

Continuous Renal Replacement Therapy in the Treatment of Acute Renal Failure: Critical Assessment Is Required

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A continuous approach to renal replacement therapy (CRRT) for critically ill patients was introduced in 1977 and was hailed almost immediately as an improved alternative to intermittent hemodialysis (IHD). Now that CRRT has been in clinical practice for three decades, it is fair to ask whether research-based evidence (rather than expert opinion) supports the use of this complex technology in comparison to IHD. Several randomized clinical trials have compared the outcomes of CRRT and IHD. In one trial, patients assigned to CRRT had a significantly higher intensive-care mortality rate. In other recent trials, there has been no significant difference in outcome. A meta-analysis of observational studies similarly shows no benefit of CRRT *versus* IHD, with recent trends actually favoring IHD. While considerable attention has been focused on perceived benefits of CRRT compared to IHD, comparatively less attention has been focused on the potential for increased risks. When examining the totality of evidence from recent observational studies and clinical trials, there is no convincing evidence to support superiority of CRRT over IHD in the treatment of critically ill patients with ARF.

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Acute renal failure (ARF), also referred to as acute kidney injury (AKI), occurs as a result of ischemic and toxic kidney injury and remains a greatly feared complication of sepsis and other syndromes that afflict patients in the intensive care unit (ICU) (1). Bywaters *et al.* (2) first described the acute loss of kidney function that occurred as a result of crush injury during the bombing of London in World War II; at that time, mortality for afflicted patients approached 100%. The use of hemodialysis as a treatment for ARF first was introduced successfully by Willem Kolff in the late 1940s and began to be used more systematically in the treatment of military casualties during the Korean War. This resulted in an overall reduction in mortality, from >90% to approximately 50% (3,4). Although circumstantial, this remains the best evidence to date that dialysis improves outcomes for critically ill patients with ARF (1).

More recently, considerable progress has been made in preventing the development and progression of ARF through improved medical triage in disaster situations, early attention to vigorous volume resuscitation, and fluid and electrolyte abnormalities and through improved monitoring of and treatment for developing hemodynamic instability (5). Nonetheless, the mortality for critically ill patients with established ARF that requires renal replacement therapy (RRT) remains high, in most series still approaching 50%. The need to initiate RRT also remains a robust adverse prognostic indicator (6). Whether RRT worsens disease processes that contribute to maintaining multiorgan dysfunction and prolongs the course of AKI,

thereby directly contributing to increased mortality, remains to be determined fully.

By the 1960s, when intermittent hemodialysis (IHD) for the treatment of ARF came into widespread clinical use, some limitations of this therapeutic approach had become apparent. For example, it was observed commonly that IHD frequently imparted additional hemodynamic instability, even to the extent that some patients could not safely receive dialysis therapy. Conger *et al.* (7) later demonstrated in experimental models that ischemic ARF is associated with a loss of renal autoregulation, thereby increasing the kidney's vulnerability to any further decrement in renal blood flow. The introduction of hemodialysis frequently "converted" nonoliguric to oliguric ARF. Solez *et al.* (8) noted that fresh renal tubular epithelial cell injury was noted on kidney biopsy specimens that were obtained after the initiation of hemodialysis, suggesting that adverse hemodynamic consequences of dialysis was contributing directly to further kidney injury. Therefore, considerable concern developed that the beneficial effects of dialysis on uremia were being attenuated or lost through complications from the dialysis procedure itself.

The problem of exacerbation of hemodynamic instability by use of IHD clearly constituted an unmet medical need; as is common in such situations, necessity became the mother of invention. Kramer *et al.* (9) first described a continuous approach to renal replacement therapy (CRRT) for critically ill patients in 1977. With CRRT, the continuous regulation of volume homeostasis could lessen the hourly rate of required ultrafiltration, thereby improving hemodynamic stability compared with IHD. Since its adoption in 1977, a myriad of different technologies, techniques, and technical advances have been introduced into CRRT. CRRT was hailed immediately as an improved alternative to IHD. Furthermore, early reports (to be

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discussed further) seem to suggest better outcomes for patients who are treated with CRRT compared with IHD. As a consequence, many investigators and clinicians who care for critically ill patients with ARF have assumed that CRRT is an inherently superior technology and therefore is the treatment of choice in this clinical setting (10). Indeed, in a recent multinational, multicenter, prospective, epidemiologic survey of ARF in patients who were in the ICU, >80% of patients received CRRT, whereas only 17% received IHD (3% of patients received either peritoneal dialysis or ultrafiltration only) (11).

