Reducing Mortality in Acute Kidney Injury Patients: Systematic Review and International Web-Based Survey

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Objective: **To identify all interventions that increase or reduce mortality in patients with acute kidney injury (AKI) and to establish the agreement between stated beliefs and actual practice in this setting.**

Design and Setting: **Systematic literature review and international web-based survey.**

Participants: **More than 300 physicians from 62 countries.**

Interventions: **Several databases, including MEDLINE/PubMed, were searched with no time limits (updated February 14, 2012) to identify all the drugs/techniques/strategies that fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealing with critically ill adult patients with or at risk for acute kidney injury, and (c) reporting a statistically significant reduction or increase in mortality.**

Measurements and Main Results: **Of the 18 identified interventions, 15 reduced mortality and 3 increased mortality. Perioperative hemodynamic optimization, albumin in cirrhotic patients, terlipressin for hepatorenal syndrome type 1, human immunoglobulin, peri-angiography hemofiltration, fenoldopam, plasma exchange in multiple-myeloma-associated AKI, increased intensity of renal replacement therapy (RRT), CVVH in severely burned patients, vasopressin in septic shock, furosemide by continuous infusion, citrate in continuous RRT, N-acetylcysteine, continuous and early RRT might reduce mortality in critically ill patients with or at risk for AKI; positive fluid balance, hydroxyethyl starch and loop diuretics might increase mortality in critically ill patients with or at risk for AKI. Web-based opinion differed from consensus opinion for 30% of interventions and self-reported practice for 3 interventions.**

Conclusion: **The authors identified all interventions with at least 1 study suggesting a significant effect on mortality in patients with or at risk of AKI and found that there is discordance between participant stated beliefs and actual practice regarding these topics.**

KEY WORDS: acute kidney failure, mortality, critical care, anesthesia, consensus, renal failure, acute renal injury, survival, web vote, consensus conference

ACUTE KIDNEY INJURY (AKI) is a major healthcare problem with impact on morbidity, mortality, and health resource utilization.[1–3] Despite considerable progress in intensive care medicine, up to 67% of critically ill patients may develop some degree of AKI, as defined by the RIFLE (risk, injury, failure, loss, end-stage renal disease) classification, and approximately 5% to 6% of ICU patients require renal replacement therapy.[1] Even small increases in creatinine levels or biomarkers[4] correlate with increased mortality, and when patients require renal replacement therapy, the risk of death rises dramatically.[2,5] It is conceivable that the speed and appropriateness of therapy might affect survival of critically ill patients. However, to date, there is no specific treatment that increases survival in patients with or at high risk of AKI.

The authors systematically identified interventions reported to increase or reduce mortality in critically ill patients with or at risk for AKI. Their aim was to establish the agreement between stated beliefs and actual practice in this setting and guide further research into such interventions. In order to achieve this goal, an innovative strategy was applied.[6,7] After first identifying of the key topics based on systematic database search and contact with experts, a web-based voting system was developed. After that, each topic was debated in a formal meeting and consensus achieved. The consensus statements were placed on the web for a second round of voting by the web-based physician community. The authors asked whether the voting physicians agreed with the statements or not, and if, independently on the statements, they would use a given treatment in their clinical setting. This method provided a new way to integrate consensus with self-reported practice.

MATERIALS AND METHODS

Pertinent papers were searched independently in PubMed, BioMedCentral, EMBASE, and Cochrane Library (updated February 14, 2012). A sensitive PubMed search with no time limits was used to systematically identify all published papers concerning interventions influencing survival in critically ill patients with or at risk for AKI. The full search strategy is available in the supplemental appendix and yielded 691 results.

Further topics were identified by a core group of experts who worked from May 2008 to February 2012 and backward snowballing, ie, cross-checking of references, was implemented to discover further interventions. Recent reviews on AKI also were studied to identify further papers, and experts in the field were contacted.

Papers were evaluated by the consensus meeting and included only if they fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealt with critically ill adult patients with or at risk for AKI, and (c) reported a statistically significant reduction or increase in mortality. During the first phase, while screening the literature, the authors preferred a comprehensive approach so that no pertinent papers would be excluded.

From January 1, 2012 to February 14, 2012, a web site allowed participants to vote in support of or against the selected interventions and to submit further topics.

A meeting was held on February 14, 2012 at the Vita-Salute University of Milan, Italy among most of the authors of the present manuscript (anesthesiologists, intensive care specialists, and nephrologists). All the suggested topics were discussed, and for each topic, it was decided if: (a) the most recent evidence had been collected, (b) the impact on mortality was supported by either randomized controlled trials or meta-analyses of randomized controlled trials, case-matched studies, or other studies, and (c) the evidence had been derived entirely or partially from patients with or at risk of AKI.

Topics then were presented by a selected reporter. After discussion, a position statement was approved describing the intervention, the reasons for the inclusion, the challenges in evaluating it, and the grading according to the GRADE classification (Table 1).[8] In this classification, each statement is defined by a number (1 or 2) and by a letter (A, B, or C). The number represents the strength of the recommendation based on comparison of known risks with expected benefits. A strong recommendation is represented by a value of 1 while a value of 2 indicates a weak recommendation or suggestion. The following letter describes the methodologic quality of the supporting evidence. A, B, and C correspond to high, moderate, and low/very low quality, respectively.[8,9] After discussion, a position statement was approved describing the intervention, the reasons for the inclusion, and the challenges in evaluating it.

Major exclusions were represented by therapies that could determine a specific mortality reduction or increase but without providing sufficient information to be able to derive data or conclusions on mortality in AKI patients.

Final statements were presented online (February 15, 2012 to April 1, 2012). Via an interactive web questionnaire, both in-person and web participants were asked again to agree or disagree with the topics and statements from the meeting (Do you agree with the statements? Yes; No; Don't know) and if they personally would consider the therapy or strategy in their daily practice (Do you recommend this therapy to increase survival? Definitely; Probably; Not sure; Probably not; Definitely not) (Fig 1).

The authors included the option "don't know" in the questionnaire to allow respondents to state that they had no opinion or had never thought about a particular issue. Since methodologic research suggests that there is no difference in response rate depending on the inclusion or exclusion of the "don't know" option (if less than 40%), the authors reported only the "yes" and "no" frequencies.[10]

Throughout the process, all participants (either those voting via web or those participating in person) were asked to disclose all potential conflicts of interest. The interactive web questionnaire asked voters to declare any potential conflict of interest for each intervention without specifying the details of the nature of this conflict. All in-person participants had to complete the same questionnaire. There was no sponsor or industry support for this consensus conference.

The consensus process through the web involved the international cohort of participants who voted on the topics before and after the Milan meeting. Double votes were prevented using the email field as the unique identifier.

Statistical Analysis

Statistical analysis was done using Stata 11. The authors compared the answers given by meeting participants and web voters. They used chi square or Fisher's exact test where appropriate. They defined a p value < 0.05 as statistically significant. The authors used Cohen's kappa to investigate the agreement between the 2 questions, ie, if evidence-based opinion agrees with self-reported clinical practice. They considered agreement to be satisfactory when $k > 0.4$ and identified disagreement when $k \leq 0.4$.

RESULTS

Overall, 311 participants from 62 countries (Supplemental Material 2) participated in the consensus process. The consensus process identified 18 topics[11–35] with at least 1 paper published in a peer-reviewed journal suggesting a statistically significant effect on mortality.

Perioperative hemodynamic optimization,[11] albumin in cirrhotic patients,[12,13] terlipressin for hepatorenal syndrome type