CHAPTER 159

Hybrid Dialysis Techniques in the Intensive Care Unit

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OBJECTIVES

This chapter will:

1. Define and give the rationale for hybrid renal replacement therapy.
2. Discuss the technical requirements of hybrid renal replacement therapy.
3. Explain the versatility and flexibility of hybrid renal replacement therapy prescription and provision.
4. Describe the effects of hybrid renal replacement therapy on control of small and larger solutes and on cardiovascular stability.
5. Review comparative outcome data.

Hybrid therapy (HT) is a newly described modality of acute renal replacement therapy (ARRT) with the following features: (1) outpatient nephrology intermittent hemodialysis (IHD) machinery is used to deliver treatments, as opposed to dedicated intensive care unit (ICU) continuous renal replacement therapy (CRRT) machinery, (2) treatment sessions may be deliberately intermittent rather than necessarily being continuous, (3) treatment sessions are of longer duration than outpatient nephrology IHD treatments, and (4) the rate of solute and fluid removal is slower than with outpatient nephrology IHD treatments but faster than with conventional CRRT.

The technical elements of HT are not novel. In the extreme, it can be argued that Kolff actually performed the first HT treatments more than 50 years ago.[1] However, the clinical context of HT is novel as a conceptual and logistic compromise between the modern applications of IHD and CRRT. With this rationale, HT first was presented 10 to 15 years ago as a way of combining the advantageous features of IHD and CRRT while minimizing their respective disadvantages.[2–5] The major advantages of IHD are that it is inexpensive and has the convenience of scheduled downtime that allows the patient to be available for out-of-unit radiologic and surgical procedures. The major advantages of CRRT are that it allows fluid removal with minimal hemodynamic instability and provides consistent solute control. In general, HT has lived up to this rationale, and reported experience has shown this modality to be effective among a wide range of patients, popular with nurses, and inexpensive.[6]

HT is used increasingly. For example, 7% of patients in the Acute Renal Failure Trial Network (ATN) Study receive HT as primary treatment, and 25% of practitioners participating in this study routinely prescribe this modality.[7] These proportions are reported to be similar in Europe on the basis of data from around the same time.[8] There is a lot of unpublished or inaccessible experience about HT in the world literature. For instance, important work has been reported in the Chinese nephrology literature, which is not listed by Medline.[9]

In this topic review, such regimens collectively are referred to as HT, although other terms used in the literature are sustained low-efficiency (daily) dialysis (SLED or SLEDD), sustained low-efficiency (daily) diafiltration (SLEDD-f or SLED-f), extended (daily) dialysis (ED or EDD), prolonged (daily) intermittent renal replacement therapy (PIRRT or

PDIRRT), slow continuous dialysis (SCD), and "go slow dialysis." There is agreement among opinion leaders that the nomenclature must be standardized. However, this is proving difficult, owing to lack of a common perspective between nephrologists and intensivists. Hybrid therapy is "low efficiency" and "prolonged" to nephrologists, but "high efficiency" and "foreshortened" to intensivists. In the authors' opinion, nomenclature is likely to remain a local affair and to depend on which of the disciplines has responsibility for the therapy in an institution. It would seem that the only two terms that would be acceptable to both disciplines are hybrid therapy and prolonged (daily) intermittent renal replacement therapy.

TECHNICAL ISSUES

An overall summary of HT programs from published literature is shown in Table 159.1.[9–19] A few key technical issues are discussed here; issues related more to prescription are discussed in Section 15.

Machinery

A fundamental feature of HT is the use of outpatient nephrology IHD machinery. Maintenance IHD programs are very common throughout the world, and hospitals that have such programs are in possession of all the technical elements necessary to an HT program. In some hospitals, there has been a clear mandate to adapt and share existing machinery between maintenance IHD and HT programs, thereby reducing the cost of program implementation and maintenance. In fact, one of the main motivating factors for nocturnal HT was the need to use the machinery in outpatient IHD facilities during the day.[16] In other hospitals (particularly where ICU provides ARRT), machinery for HT is owned and maintained by the ICU as a separate ongoing concern, although it remains the same as (or technically very similar to) that used by nephrology services.[17,18]

