Organogenesis 7:1, 2-12; January/February/March 2011; © 2011 Landes Bioscience

Renal replacement therapy review
Past, present and future

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Key words: dialysis, peritoneal dialysis, hemodialysis, renal replacement therapy, artificial kidney

Introduction

Support of renal function in modern times encompasses a wide array of methods and clinical scenarios, from the ambulatory patient to the critically ill. The ability to safely and routinely deliver ongoing organ support in the outpatient setting has, until recently, separated renal replacement therapy from other organ support. Renal replacement therapy (RRT) can be applied intermittently or continuously using extracorporeal (hemodialysis) or paracorporeal (peritoneal dialysis) methods. The purpose of this article is to familiarize the reader with the history, physiology, mode, dose, equipment and future of renal replacement therapy and not to detail the technical methods employed for blood purification.

History

Artificial support of the functions of failing organs has a history deeply rooted in the beginning of the last century. Although artificial respiration may have been used as early as Roman times by the physician Galen, and as late as 1908 by George Poe, support of the failing kidney began as early as 1913. Two scholars are credited repeatedly in the literature, Dr. John J. Abel and Dr. W. J. Kolff, as the forefathers of modern dialysis. "Vividiffusion" was coined in a paper given before the Association of American Physicians in 1913 in which the blood of animals was cleansed of intermediaries of metabolism.[1] This "vivi-diffusion" was achieved using arterial cannulation and hirudin anticoagulation in a dog with blood directed through branching glass tubing to reach a series of cellodin dialysis membranes and then back to a venous cannula. This concept was concomitantly developed by Dr. Kolff in the Netherlands and led to the first apparatus available for clinical use.[2] Dr. Kolff's drum dialyzer fed blood through cellophane tubing wrapped around a rotating drum sitting in a bath of dialysate. The rotation of the drum moved blood through the dialysis bath, and then blood flow return to the patient was controlled using a burette. Although Dr. Kolff's apparatus was used prominently as late as the 1950s during the Korean war,[3] modern dialysis today is performed using the work of Dr. Nils Alwall. The Alwall dialyzer compressed blood-filled cellophane tubing between an inner and outer cylinder. Dialysate was passed in the countercurrent direction to blood between the cylinders.[4] The authors describe dialysis in eight patients, including changes in levels of non-protein nitrogen (N.P.N.), using countercurrent exchange between blood and dialysis fluid that is still in use today in RRT.

The peritoneum was noted to be a "living dialyzer" by Dr. Tracey J. Putnam in 1923 in a series of experiments with cats receiving peritoneal dialysis.[5] He, unlike his predecessors, made a complete evaluation of the spent dialysate and remarked upon the ability of the peritoneal membrane to exchange fluid and solute in the living animal. However, despite this early success, clinical peritoneal dialysis was delayed until the 1940s with the presentation of four cases by Dr. Jacob Fine and colleagues at the American Surgical Association.[6] Widespread use of peritoneal dialysis required improvement in the dialysis catheter used, and was accomplished with the work of Dr. Quinton[7] and Dr. Tenckhoff.[8] Today, the methods and catheter designs of these pioneers are still evident in clinical practice around the world.

Continuous therapies of today have their origins in the 1960s, with early descriptions of pump-assisted continuous arteriovenous hemofiltration (CAVH) by Dr. Scribner.[9,10] Dr. Scribner found that the resistance of the hemofilter varied by design and hand manufacturing techniques, which made predictable response to therapy difficult. Additionally, dialysate was cooled for aseptic technique but re-warming blood prior to return to the patient resulted in bubble formation and clinical symptoms in the patient. Finally, a predictable method of delivering heparin for anticoagulation was required, as the standard IV pump of today was not available. Dr. Robert Bartlett utilized this therapy in the management of patients on extracorporeal membrane oxygenation (ECMO) and was among the early authors in the literature.[11-13] These pump-assisted therapies required arterial cannulation, and the success of veno-venous circulation using a pump for continuous ultrafiltration helped reduce the morbidity of the therapy. Dr. Canaud described continuous veno-venous hemofiltration for adults in 1988,[14] and Dr. Yorgin described the therapy applied to children in 1990.[15] To date, we delivery therapy in fundamentally the same fashion as described in the preceding paragraphs with some modification and refinement of technique over time.

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Submitted: 08/01/10; Accepted: 10/21/10
DOI: 10.4161/org.7.1.13997

