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## Loop Diuretics for Patients With Acute Renal Failure Helpful or Harmful?

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NTRINSIC ACUTE RENAL FAILURE (ARF) THAT DOES NOT result from primary vascular, glomerular, or interstitial disorders has been ascribed to acute tubular necrosis and accounts for approximately 45% of cases of hospital-acquired ARF.<sup>1</sup> While acute tubular necrosis usually is caused by ischemic (50%) or nephrotoxic (35%) injury to the kidney,<sup>2</sup> the cause is often multifactorial. Unfortunately, neither the occurrence of acute tubular necrosis nor the morbidity and mortality associated with it have declined despite ongoing improvement in the supportive care of patients with renal failure and the advent and availability of intermittent and continuous dialysis.<sup>3,4</sup> One reason for this lack of improvement is a change in the severity of the underlying diseases causing ARF.<sup>1,4,5</sup>

The incidence of acute tubular necrosis is particularly high in patients admitted to an intensive care unit (ICU). The spectrum of acute tubular necrosis in the ICU, compared with other settings, is indeed different. Critically ill patients develop acute tubular necrosis predominantly as part of a multiple organ dysfunction syndrome, whereas isolated ARF is the usual presentation for patients outside the ICU.<sup>6</sup> The mortality rate among critically ill patients with acute tubular necrosis has been estimated to be as high as 80% to 85% in some series.<sup>7,8</sup> Acute renal failure also complicates the medical management of hospitalized patients and contributes to their morbidity and mortality.9 Hence, a treatment that would prevent ARF or accelerate the recovery of renal function in patients with established ARF might be expected to reduce morbidity and possibly mortality and could substantially reduce the cost of medical care.

Acute tubular necrosis has traditionally been characterized as either oliguric (urine output <400 mL/d) or nonoliguric (urine output >400 mL/d); this distinction is important because of several clinically relevant associations and implications. In comparison with oliguric acute tubular necrosis, nonoliguric acute tubular necrosis is more often reported to have a nephrotoxic cause; is associated with shorter hospital stay; has fewer septic, neurologic, hemorrhagic, and

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acidemic complications; requires less dialysis; and has a lower mortality rate.<sup>2,10</sup> However, the distinction between oliguric and nonoliguric acute tubular necrosis is somewhat arbitrary, because urine flow rates in patients with acute tubular necrosis represent a continuum from very low to high values without an obvious biphasic distribution. Most probably, the residual level of glomerular filtration rate is the primary determinant of variations in urine flow rate in patients with ARF.<sup>11</sup>

Several theoretical arguments support the use of mannitol and loop diuretics for prevention or treatment of ARF. Both mannitol and loop diuretics can induce a diuresis, potentially "washing out" obstructing cellular debris and casts. Mannitol may preserve mitochondrial function by osmotically minimizing the degree of postischemic swelling and by scavenging free radicals.<sup>12</sup> Loop diuretics have been reported to improve medullary oxygenation, presumably because they selectively decrease oxygen use in this portion of the tubule by blocking active transport.<sup>13,14</sup> The ensuing decrease in energy requirements may protect the renal cell in ischemic conditions. In addition, loop diuretics may act as renal vasodilators.<sup>15,16</sup> But how theory relates to actual pathophysiology in individual patients is often unclear.

In this issue of THE JOURNAL, Mehta and colleagues<sup>17</sup> retrospectively analyzed the outcome of all ICU patients with ARF who received nephrology consultation in 4 teaching hospitals over a 6-year period. Patients who received loop diuretics or a combination of thiazide and loop diuretics at the time of nephrology consultation were compared with a group of similar patients who did not receive diuretics. After adjustment for relevant covariates and propensity scores, diuretic use was associated with a 68% increase in in-hospital mortality, and a 77% increase in the odds of death or nonrecovery of renal function. The increased risk was mainly observed in patients who were relatively unresponsive to diuretics. Moreover, the risk associated with a high ratio of diuretic dose to urine output, an index of diuretic resistance, was magnified over time. The authors suggest that the use of loop diuretics must be harmful to patients, although it also seems possible that these diuretics are used more frequently in patients who would have done worse anyway.

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### EDITORIALS

Several clinical studies have examined the use of loop diuretics in patients with ARF. Two randomized controlled studies, involving respectively 66 and 58 patients with established acute tubular necrosis, revealed that high doses of furosemide can induce a high urine output and can convert oliguric renal failure to nonoliguric renal failure in a substantial number of patients, but fail to reduce the need for dialysis, and, importantly, do not reduce mortality.<sup>18,19</sup> In a more recent randomized controlled trial, Lassnigg et al<sup>20</sup> showed that continuous infusion of dopamine was ineffective for renal protection and was not superior to placebo in preventing postoperative renal dysfunction after cardiac surgery. In contrast, continuous infusion of furosemide was associated with the highest rate of renal impairment. This study not only confirmed that renal-dose dopamine is ineffective, but also showed that furosemide is detrimental in the protection of renal dysfunction after cardiac surgery.

