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Acute Renal Failure: Diagnostic and Therapeutic Considerations

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Abstract

Introduction: Choice of renal replacement therapy modality may affect renal recovery after acute kidney injury. When acute renal failure is so severe as to require renal replacement therapy (RRT) mortality rates are as high as 63%. This review aimed to highlight the updated diagnostic and therapeutic considerations that should be considered during management of acute renal failure.

Methods: The authors performed a systematic search of the MEDLINE and EMBASE bibliographic databases to identify published studies evaluating acute renal failure. search strategies combined the medical subject heading terms "kidney failure, acute" combined with prognosis (specificity) limited to "humans," "article" and "journal article" for MEDLINE. The authors restricted their search to clinical studies performed in adult populations and published in the English language. Full-text review was independently performed by two reviewers (as above) for the following specific eligibility criteria including observational cohort and/or randomized/quasi-randomized clinical trial (RCT) design. All data were extracted independently with standardized forms with subsequent discussion of any discrepancies.

Results: A total of 494 citations were identified. After primary and secondary screen, 15 studies fulfilled all criteria for final analysis (13 articles). The authors found two randomized trials , four prospective cohort studies and nine retrospective cohort studies. Of these, 13 were published as articles in peer-reviewed journals and 2 studies were published as abstracts only. Only five had a prospectively assembled control group, four had comparable modes of RRT between the early and late initiation groups , and only three studies accounted for withdrawals/loss to follow-up.

Conclusions: We can conclude that diuretics and dopamine are clearly not helpful and may even be harmful, while volume expansion with saline is unproven but potentially beneficial. The facts are even less clear regarding mannitol in vascular surgery.

In other types of surgery, such as coronary artery bypass or biliary surgery, small studies have also been unable to demonstrate a benefit associated with mannitol. Given these considerations, and in the absence of clinical data, diuretics cannot be recommended to prevent acute renal failure.

Keywords: Renal failure, Kidney injury, Recover, Diuretics, Surgery.

Introduction

A CUTE renal failure (ARF) occurs in 20% to 25% of patients admitted to the intensive care unit (ICU) and is associated with adverse patient outcomes and high health care costs. Of patients who survive an episode of ARF in the ICU, 5% to 30% will remain on long-term dialysis therapy without renal recovery. ARF in the ICU can be managed with intermittent hemodialysis (IHD) therapy, in which intensive dialysis is performed for a few hours at variable intervals, or continuous renal replacement therapy (CRRT), during which treatment is performed continuously at lower blood flow rates [1]. Acute kidney injury (AKI) is a frequent complication in critically ill patients in intensive care units (ICU), increasing significantly both hospital mortality and morbidity. If such interventions are not effective, these patients may end up being treated with renal replacement therapy (RRT).

Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT . The growing numbers of kidney function and damage biomarkers, often showing contradictory findings, have made clinical inferences about their utility challenging . Since damage in AKI at first manifests in renal tubular cells, urinary biomarkers are considered most sensitive for AKI diagnosis. Cystatin C is considered an established marker for glomerular filtration rate (GFR) in chronic kidney disease but has also been demonstrated to detect AKI earlier than creatinine does in critically ill patients [2]. Acute kidney injury (AKI) is a frequent complication in critically ill patients in intensive care units (ICU), increasing significantly both hospital mortality and morbidity . If such interventions are not effective, these patients may end up being treated with renal replacement therapy (RRT). Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT. The growing numbers of kidney function and damage biomarkers, often showing contradictory findings, have made clinical inferences about their utility challenging [3.4]. Choice of renal replacement therapy (RRT) modality may affect renal recovery after acute kidney injury. When AKI is so severe as to require renal replacement therapy (RRT) mortality rates are as high as 63%. AKI in cardiac surgery commonly occurs within a well-defined perioperative period that includes surgery and the use of cardiopulmonary bypass (CPB). Many investigators have tested the hypothesis that concomitant administration of a pharmacological non-protective agent that improves renal perfusion, reduces renal oxygen consumption, or attenuates inflammatory injury should prevent or reduce the severity of AKI and improve clinical outcomes [5,6].