Whenever a new technology or device is introduced into medical practice, there is a natural tendency on the part of clinicians to assume that the novel approach is providing benefit. This is particularly true when it is designed to treat a condition for which clinical results are of limited benefit and not improving over time. However, this tendency must be tempered by the recognition that with many new devices and therapies, implementation may not be associated with benefit and may even be associated with harm. Therefore, even when devices and techniques are in widespread clinical use, it is necessary to assess critically periodically the utility of the therapy *versus* available alternatives.

Decisions in health care are being made increasingly on the basis of research-based evidence rather than on expert opinion or clinical experience alone. Numerous agencies, including the Agency for Healthcare Research and Quality and the United States Preventative Task Force in Medicine, have advocated for the use of a hierarchical system to rate the strength of scientific evidence. Within nephrology, the Kidney Disease: Improving Global Outcomes (KDIGO) uses a similar method for clinical practice guideline development (12). Observational studies, with larger total numbers of subjects and with groups of subjects from more diverse patient populations and practice settings, can be an important source of scientific evidence. Although observational studies are of value in providing research-based evidence, randomized, clinical trials can minimize selection bias, an important potential bias in observational studies. Well-conducted, randomized clinical trials that involve large numbers of patients can provide the highest standard of evidence. Structured systematic reviews (meta-analyses) can represent a rigorous method for compiling scientific evidence to answer questions concerning the strength of evidence. These approaches to scientific evidence are applicable to examining whether CRRT truly is superior to IHD in critically ill patients. Given that CRRT has been used in clinical practice for more than three decades, it now is fair to ask whether research-based evidence (rather than expert opinion) supports the use of complex technology in comparison with IHD.

Evidence from Randomized, Clinical Trials

Several randomized, clinical trials have compared the outcomes of CRRT and IHD in critically ill patients with ARF, although, until recently, none has been powered adequately (reviewed in reference [13]). Mehta *et al.* (14) compared CRRT and IHD in 166 critically ill patients with severe AKI, with the finding of a significantly higher ICU mortality rate in patients who were randomly assigned to CRRT (60 *versus* 42%; $P =$

0.02). However, despite randomization, patients who were assigned to CRRT were found subsequently to be more likely to have had liver failure and had a higher overall severity of illness, as determined by Acute Physiology, Age, Chronic Health Evaluation III (APACHE III) score. After adjustment for these factors, the increased risk that was attributed to CRRT no longer was statistically significant (odds ratio 1.6; 95% confidence interval [CI] 0.7 to 3.3). However, within each tertile of severity of illness, randomization to CRRT was associated with a trend toward higher rather than lower risk (Figure 1). In a meta-analysis that encompassed six published randomized, controlled trials that compared IHD with CRRT through 2002, the relative risk for mortality with IHD was 0.96 (95% CI 0.85 to 1.08; $P = 0.50$) (13). In a recently reported randomized trial, 125 patients were randomly assigned to CRRT (venovenous hemodiafiltration) or IHD from a single-center hospital ICU. In hospital, mortality rates did not differ by treatment assignment (47 *versus* 51%, venovenous hemodiafiltration *versus* IHD; $P = 0.72$) (15). Therefore, published data from randomized trials do not support the contention that CRRT is a superior therapy.

More recently, Vinsonneau *et al.* (16) from the Hemodiaf Study Group reported the results of the largest, best powered, prospective, randomized, multicenter study reported to date comparing the results of CRRT with IHD. A total of 360 critically ill patients were randomly assigned. In an intention-to-treat analysis, there was no difference in the primary end point of 60-d survival (32% in the IHD group *versus* 33% in the CRRT group; Figure 2). Of interest, the authors noted that there was an unexpected progressive and significant increase in survival rates in the IHD group over time (relative risk 0.67 per year; 95% CI 0.56 to 0.80; $P < 0.001$). This suggests that there may have been a learning curve for optimizing IHD therapy in this study environment. Perhaps if IHD therapy had been optimized from the onset of the trial, there would have been at least a trend to a better outcome with IHD compared with CRRT (as was seen in the Mehta trial). Thus, the weight of available

