CHAPTER 183

Feasibility, Efficiency, and Adequacy of Peritoneal Dialysis in Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Explain the overall role of peritoneal dialysis in acute kidney injury.
2. Describe the concept of dialysis dose and efficiency as it relates to peritoneal dialysis.
3. Discuss the shortcomings of urea kinetics in assessing the adequacy of dialysis dose in acute kidney injury.
4. Define the adequacy of peritoneal dialysis dose through the compound measures of the individual components in acute kidney injury.

Although the initial reports of peritoneal dialysis (PD) for the management of renal failure were for acute kidney injury (AKI), PD uncommonly is used as renal replacement therapy (RRT) in patients with AKI, at least in developed societies. Developments and refinements in continuous renal replacement therapies (CRRTs), principally venovenous therapy, over the last quarter of a century, along with improving safety and a belief that increasing the dose of dialysis as measured by small solute clearance would improve patient outcomes, have eroded into what was once considered a classical PD pool of patients with unstable hemodynamics and have pushed the considerations for PD mainly for children, and in those with coagulation abnormalities and/

or hemodynamic instability, where it has some distinct advantages.[1,2] Recently, surveys from providers across the world have revealed that even though about 40% to 60% of providers feel that PD is suitable for patients with AKI, fewer than 20% offer it as a therapy in their practice, and true use of PD for the AKI management is even less than that.[1,2] In these surveys, the largest gap between belief and practice was seen in Europe and North America. To the best of the authors' knowledge, PD for adult AKI in the United States and Canada is anecdotal and is used mainly in circumstances in which alternate forms of extracorporeal therapy are not feasible.

On the other hand, PD continues to be an important modality of RRT for significant populations in the world, especially in Africa, South and Southeast Asia, and South America. Economic considerations and prevalent healthcare infrastructure contribute significantly to this disparity, although similar trends of decline are evident in many urban areas.[3] However, whether the newer, more aggressive and consequently more "sophisticated" forms of extracorporeal therapies, namely hemodialysis or hemofiltration, are better in the critical care setting than PD has been difficult to compare because clinical studies comparing these modalities have been limited in numbers and generalizability.

Therefore important issues while considering PD for AKI appear to be (1) Is PD feasible in patients with AKI? (2) Can PD provide efficient clearance of fluid and solutes? (3) What is that efficient clearance (i.e., how to define the adequacy of such clearance)? (4) Is PD worth the considerations, when compared with the extracorporeal therapies in terms of effort needed to improve its availability and the medical benefits and risks?

FEASIBILITY OF PERITONEAL DIALYSIS IN ACUTE KIDNEY INJURY

Apart from a breached peritoneum, there are few absolute contraindications to PD. Thus the question of feasibility of PD in patients with AKI and intact peritoneum rests on coexistent homeostatic, mechanical, and infectious considerations. These include concerns related to the peritoneal access (which include mechanical and infectious complications) and those related to the non-physiologic presence of PD fluid within abdominal cavity (which include mechanical and metabolic issues). However, when considered as a whole, these feasibility concerns, although important, can be addressed easily by adequate applications of fundamentals of PD and provide limited hindrance to application of PD in AKI. The details of this topic are discussed at greater length in other sections of this volume (Section 26).

EFFICIENCY AND ADEQUACY OF PERITONEAL DIALYSIS IN ACUTE KIDNEY INJURY

Defining the adequacy of dialysis has been studied intensely and is a hotly debated topic in nephrology. However, despite nearly three decades of efforts, we lack a consensus in terms of acceptable markers capable of representing uremic toxins as well as the quantitative clearance considered adequate. These concerns, important in the care of end-stage renal disease (ESRD), have further limitations in the setting of AKI.[4] AKI is defined usually by a rise in serum creatinine, usually in conjunction with a decline in urine output, despite the simultaneous retention of many different uremic toxins. Handling of creatinine by the gastrointestinal (GI) tract and kidneys is altered with progressive decline in glomerular filtration rate. In addition, because creatinine is a larger molecule with more tissue compartmentalization, its kinetic modeling has been difficult, and association of its clearance indices to hard outcomes has been elusive even in ESRD. Recently, multiple novel molecules have been studied that should be able to provide early diagnostic or prognostic information. However, the utility of these in clinical decision making is still limited.

