High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis

Ryan Van Wert, MD; Jan O. Friedrich, MD, DPhil; Damon C. Scales, MD, PhD; Ron Wald, MDCM, MPH; Neill K. J. Adhikari, MDCM, MSc; for the University of Toronto Acute Kidney Injury Research Group

Objective: To determine the effect of renal replacement therapy dose on mortality and dialysis dependence in patients with acute kidney injury.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to October 2009; PubMed “Related Articles;” bibliographies of included trials; and additional information from trial authors.

Study Selection: Randomized and quasi-randomized, controlled trials in adults with acute kidney injury prescribed high- vs. standard-dose continuous renal replacement therapy (≥30 mL/kg/hr vs. <30 mL/kg/hr), intermittent hemodialysis, or sustained low-efficiency dialysis (daily vs. alternate day, or by target biochemistry).

Data Extraction: Three authors independently selected studies and extracted data on outcomes and study quality. Meta-analyses used random-effects models.

Data Synthesis: Of 5416 citations, 12 trials (n = 3999) met inclusion criteria. Modalities included continuous renal replacement therapy (7 trials), intermittent hemodialysis (3 trials), sustained low-efficiency dialysis (1 trial), and all three (1 trial). Study quality was moderate-high. Meta-analyses found no effect of high-dose renal replacement therapy on mortality (risk ratio, 0.89; 95% confidence interval, 0.77–1.03; 12 trials; n = 3954) or dialysis dependence among survivors (risk ratio, 1.15; 95% confidence interval, 0.92–1.44; 8 trials with events; n = 1743). The effect on mortality was similar (all interaction p values were nonsignificant) in patients with sepsis (risk ratio, 1.02; 95% confidence interval, 0.85–1.23; 9 trials; n = 1786) vs. without sepsis (risk ratio, 0.89; 95% confidence interval, 0.75–1.05; 8 trials; n = 1955), treated exclusively with continuous renal replacement therapy (risk ratio, 0.87; 95% confidence interval, 0.71–1.06; 7 trials; n = 2462) vs. other modalities alone or in combination (risk ratio, 0.92; 95% confidence interval, 0.70–1.21; 5 trials; n = 1492), and in trials with low (risk ratio, 0.96; 95% confidence interval, 0.85–1.09; 6 trials; n = 3475) vs. higher (risk ratio, 0.76; 95% confidence interval, 0.53–1.09; 6 trials; n = 479) risk of bias.

Conclusions: High-dose renal replacement therapy in acute kidney injury does not improve patient survival or recovery of renal function overall or in important patient subgroups, including those with sepsis. (Crit Care Med 2010; 38:1360–1369)

Key Words: acute kidney injury; acute renal failure; renal replacement therapy; renal dialysis; randomized controlled trial; meta-analysis

Severe acute kidney injury (AKI) occurs in approximately 6% of patients admitted to intensive care units (ICUs) (1) and in up to half of patients with septic shock (2). 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 [IHD]) and sustained low-efficiency dialysis (SLED), treatment dose is typically quantified by the number of sessions (or hours) per week that RRT is applied.

High-dose RRT might benefit critically ill patients with AKI by providing better clearance of toxic molecules or by attenuating the systemic inflammatory response associated with septic shock, pancreatitis, and cardiopulmonary bypass. Several randomized, controlled trials have studied the optimal dose of RRT. A recent systematic review (3) limited to two trials comparing high-dose (≥35 mL/kg/hr) vs. standard-dose (20 mL/kg/hr) continuous venovenous hemofiltration (CVVH) in patients with AKI found that high-dose therapy reduced mortality (risk ratio [RR], 0.74; 95% confidence interval [CI], 0.63–0.88). Since publication of this review, additional randomized, controlled trials have been completed. We therefore conducted an updated systematic review and meta-analysis to de-
define high-dose RRT as and consensus among the investigators, we dependence among survivors. After discussion

IHD, or SLED) and for at least 48 hrs; and 4) applied using the same RRT modality (CRRT, RRT, with both assigned dose strategies ap-

plied in the same RRT modality (CRRT, IHD, or SLED), and for at least 48 hrs: and 4) outcome: all-cause mortality or dialysis de-

pendence among survivors. After discussion and consensus among the investigators, we defined high-dose RRT as \( \geq 30 \text{ mL/kg/hr} \) of prescribed effluent flow in CRRT, or six or more sessions per week of 3–4 hrs each (IHD) or 8–12 hrs each (SLED). We defined standard-dose RRT to be \(<40 \text{ mL/kg/hr} \) of prescribed effluent flow (CRRT) or two to four sessions per week (IHD and SLED). We ac-

cepted authors’ reporting of prescribed CRRT dose without adjustment for the effects of net fluid removal or prefilter replacement fluid on dose (if hemofiltration or hemodiafiltration used). We considered for inclusion: 1) trials with cointerventions if they were applied equally in both groups; 2) trials using different modalities of RRT (i.e., CRRT, IHD, or SLED), provided that high-dose and standard-dose therapies were not delivered by exclusively different modalities; and 3) trials in which RRT was initiated at different times in the high-

dose and standard-dose groups, provided that dose clearly differed between the treatment groups throughout the entire study period (for example, differential predialysis serum creati-
nine or urea targets for intermittent RRT or different effluent flow rates for CRRT). We considered continuous venovenous hemodial-

ysis (CVVHD, CVVH, and continuous venovenous hemodiafiltration (CVVHDF) to be different modes within the same modality (CRRT) and did not exclude trials using different CRRT modes in the high-dose and stan-
dard-dose groups. We excluded crossover tri-

als in which all patients received treatment and control interventions in random order.

