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# Reducing Mortality in Acute Kidney Injury: The Democracy-Based Approach to Consensus

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## 3.1 Introduction

Evidence-based medicine (EBM) is the cornerstone of medical epistemology. This “movement,” which was born more than three decades ago, has promoted a critical revision of the clinical and scientific medical knowledge. However, the EBM approach is not free from limitations [1], and this was demonstrated in particular in the field of intensive care medicine [2].

Internal validity and generalizability of randomized clinical trials (RCTs) are limited in the intensive care setting [3, 4] due to the complexity of clinical conditions and therapeutic interventions to be investigated (and accordingly the frequent lack of “conventional” therapies to be used as control), the large amount and wide variability of concomitant treatments, and difficulties in definition of end points (with large use of composite end points) [5]. A “pendulum effect” has been proposed to define the sequence of opposite results in clinical trials [2].

Guidelines and consensus conferences have been introduced as a simple tool to summarize scientific evidences and to ensure optimal care to patients, while helping clinicians to achieve best practice in their daily clinical management. A controversy on a debated topic is normally settled by the opinion of experts in the field. This strategy, however, is not only far from the ideal approach of EBM epistemology but is being increasingly criticized for the risk of introducing expert opinion biases [6].

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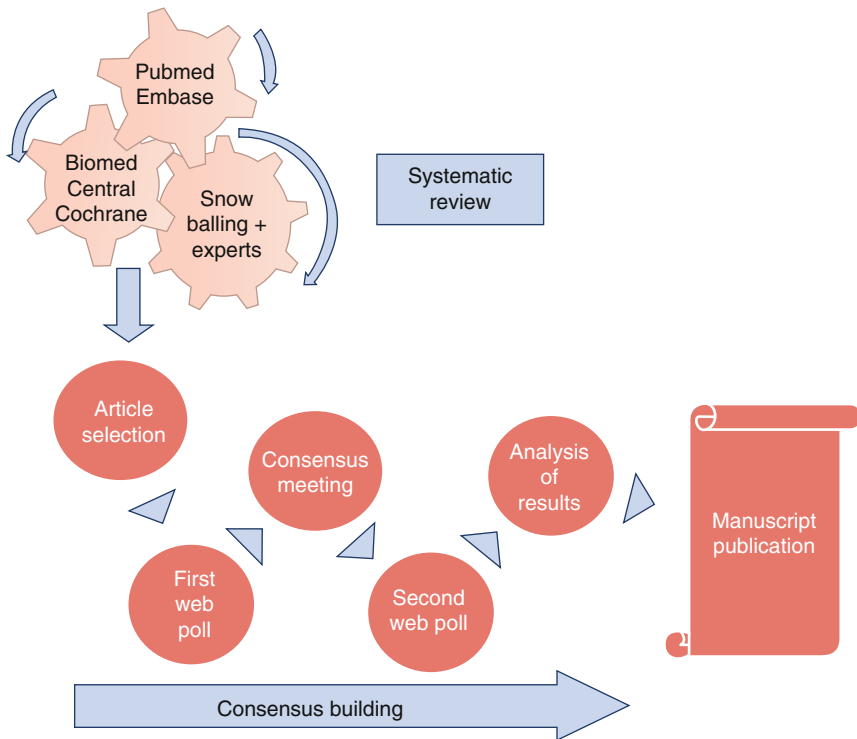
A new method to achieve consensus on medical evidence has been recently developed and already employed in various settings [8, 9] in the attempt to overcome some limits and, possibly, to improve the reliability of “classic” consensus conferences [7]. This approach has the advantage of sharing the best available evidence with a worldwide audience of clinicians, to allow them to discuss on it and propose further evidence, and to reach a final consensus through a democratic process.

This method has been also applied in the recent first international consensus conference conducted to identify the interventions (drugs, techniques, or strategies) with a statistical significant effect on mortality in critically ill patients with, or at risk for, acute kidney injury (AKI) [10]. The process of consensus building is outlined in Fig. 3.1 and is fully described in the following sections.

