Oliguria, volume overload, and loop diuretics

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Acute kidney injury (AKI) is commonly and increasingly encountered in patients with critical illness. In the past, epidemiologic studies have consistently found that oliguria further increases the risk of death from AKI. Compared with patients outside the intensive care unit (ICU), critically ill patients are more likely to have volume overload as a result of impaired solute and water excretion. Recently, broad changes have occurred in ICU practice, such as early goal-directed therapy in sepsis, which may further compound volume overload in the ICU patient with oliguric AKI. Evidence has also emerged to suggest that a positive fluid accumulation in ICU patients can unfavorably affect outcome. Thus, the ICU patient with oliguric AKI presents a dilemma with limited therapeutic options. These would include optimization of systemic hemodynamics, added fluid therapy, administration of loop diuretics, or finally, the initiation of renal replacement therapy. Interestingly, recent survey data and observational studies indicate that a majority of intensivists use loop diuretics, specifically furosemide, at some point during the course of illness in patients with AKI. Paradoxically, loop diuretics have been found in several clinical studies of patients with AKI to be potentially detrimental or, at the least, lack effectiveness for improving clinical outcomes. This contradiction between clinical practice and available evidence would suggest there is equipoise and need for higher-quality evidence to better characterize the role of loop diuretics in ICU patients with AKI. (Crit Care Med 2008; 36[Suppl.]:S172–S178)

KEY WORDS: acute kidney injury; acute renal failure; loop diuretic; furosemide; oliguria; fluid therapy; resuscitation; critically ill; randomized trial; equipoise

Acute kidney injury (AKI) severe enough to warrant renal replacement therapy (RRT) can be found in an estimated 6% of critically ill patients, and recent data indicate the incidence is rising (1, 2). In general, the development of AKI in relation to critical illness remains associated with an unacceptably high morbidity and mortality (1, 3–10). Similarly, management of intensive care unit (ICU) patients with AKI can escalate the complexity of care and health resource utilization (11, 12).

Regrettably, there are few therapeutic interventions proven to affect the clinical course and outcome for ICU patients once AKI is established (13–15). Rather, management of the ICU patient with AKI is largely supportive and predicated on removal of the stimulus contributing to AKI, averting complications, and allowing recovery to occur.

However, certainly a more problematic dilemma arises in the ICU patient with AKI who develops oliguria. Many epidemiologic studies have found the presence of oliguria, in the context of AKI, to be independently associated with mortality (4, 6, 16). The association of oliguria and mortality in these studies was likely in part explained by oliguria representing a surrogate for a more significant injury or greater severity of AKI. However, not all severe forms of AKI are characterized by oliguria (17). Nonetheless, nonoliguric AKI in ICU patients is generally portrayed as having a better prognosis compared with oliguric AKI, and thus, many clinicians opt to preserve or increase urine flow by using loop diuretics (18–20).

All forms of AKI, even mild, are associated with the potential for several complications, the most important including: volume overload due in part to impaired sodium and water excretion, disrupted acid–base homeostasis due to impaired strong-ion regulation, electrolyte disorders (hyponatremia, hyperkalemia), retention of uremic solutes, and impaired elimination of a large variety of other toxins (myoglobin, drug metabolites) (21, 22). These complications, in particular volume overload, are naturally further aggravated by the development of oliguria.

As a consequence, critically ill patients with oliguric AKI are at an important crossroads. In the absence of a mechanical obstruction, the therapeutic options available to restore urine flow are limited and generally constrained to additional fluid therapy, restoration of systemic hemodynamics with vasoactive drugs, if necessary, or the administration of diuretics such as furosemide. Finally, short of these measures, the initiation of RRT would seem indicated. In this review, we discuss the dynamics of oliguria, volume overload, and diuretics (more specifically, loop diuretics) in the context of critically ill patients with AKI.

Oliguria and Volume Overload

In general, there is broad consensus on the importance of fluid therapy in acute resuscitation. Fluids should ideally be given early and targeted to physiologic end points, such as mean arterial pressure, cardiac output, central venous pressure, and urine output (23–26). This is a clear priority in the acute resuscitative phase of critical illness (27). However, in the ensuing hours to days after correction of circulatory shock, those ICU patients with AKI may have persistence of oliguria or develop oliguria.