**Data Abstraction and Validity Assessment**

Three unblinded reviewers independently abstracted data from included trials, including patient population, RRT methods, outcomes, and study quality. We considered trials to be at low risk for bias if allocation was adequately concealed, \(<5\%\) of patients were lost to follow-up for mortality, and the trial was not stopped early for benefit. We considered trials to be at higher risk for bias if not all three criteria were present. Disagreements between reviewers at the stages of study selection and data extraction that remained after author contact were resolved by consensus.

**Data Analysis**

Our primary outcome was all-cause mor-
tality assessed at 90 or 60 days after random-

ization or, if not available, at hospital dis-

charge, 30 or 28 days after randomization, ICU discharge, or after stopping renal replacement therapy (in descending order of preference). Secondary outcomes included dialysis dependence among survivors (with the same pre-

ferred order of time point) and hypotension, as defined by the author. We anticipated that trials would report hypotension differently, precluding a pooled analysis. Pooled analyses included trials (and groups within trials) using CRRT, IHD, and SLED, with dose classified according to prespecified definitions. When a trial had more than one group receiving either high-dose or standard-dose RRT, we combined groups to create one high-dose and one standard-dose group per trial.

We used Review Manager 5.0.22 (The Co-

chrane Collaboration, Oxford, England) to calculate pooled RRs and 95% CIs for mor-
tality and dialysis dependence and R 2.7.2 (http://www.r-project.org) to create figures. We used random-effects models, which incorporate between-trial heterogeneity and thus generally give wider CIs when heterogeneity is present. We assessed statistical heterogeneity among tri-

als using \( I^2 \), the percentage of total variability across studies attributable to heterogeneity rather than chance (4, 5), and used published guidelines for low \( (I^2 = 25\% \text{ to } 49\%) \), moderate \( (I^2 = 50\% \text{ to } 74\%) \), and high \( (I^2 \geq 75\%) \) heter-

ogeneity (5). Continuous variables are expressed as mean ± sd, unless otherwise indicated.

We performed subgroup analyses for mor-
tality in patients with sepsis at randomization vs. not, treated exclusively with CRRT vs. not, and enrolled in trials with low vs. higher risk of bias. We also performed a subgroup analysis for dialysis dependence in survivors in patients treated exclusively with CRRT vs. not. We hy-

thesized that high-dose RRT would be more beneficial in subgroups of patients with sepsis (because of the extreme inflammatory re-

sponse), treated exclusively with CRRT (be-

cause of improved hemodynamic stability), and enrolled in trials at higher risk for bias (in which treatment benefits may be amplified). To test for interaction between dose and sub-


group, pooled RRs between subgroups were compared using z tests.

Finally, we anticipated that the timing of initiation of RRT after the onset of AKI might differ between high-dose and standard-dose groups of patients in some trials. We therefore conducted sensitivity analyses for the out-

comes of mortality and dialysis dependence in survivors restricted to trials and arms within trials in which patients started assigned ther-

apy at the same time after enrollment. To assess publication bias, we visually examined a funnel plot of study precision vs. effect on mortality for evidence of asymmetry.

**RESULTS**

**Study Flow**

Our search strategy yielded 5416 cita-

tions (Fig. 1). We retrieved 32 articles for detailed evaluation, of which 20 were ex-

cluded (Appendix B). Twelve trials (3999 patients) met criteria for inclusion (6–

17). The authors of eight trials provided additional data (7, 9, 10, 12–14, 16, 17); the author of one trial (8) informed us that he was unable to provide any addi-

tional information.

**Description of Included Studies**

Trials enrolled a median of 158.5 pa-

tients (range, 18–1508) and were con-

ducted in one (6, 8, 10–14, 16) or two (7, 9) centers (Tables 1 and 2), except for two recently published, large, multicenter trials (15, 17; additional details in [18–21]). En-

rolled patients had a critical illness (i.e. trauma [6], pancreatitis [12], or various [7]), or were admitted to an ICU (8–11, 13–17) with AKI, defined by abnormal bio-

chemistry (serum creatinine or urea) or a complication of oliguria (e.g., hyperkalemia or volume overload). Two trials required oliguria (9, 10). Seven trials specifically ex-

cluded patients with chronic renal failure (8, 9, 13, 16, 17) or end-stage renal disease
Patients had high illness severity (median Acute Physiology and Chronic Health Evaluation II score, 26 in 7 trials) and many had sepsis (median, 43.5% of enrolled patients in 12 trials).