Almost any IHD machine *can* be used for HT. However, blood and dialysate flow rates (Q_B and Q_D, respectively) and treatment session duration are typically different from that of conventional IHD (see Table 159.1), and machines must be capable of being changed to any of these variations in a convenient fashion. The ideal HT machine therefore is versatile over a wide range of operating conditions and easy to use. Specifically, the following features should be considered in the choice of a machine for HT:

- Flexibility of Q_D from as low as 100 mL/min up to the dialysis flow rates used for conventional IHD
- Flexibility of treatment session length from as short as those used for conventional IHD up to continuous duration
- Clear interface between machine and staff conducting treatment
- Easy transition between IHD and HT modes

In the first descriptions of HT, dialysate for treatments was produced in batches and used in now-outdated batch dialysis machinery.[2,3] In the modern practice of HT, only one such batch machine remains in common use, the GENIUS therapy system (Fresenius Medical Care, Bad Homburg, Germany).[15,20,21] This machine is sold only in Europe at present. For this machine, dialysate is generated in the outpatient nephrology dialysis unit through the use of a separate machine called a "preparator" and stored in a 75- or 90-L tank within the machine. A single roller pump is used to move dialysate and blood (max Q_B 300 mL/min) through the extracorporeal circuit at a ratio of 1:1 to 1:2. This ratio is determined by the staff conducting treatment, who choose between lines that have different lumen widths for the segments in the roller pump that provide Q_B and Q_D. Fresh dialysate is pumped from the top of the dialysate storage tank, and spent dialysate is returned to the bottom. Despite the lack of a physical barrier between these fluids, there is little mixing within the tank. Separation is maintained by small but important differences in fluid density and temperature between fresh and spent dialysate. One HT session using the GENIUS machine can last up to 15 hours with a Q_D of 100 mL/min.

The GENIUS machine has several advantages over single-pass machines. Treatments can be performed in the ICU without the need for a water supply. It is very easy to set operating parameters via independent and simple controls, allowing unlimited combinations of Q_B, Q_D, and session duration. An argument has been made that dialysate sterility in this machine is superior to that in single-pass machines, although this contention has not been proven and is not likely. Disadvantages of the GENIUS machine are its weight (approx 165 kg) and its fixed clearance, which is due to the fixed aliquot of dialysate per treatment. Nevertheless, this machine is regarded by some opinion leaders as the best HT machine on the market.[22]

Generally around the world, HT is performed using single-pass machines, whereby solutions for blood purification in HT are generated online from purified tap water and dialysate concentrate. Few of these machines are suited ideally for HT (Table 159.2), and most have some limitations around the lowest Q_D and the longest HT session length that can be provided. With regard to Q_D, these limits do not impose any critical clinical limitation. A Q_D of 300 mL/min is perfectly satisfactory in most clinical circumstances, and there are often means to reduce effective Q_D without drastically modifying machine hardware. For instance, one group of researchers has used the Gambro AK200S Ultra machine (Gambro AB, Stockholm, Sweden) in hemofiltration mode; the replacement fluid is used as countercurrent dialysate within the dialyzer at 100 mL/min, the operational QD on the machine interface set to zero (E. Fiaccadori, personal communication, September 7, 2005; P. Van Malderen, personal communication, September 9, 2005). Another group has developed a simple shunt to be used with the Fresenius 4008H machine (Fresenius Medical Care), which allows a proportion of the dialysate to bypass the hemodialyzer.[23, 24] There are probably easier and simpler ways to reduce the effective Q_D from 300 mL/min to the equivalent of 100 mL/min, such as reducing hemodialyzer size and using co-current dialysate flow.

With regard to treatment session length, many machines in North America can perform treatments for 24 hours or even continuously (e.g., Fresenius 2008K, Fresenius Medical Care North America, Lexington, MA), but most in Europe and the Asia Pacific region can perform treatments for only 10 hours (e.g., Fresenius 4008S, Fresenius Medical Care). This difference is due to different regulatory environments between the continents. This trend is changing, and some of the newer European machines from major vendors have an option for 24-hour or continuous treatment (e.g., Fresenius 5008S, Fresenius Medical Care).