## 3.2 The Process of Consensus Building

### 3.2.1 Systematic Literature Research

A systematic literature research was performed to identify any intervention influencing mortality in critically patients with AKI. PubMed, Embase, BioMed Central,



**Fig. 3.1** The democracy-based consensus process

and the Cochrane Library were searched without time limits, using the search strategy reported in Box 3.1. Further topics were proposed by a group of experts and by snowballing, i.e., backward cross-checking of article references. Any paper on critically ill patients with or at risk for AKI, published in a peer-reviewed journal, was included if reporting a statistically significant effect on mortality ( $p < 0.05$ ) at any end point. A conservative strategy was employed to avoid exclusion of any relevant article in this phase.

**Box 3.1. PubMed Search Strategy**

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((acute AND (renal OR kidney) AND (failure OR injury)) OR (renal AND replacement AND therapy)) AND ((death* OR survival OR mortality)) AND (prevent* OR reducti* OR reduci*) AND (significat* OR significan*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw]))) OR (latin square[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw])) NOT (animal[mh] NOT human[mh]))
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A total of 691 papers were analyzed as full text, and 657 were excluded due to the lack of inclusion criteria. Therefore, 34 papers were selected for further inclusion in the consensus process.

### 3.2.2 Global Voting and International Consensus Meeting

The topics of these 34 studies were subjected to a first worldwide evaluation via web polling. In the period between January 1, 2012, and February 14, 2012, a website allowed to vote in favor or against the selected topics. Moreover, participants were allowed to suggest online other interventions or relevant literature.

On February 14, 2012, a core group of experienced clinicians of various disciplines (including intensivists, anesthesiologists, and nephrologists) met at the Vita-Salute San Raffaele University (Milan, Italy) to discuss the identified papers and topics, as well as the results of the first web voting. Topics were introduced to the meeting audience by a discussant and then evaluated on:

1. The completeness of the literature review, including most recent evidence
2. The type and quality of scientific evidence supporting the influence on mortality (RCTs, meta-analyses, case-matched studies, or other)
3. The study population of included articles, to assess if it was derived entirely or partially from patients with or at risk for AKI

After thorough discussion, a position statement was produced for each topic, summarizing the intervention, the reason for its inclusion, and the challenges in evaluation, if any. Each statement also reported a recommendation, which was rated according to the grade classification on strength and quality of evidence (Table 3.1) [11]. According to the grade classification, the strength of the recommendation is defined by one of two numbers: (1) represents a strong recommendation, while (2) represents a suggestion or weak recommendation. A letter among A, B, and C indicates the quality of evidence for the recommendation, according to the type of studies from which evidence is derived:

- Level A: RCTs without important limitations or overwhelming evidences from observational studies (high-quality evidence)
- Level B: RCTs with important limitations or exceptionally strong evidence from observational studies (moderate-quality evidence)
- Level C: observational studies or case series (low-quality evidence)

Five topics were excluded during the consensus meeting, due to the lack of information or evidence about critically ill patients with or at risk for AKI.

**Table 3.1** Grade of recommendation for the 18 identified interventions.

Grade of recommendation	Intervention
1A	None
1B	Albumin in cirrhotic patients Hydroxyethyl starch ( <i>avoid</i> )
1C	Perioperative hemodynamic optimization Terlipressin in hepatorenal syndrome type 1
2A	None
2B	Fenoldopam <sup>a</sup> Periangiography hemofiltration
2C	Citrate in continuous RRT CVVH in severely burned patients Continuous RRT Early RRT Furosemide by continuous infusion Human Immunoglobulin Increased intensity of RRT Loop diuretics ( <i>avoid</i> ) <i>N</i> -acetylcysteine Plasma exchange in multiple myeloma-associated AKI Positive fluid balance ( <i>avoid</i> ) Vasopressin in septic shock

RRT renal replacement therapy

<sup>a</sup>Probably no longer to be recommended (see Chap. 13)

Fifteen interventions which were shown to increase survival, and three that might increase mortality, were finally identified during the consensus meeting. These 18 interventions, supported overall by 25 papers [12–36], are reported in Table 3.2.