Eleven trials used one modality exclusively: IHD (6–8), CRRT [CVVH (9, 10, 12); CVVH or CVVHD (11); CVVHDF (13); CVVHD (14, 15)], or SLED (16). Two of these trials used more than one CRRT mode and allocated patients to high-dose or standard-dose CVVH or CVVHD in a factorial design (11), or to high-dose CVVHD vs. standard-dose CVVH (13). One trial studied high-dose vs. standard-dose RRT and assigned patients to IHD vs. CVVHDF or SLED based on hemodynamic stability (17). Trials of CVVH or CVVHD administered replacement fluid either prefilter (12–14, 17) or postfilter (9–11, 15).

Two early trials of IHD (6, 7) targeted differential predialysis serum creatinine and urea in the high-dose and standard-dose groups, whereas other trials explicitly varied the frequency of IHD sessions (8, 17). Trials of IHD reported delivering 5.4 to 7.0 and 2.5 to 3.2 sessions per week in the high-dose and standard-dose arms, respectively (6–8, 17). Prescribed $Kt/V_{urea}$ (a dimensionless coefficient defining urea clearance per session, where $K$ is the dialyzer clearance of urea, $t$ is time, and $V_{urea}$ is the volume of distribution of urea), when reported, was 1.2 to 1.4 per session (8, 17), although the targeted $Kt/V_{urea}$ was not achieved in one trial (8). One trial of SLED defined dose by target urea (<15 mmol/L vs. 20–25 mmol/L), with patients administered the high dose receiving approxi-

Figure 1. Flow of studies through the meta-analysis. RRT, renal replacement therapy.

### Table 1. Patient characteristics in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Randomized, n</th>
<th>Centers, n</th>
<th>Age, yr</th>
<th>Male, %</th>
<th>APACHE II/III</th>
<th>Oliguria, %</th>
<th>Intensive Care Unit Days at Enrollment</th>
<th>Creatinine, μmol/L</th>
<th>Urea, mmol/L</th>
<th>Sepsis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conger (6)</td>
<td>18</td>
<td>1</td>
<td>23</td>
<td>100</td>
<td>NR</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0&quot;</td>
</tr>
<tr>
<td>Gillum et al (7)</td>
<td>34</td>
<td>2</td>
<td>56</td>
<td>85</td>
<td>NR</td>
<td>71</td>
<td>6&quot;</td>
<td>NR</td>
<td>NR</td>
<td>38</td>
</tr>
<tr>
<td>Schiff et al (8)</td>
<td>160</td>
<td>1</td>
<td>60</td>
<td>55</td>
<td>NR/87</td>
<td>46</td>
<td>NR</td>
<td>420</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Bouman et al (9)</td>
<td>106</td>
<td>2</td>
<td>68</td>
<td>59</td>
<td>23/84</td>
<td>100</td>
<td>1.3</td>
<td>NR</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Ronco et al (10)</td>
<td>425</td>
<td>1</td>
<td>61</td>
<td>56</td>
<td>23</td>
<td>100</td>
<td>2.5</td>
<td>318</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Morgera et al (11)</td>
<td>24</td>
<td>1</td>
<td>65</td>
<td>58</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
<td>254</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>Jiang et al (12)</td>
<td>37</td>
<td>1</td>
<td>54</td>
<td>57</td>
<td>NR</td>
<td>84</td>
<td>NR&quot;</td>
<td>232</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Saudan et al (13)</td>
<td>206</td>
<td>1</td>
<td>63</td>
<td>61</td>
<td>25</td>
<td>37</td>
<td>3.9</td>
<td>428</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Tolwani et al (14)</td>
<td>200</td>
<td>1</td>
<td>60</td>
<td>58</td>
<td>26</td>
<td>64</td>
<td>8</td>
<td>376</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>Bellomo et al (15)</td>
<td>1508</td>
<td>35</td>
<td>65</td>
<td>65</td>
<td>NR/102</td>
<td>60</td>
<td>2.1</td>
<td>334</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>Faulhaber-Walter et al (16)</td>
<td>157</td>
<td>1</td>
<td>51</td>
<td>63</td>
<td>32</td>
<td>73</td>
<td>5.9</td>
<td>273</td>
<td>22</td>
<td>72&quot;</td>
</tr>
<tr>
<td>Palevsky et al (17)</td>
<td>1124</td>
<td>27</td>
<td>60</td>
<td>71</td>
<td>26</td>
<td>78</td>
<td>6.8&quot;</td>
<td>362</td>
<td>24</td>
<td>63</td>
</tr>
</tbody>
</table>

APACHE, Acute Physiology and Chronic Health Evaluation [APACHE II (38); APACHE III (39)]; NR, not reported.

"Patients with septic shock causing acute kidney injury were excluded from the study, but the number of patients with sepsis (if any) was not reported; there were 6 (SD, 3) days between acute kidney injury and initiation of intermittent hemodialysis – 5 (SD, 2) days in the high-dose group and 7 (SD, 3) days in the standard-dose group; mean creatinine clearance 6 mL/min from 3-hr urine collection; one-third of the patients were in the intensive care unit; includes patients with the systemic inflammatory response syndrome; interval from onset of acute kidney injury to randomization was 3.2 (SD, 2.0) days (37)."
Continuous renal replacement therapy

