On-Line Supplement

Prevention and Management of Acute Renal Failure in an ICU Patient

Impact of resuscitation strategies on renal function (II. 1)

A study performed to analyze the effect of pulmonary artery catheters on morbidity and mortality in a mixed group of 201 critically ill patients found a higher incidence of acute renal failure on day 3 post-randomization in the pulmonary artery catheter group than in the control group (35 versus 20%, p < 0.05). The greater incidence of AKI occurred even though patients managed with pulmonary artery catheters received more fluids in the first 24 hours: median (25-75th centiles) 4.9 (3.1, 7.0) versus 4.3 L (2.5, 6.0). The results of the Fluids and Catheters Treatment Trial (FACTT) also suggest that, in selected patients with acute lung injury, conservative fluid management may not be detrimental to kidney function: conservative fluid management (goal of central venous pressure < 4 mm Hg or pulmonary artery occlusion pressure < 8 mm Hg) was compared to a liberal fluid management (goals of 10-14 mm Hg and 14-18 mmHg respectively). Mean (±SE) fluid balance over 7 days was -136 ± 491 mL in the first group and +6992 ± 502 ml in the second group. Compared to the liberal strategy, the conservative strategy increased the number of ventilator-free days, reduced the number of ICU days and had similar 60-day mortality. These benefits were not associated with an increase in the frequency of renal-replacement therapy, which occurred in 10% of the conservative-strategy group and 14% of the liberal-strategy group (p = 0.06). Yet, during the 7 days of the study, the conservative-strategy group tended to have slightly higher creatinine values than did the liberal-strategy group (p = 0.07) and had higher levels of blood urea nitrogen, bicarbonate, and calculated colloid osmotic pressure. Several points limit the application of this study in the development of recommendations on fluid administration to prevent AKI in critically ill patients. First, the study was not specifically designed to assess different fluid management strategies to prevent AKI in critically ill patients. Second, no patient with overt renal failure (and thus potentially more vulnerable to a conservative fluid
strategy) was enrolled in the study. Third, when randomized, hemodynamics and filling pressures of most patients would have been considered already optimal by most investigators. Fourth, serum creatinine was used as the marker of kidney function – but this marker has limitations in identifying patients with early AKI or in distinguishing between prerenal azotemia and AKI. Fifth, no data on the recovery of kidney function with either strategy was provided. This latter point may be particularly relevant for patients with pre-existing chronic kidney disease, an increasing segment of critically ill patients affected by AKI.

**Drugs to Prevent Contrast-Induced Nephropathy (II. 4)**

Recent recommendations to prevent CIN in non-critically patients have been published. Despite a lack of solid data regarding the optimal fluid regimen, these recommendations stress the importance of adequate fluid administration. Randomized studies, most of which enrolled a limited number of patients, have not provided conclusive evidence that vasodilators (dopamine, fenoldopam, atrial natriuretic peptides, calcium blockers, prostaglandine E1, endothelin receptor antagonist) protect against CIN and some appear to be harmful. In a recent prospective randomized study of more than 300 patients at risk for CIN (baseline creatinine clearance < 60 mL/min), fenoldopam failed to prevent CIN after contrast administration. Theophylline and aminophylline have been reported to modestly limit contrast induced rise in serum creatinine level, the clinical significance of these findings is unclear. In a recent meta-analysis, however, theophylline protective effect did not reach statistical significance (CI 0.23 to 1.06).

Administration of oral N-acetylcysteine (NAC) has been proposed as a means to prevent CIN based on a recent meta-analysis. Its role remains controversial given the inconsistent results observed across multiple studies. In addition, using different markers of renal function, it
has been suggested that NAC could have a specific effect on serum creatinine levels, dissociated from an effect on renal function. High doses of NAC may be needed to achieve a renal protection in patients at risk for CIN. 354 consecutive patients undergoing primary angioplasty were randomly assigned to N-acetylcysteine (a 600-mg intravenous bolus before primary angioplasty and 600 mg orally twice daily for the 48 hours after angioplasty), a double dose of N-acetylcysteine and to placebo. Creatinine increased 25% or more from baseline after angioplasty in 33% of the control patients, 15% of the patients receiving standard-dose NAC, and 8% of patients receiving high-dose NAC (P<0.001). Such results contrast with those of other randomized controlled trials with intravenous NAC, especially in aortic or cardiac surgery. The variable efficacy of i.v. NAC against AKI could be explained by differences in associated risk factor for AKI in the above clinical settings. These contradictory results call for need to study the potential protective effects of NAC against CIN in the critically ill patients. Intravenous NAC may lead to side effects in up to 10% of patients. Serious complications such as hypotension, angioedema, bronchospasm, hyponatremia, seizure and volume overload appear to be dose dependent.