Many vendors are selling or developing machines that switch easily and instantaneously between IHD and HT modes (so-called universal platforms). Fresenius Medical Care undoubtedly has taken the lead in this regard, having developed the two or three leading machines in terms of ease of operation—the Fresenius 2008K (US), 4008S ARrT Plus

TABLE 159.1

Hybrid Dialysis Therapy Programs Reported in Published Literature

	STUDY									
	SCHLAEPER ET AL.[19]	**FINKEL AND FORINGER**[12]	**LONNEMANN ET AL.**[15]	**MARSHALL ET AL.**[16]	**MARSHALL ET AL.**[17]	**NAKA ET AL.**[18]	**KUMAR ET AL.**[13,14]	**FIACCADORI ET AL.**[11]	**LI ET AL**[9]	**BERBECE ET AL**[10]
Hemodialysis machine	Fresenius 2008H	Fresenius 2008H	Fresenius GENIUS	Fresenius 2008H	Fresenius 4008S ARrT-Plus	Fresenius 4008S ARrT-Plus	Fresenius 2008H	Gambro AK200S Ultra	Fresenius 4008S or Toray TR123	Gambro Integra
Hemodialyzer	Fresenius F40	Fresenius F7	Fresenius F60S	Fresenius F8	Fresenius AV600S	Fresenius AV600S	Toray 1.0	Fresenius F7HPS	Fresenius AV600S	Bellco Diapes 140G
Membrane composition	Polysulfone	Polysulfone	Polysulfone	Polysulfone	Polysulfone	Polysulfone	Polymethyl methacrylate	Polysulfone	Polysulfone	Polysulfone
Area (m^2)	0.7	1.6	1.25	1.8	1.4	1.4	1.0	1.6	1.4	1.4
Flux	High	Low	High	Low	High	High	High	Low	High	High
Duration (hours)	Continuous	Continuous	8–18	12	8–10	8–10	8	8–9	10	8
Time of day	Continuous	Continuous	Nocturnal	Nocturnal	Nocturnal/ Diurnal	Diurnal	Diurnal	Diurnal	Nocturnal/ Diurnal	Diurnal
Frequency	Continuous	Continuous	Daily	Daily/5–6 days per week	Daily/5–6 days per week	Daily/5–6 days per week	Daily/6 days per week	Daily/6 days per week	Daily/alternate days	6 days per week
Blood flow rate (Q_s) (mL/min)	150–200	150	70	200	200–350	100	150–200	200	150–200	200
Dialysate flow rate (Q_D) (mL/min)	100	100	70	100	200	200	300	100	300	350
Filtration rate (Q_F) (mL/min)	0	0	0	0	100	25	0	0	0	17
Dialysate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate	Bicarbonate

TABLE 159.2

Machines From Major Vendors Used for Hybrid Dialysis Therapy

MACHINE	LOWER LIMIT OF BLOOD FLOW (mL/min)	UPPER LIMIT OF TREATMENT TIME	EASY TRANSITION TO HT MODE?
Fresenius 2008H	300[a]	Nil	N/A
Fresenius 2008H + P/N 190178	100	Nil	Yes
Fresenius 2008K	100	Nil	Yes
Fresenius 4008S	300	10[b]	N/A
Fresenius 4008S ARrT Plus	200	10[b]	Yes
Fresenius 5008S	100	Nil	Yes
Gambro AK95/100/200	300	10	N/A
Gambro Integra	350	10	N/A
Toray TR-123	300	10	N/A

HT, Hybrid dialysis therapy; *N/A,* specific HT mode not available.
[a]Can set QD 100 mL/min by manually recalibrating dialysate temperature sensors, a procedure that takes ~45 minutes (details in ref 45).
[b]Treatments can be restarted at the end of 10 hr by re-entering new treatment parameters, to effectively carry the treatment on beyond the patient's time limit without having to disinfect or drain the machine and setting up again with new lines.

(Asia Pacific), and 5008S (Europe). All of these machines allow selection of CRRT or HT from their startup screens and enable easy changes of operating parameters.

Water Quality

Fluids for blood purification in HT usually are generated online from purified tap water and dialysate concentrate. In contrast are those used in CRRT, which are pharmacy-made or commercially purchased and delivered to the point of service, for batch and single-pass machinery. A growing concern is the possibility of exposure to bacterial contaminants—and specifically endotoxin—from these fluids. Such exposure may arise during direct infusion of online replacement fluid and also from backfiltration via dialysate into the patient. It therefore generally is accepted that water quality for online fluids should conform to the same standards that are used in the outpatient nephrology IHD setting.