**Gillum et al (7)** Clinician Cr < 442; Urea < 25

**Schiff et al (8)** Clinician Daily; Kt/V ≥ 0.92/session; 9 days

**Continuous renal replacement therapy**

**Bouman et al (9)** (postfilter CVVHDF)

**Ronco et al (10)** (postfilter CVVHDF)

**Morgera et al (11)** (postfilter CVVH and CVVHD)

**Jiang et al (12)** (prefilter CVVH)

**Sussan et al (13)** (prefilter CVVH and CVVHD)

**Tolwani et al (14)** (prefilter CVVHDF)

**Bellomo et al (15)** (postfilter CVVHDF)

**Sustained low-efficiency dialysis**

**Faulhaber Walter et al (16)**

**Combined modalities**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cessation of Study RRTa</th>
<th>Prescribed Doseb</th>
<th>Delivered Dosec; Days of Study RRT</th>
<th>Biochemistry During Therapy</th>
<th>Delivered Dosec; Days of Study RRT</th>
<th>Biochemistry During Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cr = 309; Urea = 18 (pre-IHD)</td>
<td>Cr = 884; Urea = 12.2 days</td>
<td>Cr = 857; Urea = 43 (pre-IHD)</td>
</tr>
<tr>
<td>Conger (6)</td>
<td>Clinician</td>
<td>Cr &lt; 442; Urea &lt; 25</td>
<td>7.0/wk; 13.8 days</td>
<td>Cr = 309; Urea = 18 (pre-IHD)</td>
<td>Cr &lt; 884; Urea &lt; 54</td>
<td>Cr = 857; Urea = 43 (pre-IHD)</td>
</tr>
<tr>
<td>Gillum et al (7)</td>
<td>Clinician</td>
<td>Cr &lt; 442; Urea &lt; 21</td>
<td>6.1/wk; 18.3 days</td>
<td>Cr = 465; Urea = 36 (pre-IHD)</td>
<td>Cr &lt; 796; Urea &lt; 18 days</td>
<td>Cr = 804; Urea = 36 (pre-IHD)</td>
</tr>
<tr>
<td>Schiff et al (8)</td>
<td>Clinician</td>
<td>Daily; Kt/V ≥ 1.2/session</td>
<td>6.2/wk; Kt/V = 0.92/session; 21 days (time-averaged)</td>
<td>Cr = 465; Urea = 36 (pre-IHD)</td>
<td>3.2/wk; Kt/V = 0.94/session; 16 days (time-averaged)</td>
<td>Cr = 840; Urea = 37 (time-averaged)</td>
</tr>
</tbody>
</table>

| Protocol | ≥72 L/day | Protocol | 35 mL/kg/hr | Protocol | 25 mL/kg/hr | Protocol | 42 L/3/day | Protocol | 35 mL/kg/hr | Protocol | 1 L/h (14 mL/kg/hr) | Protocol | 22.0 mL/kg/hr; 22 mL/kg/hr; 20 mL/kg/hr; 18.9 mL/kg/hr; 11 days |
|----------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 72 L/day | 48.2 mL/kg/hr                   | 35 mL/kg/hr                     | 42 L/24 hr                      | 22 mL/kg/hr                    | 25 mL/kg/hr                    | 4 L/h                            | 36 (time-averaged)              | 14 mL/kg/hr                    | 20 mL/kg/hr                    | 18.9 mL/kg/hr                   | 11 days                         | 25 mL/kg/hr                    | 18.9 mL/kg/hr                   | 11 days                         |
| 1st 24 hr | NR                               | 0.94/session; 1.3/session        | 36 (time-averaged)              | NR                               | 7.7 sessions of 8.5 hrs each; 20–25 | 1 session in first 24 hrs, then target urea < 15 | 14.7 (interdialytic interval) | 22 mL/kg/hr                    | 17 mL/kg/hr                    | 9.7 days                         | 22 mL/kg/hr                    | 20 mL/kg/hr                    | 17 mL/kg/hr                    | 9.7 days                         |
| 8.9 hrs each; | Urea = 14.7                      | 24.0 mL/kg/hr                  | NR                               | 12.2 mL/kg/hr                   | 25 mL/kg/hr                    | 35 mL/kg/hr                     | 22 mL/kg/hr                    | 20 mL/kg/hr                    | 17 mL/kg/hr                    | 9.7 days                         | 20 mL/kg/hr                    | 17 mL/kg/hr                    | 20 mL/kg/hr                    | 9.7 days                         |
| NR                    | 13 (IHD)                         | 6.3 days                        | 1363Crit Care Med 2010 Vol. 38, No. 5 |

**Cesation refers to discontinuation of study renal replacement therapy by clinician discretion, by protocol (typically defining renal recovery), or when a fixed timepoint was reached:**