**Protocolized intravenous fluid administration (alone and in combination with NAC) and hemofiltration to prevent CIN (II. 4)**

Protocolized administration of intravenous fluids alone (sodium chloride 0.9% or isotonic sodium bicarbonate [sodium bicarbonate 154 mmole/L], or protocolized fluid administration plus intravenous NAC (sodium chloride or sodium bicarbonate solution) have the potential to reduce the incidence of CIN and the need for dialysis. In 119 patients with slightly elevated creatinine (at least 1.1 mg/dL (> or =97.2 micromol/L) hydration with i.v sodium bicarbonate before contrast administration was reported to be more effective than hydration with i.v. sodium chloride. In a study of 326 patients with chronic renal failure, it was found that i.v sodium bicarbonate plus oral NAC was superior to the
combination of normal saline with NAC alone or with the addition of ascorbic acid in patients at medium to high risk. Similarly, intravenous hydration with sodium bicarbonate plus oral NAC before contrast administration was found more effective and safer than saline and NAC in preventing CIN in 111 patients undergoing emergency percutaneous coronary intervention \(^{24}\). Similarly in 264 patients with a baseline creatinine level 1.2 mg/dl scheduled for cardiovascular procedures, intravenous sodium bicarbonate reduced the incidence of CIN more than intravenous sodium chloride with or without concomitant oral NAC administration \(^{25}\). Sodium bicarbonate may therefore confer more protection against CIN than saline alone and that oral NAC does not add to the renal protective effects of intravenous sodium chloride.

Finally, it was reported that hemofiltration prevents CIN in high risk patients (patient with baseline serum creatinine > 2 mg/dl [176 μmol/L] who received approximately 250 ml of i.v. contrast) \(^{26}\). The applicability of this investigation is, however, limited. First, renal function was assessed using plasma creatinine levels, a marker that is directly altered by the proposed intervention (i.e., hemofiltration). Second, patients were randomized to be treated in different settings (ultrafiltration was performed in the ICU, while routine care was performed in a step down unit). Overall, the published literature suggests that periprocedural extracorporeal blood purification has no protective effect against CIN \(^{27}\).

To what extent the protective effects of intravenous sodium chloride and sodium bicarbonate and the possible benefits of NAC observed in non-ICU patients can be extrapolated to critically ill patients remains to be determined. The safety of these protocols has not been established in critically ill patients, particularly in patients at risk of developing pulmonary edema or in those with hypotension or acid base disorders.

The choice of the contrast medium may also be important but will only be discussed briefly as the intensivist is typically not involved in the choice of contrast medium. A meta-analysis reported in 1993 that high osmolar contrast media is more nephrotoxic than low osmolar
contrast media (reduced odd ratio 0.67, CI 0.48-0.77)\textsuperscript{28} A recent meta-analysis suggested that the isosmolar compound might be slightly less nephrotoxic than low contrast medium in patients at high risk of CIN\textsuperscript{29}. In the absence of a demonstrated clinically relevant advantage of isosmolar contrast agent over low contrast medium in critically ill patients, both contrast media constitute a reasonable choice in this population for the time being.

**RRT Intensity (dose) (V. 3)**

*Details of trials*

Table 2 shows the main results of these trials. Schiffl et al. compared alternate day to daily IHD in 160 critically ill patients\textsuperscript{30}. The alternate day group received a $K_t/V_d$ per week of only 3.0 compared to 5.8 in the daily group and had a significantly higher mortality (72\textit{versus} 54\%, respectively; $P = 0.01$). Notably, the control group in this trial received a RRT dose lower than that used in any of the other RCTs testing dose and below the threshold considered safe for the management of chronic renal failure. These results may only indicate that overt under-dialysis is harmful in critically ill patients with AKF. In a single-center study, Ronco et al. investigated 425 patients randomized to CVVH at 20, 35, and 45 mL/kg/h of replacement fluid delivered post filter\textsuperscript{31}. Survival was 41\%, 57\%, and 58\% across the low, medium, and high dose groups ($P < 0.001$) at 15 days after the discontinuation of CVVH, suggesting again that a break point exists for clearance intensity, below which survival worsens. Notably, estimates of $K_t/V_d$ for the low, medium, and high dose groups were 5.3, 9.5, and 11.8 per week, respectively (Table 2)\textsuperscript{32}, all well above the minimum standard for chronic renal failure. Bouman et al. studied 106 patients assigned to early high-volume hemofiltration (72 – 96 L/24 h), early low-volume, hemofiltration (24 – 36 L/24 h), and late low volume
hemofiltration (24 – 36 L/24 h). Median ultrafiltration rates were 48.2 mL/kg/h in the early high-volume group, and 20.1 mL/kg/h in the early low-volume group, and 19.0 mL/kg/h in the late low volume group. Survival at day 28 was identical among the three study arms (Table 2). Another trial of RRT dose, compared continuous veno-venous hemofiltration to continuous veno-venous hemodiafiltration (CVVHD) with the same ultrafiltration rate, plus the addition of dialysate. This produced an estimated delivered urea clearance of 22 mL/kg/h (Kt/Vd = 6.2/week) for the CVVH group and 34 mL/kg/h (Kt/Vd = 9.4/week) for the CVVHD group. Twenty-eight day survivals were 39% and 59% (P = 0.03) in the CVVH (n = 102) and CVVHD (n= 104) groups, respectively (Table 2). A trial of CVVHD dose (20 versus 35 mL/kg/h effluent flow rate) only available in abstract recently reported no effect on survival in ICU patients (n = 200) with a mean APACHE II score of 26 (Table 2).