Indications

The primary indication for RRT is acute or chronic renal failure. However, much debate exists today regarding the optimal definition of renal failure, especially with acute renal disease. As many as 30 definitions of renal failure exist in the literature, yet recent consensus definitions and guidelines are becoming more widespread. The Kidney Dialysis Outcomes Initiative's(K/DOQI) clinical practice guidelines for chronic kidney disease[16] define end stage kidney failure as Stage 5 with glomerular filtration rate (GFR) of <15 ml/min/1.73 m^2 or the use of dialysis. GFR is estimated using serum creatinine measurement in conjunction with the Modification of Diet in Renal Disease (MDRD), Crockcroft-Gault or Schwartz equations.[17-19] The Acute Dialysis Quality Initiative (ADQI) group published a consensus definition of acute renal failure for adults,[20] with a graded severity Risk Injury Failure Loss and ESKD (RIFLE) and the recent publication of a modification for use in pediatric patients.[21] Classification is based on a change in GFR or urine output in the previous hours rather than absolute values individualizing it to the patient. Both the K/DOQI and RIFLE definitions of renal failure rely upon serum creatinine measurements, which are known to overestimate GFR.[22-25] Additionally, in acute renal injury, the rise in serum creatinine used to define organ failure is delayed approximately 24–48 hours from the insult. Although not an issue in chronic kidney disease and failure, it affects timing of definition and organ support in the acute setting. Consequently, current research is focused on an appropriate biomarker(s) that would aid in the diagnosis of acute renal failure, especially in the critically ill patient. Multiple markers are under study, some of which have performed well in select patient populations to date, and the reader is directed to comprehensive reviews of the subject.[26,27] In the future, the definition of acute renal failure will be driven by a combination of markers of organ function, including biomarkers, as is the case for myocardial infarction.

Other indications for RRT exist beyond renal failure and classically have included electrolyte or acid-base abnormalities and toxins removable by dialysis. The critically ill pediatric population has been the primary study ground for fluid overload as an indication for RRT. This idea arose from adult studies of critically ill patients in whom a mortality benefit was noted, reversal of fluid overload in the first days of illness.[28,29] Numerous observational studies of pediatric patients demonstrated fluid overload was associated with higher mortality.[30-33] In these studies, fluid overload >10% was associated with higher mortality when controlling for severity of illness. Data from the Prospective Pediatric CRRT Registry Group demonstrated again that % fluid overload was associated with mortality, and that survival was improved (76%) if dry weight was attained during CRRT as compared to those who did not attain dry weight (36%).[34]

Since the earliest animal studies of sepsis, a soluble myocardial depressant factor has been postulated to exist and is later suggested as removable from the plasma. Hemofiltration in a canine sepsis model reversed left ventricular dysfunction[35] as well as right ventricular dysfunction in porcine sepsis.[36] Re-infusion of the ultrafiltrate from hemofiltration in porcine sepsis induced the shock state in normal pigs.[37] Subsequent work has suggested cytokines to be the target of hemofiltration during the systemic inflammatory response syndrome (SIRS) of sepsis.[38] Human trials of hemofiltration during sepsis have had mixed results on despite documentation of removal of cytokines.[39-43] Success or failure to show clinical improvement has been hypothesized by some to be related to frequency of filter change, mode of clearance and dose of clearance.[44] Recent data are the first to suggest that early hemofiltration during sepsis may associated with increased mortality.[45] Investigators continue to examine hemofiltration to control the cytokine storm and hemodynamic instability of severe sepsis; however, the most recent sepsis guidelines do not include hemofiltration in the recommendations beyond renal support.[46,47] Certain subgroups with hypercytokinemia, such as patients with severe pancreatitis, may benefit from RRT for cytokine removal.[48]

Current indications for RRT in the hospitalized patient include renal failure, severe acidosis, hyperkalemia or other electrolyte abnormalities, and toxin/poisonings. Fluid overload >10% in the critically ill patient is gaining support as an indication for RRT. Cytokine modulation during SIRS remains a popular topic in the literature, yet no current data support universal application. RRT indications for chronic renal failure are currently targeted at patients with GFR <10 ml/min/1.73 m^2.

Physiology

RRT employs only two physiologies for solute and fluid movement.[49] Both methods require sequestration of blood on one side of a semi-permeable membrane. In diffusive clearance (Dialysis), solute moves down its concentration gradient, from areas of high concentration to low concentration. The solute must be of appropriate size and charge to pass through a semi-permeable membrane. By passing fluid across the membrane countercurrent to blood flow, equilibration of plasma and dialysate solute concentrations occur. This process may remove or add solute to the plasma water space depending upon the relative concentrations in dialysate and plasma. Water will also move along a gradient, in this case the osmolar or osmotic gradient, in effect "following" the solute. Diffusive clearance is more effective at removal of small solute, such as serum ions and urea, than for larger solute.

Convective clearance (hemofiltration or ultrafiltration) utilizes a pressure gradient rather than concentration gradient and has its main effect on water movement with solute movement in conjunction with water. The transmembrane pressure difference is increased as needed to "push" water through the membrane down a pressure gradient. This bulk flow of plasma water "drags" solute with it (convective mass transfer) in the formation of ultrafiltrate. Small solute removal is nearly the same as with diffusion, but fluid removal is far superior with convective clearance. Additionally, clearance of small solute is equivalent to diffusion, but convection demonstrates increased middle molecule (500–5,000 Dalton) clearance and is limited by membrane characteristics. Simply removing isotonic plasma water is considered slow continuous ultrafiltration (SCUF) but may lead to large volume shifts during therapy. To offset the large fluid shifts

of hemofiltration, convective therapies usually include a filter replacement fluid (FRF) that is administered into the patient. Fluid given is removed in equal quantities for isovolemic hemofiltration, yet the plasma composition will eventually resemble the FRF, allowing for solute management.