- **prescribed and delivered doses refer to target urea or creatinine; number of weekly sessions or R/U per session (IHD, excluding the first session in one trial (17)); or effluent flow (continuous renal replacement therapy).**
- **For trials of continuous renal replacement therapy, effluent flow rates are as reported in the publications (expressed in weight-based units, if possible), without adjustment for the effects of net fluid removal or prefiltre replacement fluid (if CVVH or CVVHDF used) on dose:**
- **patients were randomized to 1 of 3 groups: high-dose or standard-dose CVVH starting ≥ 12 hrs after meeting inclusion criteria, or standard-dose CVVH starting only for clinical indications**
- **In the last group, 6/36 (17%) patients did not receive RRT because of death (n = 10) or renal recovery (n = 8):**
- **patients were randomized to 1 of 3 CVVH dose groups, 2 high-dose groups and 1 low-dose group:**
- **patients were randomized to 1 of 4 groups: high-dose or standard-dose CVVH, or high-dose or standard-dose CVVHDF.**
- **Weight-based prescribed doses are calculated based on an assumed mean weight of 70 kg; patients were randomized to 1 of 4 groups: high-dose or standard-dose CVVH starting within 48 hrs or 96 hrs after the onset of abdominal pain.**
- **All patients had pancreatitis and acute kidney injury.**
- **Mean patient weight in each group was obtained from the author:**
- **patients were randomized to a high-dose CVVHDF group (mean replacement 24 mL/kg/hr plus mean dialysate 18 mL/kg/hr) or a standard-dose CVVHDF group (mean 25 mL/kg/hr):**
- **within the high-dose and standard-dose groups, patients received IHD if hemodynamically stable and CRRT or sustained low-efficiency dialysis (by centre preference) if unstable.**

Crit Care Med 2010 Vol. 38, No. 5
Table 3. Factors related to risk of bias of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence Generation</th>
<th>Concealment of Allocation</th>
<th>Trial Stopped Early for Benefit</th>
<th>Intention-to-Treat Analysis</th>
<th>Postrandomization Withdrawals From Mortality Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conger et al (6)</td>
<td>Quasi-randomized* (alternate allocation within each subgroup)</td>
<td>No</td>
<td>Not reported*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gillum et al (7)</td>
<td>Coin-flip to assign patients paired by etiology of acute kidney injury</td>
<td>Incomplete (second patient within pair not concealed)</td>
<td>Not reported*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Schiffl et al (8)</td>
<td>Quasi-randomized (alternate allocation)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bouman et al (9)</td>
<td>Computer-generated</td>
<td>Yes (sequentially numbered sealed opaque envelopes)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ronco et al (10)</td>
<td>Computer-generated</td>
<td>Yes (central randomization)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Morgera et al (11)</td>
<td>Not reported</td>
<td>Unclear (not reported)*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Jiang et al (12)</td>
<td>Quasi-randomized (alternate allocation)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Saudan et al (13)</td>
<td>Computer-generated</td>
<td>Yes (sequentially numbered sealed opaque envelopes)</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tolwani et al (14)</td>
<td>Computer-generated</td>
<td>Yes (sequentially numbered sealed opaque envelopes)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bellomo et al (15)</td>
<td>Computer-generated</td>
<td>Yes (central randomization)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Faulhaber-Walter et al (16)</td>
<td>Computer-generated</td>
<td>Yes (local independent randomization by statistician)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Palevsky et al (17)</td>
<td>Computer-generated</td>
<td>Yes (central randomization)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*If no patient with similar injuries had been previously treated, then the new patient was assigned by alternate allocation. If a patient’s injury pattern was similar to another patient in the protocol, then the new patient was assigned the alternate treatment. Two patients were assigned by direct investigator allocation to the standard-dose arm “because they had injuries similar to other patients in [the high-dose arm] to which they could be compared;” these trials did not report a sample size calculation; we were unable to reach the author of this trial; confirmed in correspondence with study author.

Clinicians’ discretion (6–8, 10, 12, 14), or when certain clinical criteria defined in the study protocol were met (9, 13, 15–17).

**Study Quality**

Most trials were at low risk for bias (9, 10, 14–17). All patients were analyzed according to the group (Table 3) to which they were initially assigned, and withdrawals of randomized patients from the mortality analysis either did not occur (6–14) or comprised <5% of randomized patients (15–17). Caregiver blinding was not practical in any trial. Seven trials (9, 10, 13–17) clearly concealed allocation, whereas three quasi-randomized trials used alternate allocation (6, 8, 12), one trial used a coin-flip to assign patients paired by etiology of AKI (7), and one trial did not report the method of allocation (11). The author of one trial informed us that it was stopped early for benefit (15).

**Clinical Outcomes**

Trials varied in the timing of mortality reporting: 6 mos (6), 90 days (13, 15), 60 days (17), or 28 days (16) after randomization; at discharge from the hospital (7, 9, 12, 14) or ICU (11); or 14 days (8) or 15 days (10) after cessation of RRT (which was provided for a mean of 9–16 days). Pooled mortality from 12 trials (n = 3954) showed no benefit of high-dose vs. standard-dose RRT (RR, 0.89; 95% CI, 0.77–1.03; p = .12) (Fig. 2). There was moderate statistical heterogeneity (I² = 67%) in this analysis. Visual inspection of a funnel plot did not suggest publication bias (Appendix C).

Similarly, trials varied in the timing of reporting of dialysis dependence in survivors: 6 months (6), 90 days (13, 15), 71 days (9), 60 days (17), or 28 days (16) after randomization; at discharge from the hospital (7, 12, 14); or 14 days after cessation of RRT (8). Two trials (n = 68) reported no survivors requiring dialysis at last follow-up (6, 9). Data from eight trials (n = 1743) with events showed no effect of high-dose vs. standard-dose RRT on the risk of dialysis dependence in survivors (RR, 1.13; 95% CI, 0.92–1.44; p = .23) (Fig. 3). There was no evidence of statistical heterogeneity in this analysis (I² = 0%).