Fluid Therapy in Oliguria. In these circumstances, one therapeutic option for oliguria is a fluid challenge. This option is appropriate in the AKI patient for

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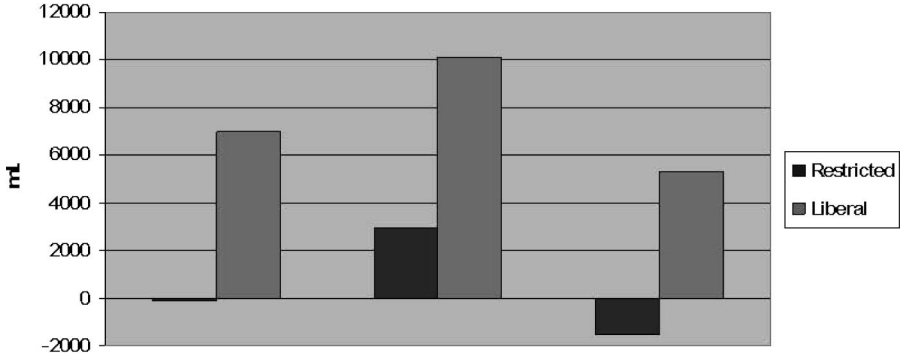

Figure 1. Summary of the 7-day cumulative fluid balance stratified by liberal and restrictive fluid regimens in intensive care unit patients with acute lung injury from the Acute Respiratory Distress Syndrome Clinical Trials Network trial. Data further stratified by the presence or absence of shock at trial enrollment. Adapted from Wiedemann et al (30).

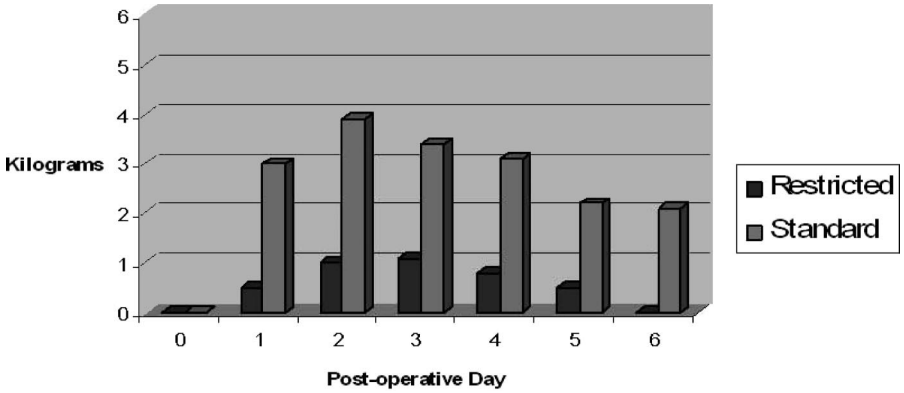

Figure 2. Summary of cumulative weight gain in the postoperative period for patients undergoing elective colorectal surgery stratified by standard and restrictive peri-operative fluid therapy strategies from the trial by Brandstrup et al (36). Adapted from Brandstrup et al (36).

correction of volume depletion. However, oliguria is not necessarily an indication for volume expansion. The distinction has clinical relevance. Although added fluid therapy may indeed temporarily increase urine flow in the resuscitated ICU patient with AKI, there is no evidence that this practice improves renal recovery or patient outcome. Moreover, there has recently been an increased recognition that "fluid responsiveness," such as a temporary increase in urine output afforded by a fluid bolus, does not necessarily constitute an indication for fluid therapy (28–30). Rather, there is evidence to suggest that the liberal use of fluid therapy, leading to fluid accumulation, in the management of ICU patients can be associated with harm (28–31). This was shown by Van Biesen et al. (29) in a small cohort of septic patients with AKI. In these patients, despite apparent optimal hemodynamics, restored intravascular volume, and an already high use of diuretics, additional fluid therapy failed to affect kidney function. Moreover, the added fluid simply contributed to a grossly positive fluid balance and significant reductions in lung function and oxygenation. A positive cumulative fluid balance has been shown in several studies to independently predict hospital mortality (28, 31, 32).

Recently, the Acute Respiratory Distress Syndrome Clinical Trials Network reported a randomized trial comparing restrictive and liberal strategies for fluid management after complete resuscitation in 1,000 ICU patients with acute lung injury, of whom most were septic (30) (Fig. 1). Globally, no difference in the primary outcome of death at 60 days was found between the strategies (25.5% for restrictive vs. 28.4% for liberal, $p = .3$). The cumulative estimates of positive total fluid balance at 72 hrs were 5100 mL in the liberal group and 400 mL in the restrictive group. Notably, however, those allocated to the restrictive strategy showed improved lung function, increased ventilator-free days, reduced ICU length of stay, and no increase in the rate of nonpulmonary organ failure or shock. The restrictive strategy also showed a trend for reduced need for RRT (10% for restrictive vs. 14% for liberal, $p = .06$) (30). Importantly, patients requiring RRT at baseline were excluded.