Although these two models suggest very simple and predictable solute and fluid movement, these processes are in reality quite complex. Diffusion gradients change depending upon blood flow rates, dialysate flow rates and starting concentration gradients. Additionally, convection allows for larger solute to be pushed/pulled through the membrane with fluid transfer, conferring additional solute clearance properties. Flow characteristics at the membrane surface also affect diffusion and are termed boundary layers. Proteins affect equilibrium of ions due to sequestration of charged proteins on one side of the membrane, termed the Gibbs-Donnan Equilibrium.[50] Finally, the combination of diffusion and convection across the membrane alter the properties of individual methods in a complex manner. A great deal of literature examines these complexities and is beyond the scope of this article to review.

Modalities

The previous sections are a prelude to the modalities available for RRT. Blood may be passed through tubing and across artificial membranes (hemodialysis or hemofiltration), or dialysate may be instilled adjacent to the peritoneal membrane (peritoneal dialysis). Peritoneal or hemo-based modalities may either be intermittent or continuous therapies. Finally, the method of clearance is also included in the description. Hence, RRT has been plagued with a confusing array of nomenclature in the literature, but includes peritoneal dialysis (PD), intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD) and continuous renal replacement therapy (CRRT). CRRT is comprised of slow continuous ultrafiltration (SCUF), continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD) or a combination of convective and diffusive therapies, continuous veno-venous hemodiafiltration (CVVHDF). PD includes Automated Peritoneal Dialysis (APD), with ~3–6 nocturnal cycles of dialysis fill and drain and a small residual dwell during the day, and Continuous Ambulatory Peritoneal Dialysis (CAPD), with frequent exchanges during the waking hours and one long dwell during the night. Hence, peritoneal dialysis may be considered CRRT in the sense it is continuous and is renal replacement therapy, although most connote hemo-based therapy when using the term CRRT. The selection of peritoneal based versus hemo-based RRT is decided using patient characteristics (age, severity of illness, comorbid illness), indication for RRT (ion removal, middle molecule clearance, fluid removal), location (inpatient, ICU, outpatient) and resources (financial, equipment, training). Although PD may be the correct choice for an outpatient with stable chronic renal dysfunction, it is also used for critically ill children in ICU after surgery for congenital cardiac disease surgery in developed countries. Conversely, CRRT is almost exclusively restrained to the intensive care unit in a developed country with significant resources; however, intermittent therapy is often employed in these circumstances.

Data regarding the modality used for RRT comes predominantly from survey results, with few publications of worldwide usage. In a 2005 survey using the Fresenius medical care network, it was estimated 1.3 million patients received RRT worldwide, of which 89% received hemodialysis and 11% received peritoneal dialysis.[51] In an international sampling of ICUs, the most frequently employed continuous modality was CVVH,[52] as was also true for patients in the United Kingdom.[53] In surveys of specific countries and regions, peritoneal dialysis remains the predominant therapy due to its relative ease and lower cost as compared to IHD.[54-56] Peritoneal dialysis is preferred in the pediatric population after surgery for repair of congenital cardiac disease[57,58] and possibly for adult cardiac transplant patients.[59] Yet, among other pediatric patients with kidney failure, PD is employed less frequently in favor of hemo-based CRRT.[60] In some instances, the modality of choice is driven by practice guidelines based on patient and disease characteristics such as hemodynamic stability and other organ failures.[61] Furthermore, cost of therapy may be a significant driving force in the choice of modality.

For critically ill inpatients with acute kidney failure, debate exists over the choice of intermittent versus continuous therapies.[62] Single center data and meta-analysis demonstrate conflicting results,[63-65] possibly due to difficulties such as sicker patients crossing over from intermittent to continuous therapies,[63] significant interruption time in continuous therapies[63] and effect of era of study.[64] As such, no definitive data exist to support one therapy over the other, and the two most recent large adult trials failed to show benefit of continuous therapy over intermittent.[66,67] One recurring concern with this comparison is the hemodynamic stability of patients and tolerance of intermittent therapy. Two studies have compared hemodynamic stability between IHD and CVVH, both demonstrating lower mean blood pressure in the IHD group, presumably due to lower blood flows and slower fluid removal during CVVH.[68,69] Newer hybrids such as extended daily dialysis had no hemodynamic instability as compared to CVVH in a more recent study, suggesting blood flow rate and fluid removal rates may be the limiting factor.[70] Hemodynamic instability is often the cited reason for CRRT use in critically ill children as compared to IHD, especially children <10 kg.[71] At least one study has suggested improved return of renal function in the continuous therapy group, although this is not a consistent finding.[63]

Cost. The cost of continuous therapy in the intensive care unit is generally felt to be greater than the cost of intermittent therapy, predominantly due to fluid expenditures.[72-74] Cost comparisons of therapy are difficult due to the complexity of the analysis, including personnel time use and costs, equipment depreciation costs, total hospital charges and country of study. Other hidden costs may not be included in analysis of intermittent therapy such as water purification system costs and maintenance. In developed countries, intermittent therapy is felt to be more costly than peritoneal dialysis, yet in developing countries, IHD may be more cost effective than PD.[75] These differences are felt to be due to costs of fluids and personnel time associated with the therapy. As

hybrid therapies gain in popularity, cost comparisons will emerge but initial studies suggest SLED is less costly than CRRT in North America and New Zealand.[76-78]

