Reducing Mortality in Critically Ill Patients

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Second Edition

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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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Contents

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

Massimiliano Greco, Maria Luisa Azzolini, and Giacomo Monti

Contents

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

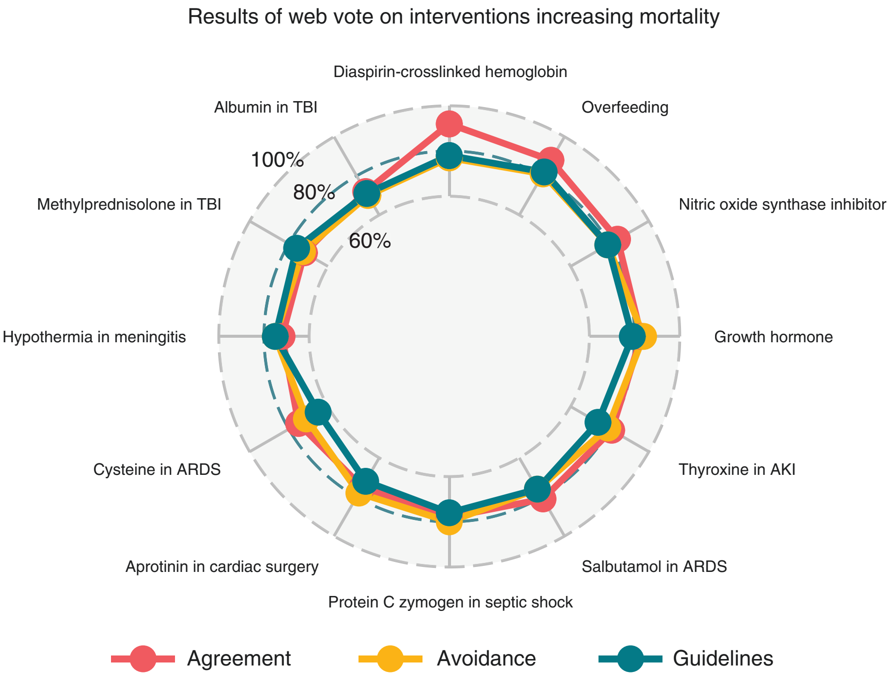

Fig. 1.1 Results of the web-vote on interventions increasing mortality. Abbreviations: AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; TBI = traumatic brain injury

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].

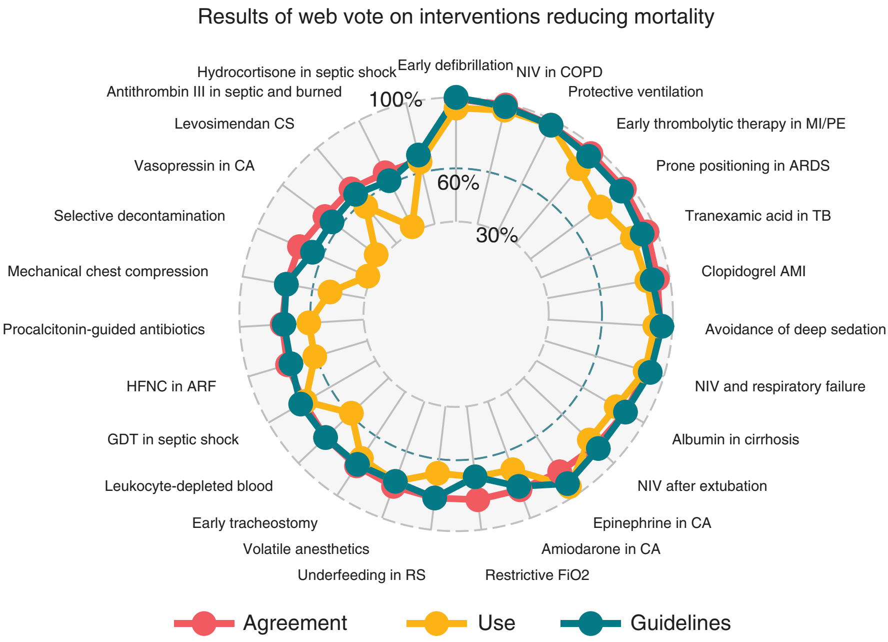

Fig. 1.2 Results of the web-vote on interventions reducing mortality. Abbreviations: *NIV* = non-invasive ventilation; *COPD* = chronic obstructive pulmonary disease; *MI* = myocardial infarction; *PE* = pulmonary embolism; *ARDS* = acute distress respiratory syndrome; *AMI* = acute myocardial infarction; *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.

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