The critical question, however, is whether water purity for ARRT actually should be higher than this standard. In the absence of any definitive clinical trial data, many opinion leaders opt for dialysate sterilization using ultrafilters in the dialysate pathway, especially if high-flux membranes are being used. These ultrafilters remove bacteria and endotoxin by virtue of a pore size of about 0.22 μm and specific adsorptive properties.[25] This decision is based on observational evidence or surrogate end points. A counter-argument has been made that bacterial contaminants are removed sufficiently by the dialyzer during backfiltration by most common membranes and that dialysate sterilization is unnecessary.[26, 27] Clearly, a definitive trial is needed urgently to determine optimal clinical practice.

There is less debate about water quality for online replacement fluid for hemodiafiltration. This fluid is a fraction of dialysate that is infused directly into the extracorporeal circuit either before or after the diafilter. The ionic composition of replacement fluid does not differ from that of dialysate. Such fluid should be sterile (no growth, endotoxin concentration < 0.03 endotoxin units). This is achieved by passing water and/or dialysate through two (Fresenius) or three (Gambro) ultrafilters before being infused. This process has been shown to yield a fluid that is at least as sterile as commercially available fluids.[28,29] The U.S. Food and Drug Administration has not approved such a process, and a similar situation exists in some European countries. In these countries, online replacement fluid preparation is not used in patients, and hemodiafiltration during HT is performed using pharmacy-made or commercially purchased fluids or, more commonly, normal saline.[10]

Hemodialyzers

Hemodialyzers used for HT can be the same as those used for conventional IHD and intermittent hemodiafiltration (IHDF). Hemodialyzer membranes can be low-flux or high-flux. High-flux membranes contain large pores that theoretically allow for greater permeability of larger putative uremic toxins. There are no comparisons of low-flux and high-flux membranes in HT; the only available data pertain to comparisons involving conventional IHDF or high-flux IHD versus low-flux IHD. In studies of ARRT in the ICU population, the more permeable membranes demonstrate no clinical or laboratory advantages over the less porous ones.[30–32] This negative result may be biased by residual confounding in these studies from unrecognized back-transport of potentially harmful waterborne molecules (see previous discussion). Alternatively, the negative results may be true, resulting from the low mass removal of larger solutes (in absolute terms) afforded by these modalities. For instance, low-flux IHD clears about 3 mL/min of β_2-microglobulin from blood water during the course of treatment, high-flux IHD clears only about 35 mL/min, and even IHDF clears only about 50 to 150 mL/min, depending on the hemofiltration (Q_F) rate.[33] Given the short duration over which these modalities are applied, a meaningful clinical effect seems unlikely. In contrast, the longer duration for HT makes a clinical effect seem more plausible, although it remains to be proven.

The effect of membrane biocompatibility on outcomes (when present) is consistently beneficial, although the data overall are conflicting.[34,35] Notwithstanding, such membranes now can be obtained cheaply, and because cost has been eliminated as a deciding factor, it is recommended that all patients be treated with these membranes.

Online hemodiafiltration is being used increasingly during HT.[10,17,18] The rationale for this technique is predicated on a survival benefit conferred by combined convection and diffusion that is not conferred by diffusion alone. This assumption has some support in the literature but is not proven. Hemofiltration rates reported

during convective HT vary from 17 to 100 mL/min. Higher convection leads to increased clearance of middle-sized and larger uremic solutes, which can amount to more than 50% of the small solute clearance. Moreover, other features of online hemodiafiltration, such as thermal energy transfer, also may affect clinical outcomes. Several groups of investigators have demonstrated the logistic feasibility of convective HT.[10,17,18,24] However, further studies still are needed to compare outcomes of this modality and diffusive HT. These studies should explore not only the relationship between removal of middle-sized and larger uremic solutes and clinical outcomes but also the role of thermal energy transfer and other features of convective ARRT in general.