**Hypotension**

Several trials reported hypotension during RRT, but widely variable definitions precluded meta-analysis. One multicenter trial (17) reported more patients in the high-dose vs. standard-dose group with hypotension requiring vasopressor therapy 81 of 563 [14.4%] vs. 56 of 561 [10.0%]; p = .02 or other intervention (212 of 563 [37.7%] vs. 168 of 561 [29.9%]; p = .006), but no difference in patients with hypotension requiring cessation of RRT (55 of 563 [9.8%] vs. 49 of 561 [8.7%]; p = .55).
We obtained supplemental information on hypotension from authors of three trials (10, 12, 16). One small trial reported a similar risk of hypotension (high-dose, 2 of 18 [11.1%] vs. standard-dose, 4 of 19 [21.2%]; p = .66 by Fisher’s exact test) (12). In the trial of SLED (16), the number of days on which mean arterial pressure declined to <70 mm Hg or vasopressor support was required was similar (high-dose 7.8 ± 7.5 days vs. standard-dose 6.8 ± 7.0 days; p = .39). One trial reported “no difference” in hypotension episodes (10).

Sensitivity and Subgroup Analyses

When analyses were restricted to trials in which both groups started RRT at the same time after randomization, there was no effect of high-dose RRT on mortality (RR, 0.88; 95% CI, 0.76–1.03; 10 trials; n = 3866) (8–17) or dialysis dependence (RR, 1.15; 95% CI, 0.92–1.44; 7 trials with events; n = 1727) (8–15) vs. other modalities, exclusively or in a combined manner (RR, 0.92; 95% CI, 0.70–1.21; 5 trials; n = 1492; interaction p = .75) (6–8, 16, 17); and 3) enrolled in trials with low risk of bias (RR, 0.96; 95% CI, 0.85–1.09; 6 trials, n = 3475) (9, 10, 14–17) vs. trials at higher risk for bias, presumably because of no or unclear allocation concealment (8–11, 12) or early stopping (13) (RR, 0.76; 95% CI, 0.53–1.09; 6 trials, n = 479; interaction p = .23). There was moderate heterogeneity (I² = 50% to 74%) in each of the subgroup and sensitivity analyses for mortality.

The effect of high-dose RRT on dialysis dependence in survivors was similar in patients treated exclusively with CRRT (RR, 1.41; 95% CI, 0.90–2.21; 4 trials with events; n = 1010) (12–15) vs. other modalities (RR, 1.07; 95% CI, 0.83–1.39; 4 trials with events; n = 733; interaction p = .30) (7, 8, 16, 17). There was no evidence of heterogeneity (I² = 0%) in either analysis.

DISCUSSION

The main results of this systematic review and meta-analysis are that high-dose RRT for patients with AKI does not reduce mortality or dialysis dependence in survivors. Our results are consistent with a large observational study (22) and with two recent, multicentered, randomized trials included in the meta-analysis (15, 17), strengthening our conclusions. Our novel finding is that results were consistent among subgroups defined by presence of sepsis and modality of RRT (continuous vs. intermittent).

RRT at different times according to different biochemical targets, and one standard-dose group in one trial (9) in which RRT was started only for clinical indications (vs. the two other groups in which RRT was started within 12 hrs of meeting inclusion criteria).

The effect of high-dose vs. standard-dose RRT on mortality was similar in patients (Fig. 4): 1) with sepsis (RR, 1.02; 95% CI, 0.85–1.23; 9 trials; n = 1786) (9–17) and without sepsis (RR, 0.89; 95% CI, 0.75–1.05; 8 trials; n = 1955; interaction p = .28 for difference between RRs) (9, 10, 12–17); 2) treated exclusively with CRRT (RR, 0.87; 95% CI, 0.71–1.06; 7 trials; n = 2462) (9–15) vs. other modalities, exclusively or in a combined manner (RR, 0.92; 95% CI, 0.70–1.21; 5 trials; n = 1492; interaction p = .75) (6–8, 16, 17); and 3) enrolled in trials with low risk of bias (RR, 0.96; 95% CI, 0.85–1.09; 6 trials, n = 3475) (9, 10, 14–17) vs. trials at higher risk for bias because of no or unclear allocation concealment (6–8, 11, 12) or early stopping (13) (RR, 0.76; 95% CI, 0.53–1.09; 6 trials, n = 479; interaction p = .23). There was moderate heterogeneity (I² = 50% to 74%) in each of the subgroup and sensitivity analyses for mortality.

The effect of high-dose RRT on dialysis dependence in survivors was similar in patients treated exclusively with CRRT (RR, 1.41; 95% CI, 0.90–2.21; 4 trials with events; n = 1010) (12–15) vs. other modalities (RR, 1.07; 95% CI, 0.83–1.39; 4 trials with events; n = 733; interaction p = .30) (7, 8, 16, 17). There was no evidence of heterogeneity (I² = 0%) in either analysis.
trials were at low risk for bias. Although the 12 included trials assessed mortality at variable times, 10 of them evaluated mortality ≥28 days after randomization or at ICU or hospital discharge. An important limitation in the mortality analyses is the moderate statistical heterogeneity, suggesting that high-dose RRT may benefit a subgroup defined by patient characteristics or RRT procedure. However, there was no benefit in two prespecified and important clinical subgroups of septic patients and patients treated exclusively with CRRT.