Dose

An important comparison between intermittent and continuous therapies is the total dose of therapy given, usually represented as a urea clearance. Although creatinine clearance is the measurement of native renal function in clinical practice, most dialytic therapies are measured by urea clearance. During diffusive clearance (K), solute rapidly equilibrates across the membrane and its instantaneous clearance is described using the equation K = (Qb) (Ci-Co)/Ci where Qb is blood flow in ml/min and C is the concentration of solute in inlet and outlet blood. This simple instantaneous clearance formula is true for situations of single pass hemodialysis with dialysate in countercurrent exchange with blood. The equation is further simplified for urea, which is not present in "fresh" dialysate, with K = (Qd) (Cd/Ci) where Qd is dialysate flow rate and C is the concentration of urea in dialysate effluent and inlet plasma. If the Qd/Qb ratio is <0.3, dialysate is considered to be fully saturated at the effluent port, whereas with a ratio >0.3 the actual K may be significantly less than calculated by the above equation. Similar formulae may be written for convective clearances of solute with K = (Qf) (Cf/Cp), where Qf is the rate of ultrafiltrate production and C is the concentration of solute in ultrafiltrate and plasma. The ratio of solute in ultrafiltrate to plasma is termed the sieving coefficient and is specific for a membrane/solute combination. Risk of excessive hemoconcentration exists with Qf/Qb ratios >0.2 and may be associated with filter clotting. In both diffusive and convective clearance, K is affected by solute size, charge of the membrane and solute, and pore size in the membrane, with characteristics specific to a solute + membrane combination. Additionally, recirculation of blood in double lumen access may affect clearance because blood in the inflow limb of the circuit may have lower solute concentration than plasma, which reduces the efficiency and efficacy of dialytic therapies.

These formulae are useful for calculating the instantaneous clearance (efficiency) of a molecule, but to describe the total clearance over an entire therapy (efficacy) the formula for Kt/V has been utilized. K is the instantaneous clearance of solute, t is the duration (time); this clearance is applied to a volume of distribution (V) of the solute in question. Kt/V values of >1 have been extracted from large observational studies and suggest that increased total dose is associated with survival; however, this has not been well documented in randomized controlled trials. The National Kidney Foundation practice guidelines recommend a minimum Kt/V of 1.2 per treatment three times a week in chronic hemodialysis; however, this is in a stable outpatient population and has not been rigorously studied in the acute renal failure population.[79] The minimal adequate dose for peritoneal dialysis has recently been modified from weekly Kt/V = 2 to 1.7.[80] For patients on continuous therapy in the intensive care unit, the minimum dose was initially extrapolated from the IHD literature with a goal Kt/V of ≥1.2 per day. This lead to modeling of urea clearance in intermittent and continuous therapies with varying degrees of urea generation, and suggested IHD had to occur 6–7 times per week to achieve and maintain equivalent time averaged urea control.[81] The optimal dose delivery in continuous convective therapies was suggested to be 35 ml/kg/hr (Kt/V ~ 1.4/70 kg) of ultrafiltration (the SC of urea is 1, hence K is approximated by Quf for urea in convective clearance), which showed benefit over 20 ml/kg/hr.[82] However, others have failed to reproduce these results.[33,67,83,84] It is now felt that there is a threshold of dose for both intermittent and continuous therapies in critically ill patients above which no further benefit is seen,[85] which appears to be between 20 and 35 ml/kg/hour based on previous studies.[67,82,84] The effects of RRT on the critically ill patient has been studied using a variety of biomarkers from urea to β2 microglobulin to cytokines, yet Kt/V for urea is the most consistently studied in large populations. However, it is unknown whether this is an adequate surrogate marker for the overall effects of blood purification that occurs during RRT in the critically ill.[85]

The instantaneous clearance (K) for intermittent therapy is much higher than continuous therapy due to operational characteristics (Qb, Qd and Qf rates), yet the efficacy of continuous therapies is greater due to the duration. This is true only if the prescribed dose is delivered and not interrupted. In the intensive care unit setting, therapy is often interrupted due to circuit malfunction or traveling outside the ICU for procedures or imaging. Hence the daily dose actually delivered may be substantially below the prescribed dose, with approximately 8 hours of "downtime" per day in continuous therapies.[63,86,87]