Hemodialyzer size is probably not critical. Two groups have reported experience with moving from a larger to smaller hemodialyzers for HT, for the purposes of reducing extracorporeal circuit clotting.[14,19] Neither group has reported any deterioration in solute control or clearance. The relationship between hemodialyzer urea mass-transfer area coefficient (K_OA), Q_D, and Q_B is not predictable during HT because of a mismatch between dialysate and blood flows resulting from incomplete fiber bundle penetration at low flows that creates a shunt within the dialyzer.[36] Further studies on this important area are needed before a recommendation can be made.

CLINICAL OUTCOMES

Solute Control

The major surrogate end point in ARRT is optimal control of solute and fluid balance, but the true clinical end points are patient mortality and recovery of renal function. As with all ARRT, outcomes studies in HT have related practice patterns mostly to the former rather than the latter outcomes. All reports of HT have shown consistently that electrolyte concentrations can be maintained within normal limits.

There are no agreed standards for solute control in ARRT. In terms of small solutes, however, strong suggestions have been made in various reports that clinical outcomes are optimized during CRRT with a urea clearance of 35 mL/kg/hr or more and during IHD with Kt/V of 0.92 at a frequency of 6.2 per week.[37,38] Although not experimentally verified, these different expressions for small solute clearance can be unified using the corrected equivalent renal urea clearance (EKRc), which reexpresses the preceding doses as a continuous clearance that provides the same time-averaged concentration of BUN for the same mass of urea removed, corrected for a urea redistribution volume of 40 L.[39,40] Expressed in this way, the values for EKRc that correspond to the two suggestions above are 35.9 mL/min for CRRT and 20.7 mL/min for IHD (assuming V = 0.65 × body weight).[41] Readers are referred to the chapters in this book on ARRT quantification for a more detailed explanation of these concepts and calculations.

The small solute clearance achieved in the first 100 patients in the HT program at Middlemore Hospital, New Zealand, is illustrated in Fig. 159.1. Small solute kinetics from other published HT experiences are shown in Table 159.3.[9–19,39,40,42] In general, metabolic control in most case series is comparable to that observed during CRRT, with one quasi-randomized controlled trial also reporting similar conclusions.[14]

Multicompartmental effects resulting from urea dysequilibrium do not occur to a significant degree during HT, as indicated by the parity between whole-body and hemodialyzer urea clearances, minimal postdialysis blood urea nitrogen (BUN) rebound, conformity between observed intradialytic time-concentration BUN profiles and those predicted from a standard single-pool urea kinetic model, and monoexponential dialysate urea nitrogen time-concentration profile (Fig. 159.2). These findings all indicate minimal urea dysequilibrium.[36,43]

Small solute clearance actually is reduced by hemodialyzer clotting. In fact, the online clearance or ratio of dialysate/filtrate (effluent) urea nitrogen to BUN (i.e., EUN/BUN) has been used to permit an elective change of a failing filter before it clots. This strategy is based on the observation that there is a decline in EUN/BUN over the treatment course, probably because of a combination of concentration repolarization and diafilter clotting. Although this issue has not been validated prospectively, it is the firm recommendation from other authors that a EUN/BUN less than 60% mandates diafilter replacement (R. Mehta, personal communication, July 15, 1999).

There are fewer data on larger solute clearance during HT. As discussed previously, interest in these particular solutes arises from the potential for removal of middle-molecule inflammatory mediators. Notwithstanding, the greatest removal of such molecules can be achieved with hemodiafiltration, although some removal also occurs with HT based on high-flux dialysis without filtration. The literature as a whole suggests that clearance of larger solutes is between 50% and 66% of that of small solutes using high-flux HT or hemodiafiltration, and very low with low-flux HT.[17,21,44,45] Support for beneficial immunomodulation by HT can be found in one study reporting restoration of function for stimulated but exhausted circulating monocytes,[46] and in two studies showing improvement in the ratio of antiinflammatory to proinflammatory mediators.[9,47]

COMPARATIVE CLINICAL OUTCOMES

Although the Kidney Disease Improving Global Outcomes guidelines for acute kidney injury (AKI) recommend CRRT for patients with hemodynamic instability or intracranial hypertension, studies have shown that the choice of dialysis modality in the ICU setting continues to be based on a number of clinician and patient-specific factors.[51] It has previously been thought that CRRT is superior to IHD, based on the theoretical advantages of increased hemodynamic stability allowing for greater volume removal, better solute clearance, and increased rates of renal recovery.[52–55] These advantages have yet to be demonstrated in randomized controlled trials (RCTs). Here, we summarize evidence regarding critical outcomes and clinical endpoints in studies comparing IHD, hybrid therapies and CRRT where doses ranged from 20–35 mL/kg/h.