Most studies have not shown a beneficial effect of forced diuresis induced by loop diuretics in the prevention of contrast nephropathy. However, Stevens et al<sup>21</sup> demonstrated that forced diuresis with diuretics and low-dose dopamine in patients at high risk for contrast nephropathy and in whom the intravascular volume was maintained constantly can increase postprocedure urine flow rates and provides a modest protective effect. The study was limited by small sample size and consequently was underpowered. Although high doses of a loop diuretic do not affect the prognosis of patients with ARF,22-24 conversion of oliguric ARF to nonoliguric ARF simplifies patient management. If diuresis ensues, it is associated with a more liberal fluid intake and easier administration of parenteral nutrition. However, the conversion does not alter the natural history of the disease, but instead provides prognostic information that the patient had less severe ARF.

It has long been known that loop diuretic treatment in the setting of acute tubular necrosis can be hazardous. From an experimental point of view, furosemide may promote the aggregation of Tamm-Horsfall protein in the lumen of the tubules, a mechanism thought to cause intratubular obstruction.<sup>25</sup> In addition, large doses of furosemide or ethacrynic acid may cause deafness, which sometimes may become permanent. Coadministration of aminoglycosides increases the risk of ototoxicity. However, the incidence of permanent hearing loss is low and mostly reported when high doses were given in bolus injections.<sup>26</sup>

Although previous studies have pointed out the limitations of diuretics for prevention and treatment of patients with ARF, no study to date has shown that diureticinduced forced diuresis is associated with a higher risk of death or nonrecovery of renal function in critically ill patients with ARF, as the findings reported by Mehta et al suggest. As a possible explanation for this deleterious effect, the authors suggest that use of diuretics to convert an oliguric form to a nonoliguric form may have delayed the recognition of ARF or underestimated its severity. This in turn may have delayed the time for obtaining consultation of the nephrologist or initiation of dialysis. However, 12% of the patients had diuretics prescribed after the nephrological consultation.

While this explanation seems plausible, it is surprising that the poor results were more frequent in patients who did not respond to the diuretic challenge. It seems that the intensivist would contact the nephrologist earlier for patients who remain oliguric after a diuretic challenge, so that dialysis would have been started earlier in oliguric patients. Since no further information is available on the causes of death, the time interval until starting dialysis, or the type of dialysis, it is possible that the higher mortality was not associated with diuretic use but may have been related to, for example, the dialysis therapy.

Furthermore, there is wide variation in the physiologic parameters of "hydration" in the patients included in this study, suggesting that many of them were not adequately hydrated, despite receiving diuretics. In addition, the nephrological consultation was requested rather late in the course, when the serum creatinine level was on average 3.6 mg/dL (318 µmol/L) in patients who received diuretics and 4 mg/dL (354 µmol/L) in those who did not. Since the mean age and the prevalence of congestive heart failure and respiratory failure were higher among patients who received diuretics, some of these patients must have been more ill than those constituting the comparison group, even though both groups had similar Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores. However, commonly used scoring methods, like the APACHE II, are not very reliable in ICU patients with ARF.7

Despite these limitations, the study by Mehta et al is timely and clinically important because administration of diuretics to oliguric patients in the ICU is still a relatively common practice. Until data from a sufficiently powered clinical trial can properly answer the question of whether critically ill patients are harmed by loop diuretics, the practice of routine administration of these agents to such patients should be discouraged. Accordingly, physicians should think twice before prescribing loop diuretics for critically ill patients with ARF. A trial of high-dose loop diuretics in an oliguric patient should only be attempted after careful correction of the volume status, should be limited in time, and, more important, should not postpone obtaining consultation with a nephrologist experienced in ARF. Nephrologists and intensivists should also realize that even successful conversion of oliguria to diuresis only reflects the existence of a milder form of ARF, has no prognostic effect, and does not justify postponing dialysis when needed.

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# Protocols to Improve the Care of Critically III Pediatric and Adult Patients

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N ADDITION TO THE CELEBRATED TECHNOLOGICAL AND PHARmaceutical advances in intensive care, an unassuming type of research testing the use of protocols in care has yielded some of the most important improvements in patient mortality and morbidity, and in the costs of critical illness. The basic concept is that routine clinical care is enhanced when interdisciplinary teams of health professionals use evidencebased protocols to complement their clinical judgment.<sup>1</sup> Perhaps the greatest value obtained from the use of protocols is that of reducing unnecessary variations in intensive care practice. Positive randomized trials now support the role of protocols for critical care interventions such as lung-protective ventilation,<sup>2</sup> weaning from mechanical ventilation,<sup>3-8</sup> transfusion of blood products,<sup>9</sup> sepsis resuscitation,<sup>10</sup> glycemic control,<sup>11</sup> and sedation and analgesia.<sup>12,13</sup>

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The benefit of protocols has been shown most consistently in approaches for weaning from mechanical ventilation. A recent review of the literature found that 4 randomized trials and 11 additional controlled studies have shown favorable outcomes such as a reduced duration of mechanical ventilation and an increased rate of successful extubation in critically ill adults.<sup>14</sup> Similar findings have been reported among critically ill children randomly assigned to protocol-directed vs physician-directed weaning.<sup>15</sup> Among the larger trials of weaning from mechanical ventilation (N $\geq$ 300),<sup>5-7,15</sup> these consistent effects were both statistically significant and clinically important.

The implications of protocols for improving the care of critically ill patients appear substantial: reduced time re-

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