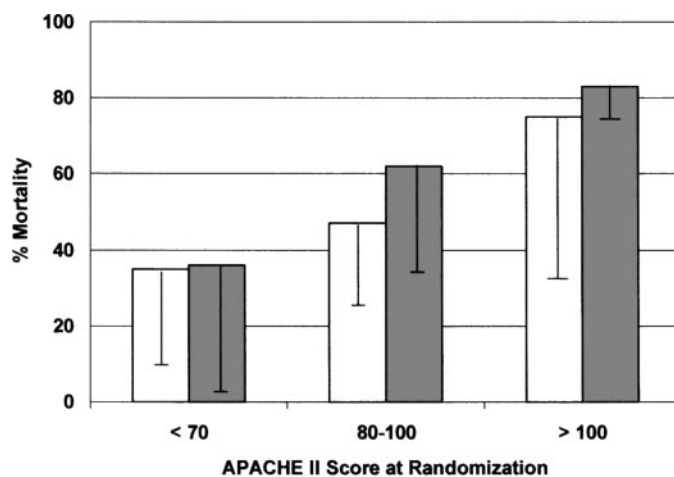
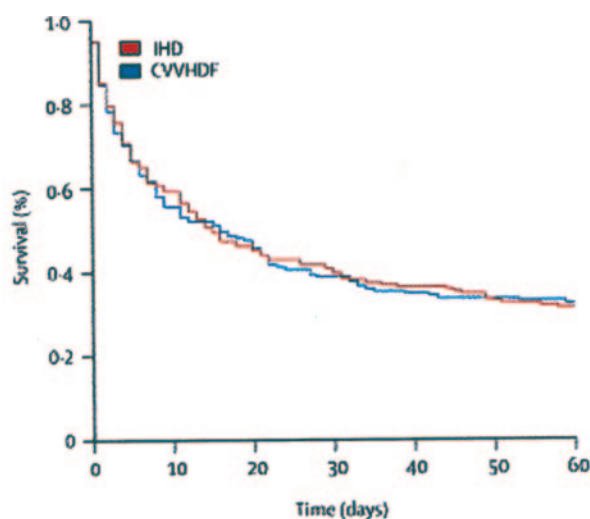


Figure 1. Relationship between severity of illness and mortality by renal replacement therapy (RRT) modality in a randomized, clinical trial. □, intermittent hemodialysis (IHD); ■, continuous RRT. Adapted from reference (14), with permission.



Numbers at risk

IHD	184	85	68	58
CVVHDF	175	83	62	57

Figure 2. Comparison of survival characteristics between continuous venovenous hemodiafiltration (CVVHDF) and IHD in a randomized, clinical trial. Reprinted from reference (16), with permission.

evidence, including the most recent evidence from randomized, clinical trials, provides no convincing evidence to support superiority of CRRT over IHD.

Evidence from Observational Studies

A number of observational cohort studies also previously compared outcomes with CRRT or IHD in critically ill patients with severe AKI. The early published literature that compared results of CRRT and IHD seem to confirm significant superiority of CRRT on the basis of overall patient survival (reviewed in reference [13]). However, these studies generally were retrospective and often used noncontemporaneous controls for assessment of results in the IHD group. Furthermore, IHD often was delivered using less biocompatible cellulosic membranes, which may have exacerbated the systemic inflammatory process and reduced the likelihood of renal functional recovery (17). Several of these reported studies used acetate-based dialysate, further increasing the likelihood that intradialytic hypotension would develop with IHD. In a meta-analysis that included several of these studies, the overall relative risk for mortality with the provision of IHD *versus* CRRT was 1.00 (95% CI 0.92 to 1.08). However, it is instructive perhaps that of the five studies performed within the past decade, two revealed significantly higher adjusted risk for mortality with the provision of CRRT, and two additional studies displayed a trend toward a higher relative risk for mortality with CRRT (Figure 3). Although overall these data suggest that there may be equipoise in comparing CRRT with IHD, recent trends actually favor IHD.

Recently, the Program to Improve Care in Acute Kidney Disease (PICARD) Group extended the previous work in this

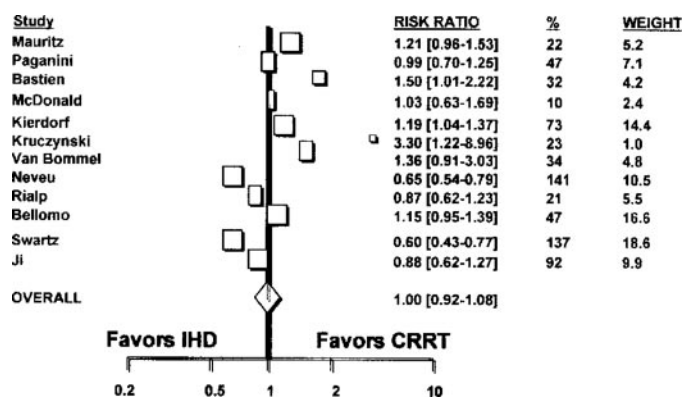


Figure 3. Meta-analysis of the relationship between RRT modality and mortality. Recent studies trend toward improved outcome with IHD. Reprinted from reference (13), with permission.

area comparing dialysis modalities by incorporating into an analysis for the first time multiple sites, multivariable regression analysis, and the propensity score approach to address residual confounding (18). In this multicenter, prospective, observational cohort study in critically ill patients with AKI, the provision of CRRT in comparison with IHD was associated with a significantly higher relative risk for mortality. The higher relative risk for mortality using CRRT was noted in fitted models that were adjusted for covariates only, propensity score only, and a combination of covariates plus the propensity score. Furthermore, the mortality risks were nominally higher, with assignment to CRRT across tertiles reflecting mortality risk (although this did not reach statistical significance in the middle tertile). These data corroborate other recent observational studies that provide no evidence for a survival benefit afforded by CRRT and suggest that under some circumstances, the use of CRRT may have been associated with harm.