These difficulties have given rise to hybrid techniques combining a portion of the instantaneous clearance (K) of IHD with the longer duration of therapy and slower fluid shifts of CRRT. These include Sustained Low Efficiency Daily Dialysis (SLEDD) and Extended Daily Dialysis (EDD).[88] Hybrid techniques utilize a lower Qb and Qd than IHD, with Qb 200 ml/min and Qd 100–200 ml/min as compared to 500–800 ml/min during IHD. An early publication in 2000 described EDD with a Qb 200 ml/min, Qd 300 ml/min over 6–8 hours with improved urea clearance as compared to continuous hemofiltration.[89] Although not published until 2001, SLED experience began in 1998 at a single institution and demonstrated a Kt/V 1.36 delivered over 10 hours with Qb 200 ml/min and Qd 100 ml/min.[90] In both these publications, the therapy was hemodynamically tolerated, and an adequate dose of therapy was delivered. In a single institution study, SLEDD was not associated with an increased patient mortality compared to mortality predicted by acute physiology and chronic health evaluation scores (APACHE II).[90] The addition of convective clearance (hemofiltration) to the therapy has been termed Sustained Low Efficiency Diafiltration (SLEDD-f) and has the goal of improving middle molecule clearance.[91] Although some centers have migrated from CRRT to a hybrid therapy, this is not yet universal. In the recent, large adult study to investigate effects of dose intensity, only 2.5% of 11,602 total RRT therapies were a hybrid technique in the Veterans Administration system in the United States.[67] However, in three ICUs in Australia, New Zealand and Italy, hybrid techniques have come to represent 50–100% of RRT delivered to adult patients over the past

decade.[92] Additionally, anecdotal experience shows this to be the treatment of choice in practices outside of academic centers in the United States.

The approach to RRT modality in the intensive care unit is still under debate. No study has clearly shown unbiased results that support one therapy over another at equivalent dose. Adjustment of the technique to facilitate patient stability was the driving force of the expansion of CRRT, and further work with hybrid techniques may provide further benefits in terms of cost and personnel. Whichever modality is employed, it can only be described in a few categories as intermittent or continuous, blood or peritoneal-based, using convective and/or diffusive clearances.

Equipment and Fluids

The most significant changes in RRT delivery have centered around equipment technology. Although roller pump technology has changed little, machine safety and therapy monitoring continue to improve. With microprocessor technologies advancing, user interface has changed dramatically, now automating therapy after a few input variables. Additionally, synthetic membranes have been developed and nearly universally adopted into practice. Tubing is exclusively polyvinylchloride (PVC) and designed for single use only. Fluids for continuous therapies have been developed for mass production, eliminating the need for on-site fluid preparation. However, for IHD and hybrid therapies, on-line dialysate production remains the standard.

Machines. The differences between individual machines by various makers are vast and at the same time limited. Operational characteristics are altered by adjusting fluid rates to achieve the desired effect. Blood flow is driven and adjusted using a single roller pump. Dialysate flow is driven by a pump on the inlet port, and ultrafiltrate is generated by creating relative negative pressure at the outlet port by a third pump spinning faster than the inlet pump. Alternatively, dialysate and ultrafiltrate flow rates may be adjusted using a series of valves. Some form of adjusting the operational characteristics are universally shared by machines used for blood purification (peritoneal dialysis cyclers only adjust the dialysate influx and efflux rates), and it is the user interface and machine programming that differs between manufacturers. The two major categories of machines are those used for continuous therapies and those for intermittent therapies. These differences will not be reviewed here due to scope of the article and to avoid industry bias; however, numerous companies exist worldwide with excellent products.[93]

Fluids. Intermittent therapy (IHD and SLEDD) uses an on-line dialysate and FRF production system, whereas continuous therapies use pre-prepared fluids. On-line dialysate and FRF production allows for instantaneous adjustment of solute control without wasting or changing large bags of fluid. For continuous therapies, industry manufactured solutions are available with a variety of solute compositions. These fluids are regulated differently in the United States, with FRF categorized as a medication and dialysate as a device. Because of industry and regulatory standards, the composition, quality and sterility of these fluids is ensured; however, this comes at significant cost.

The ultimate goal for fluid composition during RRT is precise management of the solute composition of the plasma. This may be achieved through creation of concentration gradients in dialysate for effective transfer of solute to and from the patient or composition of FRF to mimic goal plasma solute concentrations. Within this framework, the standard cations remain sodium, potassium, magnesium and calcium, with standard anions chloride, bicarbonate and occasionally phosphorus. The base included in the solution has undergone a great deal of study, mostly in continuous therapies, with extensive comparisons between lactate and bicarbonate. Acidosis during CVVH occurs as a consequence of fluid composition with lower pH, as seen with acetate >lactate>bicarbonate based solutions.[94-96] Failure to resolve acidosis during RRT is associated with increased mortality, hence this choice is important.[96-98] Lactate is noted to rise during lactate-based RRT and may have deleterious cardiovascular side effects and is associated with poor outcomes.[95,96,98-101] It is unclear whether lactate induces injury or is simply a marker of dysoxia and abnormal liver metabolism of lactate during critical illness hence its association with mortality. Although some fluids still contain minimal lactate (~3 mEq), most fluids are bicarbonate (20–24 mEq/L) based. For on-line IHD fluid generation, bicarbonate is used exclusively as the base with a small amount of acidifying acetate added for solution stability.[102]

