Selection of Modality of Renal Replacement Therapy

Tania Abi Antoun* and Paul M. Palevsky*†
*Renal-Electrolyte Division, University of Pittsburgh School of Medicine and †The Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

ABSTRACT
The proliferation of new technologies has led to the availability of a broad range of options for the management of renal replacement therapy (RRT) in patients with acute kidney injury. We provide a review of the published literature comparing the continuous RRTs (CRRT) with other modalities of renal support, including intermittent hemodialysis and the more recently described “hybrid” therapies such as sustained, low efficiency dialysis as well as compare arteriovenous and venovenous and convective and diffusive modalities of CRRT. While there is clear evidence that venovenous therapies are superior to arteriovenous therapies, current evidence does not support superiority of convective when compared with diffusive therapies or greater survival or recovery of kidney function with any individual modality of RRT. Selection of modality of RRT should therefore rely on the resources and expertise available.

Acute kidney injury (AKI) afflicts 20–30% of patients admitted to the intensive care unit (ICU) and is associated with substantial added morbidity and mortality (1–3). Patients with AKI requiring renal replacement have mortality rates in excess of 50% (1,4–6), a prognosis that has remained stable over several decades despite multiple advances in the practice of critical care medicine and nephrology. In addition to uncertainty regarding the optimal timing of initiation of renal replacement therapy (RRT), the proliferation of modalities of RRT over the past three decades has provided nephrologists and intensivists with an increasing selection of options for managing renal support. RRT can be provided as hemodialysis, hemofiltration, or a combination thereof and as short intermittent treatments, continuous therapy or, more recently, as more prolonged, but intermittent, treatments. The medical literature is brimming with studies designed to demonstrate superiority of one regimen over the others, but few questions have been answered thus far. It remains incumbent on the provider to sieve through the available data to decide on the modality of RRT to use in an individual critically ill patient.

Comparison of CRRT with Other Modalities of Renal Replacement Therapy

Comparison with Intermittent Hemodialysis
Since their initial description in 1977 (7), the continuous RRTs (CRRT) have gained wide application in intensive care units (ICUs), often supplanting intermittent hemodialysis (IHD) because of the belief that CRRT provides more efficient solute clearance, more sustained correction of electrolyte disturbances, and allows for better volume management. Advocates of CRRT also contend that it is better tolerated in hemodynamically unstable patients, making it their modality of choice in the critically ill. However, the evidence in support of this view is somewhat tenuous, with the validity of many supporting studies limited by nonrandomized or retrospective designs (Table 1) (8–24).

Unadjusted analyses have suggested that patients treated with CRRT have worse survival than those who receive IHD, an observation which may be explained by a greater disease burden in patients who are treated with CRRT when compared with IHD. In an attempt to eliminate this bias, Swartz et al. (18) performed a retrospective outcome analysis of 349 patients with AKI requiring renal replacement at the University of Michigan Medical Center between 1995 and 1996. Whereas initial univariate analysis showed that odds of death for initial treatment with continuous venovenous hemofiltration (CVVH) was greater than 2.03 when compared with IHD \( (p < 0.01) \), adjustment for greater severity of illness using a multivariate model provided an adjusted odds of death among patients assigned to initial CVVH
TABLE 1. Studies comparing CRRT and IHD