ICU LENGTH OF STAY

Two studies compared ICU length of stay between patients receiving CRRT or IHD and found no significant differences.[56,57]

HEMODYNAMICS

Regarding hemodynamics alone, some studies have shown that CRRT is superior to PIRRT, although it does not appear

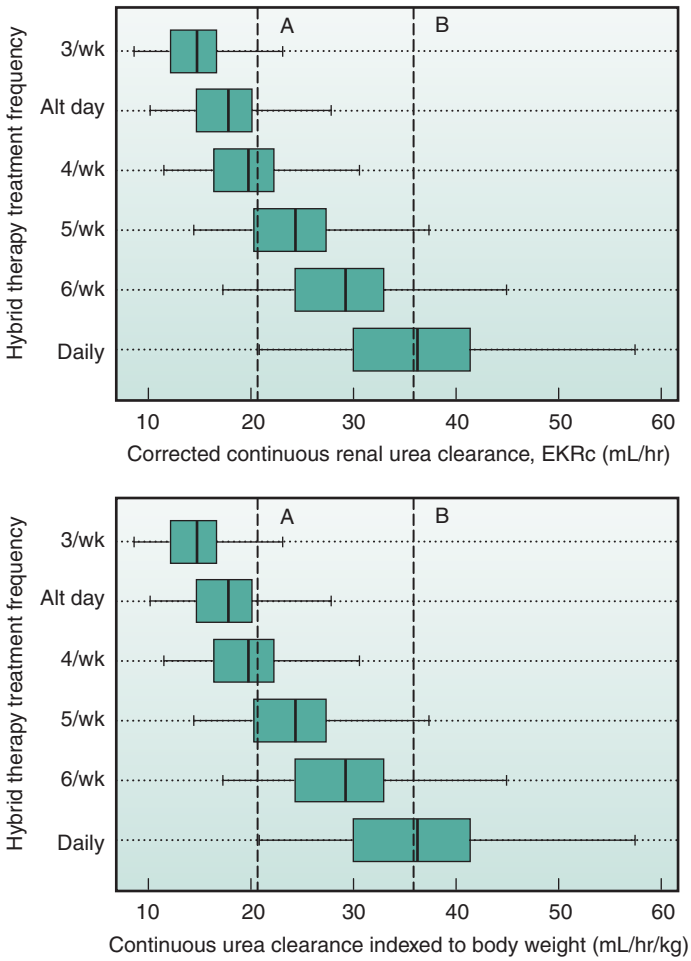

FIGURE 159.1 Small solute clearance achieved in the first 100 patients in the hybrid therapy program at Middlemore Hospital, New Zealand.

TABLE 159.3

Reported Rates of Small Solute Clearance Delivered by Hybrid Dialysis Therapy

	STUDY									
	SCHLAEPER ET AL.[19]	FINKEL AND FORINGER[12]	LONNEMANN ET AL.[15]	MARSHALL ET AL.[16]	MARSHALL ET AL.[17]	NAKA ET AL.[18]	KUMAR ET AL.[13,14]	FIACCADORI ET AL.[11]	LI ET AL.[9]	BERBECE ET AL.[10]
BUN (mg/dL):										
Before treatment	21[a]	17[a]	82	71.6	54.9	53.8	24	75	69.5	26.6
After treatment	N/A	N/A	38	31	20.4	37.0	N/R	37	12.5	10.4
Serum creatinine (mg/dL):										
Before treatment	1.7[a]	1.5[a]	3.93	3.4	3.85	3.1	2.5	N/R	8.74	1.07[a]
After treatment	N/A	N/A	1.96	1.6	1.81	2.43	N/R	N/R	1.87	N/R
spKt/V per treatment	2.4 (daily)	24 (daily)	1.25[b]	1.45	1.43	0.56[b]	1.14	1.17[b]	1.60[c]	1.39
EKRc per treatment (mL/min)	54[d]	N/R	31.68[e]	31.9[d]	35.7	15.5[e]	25.1[f]	28.9[e]	39.6[e]	29[d]
Urea nitrogen removed (g/day)	N/R	N/R	33.1	28.6	N/R	N/R	N/R	N/R	N/R	N/R