On-line dialysate production allows for alteration of the composition, which may improve patient outcomes. Data regarding sodium concentration has been associated with interdialytic volume status and potassium concentration with arrhythmias during therapy. Additionally, glucose-based dialysis solutions have undergone much investigation, with recent data suggesting that a minimal amount of glucose limits extensive glucose losses with nutritional consequences without creating hyperglycemia and hyperinsulinemia associated with high glucose dialysate concentrations.[103,104] Hence, individualization of dialysate composition may improve individual patient outcomes and is recommended for on-line dialysate production.[103,105,106] Commercial fluid compositions for CRRT also vary the amount of potassium, glucose and calcium but with less flexibility of choice, however, as compared to on-line fluid production.[107] Calcium and bicarbonate content becomes important for patients on regional citrate anticoagulation (see section on anticoagulation), as calcium in dialysate counteracts the effects of citrate at the membrane and alkalosis may develop due to citrate metabolism and increased bicarbonate load. The variety of solutions available commercially are too extensive to list here, and the choice of fluids for CRRT is individualized to an institution with consideration of method of anticoagulation, degree of flexibility required, cost of stocking multiple fluids, solute composition and regulatory body approval status.

Water purity. For intermittent therapies using on-line fluid generation, water purity is an issue of paramount importance. Dialysate production in the earliest days utilized tap water as the basic ingredient; however, water quality varies based on local regulations and facilities. An average adult patient on IHD is exposed to ~24,000 liters of water per year in dialysate, hence minute impurities become magnified, and it is now understood

that the purity or quality of dialysate is associated with patient outcomes.[102,103,108-110] The addition of reverse osmosis technology greatly improved water purity for hemodialysis and has been the standard for sometime. This process uses pressure to filter water through highly selective membranes that limit solute transfer, resulting in water with minimal impurities. Using this technology, the standard for hemodialysis water quality, including metals, micronutrients and bacteria, has been set in the United States by the Association for the Advancement of Medical Instrumentation (AAMI).[111] These standards allowed for <100 colony forming units of (CFU) of microorganisms per milliliter (ml) of fluid and <2 endotoxin units (EU) per milliliter and remain in force in the United States. Recent data have given rise to more stringent standards in Europe of <0.1 CFU/ml and <0.03 EU/ml for dialysate fluids that are associated with improved patient outcomes.[112] Chronic exposure to bacteria and bacterial byproducts (such as endotoxins) increases the inflammatory response and leads to chronic inflammatory processes as well as ongoing oxidative stress.[108-110,112,113] Hence, more stringent standards have been incorporated into the International Organization for Standardization publications regarding water quality and water treatment devices/equipment[114-116] and are being adopted by other agencies as standards for dialysate fluid as data emerges regarding patient outcomes.[108] To achieve these standards it is necessary to include filtration of endotoxins and routine decontamination of the system.[108,109,112,113] The technical aspects of decontamination will not be reviewed here; however, this does include the eradication of biofilms that develop in the transport and circulation systems of water treatment equipment. Hence, although ultrapure water is generated through a series of filtrations, stagnation within the system may lead to the formation of microbe-releasing biofilms. A variety of approaches have been recommended, including chemical, heat and ultraviolet treatment of water purifying equipment. Of utmost importance is a regular decontamination schedule and frequent monitoring. Of note, the monitoring of such systems is also complicated by differing results of CFU counts dependent upon isolation technique, which will require appropriate techniques for evaluation of maintenance of published standards.[112,117]

Peritoneal dialysis equipment. The equipment and fluids necessary for peritoneal dialysis require specific mention. Fluid for peritoneal dialysis must dwell for an extended period of time and hence requires more pronounced osmotic gradients to produce adequate fluid shift from the patient. This requirement has been partially altered by continuous flow peritoneal dialysis, which increases total clearance due to frequent dialysate replenishment. Glucose has traditionally been the agent of choice; however, hyperglycemia remains a concern, as well as accelerated changes of the peritoneal membrane. Additionally, the heat sterilization process for PD fluids produces glucose degradation products that enhance detrimental changes to the peritoneal membrane. Newer approaches have included amino acids as the osmotic agent. Despite improving nitrogen balance, this may increase azotemia and acidosis in the patient and affect changes to the peritoneum.[118-120] Other agents have been studied, and icodextrin appears to improve glucose-related dyslipidemia and hyperinsulinemia in patients requiring long dwell times for chronic renal support. It is a large molecular weight glucose polymer that exerts its effects as an oncotic gradient rather than osmotic agent with few side effects.[121] A minimal amount is absorbed via the lymphatics and metabolized by amylases to metabolites with renal clearance of parent and intermediate compounds.[122-124] Machines used for peritoneal dialysis are relatively simple, yet may be automated with a series of valves that allow for filling and emptying through the same catheter while keeping fresh and spent dialysate separate as during APD. Again, the choices of manufacturers are too varied to review in this manuscript.