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT</th>
<th>Number of IHD patients</th>
<th>Number of CRRT patients</th>
<th>IHD mortality (%)</th>
<th>CRRT mortality (%)</th>
<th>Odds of death with IHD (95% confidence interval)</th>
<th>Risk adjusted odds/risk of death with IHD (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauritz et al. (8)</td>
<td>No</td>
<td>22</td>
<td>36</td>
<td>91</td>
<td>75</td>
<td>3.3</td>
<td>NR</td>
</tr>
<tr>
<td>Paganini et al. (9)</td>
<td>No</td>
<td>47</td>
<td>27</td>
<td>81</td>
<td>82</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>McDonald et al. (10)</td>
<td>No</td>
<td>10</td>
<td>22</td>
<td>70</td>
<td>82</td>
<td>0.5</td>
<td>NR</td>
</tr>
<tr>
<td>Kierdorf et al. (11)</td>
<td>No</td>
<td>73</td>
<td>73</td>
<td>93</td>
<td>78</td>
<td>3.8</td>
<td>NR</td>
</tr>
<tr>
<td>Bastien et al. (12)</td>
<td>No</td>
<td>32</td>
<td>34</td>
<td>75</td>
<td>50</td>
<td>3.0</td>
<td>NR</td>
</tr>
<tr>
<td>Kruczynski et al. (13)</td>
<td>No</td>
<td>23</td>
<td>12</td>
<td>83</td>
<td>33</td>
<td>9.5</td>
<td>NR</td>
</tr>
<tr>
<td>Bellomo et al. (14)</td>
<td>No</td>
<td>84</td>
<td>10</td>
<td>70</td>
<td>61</td>
<td>1.5</td>
<td>NR</td>
</tr>
<tr>
<td>van Bommel et al. (15)</td>
<td>No</td>
<td>34</td>
<td>60</td>
<td>41</td>
<td>57</td>
<td>0.5</td>
<td>NR</td>
</tr>
<tr>
<td>Rialp et al. (16)</td>
<td>No</td>
<td>21</td>
<td>43</td>
<td>67</td>
<td>76</td>
<td>0.6</td>
<td>NR</td>
</tr>
<tr>
<td>Neveu et al. (17)</td>
<td>No</td>
<td>141</td>
<td>28</td>
<td>58</td>
<td>89</td>
<td>0.2</td>
<td>NR</td>
</tr>
<tr>
<td>Swartz et al. (18)</td>
<td>No</td>
<td>137</td>
<td>90</td>
<td>41</td>
<td>68</td>
<td>0.3</td>
<td>Not significant</td>
</tr>
<tr>
<td>Bellomo et al. (19)</td>
<td>No</td>
<td>47</td>
<td>47</td>
<td>70</td>
<td>53</td>
<td>1.2</td>
<td>NR</td>
</tr>
<tr>
<td>Mehta et al. (20)</td>
<td>Yes</td>
<td>82</td>
<td>84</td>
<td>48</td>
<td>66</td>
<td>1.0 (0.1–6.6)</td>
<td>0.63 (0.3–1.4)</td>
</tr>
<tr>
<td>John et al. (52)</td>
<td>Yes</td>
<td>20</td>
<td>10</td>
<td>70</td>
<td>70</td>
<td>1.0 (0.1–6.6)</td>
<td>0.63 (0.3–1.4)</td>
</tr>
<tr>
<td>Ji et al. (20)</td>
<td>No</td>
<td>92</td>
<td>101</td>
<td>36</td>
<td>41</td>
<td>0.8</td>
<td>NR</td>
</tr>
<tr>
<td>Guerin et al. (21)</td>
<td>No</td>
<td>233</td>
<td>354</td>
<td>59</td>
<td>79</td>
<td>0.4</td>
<td>Not significant</td>
</tr>
<tr>
<td>Chang et al. (22)</td>
<td>No</td>
<td>95</td>
<td>53</td>
<td>54</td>
<td>79</td>
<td>0.3</td>
<td>NR</td>
</tr>
<tr>
<td>Augustine et al. (27)</td>
<td>Yes</td>
<td>40</td>
<td>40</td>
<td>70</td>
<td>68</td>
<td>1.12 (0.43–3.2)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Gangi et al. (23)</td>
<td>No</td>
<td>66</td>
<td>36</td>
<td>58</td>
<td>64</td>
<td>0.8</td>
<td>Not significant</td>
</tr>
<tr>
<td>Swartz et al. (24)</td>
<td>No</td>
<td>183</td>
<td>200</td>
<td>40</td>
<td>65</td>
<td>0.4</td>
<td>Not significant</td>
</tr>
<tr>
<td>Uehlinger et al. (28)</td>
<td>Yes</td>
<td>55</td>
<td>70</td>
<td>51</td>
<td>47</td>
<td>1.16 (0.5–2.5)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Vinsonneau et al. (29)</td>
<td>Yes</td>
<td>184</td>
<td>175</td>
<td>68</td>
<td>67</td>
<td>1.05 (0.6–1.7)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