Trials included in this review varied in RRT modality, dose, and timing of initiation, reflecting the diversity of clinical practice informing trial methodology. The dose arms within each trial shared the same modality, except for one trial that applied different modalities based on hemodynamic considerations unrelated to RRT dose (17). To investigate modality as a modifier of the effect of high-dose RRT, we performed a subgroup analysis of trials applying continuous vs. intermittent therapies and found no difference in effect. We considered performing a subgroup analysis to assess whether high-dose RRT benefits patients when started early, but variable definitions of AKI precluded a reliable assessment of timing of RRT initiation. Other recent meta-analyses have not found differential outcomes based on RRT modality or timing of initiation (3, 23, 24). Trials also varied in the RRT doses being compared. We categorized arms within trials as high-dose and low-dose based on consensus among the investigators. More fundamentally, the concept of RRT dose as defined by urea clearance does not incorporate other considerations, such as clearance of inflammatory mediators or achievement of desired fluid balance. It also presents operational challenges because there is no commonly accepted method of expressing dose across RRT modalities. For example, the Kt/Vurea measure used for IHD is based on steady-state assumptions for chronic hemodialysis and may underestimate actual urea clearance for intermittent therapies in patients with AKI (25). Despite these limitations, urea clearance remains widely used to measure RRT dose.

The results of our review support current clinical practice (26–28). In the United States, a survey (26) of 27 ICUs enrolling patients in a clinical trial (17) reported that most clinicians (>80%) prescribed a standard fixed dose of CRRT (median, 1825 mL/hr; interquartile range, 1200–2400 mL/hr; or 22 mL/kg/hr; 14–29 mL/kg/hr, assuming a mean patient weight of 84 kg [17])

Figure 4. Effect of high-dose vs. standard-dose renal replacement therapy on mortality. Subgroup analyses are shown for (A) patients with and without sepsis (interaction p = .28 for difference between risk ratios), (B) patients treated exclusively with continuous renal replacement therapy (CRRT) vs. other individual or combinations of modalities (interaction p = .75), and (C) studies with low risk for bias vs. higher risk for bias (interaction p = .23). Pooled risk ratios were calculated using random-effects models. Weight refers to the contribution of each study to each subgroup's estimate of treatment effect. In the Saudan 2006 study (13), the sepsis group in (A) includes patients specifically with sepsis-induced acute kidney injury. In (B), all patients in the Palevsky 2008 study (17) are included in the “other” subgroup. Alternatively, if the patients who received CRRT/sustained low-efficiency dialysis as initial modality in this trial are included in the “CRRT only” subgroup, then results are similar, i.e., CRRT only vs. other therapies: risk ratio, 0.89; 95% confidence interval (CI), 0.76–1.04 vs. risk ratio, 0.89; 95% CI, 0.68–1.09; interaction p = .81. Note that the CRRT group for this trial includes patients who received sustained low-efficiency dialysis, although the number of sustained low-efficiency dialysis treatments was small (5% of the number of CRRT sessions) (17).
and three to four sessions of IHD per week. Another survey of 34 ICUs in Australia and New Zealand (27) enrolling patients in a trial (15) estimated the mean prescribed CRRT dose as 24 mL/kg/hr; all sites prescribed dose independent of weight. Finally, a multicenter cohort study (54 ICUs in 23 countries) of CRRT practice (28) reported that only 12% of patients received doses exceeding 35 mL/kg/hr.

High-dose therapy is of theoretical interest for patients with sepsis-induced AKI, in whom proinflammatory mediators are increased (29). We detected no effect of high-dose RRT in patients with AKI and sepsis. However, our review does not address the role of RRT in patients with sepsis who have not yet developed AKI. Several trials have studied hemofiltration in patients with early sepsis or the systemic inflammatory response syndrome, but the effects are inconsistent (30–33). Another unanswered question is whether very-high-dose RRT improves outcomes compared to high-dose RRT. A 20-patient, randomized, controlled trial found that norepinephrine administration is independent in patients with AKI who re-

dependence in patients with AKI who re-


son of standard versus intensified extended di-


ACKNOWLEDGMENTS

CONCLUSION

Current evidence does not demonstrate reduced mortality or dialysis de-

pendence in patients with AKI who re-

ceive high-dose RRT. This finding is consistent across modalities of RRT and in patients with sepsis.

