*. 1984;251(13):1723. <https://doi.org/10.1001/jama.1984.03340370055030>.
27. Hallstrom AP, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med*. 2004;351(7):637–46. <https://doi.org/10.1056/nejmoa040566>.
28. Lin S-MM, Da Huang C-D, Lin H-CC, Liu C-YY, Wang C-HH, Kuo H-PP. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock. *Shock*. 2006;26(6):551–7. <https://doi.org/10.1097/01.shk.0000232271.09440.8f>.
29. Ferrer M, Sellarés J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*. 2009;374(9695):1082–8. [https://doi.org/10.1016/S0140-6736\(09\)61038-2](https://doi.org/10.1016/S0140-6736(09)61038-2).
30. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe Sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–77. <https://doi.org/10.1056/nejmoa010307>.
31. Annane D. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862. <https://doi.org/10.1001/jama.288.7.862>.
32. Bilgin YM, van de Watering LMG, Eijssman L, et al. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. *Circulation*. 2004;109(22):2755–60. <https://doi.org/10.1161/01.cir.0000130162.11925.21>.
33. van de Watering LMG, Hermans J, Houbiers JGA, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery. *Circulation*. 1998;97(6):562–8. <https://doi.org/10.1161/01.cir.97.6.562>.
34. Fuhrmann JT, Schmeisser A, Schulze MR, et al. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction*. *Crit Care Med*. 2008;36(8):2257–66. <https://doi.org/10.1097/ccm.0b013e3181809846>.
35. Levin RL, Degrange MA, Porcile R, et al. The calcium sensitizer levosimendan gives superior results to dobutamine in postoperative low cardiac output syndrome. *Rev Española Cardiol*. 2008;61(5):471–9. [https://doi.org/10.1016/s1885-5857\(08\)60160-7](https://doi.org/10.1016/s1885-5857(08)60160-7).

36. Cohen TJ, Goldner BG, Maccaro PC, et al. A comparison of active compression-decompression cardiopulmonary resuscitation with standard cardiopulmonary resuscitation for cardiac arrests occurring in the hospital. *N Engl J Med.* 1993;329(26):1918–21. <https://doi.org/10.1056/nejm199312233292603>.
37. Gao C, Chen YY, Peng H, Chen YY, Zhuang Y, Zhou S. Clinical evaluation of the AutoPulse automated chest compression device for out-of-hospital cardiac arrest in the northern district of Shanghai, China. *Arch Med Sci.* 2016;3(3):563–70. <https://doi.org/10.5114/aoms.2016.59930>.
38. Tucker KJ, Galli F, Savitt MA, Kahsai D, Bresnahan L, Redberg RF. Active compression-decompression resuscitation: effect on resuscitation success after in-hospital cardiac arrest. *J Am Coll Cardiol.* 1994;24(1):201–9. [https://doi.org/10.1016/0735-1097\(94\)90564-9](https://doi.org/10.1016/0735-1097(94)90564-9).
39. Wolcke BB, Mauer DK, Schoefmann MF, et al. Comparison of standard cardiopulmonary resuscitation versus the combination of active compression-decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. *Circulation.* 2003;108(18):2201–5. <https://doi.org/10.1161/01.cir.0000095787.99180.b5>.
40. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. *Ann Intern Med.* 1998;128(9):721–8. <https://doi.org/10.7326/0003-4819-128-9-199805010-00004>.
41. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure. *Am J Respir Crit Care Med.* 2003;168(12):1438–44. <https://doi.org/10.1164/rccm.200301-072oc>.
42. L'Her E, Duquesne F, Girou E, et al. Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. *Intensive Care Med.* 2004;30(5):882–8. <https://doi.org/10.1007/s00134-004-2183-y>.
43. Nava S, Grassi M, Fanfulla F, et al. Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial. *Age Ageing.* 2011;40(4):444–50. <https://doi.org/10.1093/ageing/afr003>.
44. Park M, Sangean MC, Volpe MS, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Crit Care Med.* 2004;32(12):2407–15. <https://doi.org/10.1097/01.ccm.0000147770.20400.10>.
45. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ. Out-of-hospital continuous positive airway pressure ventilation versus usual care in acute respiratory failure: a randomized controlled trial. *Ann Emerg Med.* 2008;52(3):232–241.e1. <https://doi.org/10.1016/j.annemergmed.2008.01.006>.
46. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1995;333(13):817–22. <https://doi.org/10.1056/nejm199509283331301>.
47. Ferrer M, Esquinas A, Arancibia F, et al. Noninvasive ventilation during persistent weaning failure. *Am J Respir Crit Care Med.* 2003;168(1):70–6. <https://doi.org/10.1164/rccm.200209-1074oc>.