Membranes. The membrane used during hemodialysis/hemofiltration has evolved significantly since the earliest reports. Initial membranes were natural materials, such as cellulose, or simple synthetic compositions, such as polysulfone, with symmetric structures and good performance for small solute passage.[125] However, these membranes include significant interactions with the complement pathway and immune response. Modifying the hydroxyl groups on cellulose membranes gives similar performance characteristics and less bioactivity and includes cellulose diacetate and hemophan membranes. With improvements in chemical engineering and manufacturing, cellulose-based membranes have yielded to synthetic membranes. The most popular membranes in use today are polyacrylonitrile (AN69) and polysulfone; however, polyamide, polycarbonate and polymethylmethacrylate are available. These materials have improved biocompatibility and reduce complement activation; however, they may enhance protein adsorption to the membrane in the absence of further modification. Despite the improved compatibility of synthetic membranes, the most recent large review does not demonstrate benefits conveyed by bio-compatibility.[126] The ultrastructure of membranes is predominantly the capillary design, or hollow fiber structure, in which blood flows through a series of small tubes held together in a bundle. This allows for a low resistance, high surface area membrane. Membrane properties such as charge, wall thickness and pore size affect function. The radius of the pore is related to the ultrafiltrate flow through the membrane, but overall fluid transfer is a function of the mean pore size. The number or density of pores and the radius of the pore affects solute transfer in diffusive clearances. Membrane characteristics such as flux (range and efficiency of solute transfer) and permeability to water are determinants of pore characteristics and wall thickness. The reader is directed to an excellent brief review for further study.[127]

Reuse of dialysis membranes has been commonplace in maintenance IHD since the inception of the therapy.[128] Initially it was driven by the time consuming process of assembling a circuit and later by the cost of industry produced equipment. Multiple methods have been used to sterilize the dialyzers, including heat, cold and chemicals as well as the invention of machines that automate the sterilization process. This process, originally driven by cost and convenienc,e was thought by some to improve intra-dialytic symptoms such as nausea, back pain, cramping, headaches, chest pain, dyspnea and headaches. No consistent evidence exists to support claims of improved morbidity by the reuse of dialyzers

nor is there any concomitant increase in mortality.[129-132] A recent study suggests reuse of dialyzers may convey a reduced mortality risk; however, this was a short study in a single center and caution is warranted regarding generalization of results.[133] Dialyzer reuse continues worldwide using predominantly chemical processing, most commonly peracetic acid and formaldehyde.[128]

Anticoagulation. Anticoagulation of the CRRT circuit varies by modality and local practice. Systemic heparinization remains the mainstay of anticoagulation for IHD and is still used by many for anticoagulation of RRT circuits. Citrate regional anticoagulation has gained significant popularity over the previous decade and is used exclusively in some centers for CRRT.[134-136] Two studies document the safety of citrate, avoiding anticoagulation and bleeding, with improved circuit survival compared to heparin in adults.[135,136] Citrate is delivered pre-filter as tri-sodium citrate, which chelates calcium in the circuit with the goal of 0.4 mmol/l ionized calcium at the filter, and calcium is re-infused to the patient to prevent systemic hypocalcaemia. Citrate is metabolized by the liver to ~3 moles of bicarbonate, and hence, the infusion may induce hypernatremic alkalosis. Low concentration citrate protocols have been developed to prevent these complications[137] as have protocols for other modalities, such as high-flux hemodialysis and SLED.[138-140] In patients with liver disease, citrate may accumulate if citrate infusion is greater than total clearance (filter and liver combined), and this complication may have significant effects in pediatric patients who often experience hypotension with hypocalcaemia. Hypocalcaemic Citrate Toxicity (HCCT) occurred in up to 17% of pediatric CRRT treatments without increased mortality risk.[141] However, citrate remains the preferred agent of anticoagulation even in liver disease and requires attention to infusion and clearance rates of citrate. From both adult and pediatric studies it is evident that heparin or citrate use prolongs filter life compared to no anticoagulation in CRRT.

Future Trends

Renal transplantation is the ultimate step for end stage renal failure management, as it replaces native renal function completely, yet availability of organs limits the widespread use of transplantation for the millions of patients worldwide on RRT. Although current RRT is able to mimic or exceed the bulk solute clearance of the native kidney, it does so using significant volumes of fluids that require tethering to static water and power sources. Although the native kidney produces ~140 liters per day of ultrafiltrate, it excretes only 1–2 liters per day of urine, reclaiming >98% of ultrafiltrate produced. This type of fluid reclamation is prominent in artificial kidney research, which would un-tether the patient from a fluid source. Additionally, the kidney is able to modulate the solute concentration during the fluid reclamation process, another trend in artificial kidney research. Finally, the native kidney has metabolic and endocrine functions beyond simple filtration, with the production of the antioxidant glutathione and formation of active 1–25 OH-Vitamin D as well as epoprotein. Current trends in artificial kidney research are addressing each of these issues with the lofty goal of a small device, preferably implanted with little or no maintenance required by the wearer that would deliver safe and highly effective renal replacement therapy including metabolic and endocrine functions.