The high incidence of AKI in the aging can be attributed mainly to the 2 following reasons: comorbidities accumulate with age; several age-related comorbidities will induce AKI directly (obstructive prostate conditions and multiple myeloma), and other disorders will necessitate procedures, drugs, and surgery that function as renal stressors and nephrotoxins; and changes in kidney function and anatomy; in the absence of a specific disease, the kidney undergoes age dependent structural and functional alterations leading to a significant decrease in renal mass, functioning nephron numbers, and baseline kidney function. However, in the setting of pathophysiological challenges, the older kidney lacks sufficient functional reserve and is more likely to develop clinically relevant damage. Although numerous studies have addressed age-dependent changes in mortality rates, whether age is a significant predictor for recovery of kidney function after AKI has not been investigated systematically. In this study, the

authors focus on the recovery of adequate kidney function to remain dialysis independent, which is the second most important outcome parameter of AKI after survival. Although AKI can be fully reversible, the renal repair process also can be incomplete and result in chronically decreased kidney function. This can range from subclinical decreases in glomerular filtration rate to dialysis-dependent end-stage renal disease. Incidence rates of end-stage renal disease after AKI differ widely among studies, ranging from less than 1% to greater than 40%. 17- It currently is not clear whether age per se has a role in this marked variability because previous efforts to predict outcome in aged populations were controversial and limited by small sample sizes [7]. Since damage in AKI at first manifests in renal tubular cells, urinary biomarkers are considered most sensitive for AKI diagnosis. Cystatin C is considered an established marker for glomerular filtration rate (GFR) in chronic kidney disease but has also been demonstrated to detect AKI earlier than creatinine does in critically ill patients. Severe acute kidney injury occurs in approximately 6% of patients admitted to intensive care units and in up to half of the patients with septic shock. For patients who require renal replacement therapy, the treatment dose or intensity (referring to small molecule clearance) may affect outcomes [8].

Data have emerged to suggest that earlier RRT initiation may attenuate kidney-specific and non-kidney organ injury from acidemia, uremia, fluid overload, and systemic inflammation . Unfortunately, in the absence of refractory acidemia, toxic hyperkaliemia and intravascular fluid overload contributing to respiratory failure, there is limited evidence to guide clinicians on when to initiate RRT in critically ill patients with AKI. The question of timing of initiation of RRT (that is, "early" versus "late") has seldom been the focus of high-quality or rigorous evaluation . As a consequence, initiatives aimed at identifying the "optimal timing of initiation of RRT" in AKI have been given the highest priority for investigation by the Acute kidney injury Network [9,10]. Hence, this review aimed to highlight the updated diagnostic and therapeutic considerations that should be considered during management of acute renal failure.

Methods

The authors performed a systematic search of the MEDLINE and EMBASE bibliographic databases to identify published studies evaluating acute renal failure. search strategies combined the medical subject heading terms "kidney failure, acute" combined with prognosis (specificity) limited to "humans," "article" ("journal article" for MEDLINE), and "adult or aged" ("adult" or "middle aged" or "aged" for MEDLINE). The authors identified potentially relevant studies by using a manual search of references from all eligible studies, review articles Science Citation Index Expanded on the web of Science, and searching the top 50 citations for each report through the "related articles" feature of PubMed.

The Cochrane Central Registry of Controlled Trials web of Science, and Scopus to identify randomized trials and cohort studies that assessed the timing of initiation of RRT in critically ill patients with AKI. The authors restricted their search to clinical studies performed in adult populations and published in the English language. Full-text review was independently performed by two reviewers (as above) for the following specific eligibility criteria including observational cohort and/or randomized/quasi-randomized clinical trial (RCT) design. Other inclusion criteria such as adult critically ill population, diagnosis of AKI, description of factors related to timing of initiation of RRT, description of mortality and/or clinically relevant secondary outcomes. Disagreements between reviewers were resolved by a third reviewer or by discussion and consensus. All data were extracted independently with standardized forms with subsequent discussion of any discrepancies. Data were collected on study characteristics and quality, demographics and baseline characteristics. The data, therefore, are synthesized qualitatively.

Results and discussion

A total of 494 citations were identified. After primary and secondary screen, 15 studies fulfilled all criteria for final analysis (13 articles). The authors found two randomized trials , four prospective cohort studies and nine retrospective cohort studies. Of these, 13 were published as articles in peer-reviewed journals and 2

studies were published as abstracts only. Only five had a prospectively assembled control group, four had comparable modes of RRT between the early and late initiation groups , and only three studies accounted for withdrawals/loss to follow-up . Continuous renal replacement therapy (CRRT) was used as the principle modality for RRT in eight studies , while a combination of IHD and CRRT were used in the remaining studies. Six studies defined timing of initiation of RRT based on cut-offs in serum urea , two studies based on cut-offs in serum creatinine , one study based on the Risk-injury failure Loss End-stage (RIFLE) criteria , and four based on urine output.