BUN, Blood urea nitrogen; *EKRc,* corrected equivalent renal urea clearance; *N/A,* not applicable; *N/R,* not reported; *spKt/V,* single-pool Kt/V.
[a]Steady state solute concentrations.
[b]spKt/V calculated using reported data either (a) from direct dialysate quantification using reported pre- and posttreatment BUN and urea nitrogen mass removal, or (b) iteratively by formal single pool urea kinetic modeling using reported pre- and posttreatment BUN combined with hemodialyzer clearance calculated using manufacturer reported KoA.
[c]spKt/V calculated using reported data from pre- and post-treatment BUN by method of Basile et al.[42]
[d]EKRc calculated from reported continuous urea clearances or EKR by correcting for V = 40L with correction for urea non-steady state by method of Casino and Marshall.[40]
[e]EKRc calculated from Kt/V values using nomogram method of Casino and Lopez assuming daily treatments.[39]
[f]EKR as originally reported unable to be corrected to V = 40L.

Hours	0	2	4	6	8	10	12	13
○ Modeled BUN	76.9	64.5	54.5	46.4	39.9	34.7	30.4	32.6
□ Observed BUN	76.9	62.1	52.2	44.4	38.6	33.7	30.2	33.9

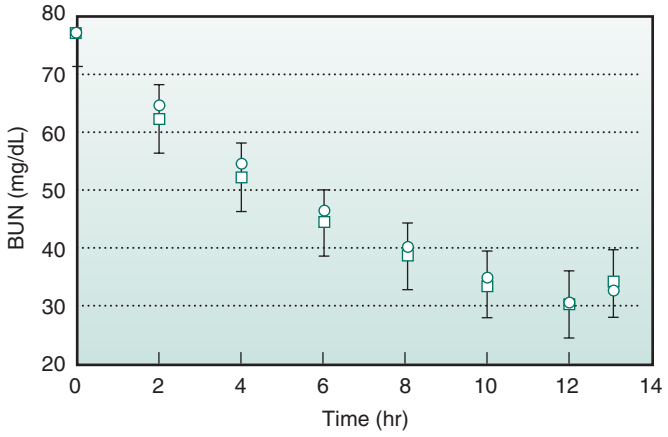

FIGURE 159.2 Graphic description of BUN profiles during hybrid renal replacement therapy under the condition of single pool urea kinetics, with *hollow squares* representing observed BUN profile and *hollow circles* representing the modeled BUN profile. Points of data are presented in graph as mean +/−standard error and in tabulated form as mean (n = 9; correlation coefficient = 0.99).

to convey a survival advantage.[54,58,59] Other observations are conflicting. Many analyses have failed to demonstrate that CRRT results in a better hemodynamic profile. Patients in the Cleveland Clinic RCT had a significant decrease in mean arterial pressure (MAP) on IHD, and those randomized to CRRT had a decreased vasopressor requirement despite greater net volume removal.[60] In the large, prospective, international BEST study, patients first treated with CRRT required more frequent vasopressor support.[61] In the Hemodiafe study, IHD patients experienced no worsened hemodynamics, attributed to slow ultrafiltration and the use of cool and/or hypernatremic dialysate.[56] Several RCTs comparing IHD to CRRT have not demonstrated hemodynamic differences.[56,62,63] Meta-analyses concur.[64,65] Some of the advantages observed in CRRT may be attributed to its inherent cooling. Additionally, several studies excluded severe hemodynamic instability prior to initial randomization, which may have attenuated any differences that would have otherwise been observed.