Recently, the VA/NIH Acute Renal Failure Trial Network reported their investigation of low and high doses of RRT in critically ill patients (Table 2). The study was large (N = 1124) and employed an innovative flexible design allowing patients to move between IHD (three times/week versus six times/week; each session Kt/Vd = 1.2 to 1.4), SLED and CVVHD (20 mL/kg/h versus 35 mL/kg/h; replacement component for both pre-filter) within each dosing arm, as hemodynamic status changed. Death from any cause by day 60 was 53.6% with intensive therapy and 51.5% with less-intensive therapy (P = 0.47). Sensivity analysis failed to identify any patient subgroups that benefited from intensive therapy. From these results, it appears that RRT doses ≥ 3.6 Kt/Vd for IHD and ≥ 20 mL/kg/h for CRRT are adequate for the vast majority of ICU patients with AKF. Another large study is ongoing and likely to provide additional important data regarding the impact of RRT intensity on the outcome of patients with AKF in the ICU. The RENAL study in Australia and New Zealand is comparing two doses of CVVHD (25 and 40 mL/kg/h) in 1,500 patients. The Acute Renal Failure Trial Network study in the U.S. is investigating low and high doses of RRT using a
flexible design allowing patients to move between intermittent (three times/week versus six times/week; each session Kt/Vd = 1.2 to 1.4), SLED and CVVHD (20 mL/kg/h versus 35 mL/kg/h; replacement component for both pre-filter) within each dosing arm, as hemodynamic status changes (cardiac SOFA score 0-2 or 2-4) 37.

RRT Mode (V. 4)

Details of the prospective randomized trials

To date six prospective randomized studies have been published 39-45 (Table 4). Abundant methodological information concerning these trials are available in a recent meta-analysis 46. Mehta et al. 40 reported a higher mortality in patients assigned to CRRT, but study groups (IHD vs. continuous arterio-venous hemodiafiltration or CVVHD) were not comparable for several covariates (e.g. % liver failure, gender, APACHE III score). After adjusting for these unbalanced covariates, multivariate analysis showed no relationship between the mode of RRT and mortality. While CRRT was associated with a higher rate of complete renal recovery in a subgroup of surviving patients (adequate trial of mode with no crossover), there were no differences in renal recovery among all survivors or using an intent to treat analysis. Cohort studies have suggested that the recovery of renal function may be better in patients treated with CRRT compared to IHD 47,48. The mortality rate, however, was also higher in those treated with CRRT and using a composite endpoint of survival or recovery of renal function showed no difference between the two modalities.

Among more recent trials of RRT mode, Augustine et al. 39 reported no difference in renal recovery or survival among 80 cases (mostly postoperative patients) randomized to either mode (CVVHD or IHD) after stratification according to the Cleveland Clinic Foundation score (survival score for hospitalized patients with AKF initiating dialysis) 49. However,
volume control was superior in the CVVHD group and a significant decrease in mean arterial pressure was associated with IHD. Uehlinger et al. compared IHD to CVVHD in a single center study. Polysulfone membranes and bicarbonate-buffered dialysate were used for IHD while polyacrylnitrile membranes and lactate-buffered dialysate were used for CVVHD. ICU and in-hospital mortalities were similar. Hemodynamic tolerance of RRT and rates of renal recovery were not influenced by mode. Vinsonneau et al. compared IHD to CVVHD (using polyacrylonitrile membranes in both groups) in 360 critically ill patients. Notably, this trial used a practice protocol developed by Schortgen et al. to improve the hemodynamic tolerance of IHD in ICU patients. Mortality, and renal support duration was not different between the two groups, but again net ultrafiltration was better with CRRT. Except for hypothermia, which was more frequent in patients receiving CVVHD, the incidence of other adverse events including hypotension was not different. However, changes in vasopressor dose and the need for fluid boluses during IHD were not recorded. Throughout the duration of the study, it was noticed that survival significantly increased in IHD, but not CRRT patients, which might have been due to an increase in the frequency and duration of dialysis sessions during the first 8 days of treatment.
References


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