Complications of Volume Overload in ICU Patients. Volume overload, although a recognized complication of AKI in ICU patients, can also contribute to numerous adverse effects. Moreover, ICU patients are at increased risk for fluid imbalance, often as a result of widespread systemic inflammation, reduced plasma oncotic pressure, and an increased propensity for capillary leak. These patients are more likely to develop edema, such as peripheral dependent interstitial edema, ascites, and pleural effusions (33). Such fluid accumulation may contribute to additional cardiopulmonary complications, for instance, congestive heart failure, pulmonary edema, increased pulmonary restrictive defects, and reduced pulmonary compliance.

Moreover, there are several additional complications that may be indirectly caused by volume overload. This has been more evident in studies of patients undergoing elective general surgical procedures. Current surgical practice is largely characterized by the administration of perioperative fluid therapy that greatly exceeds measured fluid losses (34). This is generally substantiated by patients shown to gain in excess of 3–7 kg in weight in the early postoperative period (35). In an elegant study, Brandstrup et al. (36) randomized 172 patients scheduled for elective colorectal surgery to either a restrictive or standard intraoperative and postoperative fluid therapy regimen. The restricted regimen aimed to maintain preoperative weight, whereas the standard regimen reflected usual care. Overall, postoperative complications were dramatically reduced for those receiving the restrictive regimen (33% vs. 51%, $p = .01$). The patients allocated to the restrictive regimen experienced fewer cumulative major (i.e., anastomotic leak, sepsis, bleeding requiring transfusion or return to theater, pulmonary edema requiring mechanical ventilation) and minor complications (i.e., wound infection or dehiscence) (Fig. 2). These findings have since been corroborated in a similar trial of 152 patients undergoing elective major gastrointestinal surgery (37). The restrictive fluid regimen used in

these trials of gastrointestinal surgery was not truly restrictive but rather a goal-oriented replacement of measured fluid losses (34). Accordingly, the practice of giving additional fluid in excess of these measured losses and resulting in postoperative weight gain (fluid overload) is not supported by evidence, seems unnecessary, and likely only contributes to perioperative complications. Thus, although these patients may be responsive to a fluid challenge by an increase in blood pressure and urine output, it should be highlighted that this does not necessarily translate into a need for additional fluid therapy.

This approach should now be extended to and certainly evaluated further in ICU patients, in particular those with oliguric AKI. Moreover, this approach probably has even greater importance when considering recent changes in ICU practice that have been broadly endorsed (23, 24, 38, 39). In the trial by Rivers et al. (24), subjects allocated to early goal-directed therapy received approximately 5 L of total fluid therapy within 6 hrs and >13 L by 72 hrs compared with 3.5 L in 6 hrs and also 13 L by 72 hrs in the control group. These observations highlight a high level of reliance on fluid therapy during resuscitation rather than vasopressor therapy, which was only given to approximately 30% of patients in the first 6 hrs. Regrettably, cumulative fluid balance, urine output, diuretic therapy, and kidney outcomes were not reported, but notably, serum creatinine was significantly elevated at presentation, suggesting that many, if not all, of these septic patients had AKI. Early goal-directed therapy with large volumes of fluid therapy, as performed in this trial, would have the potential to precipitate complications much earlier in the oliguric patient with AKI.

In the SAFE trial (39), nearly 7,000 patients were randomized to receive either 0.9% saline or 4% albumin solution for fluid resuscitation in the ICU. The study found no significant difference in 28-day mortality between arms. Of note, those allocated to albumin received less fluid overall and had a lower cumulative fluid balance. However, this difference failed to translate into any meaningful difference in the proportion receiving RRT or other secondary outcomes. Thus, colloid resuscitation with albumin was not necessarily advantageous; however, it would be more costly and could be associated with the inherent risks of transfused products. This, coupled with some concern of hydroxyethyl starch contributing to AKI (40–42), may lead to a return to a predominant use of crystalloid for fluid resuscitation (27).