48. Ornico SR, Lobo SM, Sanches HS, et al. Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. *Crit Care.* 2013;17(2):R39. <https://doi.org/10.1186/cc12549>.
49. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med.* 1998;338(6):347–54. <https://doi.org/10.1056/nejm199802053380602>.
50. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001;345(8):568–73. <https://doi.org/10.1056/nejmoa010043>.
51. Mansouri P, Javadpour S, Zand F, et al. Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: a randomized clinical trial. *J Crit Care.* 2013;28(6):918–22. <https://doi.org/10.1016/j.jcrc.2013.06.019>.

52. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med*. 2006;34(5):1311–8. <https://doi.org/10.1097/01.ccm.0000215598.84885.01>.
53. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit. *JAMA*. 2016;316(15):1583. <https://doi.org/10.1001/jama.2016.11993>.
54. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery. *Anesth Analg*. 2012;115(4):849–54. <https://doi.org/10.1213/ane.0b013e3182652a51>.
55. Brown CH, Azman AS, Gottschalk A, Mears SC, Sieber FE. Sedation depth during spinal anesthesia and survival in elderly patients undergoing hip fracture repair. *Anesth Analg*. 2014;118(5):977–80. <https://doi.org/10.1213/ane.0000000000000157>.
56. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. *BMJ*. 1992;305(6853):548–53. <https://doi.org/10.1136/bmj.305.6853.548>.
57. Jerjes-Sanchez C, Ramírez-Rivera A, de Lourdes GM, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227–9. <https://doi.org/10.1007/bf01062714>.
58. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian region early anistreplase trial (GREAT). *J Am Coll Cardiol*. 1997;30(5):1181–6. [https://doi.org/10.1016/s0735-1097\(97\)00299-4](https://doi.org/10.1016/s0735-1097(97)00299-4).
59. Bösel J, Schiller P, Hook Y, et al. Stroke-related early tracheostomy versus prolonged orotracheal intubation in neurocritical care trial (SETPOINT). *Stroke*. 2013;44(1):21–8. <https://doi.org/10.1161/strokeaha.112.669895>.
60. Rumbak MJ, Newton M, Truncala T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged trans-laryngeal intubation (delayed tracheotomy) in critically ill medical patients*. *Crit Care Med*. 2004;32(8):1689–94. <https://doi.org/10.1097/01.ccm.0000134835.05161.b6>.
61. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32. [https://doi.org/10.1016/s0140-6736\(10\)60835-5](https://doi.org/10.1016/s0140-6736(10)60835-5).
62. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374(18):1711–22. <https://doi.org/10.1056/NEJMoa1514204>.
63. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med*. 2009;169(1):15. <https://doi.org/10.1001/archinternmed.2008.509>.
64. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest. *JAMA*. 2013;310(3):270. <https://doi.org/10.1001/jama.2013.7832>.
65. De Hert S, Vlasselaers D, Barbé R, et al. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. *Anaesthesia*. 2009;64(9):953–60. <https://doi.org/10.1111/j.1365-2044.2009.06008.x>.
66. Sarullo M. Ospedale Bucchini la Ferla F. [The safety and efficacy of systemic salvage thrombolysis in acute myocardial infarct]; 2000. <http://www.researchgate.net/publication/12486256>. Accessed 20 Aug 2020.
67. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126–34. [https://doi.org/10.1016/S0140-6736\(08\)60105-1](https://doi.org/10.1016/S0140-6736(08)60105-1).

68. Zhu G, Wang D, Liu S, Jia M, Jia S. Efficacy and safety of noninvasive positive pressure ventilation in the treatment of acute respiratory failure after cardiac surgery. *Chin Med J.* 2013;126(23):4463–9.
69. Doig GS, Simpson F, Heighes PT, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med.* 2015;3(12):943–52. [https://doi.org/10.1016/S2213-2600\(15\)00418-X](https://doi.org/10.1016/S2213-2600(15)00418-X).
70. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis.* 2016;16(7):819–27. [https://doi.org/10.1016/S1473-3099\(16\)00053-0](https://doi.org/10.1016/S1473-3099(16)00053-0).
71. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation.* 2011;82(9):1138–43. <https://doi.org/10.1016/j.resuscitation.2011.06.029>.
72. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyroxine in acute renal failure. *Kidney Int.* 2000;57(1):293–8. <https://doi.org/10.1046/j.1523-1755.2000.00827.x>.
73. López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med.* 2004;32(1):21–30. <https://doi.org/10.1097/01.CCM.0000105581.01815.C6>.