REFERENCES

tinational, multicenter study. JAMA 2005; 294: 813–818


4. Higgins JP, Thompson SG: Quantifying het-


6. Conget JD: A controlled evaluation of pro-

phylactic dialysis in post-traumatic acute re-


8. Schiff H, Lang SM, Fischer R: Daily hemo-
dialysis and the outcome of acute renal fail-


11. Morgera S, Slowinski T, Melzer C, et al: Re-

nal replacement therapy with high-cut-off he-


the course of acute pancreatitis. World J Gastroenterol 2005; 11:481–482

13. Saudan P, Niederberger M, De Seigneur S, et al: Adding a dialysis dose to continuous hemo-

filtration increases survival in patients with acute renal failure. Kidney Int 2006; 70:

1312–1317


son of standard versus intensified extended di-


20. Renal Replacement Therapy Trial Investigators, Bellomo R, Cass A, et al: Screening and study enrolment in the Randomized Evalua-


donized Evaluation of Normal versus Aug-

mented Level Replacement Therapy (RENA) Trial: High-dose versus standard-dose hemo-

filtration in acute renal failure. Blood Puri-

fication 2008; 26:407–416


23. Bagshaw SM, Berthiaume LR, Delaney A, et al: Continuous versus intermittent renal re-


apy in acute kidney injury: A survey of prac-


APPENDIX A

Search Strategy

We searched the following databases: Ovid MEDLINE 1950 to October 2009, week 5; EMBASE Classic and EMBASE 1947 to week 44, 2009; and EBVM Reviews – Cochrane Central Register of Controlled Trials Third Quarter 2009.

1. (CRRT or CVV$ or CAHV or CAVHD or IHD or SCUF).mp.
2. (contin$ adj4 (dialy$ or diafilt$ or hemodiafil$ or hemofilt$ or filt$ or ultrafilt$ or arterioven$ or venoven$)).mp.
3. (((non-continu$ or noncontinu$ or discontinu$) adj4 (dialy$ or diafilt$ or hemodiafil$ or hemofilt$ or filt$ or ultrafilt$ or arterioven$ or venoven$)).mp.
4. (SLEDD or SLEDDF or SLEDDF).mp.
5. (sustained or slow) adj4 (low efficiency or low-efficiency) adj4 (daily dialy$ or daily dialy$ or dialy$ or diafilt$ or hemodia$ or hemodia$ or hemofilt$ or hemofilt$).mp.
6. renal replacement therapy/or renal dialysis/or hemodiafiltration/or hemofiltration/or hemodialysis/or continuous renal replacement therapy/or extended daily dialysis/
7. or/1–7 [RRT terms]
8. exp sep$ or exp systemic inflammatory response syndrome/or exp septic shock/or exp shock, Septic/or exp Multiple Organ Failure/
9. exp Critical Illness/or exp critical care/or exp intensive care/or exp Intensive Care Units/or exp intensive care unit/
10. (sepsis or SIRS).mp.
11. or/9–11 [sepsis and ICU terms]
13. Exp Kidney Failure, Acute/
14. (acute renal failure or acute renal injury or acute renal insufficiency or acute kidney injury or acute kidney failure or acute kidney insufficiency).mp.
15. 13 or 14 [AKI terms]
16. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. [MEDLINE sensitive filter for randomized trials]
17. random:.tw. or clinical trial:.mp. [EMBASE sensitive filter for randomized trials]
18. 8 and 12 and (16 or 17)
19. 8 and 15 and (16 or 17)
20. remove duplicates from 18
21. remove duplicates from 19
22. 20 or 21
23. remove duplicates from 22

Notes: ‘$’ retrieves unlimited suffix variations; the .mp. extension includes the title, original title, abstract, and subject heading fields in all databases; .tw. refers to textword. Filters for MEDLINE and EMBASE (lines 2 and 5) are based on published sensitive strategies for retrieving randomized trials (40, 41). We also used British spelling of all textwords whenever relevant (i.e. “haemodia$” in item 2).

Appendix B. Reasons for exclusion of retrieved studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Main Reason For Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellomo (42)</td>
<td>1994</td>
<td>Not a parallel group, randomized, controlled trial</td>
</tr>
<tr>
<td>Booth et al (43)</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Brause et al (44)</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Hirasawa et al (45)</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Hiyayama et al (46)</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Hubsher et al (47)</td>
<td>1986</td>
<td></td>
</tr>
<tr>
<td>Lins et al (48)</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Maher et al (49)</td>
<td>1988</td>
<td></td>
</tr>
<tr>
<td>Storck et al (50)</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Raja et al (51)</td>
<td>1986</td>
<td></td>
</tr>
<tr>
<td>Zhang et al (52)</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Daud et al (53)</td>
<td>2006</td>
<td>Dose-equivalent renal replacement therapy interventions</td>
</tr>
<tr>
<td>Favre et al (54)</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Koo et al (55)</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Pettila et al (56)</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Pursnani et al (36)</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Alamartine et al (35)</td>
<td>1994</td>
<td>Short-term intervention (&lt;48 hrs) and no outcome data available</td>
</tr>
<tr>
<td>Davenport et al (57)</td>
<td>1993</td>
<td>Intermodal comparison</td>
</tr>
<tr>
<td>Riegel et al (58)</td>
<td>1995</td>
<td>Control group did not receive renal replacement therapy</td>
</tr>
<tr>
<td>Inthorn et al (59)</td>
<td>1991</td>
<td>Duplicate of Storck 1991 (50)</td>
</tr>
</tbody>
</table>

*aThis trial was incompletely randomized because some patients were directly assigned to one group depending on device availability; *author provided additional information; *author confirmed that no additional clinical outcomes data were available.