Overall, the implications of the above studies are two-fold: 1) the incidence of AKI is rising, and 2) volume overload is an important clinical problem that will also likely increase in modern ICU practice. Again, at this point, after the acute resuscitative phase, our options are narrowed to either diuretic therapy or initiation of RRT. The next logical question is what evidence exists on the role of diuretic therapy in the management of the ICU patient with AKI.

Oliguria and Loop Diuretics

The use of loop diuretics, in particular furosemide, in critically ill patients with AKI is a long-standing and widespread clinical practice (29, 43–45). Most intensivists are familiar with its administration, pharmacology, and adverse effects (43). However, regrettably, the role of furosemide in the management of ICU patients with AKI is, by and large, poorly understood.

Theoretical Basis for Use of Furosemide in Critically Ill Patients with AKI. Loop diuretics, such as furosemide, act at the medullary thick ascending loop of Henle to inhibit the $Na^+/K^+/Cl^-$ pump on the luminal cell membrane surface and can theoretically reduce renal tubular oxygen demand (46–48). Consistent with older reports, a recent study in a rat model of ischemia/reperfusion–induced AKI has shown that low-dose furosemide can reduce injury by improving renal hemodynamics and attenuation of ischemia-induced apoptosis and related gene transcription (49, 50). Although these findings add credibility to the theoretical role of furosemide, these findings in experimental animals are certainly not universal (51–55). Data have been contradictory and may be dependent on additional factors, such as the animal model, methods to induce AKI, and other experimental conditions (47, 49, 50, 56–59). Interestingly, *in vitro* studies of peripheral blood mononuclear cells stimulated with lipopolysaccharide have shown that high concentrations of furosemide have immunosuppressive and cytotoxic properties characterized by reduced expression of tumor necrosis factor-α, interleukin-6, and interleukin-8 (60). The clinical implications of these findings are unknown. Thus, at least theoretically, the timely administration of furosemide might attenuate or reduce the severity of kidney injury. Likewise, furosemide may also aid in the management of volume overload by augmenting natriuresis and diuresis, for maintaining acid–base and potassium homeostasis, and aid in delivery of adequate nutritional support.

Practice Patterns of Use of Furosemide in ICU Patients with AKI. Furosemide use is common in the ICU. In a multicenter observational study involving 552 ICU patients with AKI, 59% were found to have received diuretic therapy before consultation with a nephrologist (44). Of diuretics given, 62% received furosemide, with a median (interquartile range) single dose of 80 mg (20–320 mg). In another large, multicenter, multinational, observational study of >1,700 ICU patients with AKI, 70% had received diuretics at the time of study enrollment (45). Furosemide was the primary diuretic used in 98% of cases. In a small prospective evaluation of septic ICU patients developing AKI, 72% were found to have received diuretic therapy (29). A recent multinational survey of 331 ICU physicians and nephrologists was performed to better characterize how and when diuretics are used in ICU patients (43). This study found that furosemide was by far the most common diuretic used, almost always administered by the intravenous route, and generally titrated to a urine output goal in the range of 0.5–1.0 $mL \cdot kg^{-1} \cdot hr^{-1}$. This study also found that most clinicians did not believe diuretic use in AKI would lead to improved clinical outcomes (i.e., mortality, need for RRT, or renal recovery); however, an estimated 23–27% expressed uncertainty about the available evidence.

Clinical Data on Loop Diuretics in ICU Patients with AKI. Numerous studies have evaluated loop diuretics in the treatment of AKI (61–79) (Tables 1 and 2). The majority have failed to find clinical benefit. Moreover, two recent large observational studies in ICU patients have discrepant conclusions on the effect of loop diuretics on mortality and renal recovery (44, 45). Importantly, both these observational studies estimated risk ratios for mortality at >1.0, implying an increased mortality with their use in AKI. Mehta et al. (44) performed a prospective observational study at five academic hospitals from 1989 to 1995 that enrolled a total of 552 ICU patients with AKI. This study suggested an increased risk of death

Table 1. Summary of non-randomized studies of loop diuretics in acute kidney injury