Together these have resulted in the use of blood urea nitrogen (BUN), as in Kt/V_{urea} (Kt/V), as the most commonly used marker to represent the efficiency of dialysis. However, for a variety of reasons, this choice is more a reflection of historical precedence rather than medical significance or desirable kinetics. First, limited data exist implicating BUN to the adverse outcomes in renal failure. Second, the BUN values are affected by many factors other than renal function, especially in conditions leading to AKI, including protein malnutrition, hypercatabolic state because of either endogenous hormones or exposure to extracorporeal circuits, GI bleeding, and systemic inflammation.[5] Third, the very concept of urea kinetic modeling (UKM) is poorly validated in the settings of AKI. Variations in urea generation, inconsistent estimation of volume (V) by any standard formula,[3] and significant tissue compartmentalization are significant limitations in using urea-based kinetics in patients with critical illness.[6]

Perhaps the biggest concern using urea clearance indices to define the efficiency or adequacy of dialysis in AKI lies, at least from the PD perspective, in the fact that it focuses on the small solute clearances. The last two decades have shown us that the strength of PD lies in effects other than the removal of small solutes, and indices of small solute clearance such as Kt/V_{urea}, beyond a basic minimum, have little correlation to outcomes of PD.[7,8]

Because of these factors as well as the inconsistent and largely negative results of the randomized studies examining the impact of the dose of dialysis as reflected by urea clearance indices on AKI outcomes, Kt/V_{urea} is considered a poor marker for dialysis adequacy, especially PD adequacy. On the other hand, PD, like other modalities of CRRT, allows for constant ongoing equilibration among different body compartments and thus has much less tendency for discrepancy between the targeted and the true delivered dose as defined by Kt/V. These changes in understanding have been incorporated in recent adequacy guidelines for ESRD, and greater emphasis has been placed on a more holistic approach toward the control of multiple clinical and biochemical parameters.[9] One such important but infrequently reported example of adequacy is the management of fluid overload. Outcome studies in AKI show a consistent relationship between fluid overload and mortality.[10,11] Brown et al. showed the importance of management of fluid overload in ESRD among patients on chronic PD. In this study, investigators showed that among those with equivalent small solute (creatinine) clearances, a higher daily ultrafiltration (UF), defined as being greater than 750 mL, was associated with reduction in mortality.[12] Similar improvements in the outcomes associated with volume removal have been shown in those with AKI on different types of renal replacement therapies, again including PD.[13] Despite these findings, targets for fluid balance have been difficult to incorporate into adequacy guidelines because the requirements of fluid

management are dynamic in AKI and assessment of fluid status and optimal goals are defined poorly.

ADEQUACY AND OUTCOMES OF PERITONEAL DIALYSIS IN ACUTE KIDNEY INJURY

A number of clinical studies have reported outcomes of PD in AKI patients. Although a majority of these are cohort to small-scale randomized controlled trials (RCTs), they show a trend toward comparable outcomes for AKI with PD and other extracorporeal blood purification (ECBP) therapies in the modern era. We focus on the new data and how they reconcile with the older literature.

As highlighted above, in the absence of a well-defined marker(s), the adequacy of dialysis in AKI has been judged by the clearance indices established for conventional thrice-weekly hemodialysis (HD). Similar to the choice of marker, there is uncertainty as to how the dosing of the therapy should be calculated. A pragmatic definition of adequacy could be: the ability of a therapy to negate the adverse effects of the disease process and achieve outcomes comparable to those without the disease, or available with alternate therapies. By these measures, a dialysis therapy (PD) that focuses mainly on removal of toxins accumulated during the process of AKI can be considered adequate if its capacity to clear uremic toxins fulfills the needs of clinical care. The early reports on PD spanning from 1960s through the 1980s reported that PD could deliver adequate clearance on the target parameters.[14–18] In fact, Indraprasit et al., in their metabolic studies, found an equivalence in urea clearance comparing continuous PD urea clearance of approximately 12 mL/min and alternate-day HD clearance of 120 mL/min for a 5-hour session.[18] However, with the technologic advances in hemodialysis and CRRT techniques, concerns were raised about the ability of PD to control adequately the degree of uremia, especially comparing its speed of small solute clearance (clearance per unit of time) to hemodialysis and discounting its constant nature. Phu et al. in a randomized trial compared the practice of intermittent peritoneal dialysis (IPD) to continuous veno-venous hemofiltration (CVVH) in 70 adults (48 with severe falciparum malaria and 22 with sepsis).[19] They randomized 34 patients to hemofiltration and 36 to IPD and found that those treated with IPD had substantially higher mortality (47%) compared with those treated with CVVH (15%, $p = .05$). Secondary outcomes as well, such as correction of acidosis and solute clearance, were significantly better in the hemofiltration group. However, this study had several methodologic problems. The study used suboptimal PD practices. (Old PD technology with rigid catheter, open system, manual exchanges, locally prepared acetate buffered dialysate, with higher Na [141 meq/L]/), had inefficient PD prescription (70 L dialysate over 24 hours with less than 30 minutes' dwell), and were thought clinically to have had a high peritonitis rate; and compared it with a state of the art CVVH system with commercially manufactured dialysate.