RENAL RECOVERY

Hemodynamics protect renal function. Autoregulation is lost during AKI, and hypotension decreases glomerular perfusion and further delays renal recovery. As IHD has been associated with increased episodes of hypotension, it was hypothesized that CRRT would result in better preservation of renal function. In BEST, unadjusted dialysis independence at hospital discharge was higher in those patients who first received CRRT.[61] Although an improvement in renal recovery was analyzed as a secondary endpoint in most RCTs and studies may not have had an adequate power to detect a statistically-significant difference, no RCT has been able to show a difference.[56,57,60,63] Two large retrospective cohort studies suggest the possibility of better renal recovery among patients who receive CRRT.[66,67] A Swedish study showed less dialysis dependency at 90 days in those patients who initially received CRRT.[66] In a Canadian study, patients who received IHD as an initial dialysis modality had a higher risk of dialysis dependence at 90 days as compared to CRRT, an association strengthened by the presence of preexisting kidney disease.[67] Although some of the observational studies suggested that patients who received IHD suffered from a higher rate of dialysis dependence, meta-analyses conclude otherwise.[49,64,65,68]

MORTALITY

Much of the literature comparing CRRT to intermittent therapies demonstrates no survival benefit. Some observational studies have suggested that CRRT is associated with increased mortality as compared to IHD,[69] but when adjusted for severity of illness, mortality is similar.[59,70,71] In BEST, unadjusted hospital survival was lower in patients who first received CRRT,[61] but the San Diego study found the opposite.[72] The latter study saw a high crossover rate and significant differences in gender, liver failure, number of failed organ systems, and APACHE scores despite randomization. Several RCTs demonstrated no mortality differences using a variety of definitions.[56,60,62,73] Meta-analyses reveal no difference in mortality between the two modalities.[48,49,64,65,74]

Patient selection is a large bias in observational studies comparing modalities (confounding by indication). For example, triage to CRRT was associated with an increased relative risk of in-hospital death.[75] In another study, patients who received CRRT tended to be younger, female, and had increased rates of sepsis.[76] These characteristics were adjusted for in the final analysis, which also confirmed higher costs for CRRT patients. In a RCT unique for its large sample size and stratification there was no difference in mortality on multivariate analyses, even when adjustments were made for age, sepsis, and presence of heart failure.[57] In a large multi-centered study, no significant association was demonstrated between ARRT dose and mortality when a median CRRT dose of 27.1 mL/kg/hour was compared to a median IHD dose of 7 sessions per week. However, survivors in the more intensive ARRT group had a shorter ICU stay and a decreased duration of mechanical ventilation.[77] The aforementioned data do not include patients with acute brain injury or concurrent liver failure, two conditions in which CRRT has been shown to be preferred.[78,79] Also, critically ill patients with life-threatening hyperkalemia or toxic ingestions benefit from IHD for rapid solute removal.

INTRODUCING HYBRID THERAPIES (HTS)

Compared to CRRTs, hybrid therapies (HTs) are associated with decreased costs, less need for anticoagulation, and lower MAPs, but have similar solute clearance, net

ultrafiltration, and rates of renal recovery.[10,13,14,21,80–83] Mortality and other outcome comparisons are less definitive. Hospital survival and renal recovery have been shown to be better in HTs.[84–86] CRRT patients had a higher rate of renal recovery but similar mortality in other studies.[87–90] A large single center observational study demonstrated the clear clinical efficacy of HTs but patient selection confounds all such observational studies.[91] Meta-analyses of RCTs that compare CRRTs to HTs find no mortality differences but note variable differences in other outcomes.[92,93]

CONCLUSION

CRRT requires specialized nursing, increases costs, often requires anticoagulation, and results in patient immobilization. Hybrid therapies are of lower complexity and allow for free intervals for procedures and interruption of continuous anticoagulation. As overall outcomes tend to be similar, hybrid therapies may be the more attractive renal replacement therapy option for the critically ill.

Key Points

1. Hybrid renal replacement therapy is a conceptual and logistic compromise between the modern applications of intermittent hemodialysis and continuous renal replacement therapy.
2. Most outpatient nephrology IHD machinery can be used to perform hybrid therapy, although one should be aware of the limitations of the machines in terms of the lowest dialysis flow rate and the longest hybrid therapy session length that can be provided.
3. The prescription and provision of hybrid therapy is very flexible and can be varied when desired to suit the requirements of the institution and patient.
4. Hybrid renal replacement therapy provides high small solute clearance and significant larger solute clearance.
5. This modality allows ultrafiltration with a minimum of cardiovascular instability and is well tolerated by patients with severe illness.

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