Study, First Author (Reference No.)	Year	No. Patients	Loop Diuretics Protocol	Toxicity	Comment
Beroniade (61)	1969	24	Furosemide, 60–480 mg	None reported	Not ICU
Cantarovich (66)	1973	105	Furosemide, 100–3200 mg IV, fixed/progressive daily	None reported	Not ICU Anuric for >2 days before enrollment All on RRT at enrollment
Chandra (69)	1975	28	Furosemide, 200–2000 mg IV, fixed/progressive daily	Deafness (n = 2)	Not ICU Oligo-anuric for >5 days before enrollment
Minuth (74)	1976	104	Furosemide, 40–500 mg IV	None reported	Not all ICU
Borirakchanyavat (62)	1978	14	Furosemide, 2000 mg IV daily	None reported	Not all ICU No patient died or needed RRT
Lumlertgul (73)	1989	23	Furosemide, 200 mg IV every 6 hrs	None reported	Not all ICU Co-intervention (DA) No patient died
Mehta (44)	2002	552	80 mg (20–320)[a]	None reported	Secondary question of study
Uchino (45)	2004	1743	240 mg (80–500)[b]	None reported	Secondary question of study

IV, intravenous; DA, dopamine; RRT, renal replacement therapy; ICU, intensive care unit.
[a]Median (intraquartile range) dose before consultation with nephrologist; [b]median (intraquartile range) dose in 24 hrs before enrollment.

Table 2. Summary of randomized studies of loop diuretics in acute kidney injury

Study First Author (Reference No.)	Year	No. Patients	Loop Diuretics Protocol	Toxicity	Comment
Cantarovich (65)	1971	47	Furosemide, 100–3200 mg IV fixed/progressive daily	Tinnitus[a]	All on RRT at enrollment
Karayannopoulos (70)	1974	20	Furosemide, 1000–3000 mg IV daily	None reported	Not ICU
Kleinknecht (71)	1976	66	Furosemide, 3 mg/kg IV load, 1.5–6.0 mg/kg IV every 4 hrs	Tinnitus, deafness, vertigo[a]	Not ICU Co-intervention (MA) Most already on RRT
Brown (63)	1981	56	Furosemide, 2 mg/min IV or 1000 mg every 8 hrs orally	Deafness (n = 2)	Not ICU Furosemide given to both
Shilliday (76)	1997	92	Furosemide or torsemide, 3 mg/kg IV every 6 hrs	Deafness (n = 1)	Co-interventions (DA, MA)
Cantarovich (67)	2004	330	Furosemide, 25 $mg \cdot kg^{-1} \cdot day^{-1}$ IV or 35 $mg \cdot kg^{-1} \cdot day^{-1}$ orally	Deafness (n = 4)	All on RRT at enrollment

IV, intravenous; RRT, renal replacement therapy; ICU, intensive care unit; DA, dopamine; MA, mannitol.
[a]Estimates of occurrence of toxic effect were not reported. In these studies, ototoxicity may have been confounded by concomitant use of aminoglycosides. Symptoms were reported to occur temporally within a few hours after furosemide administration. No long-term sequelae were reported.

and/or nonrecovery of kidney function with loop diuretics. Notably, however, this study included only those patients having had a nephrology consultation while admitted to the ICU, excluded patients with "hypovolemia," failed to report the proportion requiring RRT, and included data on only 64% of potentially eligible ICU patients from the entire cohort (n = 851). These factors could lead to significant selection and observation bias and, moreover, suggest the study may be limited in terms of generalizability to broader ICU practice worldwide (80). Uchino et al. (45) performed a prospective observational study that enrolled 1,743 ICU patients with AKI from 54 ICUs in 23 countries. Similar to the findings of Mehta et al. (44), the risk ratio estimate in this study was approximately 1.2. However, unlike the study by Mehta et al. (44), the result was nonsignificant and continued to be nonsignificant after adjustment in three distinct multivariable regression models that included controlling for residual confounding by propensity analysis and compensation of collinearity in model variables (45).

Additional small clinical trials have suggested that diuretics might shorten the duration of AKI, improve the rate of renal recovery, or possibly delay or ameliorate need for RRT (65, 66, 70, 71, 76, 78). However, thus far, the potential for improvement in survival, renal recovery, or any clear patient-centered end point has yet to be established by high-quality clinical trials. Accordingly, there is ongoing controversy as to whether diuretics can affect clinical outcomes and should be used in ICU patients with AKI (81–86).

A recent meta-analysis concluded that furosemide was not associated with any significant clinical benefit and perhaps an increased risk of harm (87). Unfortu-

nately, this meta-analysis included studies in which furosemide was administered to both prevent and treat AKI and one study in which furosemide was given to both the treatment and control groups. Further, it included duplicated control data from one study with three treatment groups and provided approximated or estimated rates of toxicity in another (88). Thus, inferences from this meta-analysis are limited.