However, since the publication of this report, multiple other investigators have reported different findings. Chitalia et al. from India reported the results of a randomized crossover study in 87 patients with mild to moderate hypercatabolic AKI, with access to peritoneal cavity obtained by a trocar-based stiff PD catheter.[20] They compared the manual open system of continuous equilibrated PD (CEPD) with the automated and closed system of tidal PD (TPD) in 236 PD sessions (118 in each treatment arm) and used a total of 26 L of dialysate per day, in 2-L dwells. They found that TPD and CEPD are reasonable options for mild-moderate hypercatabolic AKI, achieving daily UF of 2.9 L and 1.9 L, respectively, and calculated weekly urea Kt/V of 2.43 and 1.8. Although mortality data were not reported, the researchers reported *technique failure* in 4 out of 87 (4.5%) patients, 3 of whom had snake bite and had very low indices of clearances (daily Kt/V of 0.12 to 0.18). A detailed analysis regarding the cause of such low clearances was not reported. In another report from India, George et al. randomly allocated 55 patients to receive continuous venovenous hemodiafiltration (CVVHDF) at 20 mL/kg/hr or IPD performed through a trocar-based rigid catheter with closed manual exchange system.[21] After censoring the deaths within first 6 hours of initiation (four in the CRRT group and one in the PD group), they had 25 patients randomized in each group. The authors reported that despite a higher urea clearance with CRRT (mean 21.8 mL/min vs. 9.4 mL/min for PD), both modalities achieved equivalent outcomes when a composite score for clearance accounting for correction of acidosis, electrolyte disturbances, and ultrafiltration were considered, with both groups achieving daily UF rates of 2.9 L and 2.8 L, respectively.

Gabriel Ponce et al. have published a series of reports from Brazil for their acute PD program, which used percutaneous nephrologist-inserted flexible PD catheters for peritoneal access, and blind automated cycler–based closed systems. After finding encouraging results in an earlier study,[22] they conducted an RCT, allocating 120 critically ill patients to either high-volume PD (HVPD) (n = 60) or daily HD (dHD) (n = 60).[23] The HVPD arm used 35 L per day of dialysate in 2-L dwells. They were able to achieve a weekly Kt/V_{urea} of 3.6 and 4.7 and daily UF rates of 2.1 and 2.4 L with HVPD and dHD, respectively. The primary outcomes (mortality and rates of renal recovery) were found to be similar in both groups. Secondary outcomes of serial progression of the metabolic profile (including BUN, creatinine, bicarbonate, potassium, and glucose) were equivalent, at each 24-hour mark over the first 5 days. However, when examined for the time to renal recovery, PD was found to be superior compared with dHD. In a follow-up report designed to examine the intensity of PD, the same group reported their experience of a smaller RCT involving 61 critically ill patients randomized to receive high-intensity versus lower-intensity PD, with targeted weekly Kt/V of 5.6 versus 3.5, respectively.[24] Despite achieving a lower-than-targeted clearance (weekly Kt/V of 4.13 in high-intensity and 3.01 in lower-intensity group), the outcomes in the form of daily UF (2.4 L vs. 2.1 L), serial parameters of metabolic control, rates of infectious or mechanical complications, duration of therapy, recovery of renal function, and overall mortality did not differ significantly between the two groups in this small study. Finally, a recent publication from this group recounts their experience with PD for AKI over a longitudinal 10-year period.[13] This retrospective analysis covers a total of 1231 patients with AKI treated by dialysis, of whom 301 (24.4%) were treated by HVPD protocol. Unfortunately, the indications and circumstances under which the modality choice was made were unclear. However, a majority of those treated with PD were critically ill (67% in intensive care unit, 63% requiring vasopressor drugs, and 70% requiring mechanical ventilation). Overall, 31 patients (10.3%) developed peritonitis, and 44 (14.6%) developed mechanical complications. Nearly half of those complications were treatable, and the technique failure occurred in 51 (16.9% of) patients. The mean delivered Kt/V_{urea} over the 10-year study was 3.9+/-0.8 per week.

The experience highlighted a progressive stabilization of the metabolic parameters over the first three sessions of HVPD, reaching a steady state by the fourth session. Interestingly, the authors showed a progressive improvement in daily ultrafiltration as well, over the initial few (3) days with an optimization appearing by the fourth session, possibly suggesting an evolution of peritoneal membrane ultrafiltration over the early PD period.

Although the outcomes of those treated with ECBP were not available for comparison within the publication, the authors did publish separately their experiences with the contemporary ECBP cohort, in which they found similar trends for metabolic control, reaching stabilization of parameters by day 4, and what appeared to be similar trends in hard outcomes. However, these comparisons across two separately published retrospective and uncontrolled analyses likely are fraught with significant methodologic limitations and should not be taken as hard evidence.