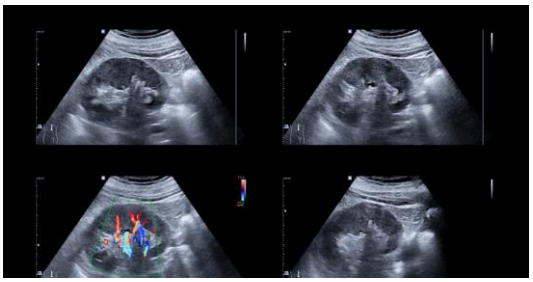
After inspecting the included studies the authors defined the following subgroups: mixed trauma, traumatic brain injury (TBI), and military casualties. Some uncertainty regarding diagnosis of AKI was prevalent: 11 of 24 studies used modified AKI criteria (Table 1) and pre-injury creatinine levels often were unknown; thus exclusion of patients with CKD pre-injury was not ensured. Time from trauma to AKI diagnosis was 3 days (range 1-6) . Risk factors for AKI extracted from the various studies were patient age [11]. Trials for which an RR for mortality or renal recovery could not be determined, that involved multiple experimental interventions, or that included children were excluded. The remaining studies either did not compare IHD and CRRT directly or did not provide data on mortality or renal recovery. Finally, excluding the RCT in which substantial baseline differences were observed between treatment groups 21 did not change the pooled RR (mortality) [12]. In one study, on the same day that the criterion for meeting the RIFLE-R definition of AKI (rise in serum creatinine X50%) was observed, the positive predictive value of elevations in serum cystatin C for the need for renal replacement therapy (RRT) was 78% and the AUC was (0.76).

Mild AKI defined as increase in creatinine level greater than 25% or decrease in creatinine clearance greater than 10%; moderate AKI, increase in creatinine level greater than 50%, greater than 100%, greater than 1.0 mg/dL, or creatinine level greater than 1.7 mg/dL; severe AKI, need for RRT; transient AKI Welten et al 34 defined it as worsening of creatinine clearance greater than 10% at day 1 or day 2, but recovery within 10% of baseline value by day 3. It is clear that serum creatinine value of 1.4 mg/dL or greater at the time of hospital discharge; Loef et al 36 defined it as a 25% or greater increase in postoperative serum creatinine value that returned to preoperative level at hospital discharge; persistent AKI. Another cut-off point is a greater than 10% decrease in creatinine clearance without recovery to within 10% of baseline value by day 3. Another study defined it as AKI serum creatinine value greater than 1.4 mg/dL at hospital discharge. Some defined it as a 25% or greater increase in postoperative creatinine level that did not return to preoperative level at hospital discharge.

The rate of CKD after an episode of AKI was 7.8 events/100 patient-years, and the rate of ESRD was 4.9 events/100 patient-years. No study compared the rate of CKD or ESRD after AKI with patients within the same cohort without AKI; thus, the authors could not determine the RR for CKD or ESRD after an episode of AKI. No study examined the incidence or rate of CKD after AKI that resolved compared with AKI without recovery [13]. Accounting for post-AKI recovery from AKI (eg, return of creatinine to within 20% pre-AKI creatinine 2) may assist future risk assessment. Definitions of renal recovery also varied: with definitions of its timing ranging from 3 days 26 to 3 months; and its extent from within 50% of baseline 20 to within 10% of baseline, or below a pre-AKI value. AKI was associated with increased mortality in all but one study regardless of pre-AKI baseline or recovery of renal function. Five studies did not report non-AKI comparators or risk ratios. Of the three studies stratified by pre-AKI baseline function, in two the overall prognosis was worse in patients with AKI with prior CKD with doubling of HRs with respect to a non-AKI non-CKD comparator. However, in a third study, where comparators were also stratified by eGFR, the independent mortality risk from AKI diminished with advancing CKD. Six studies compared mortality stratifying either by post-AKI recovery (four studies) or by AKI duration (two studies). All but one were postoperative studies with different thresholds for defining recovery [14]. Despite considerable research efforts, it is still unclear whether and when RRT should be commenced to improve the outcomes of these critically ill patients with AKI. Early initiation of RRT may reduce

mortality but it comes with a higher risk of treatment-related complications, such as catheter-related bloodstream infections. Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT. Since damage in AKI at first manifests in renal tubular cells, urinary biomarkers are considered the most sensitive for AKI diagnosis. Generally, biomarker research evaluates the necessity of a certain treatment (e.g. However, the studies in this review aimed to predict a clinical diagnosis (e.g. Despite considerable research efforts, it is still unclear whether and when RRT should be commenced to improve the outcome of these critically ill patients with AKI. Early initiation of RRT may reduce mortality but it comes with a higher risk of treatment-related complications, such as catheter-related bloodstream infections. Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT. Since damage in AKI at first manifests in renal tubular cells, urinary biomarkers are considered the most sensitive for AKI diagnosis. Generally, biomarker research evaluates the necessity of a certain treatment (e.g. However, the studies in this review aimed to predict a clinical diagnosis [15].