NR, not reported; CRRT, continuous renal replacement therapies; IHD, intermittent hemodialysis; RCT, randomized controlled trials.

comparable to patients receiving initial IHD (1.09, p = 0.72). Although suggesting that the poor outcomes associated with CRRT can be ascribed to the underlying condition that prompted triage to CRRT and not the treatment modality itself, this analysis fails to support any intrinsic advantage of CVVH over IHD. Similar analyses by Guerin et al. (21) also demonstrated that the increased mortality associated with CRRT could be explained by the increased disease severity associated with its selection.

Five randomized controlled trials (RCTs) comparing IHD and CRRT have been published in peer-reviewed journals. One small RCT compared the effects of CVVH and IHD on systemic hemodynamics and splanchic regional perfusion in septic patients with AKI (25). Thirty patients with similar baseline characteristics were assigned to CVVH (n = 20) or IHD (n = 10). After 24 hours of therapy and despite CVVH causing an increase in systemic vascular resistance and a decrease in cardiac output, no differences were found in intramucosal pCO2 and pH, surrogate markers of splanchic perfusion, suggesting that CVVH does not improve tissue oxygenation and mortality in septic patients with AKI. Although not the primary study endpoint, ICU mortality was the same (70%) in both treatment groups.

In the first multicenter RCT designed to assess the impact of modality of RRT on outcomes in AKI, Mehta et al. (26) randomized 166 critically ill adults with AKI to IHD or CRRT [continuous arteriovenous hemodiafiltration (CVVHDF) in 84.5%], excluding patients with hemodynamic instability, defined as a mean arterial pressure less than 70 mmHg. In the intention-to-treat analysis, mortality was greater in the CRRT group when compared with IHD group (28-day all-cause and ICU mortality: 59.5% versus 41.5%, p = 0.02; in-hospital mortality: 65.5% versus 47.6%, p = 0.02). Despite randomization, patients assigned to CRRT had higher APACHE (acute physiology and chronic health evaluation) III scores and more organ system failures and a greater proportion had liver failure, all of which were independently associated with mortality. After adjustment for these unbalanced covariates, the odds of death associated with CRRT was 1.58 (95% confidence interval 0.7–3.3), suggesting that baseline severity of disease accounted for the difference in mortality between CRRT and IHD. Complete renal recovery in survivors was more likely in patients who received CRRT and was also strongly influenced by the APACHE scores. In addition to the issues associated with imbalanced randomization, interpretation of this study is additionally confounded by a high rate of crossover between treatment modalities in both study arms.

A single center randomized prospective trial conducted at the Cleveland Clinic compared continuous and intermittent RRT in 80 patients assigned to either continuous venovenous hemodialysis (CVVHD) or IHD after matching for baseline illness severity (27). Although this study found some differences with respect to greater fluid removal and decreased vasopressor requirement in patients assigned to CVVHD, mortality was similar in CVVHD and IHD arms (67.5% versus 70% respectively, p > 0.99) as was the rate of kidney recovery.

In another single-center study, Uehlinger et al. (28) randomized 125 patients with AKI admitted to an ICU at a university hospital in Switzerland between 1998 and
2000 to CVVHDF \( (n = 70) \) or IHD \( (n = 55) \). The two groups were comparable at initiation of therapy with respect to gender, severity of illness, etiology, and markers of AKI. No differences were found in ICU mortality (34% CVVHDF versus 38% IHD, OR 1.16, \( p = 0.71 \)) or in-hospital mortality (47% CVVHD versus 51% IHD, OR 1.18, \( p = 0.72 \)). There was also no difference in hemodynamic stability, use of vasopressor agents, fluid balance, duration of RRT, recovery of kidney function, or length of stay. Of note, to avoid inciting or exacerbating hemodynamic instability, IHD was provided using short (2–3 hours) treatments with limited ultrafiltration during the first days of therapy, resulting in a requirement for daily IHD sessions for the majority of patients. Over the duration of treatment, the median frequency of IHD was 5 sessions/week.