74. Morris PE, Papadakos P, Russell JA, et al. A double-blind placebo-controlled study to evaluate the safety and efficacy of L-2-oxothiazolidine-4-carboxylic acid in the treatment of patients with acute respiratory distress syndrome. *Crit Care Med.* 2008;36(3):782–8. <https://doi.org/10.1097/CCM.0B013E318164E7E4>.
75. Oлдashi F, Muzha I, Filipi N, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet.* 2004;364(9442):1321–8. [https://doi.org/10.1016/S0140-6736\(04\)17188-2](https://doi.org/10.1016/S0140-6736(04)17188-2).
76. Braunschweig CA, Sheean PM, Peterson SJ, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). *J Parenter Enter Nutr.* 2015;39(1):13–20. <https://doi.org/10.1177/0148607114528541>.
77. Mourvillier B, Tubach F, Van De Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. *J Am Med Assoc.* 2013;310(20):2174–83. <https://doi.org/10.1001/jama.2013.280506>.
78. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med.* 1999;341(11):785–92. <https://doi.org/10.1056/NEJM199909093411102>.
79. Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med.* 2008;358(22):2319–31. <https://doi.org/10.1056/NEJMoa0802395>.
80. Pappalardo F, Crivellari M, Di Prima AL, et al. Protein C zymogen in severe sepsis: a double-blinded, placebo-controlled, randomized study. *Intensive Care Med.* 2016;42(11):1706–14. <https://doi.org/10.1007/s00134-016-4405-5>.
81. Smith F, Perkins G, Gates S, Young D, Lancet DM-T. Effect of intravenous β -2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet.* 2012;379:229–35. [https://doi.org/10.1016/S0140-6736\(11\)61623-1](https://doi.org/10.1016/S0140-6736(11)61623-1).
82. Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. *J Am Med Assoc.* 1999;282(19):1857–64. <https://doi.org/10.1001/jama.282.19.1857>.
83. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med.* 2007;357(9):874–84. <https://doi.org/10.1056/NEJMoa067514>.

84. Sartini C, Lomivorotov V, Pieri M, et al. A systematic review and international web-based survey of randomized controlled trials in the perioperative and critical care setting: interventions reducing mortality. *J Cardiothorac Vasc Anesth*. 2019;33(5):1430–9. <https://doi.org/10.1053/j.jvca.2018.11.026>.
85. Sartini C, Lomivorotov V, Pisano A, et al. A systematic review and international web-based survey of randomized controlled trials in the perioperative and critical care setting: interventions increasing mortality. *J Cardiothorac Vasc Anesth*. 2019;33(10):2685–94. <https://doi.org/10.1053/j.jvca.2019.03.022>.
86. Landoni G, Rodseth RN, Santini F, et al. Randomized evidence for reduction of perioperative mortality. *J Cardiothorac Vasc Anesth*. 2012;26(5):764–72. <https://doi.org/10.1053/j.jvca.2012.04.018>.
87. Landoni G, Pisano A, Lomivorotov V, et al. Randomized evidence for reduction of perioperative mortality: an updated consensus process. *J Cardiothorac Vasc Anesth*. 2017;31(2):719–30. <https://doi.org/10.1053/j.jvca.2016.07.017>.
88. Landoni G, Lomivorotov V, Silvietti S, et al. Nonsurgical strategies to reduce mortality in patients undergoing cardiac surgery: an updated consensus process. *J Cardiothorac Vasc Anesth*. 2018;32(1):225–35. <https://doi.org/10.1053/j.jvca.2017.06.017>.
89. Landoni G, Bove T, Székely A, et al. Reducing mortality in acute kidney injury patients: systematic review and international web-based survey. *J Cardiothorac Vasc Anesth*. 2013;27(6):1384–98. <https://doi.org/10.1053/j.jvca.2013.06.028>.
90. Pisano A, Landoni G, Lomivorotov V, et al. Worldwide opinion on multicenter randomized interventions showing mortality reduction in critically ill patients: a democracy-based medicine approach. *J Cardiothorac Vasc Anesth*. 2016;30(5):1386–95. <https://doi.org/10.1053/j.jvca.2016.05.005>.
91. Landoni G, Comis M, Conte M, et al. Mortality in multicenter critical care trials: an analysis of interventions with a significant effect. *Crit Care Med*. 2015;43(8):1559–68. <https://doi.org/10.1097/CCM.0000000000000974>.
92. Landoni G, Augoustides JG, Guarracino F, et al. Mortality reduction in cardiac anesthesia and intensive care: results of the first international consensus conference. *Acta Anaesthesiol Scand*. 2011;55(3):259–66. <https://doi.org/10.1111/j.1399-6576.2010.02381.x>.
93. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *J Am Med Assoc*. 2001;286(15):1869–78. <https://doi.org/10.1001/jama.286.15.1869>.