Claims for better outcomes from CRRT always have been based on the concept that CRRT can provide more hemodynamic stability, better control of circulating volume, increased convective clearance, and the ability to provide nutritional support, BP support, and other obligate fluids more fully. Because available recent data do not support the hypothesis that CRRT will provide better outcomes than IHD, it may be worthwhile to reassess this concept critically. In the past two decades, a number of technical advances have allowed for safer delivery of IHD therapy. These include the introduction of volumetric control, the use of lower dialysate temperature to minimize intradialytic hypotension, the use of more compatible dialysate, and the widespread use of more biocompatible high-flux synthetic dialysis membranes. Several reports have indicated that it now is possible to deliver IHD therapy with improved hemodynamic tolerance even in critically ill patients. In the only randomized, crossover study reported to date, the hemodynamic response to IHD and continuous hemofiltration were similar (19). Schortgen *et al.* (20) also demonstrated that implementation of clinical practice guidelines that are designed to improve hemodynamic tolerance can lessen hemodynamic in-

stability and may improve outcome in patients with ARF. Therefore, the original rationale that led to the development of CRRT techniques may have dissipated over time.

Potential Risks Associated with CRRT

Although much attention has been focused on perceived benefits of CRRT compared with IHD, comparatively less attention has been focused on the potential for increased risks with CRRT therapy. Because CRRT is a continuous extracorporeal therapy, there frequently is a requirement for prolonged anticoagulation therapy, which may increase bleeding risk. Clotting of the extracorporeal circuit occurs frequently with CRRT, which may increase blood loss and exacerbate anemia. Recently, several safety concerns have been raised with a CRRT delivery device (21). In some circumstances, CRRT is performed by personnel who are less experienced in the procedure than trained nurses who perform IHD. The use of CRRT may enhance removal of amino acids, vitamins, small peptide hormones, catecholamines, and other solutes with beneficial function in critically ill patients.

Reassessment of the Utility of the Pulmonary Artery Catheter: Analogous to CRRT?

An excellent example of a process of critical reassessment is the use of the pulmonary artery catheter, introduced as a novel technology for use in critically ill patients in the 1970s (22). The introduction of right heart catheterization in 1929 by Forssmann, followed by the work of Cournand and Richards in the 1940s, provided tremendous advances in understanding cardiopulmonary physiology, cardiovascular hemodynamics, and gas exchange. In 1956, Forssman, Cournand, and Richards shared the Nobel Prize for this seminal work. By 1970, the Swann-Ganz balloon-tipped flow-directed pulmonary artery catheter further brought cardiopulmonary physiology to the bedside, achieving near instantaneous widespread use in the ICU environment (23). Acceptance of the utility of the Swann-Ganz catheter in improving patient outcomes went unquestioned until a now-famous editorial entitled “The Cult of the Swann-Ganz Catheter: Overuse and Abuse of Pulmonary Flow Catheters” was published by Robin in 1985 (24). Although highly controversial at the time it was written, it stimulated the development of large, prospective, observational cohort studies and eventually randomized, clinical trials. A decade after this editorial was published, a large cohort study suggested that the use of pulmonary artery catheters in ICU settings actually might increase morbidity and mortality (25). In the past decade, three studies now have reported no benefit to the use of pulmonary artery catheters in patients who have congestive heart failure or undergo high-risk surgery and in the management of acute respiratory distress syndrome (26–28). Although there still is a clinical role for the use of pulmonary artery catheters (particularly in the management of primary pulmonary hypertension), the range of clinical scenarios in which the use of these catheters is beneficial has been circumscribed narrowly compared with its original use. In the case of pulmonary artery

catheters, three decades of clinical use and careful research has evolved the use of these catheters from unbridled enthusiasm to a more careful, sober, evidence-based recognition of risk-benefit ratio in diverse clinical settings (22).

There are other examples in which technologies, devices, and drugs that have been introduced into medical practice on the basis of a sound rationale subsequently were demonstrated through clinical practice and research not to be associated with benefit and perhaps even to be associated with harm. Recent examples include liberal use of blood transfusions in the ICU (29), the use of certain antiarrhythmic agents for sudden death prevention (30), the use of cyclooxygenase-2 selective nonsteroidal anti-inflammatory agents (31–34), and the use of selected inotropes and vasodilators in the treatment of congestive heart failure (35). When examining the results of recent observational studies and clinical trials, there is no convincing evidence to support superiority of CRRT over IHD in the treatment of critically ill patients with ARF.

Disclosures

None.

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