Another systematic review of randomized trials assessing loop diuretics in AKI, with a focus on ICU patients, included five trials enrolling 555 patients (89). This study found loop diuretics have no significant effect on mortality or renal recovery; however, their use was associated with a shorter duration of RRT, a shorter time to spontaneous decline in surrogate measures of kidney function (i.e., serum creatinine), and a greater increase in urine output from baseline. Because of inadequate data, this study was not able to comment on whether loop diuretics had any effect on acid–base status, duration of mechanical ventilation, secondary organ dysfunction, hospital length of stay, or health costs.

More importantly, however, this study drew attention to the poor overall trial quality and the lack of generalizability of this evidence to modern ICU patients with AKI. For example, the trials were generally small, confounded by cointerventions (i.e., mannitol, dopamine), and typically characterized by delayed or late intervention, with either prolonged periods of oligo-anuria or use of RRT at the time of enrollment (66, 67, 70, 71, 76). The latter point should be emphasized, as observational data suggest that delay in RRT is associated with increased mortality and reduced likelihood of renal recovery (90–92). Likewise, in these trials, furosemide was often given by large intravenous bolus doses, for which no specific titration of therapy to physiologic end points such as fluid balance was performed. Finally, these trials often did not include ICU patients, thus greatly limiting their applicability and generalizability to modern ICU patients with AKI (93). Regrettably, these limitations are likewise evident for the majority of other investigations of loop diuretics in AKI (61–63, 65, 68, 73, 74).

Recently, Sampath et al. (94) performed a systematic review and Bayesian evidence synthesis of 13 randomized and nonrandomized studies on diuretic use in AKI. This meta-analysis described comparable findings on the effect of loop diuretics on mortality, duration of AKI, and diuresis (89). This study calculated an estimate of the probability that loop diuretics were associated with a risk ratio for mortality of >1.0. The authors found an 83% probability of a risk ratio of >1.0 for mortality with loop diuretics. However, again it should be highlighted that this finding was based on data extracted from the same aforementioned studies (44, 45, 61–63, 65–68, 70, 71, 73, 74, 76).

Interestingly, the evidence from these trials largely forms the basis for the prevailing view that furosemide does not improve outcome in AKI. However, despite this view, survey data would imply that clinicians do routinely use loop diuretics and generally do not administer them in a manner consistent with how they were administered in these trials. If this is true, then naturally one asks: Are ICU clinicians mistaken to use furosemide or is the evidence on the effectiveness of furosemide misleading?

These findings overall would point toward evidence of clinical equipoise for additional investigations evaluating furosemide in ICU patients with AKI (45, 84, 88, 89, 94). Moreover, to appropriately overcome the limitations of current data and obtain high-quality evidence on whether loop diuretics have a role in the management of AKI, a suitably powered multicenter randomized controlled trial is needed. Such a trial should ideally incorporate clinically relevant and patient-centered outcomes, such as progression of AKI, need for RRT, or renal recovery. In addition, such trials should include important secondary outcomes focused on issues of harm, dose-response, and physiologic end points (i.e., fluid balance). Given sample size requirements, mortality, as a primary end point, may not be ideal. Moreover, the patient population included should be chosen carefully. For example, all patients should be critically ill and admitted to the ICU, all should be identified as having early oliguric AKI, and there may be value in stratification by the presence of sepsis. Furthermore, loop diuretics could be dosed as a continuous infusion and targeted to fluid balance with close hourly monitoring.

CONCLUSIONS

AKI is common and increasingly encountered in ICU patients. Oliguria likely contributes to added morbidity and possibly mortality. Recent trends in ICU practice, such as early goal-directed therapy, may further compound volume overload in patients with oliguric AKI. Moreover, emerging evidence has suggested that positive fluid accumulation in ICU patients can adversely affect outcome. Therapeutic options for the oliguric ICU patients with AKI are limited to optimization of systemic hemodynamics, fluid therapy, diuretics, or initiation of RRT. Survey and observational data indicate that a majority of ICU patients with AKI receive loop diuretics, specifically furosemide, at some point during their illness. However, furosemide has been shown in several studies to be potentially detrimental or to lack clear effectiveness for improving survival or renal recovery. It remains unclear what drives this practice and raises the important question: Are ICU clinicians mistaken to use furosemide or is the evidence on the effectiveness of furosemide misleading? This paradox would suggest there is equipoise for additional study and that higher-quality evidence is needed.

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