More recently, the results of the Hemodiafe Study, the largest prospective randomized controlled study comparing CRRT and IHD have been reported (29). This study enrolled 360 patients in 21 ICUs in France between 1999 and 2003. Among the 359 patients who received their assigned treatment (IHD: \( n = 184 \); CVVHDF: \( n = 175 \); one patient randomized to CVVHDF withdrew consent prior to treatment) there was no difference in the primary study endpoint of 60-day survival between treatment groups (31.5% in IHD versus 32.6% in CVVHDF; \( p = 0.98 \)). Treatment modality also had no significant effect on length of stay, rate, and time to recovery of kidney function or frequency of adverse events (except for hypothermia which was more common during CVVHDF). Interestingly, despite the hemodynamically unstable population (vasopressors were used in greater than 85% of patients), IHD was not associated with increased frequency of hypotension, a finding the Hemodiafe study group ascribed to standardized use of synthetic membranes, bicarbonate buffers and adherence to strict guidelines including gradual ultrafiltration, and use of cool dialysate with a high sodium concentration. This led the investigators to conclude that virtually all patients can be treated with IHD under standardized conditions.

Multiple meta-analyses comparing outcomes with IHD and CRRT have been published. A 2002 meta-analysis by Kellum et al. (30) that included 13 studies (of which only three were RCTs) suggested that CRRT might be associated with a lower relative mortality risk after adjustment for severity of illness and study quality. In contrast, Tonelli et al. (31) concluded that CRRT does not seem to offer any survival advantage over IHD, restricting their meta-analysis to RCTs. Three more recent meta-analyses reached the same conclusion after including the RCTs by Uehlinger et al. and the Hemodiafe study group. A Cochrane review in 2007 analyzed 15 RCTs and found that mortality, renal recovery, and episodes of hypotension did not differ between modalities although mean arterial pressures were higher in patients on CRRT (32). A meta-analysis by Bagshaw et al. (33) included nine RCTs and again showed no differences in mortality or recovery of kidney function, although CRRT was associated with less hemodynamic instability and greater volume removal. The authors raised concern, however, that multiple flaws in design, conduct, and quality of the included studies prevented them from drawing any definitive conclusions about the effect of modality on outcome. Finally, a systematic review by Pannu et al. (34) examined data from 30 RCTs and eight prospective cohort studies, and found no differences in survival, hypotension, or recovery of kidney function in patients treated using CRRT when compared with IHD. However, they calculated greater costs associated with CRRT and therefore concluded that IHD may be preferable to CRRT in AKI patients.

Comparison with Hybrid Therapies
Sustained, low efficiency dialysis (SLED) and extended daily dialysis (EDD) are modified forms of IHD, sometimes referred to as hybrid therapies, devised to utilize standard IHD machine technology while providing the slower solute and fluid removal of CRRT. In these modalities, solute clearance and volume removal are extended over 6–16 hours using conventional hemodialysis machines with dialysate and blood flows that are intermediate between IHD and CRRT. Observational prospective studies have shown that SLED is safe and an effective method of treating AKI in critically ill patients with decreased cost when compared with CRRT (35). Although no studies have evaluated outcomes with these modalities, several studies have evaluated intermediate parameters. Keilstein et al. (35) randomized 39 patients to 12 hours of EDD or CVVH and observed no difference in efficiency or hemodynamic tolerability. In a second study, Kumar et al. (36) assigned 54 patients with AKI to either CRRT or EDD. EDD was found to be a safe and effective alternative to CRRT with comparable hemodynamic and solute clearance profile but with decreased incidence of clotting and lower anticoagulation requirements.