This failure is caused in part by the lack of real-time sensitive and specific renal biomarkers to allow the early diagnosis of impending AKI. In current clinical practice, serum creatinine level and urine output are the most frequently used indicators of renal dysfunction despite their known limitations. They have limited sensitivity and specificity and creatinine level has a slow rate of change, thus limiting their usefulness in the early detection of AKI. Consensus groups, such as the Acute Dialysis Quality Initiative (ADQI), the AKI Network (AKIN), and the American Society of Nephrology, have set the development and validation of novel biomarkers of AKI as a priority. Genomic, transcriptomic, and proteomic techniques have identified neutrophil gelatinase associated within lipocalin (NGAL) as an early marker of AKI. In experimental and clinical studies NGAL has been investigated extensively and would appear to be one of the most frequently investigated and most promising early biomarkers of AKI. NGAL has been investigated across a range of different clinical settings of AKI, such as after cardiac surgery, in critically ill patients, 18,19 in patients receiving intravenous contrast media infusion for coronary angiography, 20,21 and in patients admitted to the emergency department [16,17].



The growing numbers of kidney function and damage biomarkers, often showing contradictory findings, have made clinical inferences about their utility challenging . Importantly, few studies have specifically evaluated the value of biomarkers to inform about the likelihood a patient with AKI will worsen or persist and progress to receive RRT. Preliminary results of a meta-analysis have been previously partially presented as an abstract . Some studies reported combinations of biomarkers or combinations of a biomarker with clinical parameters. Since damage in AKI at first manifests in renal tubular cells, urinary biomarkers are considered most sensitive for AKI diagnosis. Therefore a promising approach seems to be the combination between biomarkers and clinical parameters. The growing numbers of kidney function and damage biomarkers, often showing contradictory findings, have made clinical inferences about their utility challenging.

Importantly, few studies have specifically evaluated the value of biomarkers to inform about the likelihood a patient with AKI will worsen or persist and progress to receive RRT [18, 19]. Of patients who survive an episode of ARF in the ICU, 5% to 30% will remain on long-term dialysis therapy without renal recovery. ARF in the ICU can be managed with intermit-tent hemodialysis (IHD) therapy, in which intensive dialysis is performed for a few hours at variable intervals, or continuous renal replacement therapy (CRRT), during which treatment is performed

continuously at lower blood flow rates [20, 21].Despite considerable research efforts, it is still unclear whether and when RRT should be commenced to improve outcome of these critically ill patients with AKI. Early initiation of RRT may reduce mortality but it comes with a higher risk of treatment-related complications, such as catheter-related bloodstream infections . Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT . Generally, biomarker research evaluating the necessity of a certain treatment (e.g. RRT) on the basis of biomarker profiles, without examining the impact this treatment has on the outcome. Despite considerable research efforts, it is still unclear whether and when RRT should be commenced to improve outcome of these critically ill patients with AKI. Early initiation of RRT may reduce mortality but it comes with a higher risk of treatment-related complications, such as catheter-related bloodstream infections . Likewise, clinicians have few tools to know with certainty whether kidney recovery is imminent or likely that can be integrated to guide decision-making for use of RRT . Generally, biomarker research evaluating the necessity of a certain treatment (e.g. RRT) on the basis of biomarker profiles, without examining the impact this treatment has on the outcome [22].

For patients who require renal replacement therapy (RRT), the treatment dose or intensity (referring to small molecule clearance) may affect outcomes. For continuous RRT (CRRT), dose is approximated by the effluent flow rate, whereas for intermittent RRT (most commonly intermittent hemodialysis and sustained low-efficiency dialysis (SLED), treatment dose is typically quantified by the number of sessions (or hours) per week that RRT is applied [23]. The authors hypothesized that high-dose RRT would be more beneficial in subgroups of patients with sepsis because of the extreme inflammatory response, treated exclusively with CRRT (because of improved hemodynamic stability), and enrolled in trials at higher risk for bias, in which treatment benefits may be amplified [24].

Conclusions

We can conclude that diuretics and dopamine are clearly not helpful and may even be harmful, while volume expansion with saline is unproven but potentially beneficial. The facts are even less clear regarding mannitol in vascular surgery. No recent studies have been carried out to address this issue and it is unlikely that any will. In other types of surgery, such as coronary artery bypass or biliary surgery, small studies have also been unable to demonstrate a benefit associated with mannitol. Given these considerations, and in the absence of clinical data, diuretics cannot be recommended to prevent acute renal failure.

Conflict of interests

The authors declared no conflict of interests.

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