Fluid reclamation has been addressed using sorbent technology to remove waste products from ultrafiltrate or dialysate. The earliest of these systems was the Recycled Dialysis (REDY) system,[142-144] and the next iteration was the Alliant Hemodialysis System.[145] These cartridges use a series of layers to process fluids, first filtering through a layer of activated charcoal for initial purification and removal of organic molecules and heavy metals. The next layer contains urease to convert urea to ammonium, which is adsorbed in the subsequent zirconium phosphate layer. This layer is also responsible for the majority of active ion adsorption. The final zirconium oxide layer adsorbs phosphate and residual heavy metal and generates bicarbonate and acetate in a pH dependent reaction.[146] Miniaturization of the cartridges and placement in series allows reclamation cartridges to be included in smaller devices than previously marketed.

Reclamation technology has been applied to the Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)[147] and the Wearable Artificial Kidney (WAK).[148] The WAK has performed well in eight patients for a short term pilot study, with low but adequate urea clearance during continuous ambulatory hemodialysis. Low urea clearances were felt to be due to Qb and Qd rates achievable with a 9 volt miniaturized pump. Further modifications have improved this design, and the WAK V1.1 uses pulsatile blood and dialysate flows half a cycle apart such that blood flow peaks as dialysate flow ebbs and vice versa in a device weighing <1 kg. This, which the authors term "pulsatile push-pull internal hemodiafiltration," creates very high instantaneous Qb and Qd, allowing for improved hemodiafiltration achieving K_{urea} 55 ml/min.[149] Currently, the WAK technology utilizes established dialysis techniques with miniaturized components and sorbent-based fluid reclamation.

Although adequately replacing the filtration and waste elimination, functions of the kidney, endocrine and metabolic activities are not replaced. Specifically glutathione (antioxidant effects) and vitamin D (bone mineralization) replacement is felt to be important. Proximal renal tubule cells are the primary source for these functions in the native kidney and have been incorporated into the bioengineering solution of renal support. Two primary sources of cells have been reported, including harvesting from whole organs and cultured cell lines. Whole organ procurement in the lab setting is reported from porcine kidneys[150] and human kidneys procured but unsuitable for transplantation.[151] Investigational cell lines have been utilized, specifically Madin-Darby canine kidney (MDCK) cells and Lewis lung cancer-porcine kidney 1 (LLC-PK_1) cells.[152,153] Renal tubule cells are cultured on an ultrastructure, typically an existing hollow fiber membrane or a newer engineered membrane. The Renal Assist Device (RAD) utilizes human tubule cells, which are attached to a polysulfone high-flux membrane coated with pronectin-L.[150] Others have used nanopore silicone membranes with collagen coating to attach human renal tubule cells.[154] The membrane serves both structural and protective functions as humoral and cellular immune components are excluded from the cultured

tissue environment by the membrane allowing cultured xenograft-allograft cells to survive.

The RAD system has been the most extensively studied with evidence of both glutathione and Vitamin D metabolism in the artificial organ.[150,155] This more "complete" renal replacement was felt to be safe[151] and to convey 180 day survival and return of renal function benefits to a small group of ICU patients enrolled in an open-label trial for CVVH with RAD augmentation.[156] Phase III trials have not been published but are planned according to the authors. However, the RAD is a long way from the criteria for ultimate renal replacement support, as it is used in conjunction with standard, machine-based hemofiltration whereby the ultrafiltrate is shuttled through the RAD with reclamation of approximately 25% of solute and fluid prior to return to the patient.

Unlike the sorbent reclamation system of the WAK, the RAD uses cellular-based fluid reclamation. A biofilm of renal tubule cells attached to a semi-permeable membrane has beneficial fluid transport properties, and a small osmotic gradient creates sufficient transfer of isosmotic fluid across the tubule cells.[153] This reclamation process allows therapy to be delivered without large volume fluid replacement, freeing the patient from water sources. Membrane characteristics have also been altered to alter solute transfer properties, thus allowing for selective hemofiltration. Microelectromechanical systems (MEMS) allow the creation of nanopore silicone membranes. These membranes contain pores with highly controlled pore size, within 1 nanometer over a wide range of pore sizes from 8–90 nanometers.[154] Pore size and density control selectivity of solute transfer and water permeability, hence desirable characteristics can be engineered into small devices. A dual membrane system has been designed using nanotechnology that has incorporated hydrophobicity into the pore design.[157] This allows for selection of ion passage based on molecular weight and "hydration shell," the molecular arrangement of water around the ion. Hence, membranes with engineered specificity may be designed and miniaturized.

The complete artificial kidney has not been created, but work in this area looks promising for the future. Efficient fluid management with reclamation and selective membranes in conjunction with metabolic and endocrine function replacement in a miniaturized package is a possibility.

Conclusion

Renal replacement therapy continues to evolve. Although some indications for therapy in the acute setting are well established, other indications emerge as we care for critically ill patients. The choice of RRT for both inpatients and outpatients should best meet the needs of the patient, adequate clearance at minimal inconvenience as well as fit the financial and resource allocations of the region. Although filtration functions have been adequately mimicked in current RRT, the replacement of endocrine and metabolic functions are not yet mainstream. Current fluid reclamation and nanotechnology continue to evolve, making the implantable artificial kidney a possibility for the future.

Acknowledgements

I would like to thank Dr. Thomas Golper for his role as mentor and editor in the preparation of this manuscript.

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