Comparison of Arteriovenous and Venovenous Therapies
Continuous renal replacement therapies were historically delivered via an arteriovenous circuit (7,37–39). Reliance on systemic pressure to drive blood flow through the extracorporeal circuit permitted the use of a technologically simple device extracorporeal circuit but imposed important limitations on achievable effective solute clearance. This was particularly problematic in the critically ill patient with hemodynamic instability in whom low systemic arterial pressure limited blood flow. In addition, the prolonged arterial cannulation required was associated with high rates of complications, including bleeding and arterial thrombosis (40).

As a result of the problems with the arteriovenous approach, venovenous modalities of the continuous therapies were developed (41–43). Using a single dual-lumen venous catheter for access, the venovenous modalities require a blood pump to provide a constant blood flow independent of mean arterial blood pressure. However, the use of a pump-driven extracorporeal circuit necessitates more sophisticated instrumentation, including pressure monitors and air-leak detectors. With
the addition of balancing mechanisms for ultrafiltration control, the technological simplicity of continuous arteriovenous hemofiltration has been replaced by equipment that approaches the complexity of conventional hemodialysis machines. Given the more efficient solute clearance, more precise regulation of ultrafiltration and avoidance of prolonged arterial cannulation, with its potential complications of arterial injury, thrombosis and hemorrhage, the venovenous modalities of CRRT have virtually replaced the arteriovenous therapies (44).

An expert consensus conference held in 2000 concluded that pump-driven venovenous therapy is the preferred modality for CRRT whenever the needed equipment and expertise for its implementation are available (45).

Comparison of Convective and Diffusive Therapies

Continuous therapy can be provided as hemofiltration, hemodialysis, or hemodiafiltration. Continuous hemofiltration relies on convective solute clearance, whereas continuous dialysis provides primarily diffusive clearance (Fig. 1). Hemodiafiltration employs a variable combination of both mechanisms. Convection provides better clearance of middle molecules or solutes with molecular weights above 500–1000 Da. It was proposed that convective modalities (continuous hemofiltration and hemodiafiltration) modulate the immune response by clearing the cytokines that promote and perpetuate the systemic inflammatory response syndrome (SIRS) (46,47). Indeed, CVVH was associated with lower levels of plasma tumor necrosis factor-α (TNF-α) and IL-6 levels, although not to a significant extent (9). It has been argued, however, that cytokine clearance during hemofiltration is inconsequential in comparison to their endogenous production and that anti-inflammatory and pro-inflammatory cytokines are both removed by hemofiltration (50). In addition, membrane adsorption has contributes substantially to cytokine removal during CVVH, particularly when polyacrylonitrile membranes are used, and that saturation occurs rapidly, within the first 1–2 hours (51). Thus, in the absence of outcome data, no recommendations can be made to favor either convective or diffusive modalities.

Conclusions

The available evidence does not support any robust recommendations regarding the choice of RRT in the ICU. Continuous therapies may not offer a convincing survival advantage but have not been shown to be inferior therapy to IHD, either. With the wide availability of CRRT machines and the increasing complexity of critically ill patients, it is likely to remain one of the preferred modalities of renal replacement in the ICU. This is especially true in certain categories of patients, such as those with fulminant liver failure. The use of new hybrid modalities, such as SLED, is increasing as more centers develop familiarity with this technique. SLED may also serve as a bridging modality, as patients are transitioned from CRRT to conventional IHD. As no single modality has emerged as the standard of care, choosing a renal replacement strategy for the critically ill patient relies primarily on the resources available and personal expertise in any given institution. Future focus should be directed towards

Fig. 1. Mechanisms of solute transport by diffusion (hemodialysis) and convection (hemofiltration). During hemodialysis, solutes diffuse down their concentration gradient from blood into dialysate. Solute removal for low molecular weight solutes is more efficient than for higher molecular weight solutes. During hemofiltration, solutes are transported entrained in the flow of plasma water during ultrafiltration (solvent drag) and passively cross the membrane in the absence of a concentration gradient. Solute removal for low and high molecular weight solutes is similar until the solute diameter approaches the membrane pore size.
optimizing the currently available modalities, improving the safety and effectiveness of their use to improve the survival of patients with the ominous prognosis associated with AKI.

References