### 3.2.3 Global Appraisal of Consensus Statements

Between February 15, 2012 and April 1, 2012, the second web poll was conducted. The consensus website hosted the poll on the topics and the recommendations thereon, which were issued during the Milan consensus meeting. A large cohort of participants, including the first web voters and the participants to the consensus meeting, were invited to vote if they agreed or not with interventions and recommendations. Moreover, voters could express on a Likert scale (“definitely,” “probably yes,” “don’t know,” “probably not,” “definitely not”) if they would follow these recommendations in their clinical practice. Multiple voting was prevented through registration of e-mail address, and all participants were asked to declare any relevant conflict of interest.

### 3.2.4 Consensus Final Results

A total of 311 participants from 62 different countries took part in the Democratic Consensus Conference. After the final web poll, data were analyzed and results were made available to the authors.

**Table 3.2** The 18 interventions affecting mortality identified by the democracy-based consensus process

Increasing survival	Increasing mortality
Perioperative hemodynamic optimization [12]	Positive fluid balance [13, 14]
Albumin in cirrhotic patients [15, 16]	Hydroxyethyl starch [16, 17]
Terlipressin in hepatorenal syndrome type 1 [18]	Loop diuretics [19]
Human immunoglobulin [20]	
Periangiography hemofiltration [21]	
Fenoldopam [22]	
Plasma exchange in multiple myeloma-associated AKI [23]	
Increased intensity of RRT [24–26]	
CVVH in severely burned patients [27]	
Vasopressin in septic shock [28, 29]	
Furosemide by continuous infusion [30]	
Citrate in continuous RRT [31]	
<i>N</i> -acetylcysteine [32, 33]	
Continuous RRT [34]	
Early RRT [35, 36]	

The agreement between global polling and consensus meeting recommendations was high in most topics. However, there were several topics (plasma exchange in multiple myeloma, vasopressin in septic shock, furosemide by continuous infusion, citrate in continuous renal replacement therapy, *N*-acetyl-cysteine, and loop diuretics) for which the agreement was significantly lower among web voters than among consensus meeting participants.

The 18 selected topics with a significant impact on survival in critically ill patients with AKI, the consensus statements, and the results of the web survey were included in a paper recently published as a special article in the *Journal of Cardiothoracic and Vascular Anesthesia* [10].

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## Conclusion

This was the first International Consensus Conference on mortality reduction in critically ill patients with or at risk for AKI, and it was conducted through the new idea of democracy-based medicine. There are several advantages with this approach: (a) the consensus conference is grounded on a full systematic review of the available literature, conducted *ex novo* and fully updated; (b) it includes the opinion of experts, but it overcomes the limitations of a “classic” consensus conference conducted by experts only, as it includes a double global voting that allows for a democratic assessment of recommendations; and (c) it allows to highlight the gap between the “theory” from literature evidence and the daily clinical practice reported by respondents.

The democracy-based consensus process identified a total of 18 interventions (drugs/techniques/strategies) with a significant impact on survival in critically ill patients with or at risk for AKI: 15 interventions have been shown to increase survival and 3 might increase mortality. A graded recommendation was provided for all of them.

The following 18 chapters of this book (Chaps. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21) will unfold the main evidences, general principles, pharmacological/pathophysiological aspects, and therapeutic use of each of the identified interventions, providing the reader with a valuable resource to guide his/her clinical practice and opening the door for future lines of research.

Finally, an updated review of papers dealing with interventions which may significantly affect mortality in AKI patients, identified after the consensus process according to the same search strategy, is reported in Chap. 22.

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