At the same time, it is to be expected that the physiologic principles driving the clearance in PD preclude rapid fluxes in solute and thus are probably unsuitable for conditions requiring "aggressive," time (hours)–based control of the metabolic or volume disturbances. Unstable conditions such as hyperkalemia with cardiac manifestations, severe pulmonary edema, poisonings or intoxications, tumor lysis syndrome, snake bites, or severe sepsis may require some form of acute hemodialysis for metabolic control at the outset. However, as recently demonstrated by Ghaffari et al., transition to PD in those initiated urgently on hemodialysis can be achieved,[25] especially if the expected course of RRT is prolonged. In addition, because the data driving some of these conclusions are derived from an older era, or from the studies using suboptimal PD technology (rigid catheter, open system, manual exchanges), a risk for overemphasis of PD limitations is likely.

Augmentation of dialysis dose for stable hypercatabolic renal failure, on the other hand, can be accomplished by modifications in PD prescription as shown by multiple studies from Asia and South America. Frequent cycling is the most commonly employed remedy in such situations and, if employed correctly with preservation of dwell times, can improve substantially even small solute clearance as shown by Gabriel Ponce et al.[13] However, increasing the frequency also increases the relative "dead time" on dialysis, which is the time spent in the process of exchanges, limiting the true contact time with the peritoneal membrane. Overzealous increase in frequency could be counterproductive and may have been one of the reasons behind negative outcomes associated with the study by Phu et al.[19]

Dose escalation also can be achieved by modifications in the PD regimen, such as introduction of tidal PD (TPD) or application of continuous-flow PD (CFPD), which also limit "dead time." A successful application of TPD to achieve adequate control of hypercatabolic renal failure was demonstrated by Chitalia et al.[20] On the other hand, CFPD with access to the peritoneum, via either two separate catheters or a double-lumen peritoneal catheter with distant tips providing separate portal for inflow and outflow of PD fluid, has been shown to substantially increase the small solute clearances comparable with the quotidian dialysis.[26] Logistics of catheter insertion, limited preliminary data, and lack of correlations with hard outcomes however make the application of CFPD investigational for patients with AKI.[27] Taken together, these reports strongly suggest that PD in the modern era, at least for a significant proportion of individuals with AKI, is able to provide adequate metabolic control of electrolytes and acid-base imbalances and provide small solute clearance indices comparable to those achieved with ECBP therapies. It further emphasizes that when evaluated for hard outcomes in terms of renal recovery and mortality, PD is at least equivalent to ECBP therapies and may even have an advantage when time to renal recovery is considered.

OVERALL ROLE OF PERITONEAL DIALYSIS IN ACUTE KIDNEY INJURY

When considered in their entirety, the targets for adequacy of RRT in AKI continue to remain ill defined. Studies examining the relationship between the dose of dialysis (as reflected by the Kt/V_{urea}) and mortality and renal recovery have produced conflicting results. It is believed that the clearance of small solutes in AKI has limited implications on ultra-short (hours to days) or long-term outcomes (mortality vs. recovery), which are dictated more by fluid and electrolyte control, and presence and progression of the multiple other organ system dysfunction respectively. Thus individuals critically ill and at the height of metabolic needs may require aggressive or higher clearances, whereas once stabilized, may do well with conventional anephric measures. In other words, the adequacy of dialysis (as in solute clearance or fluid clearances) may change during the course of an illness. This minimum recommended dosing standard,[28] when converted to a time-averaged clearance, provides an equivalent PD clearance (std Kt/V) of 2 to 2.1. As highlighted earlier, modulation of PD prescription in AKI can allow for nearly twice as much small solute clearance with weekly Kt/Vurea in the range of 1.8 to 4.13,[13,20,23] providing the flexibility to titrate the dose as per the metabolic needs.

Management of fluid imbalance is another frequently cited example for underutilization of PD. However, clinical studies cited earlier show that undermanagement of fluid overload or complications in terms of respiratory distress are equivalent between different therapies and are largely noninterfering with acute PD.[13,29] These studies further report daily UF in the range of 2 to 3 L, which are comparable to those achieved on CRRT and with conventional HD regimens, especially considering the constant nature of PD, and are appropriate for the care of a critically ill patient.[13,20,23] However, there appears to be a possible evolution of peritoneal membrane function through the initial period on acute PD, reaching an optimal UF profile by the fourth session.[13]

Finally, these concerns, although important, must be examined with reference to the hard outcomes on PD compared with ECBP therapies. In this regard, there are no well-designed, large-scale head-to-head studies in the adults comparing these modalities, and the available cohorts[30] and small RCTs[21,23] have shown comparable outcomes with PD to then-prevalent ECBP populations. It is well recognized that outcomes of dialysis requiring AKI are poor and are largely related to burden of disease.[30,31] Synthesizing the mortality data, Chionh et al. recently performed a systemic review of the outcomes of PD in AKI, examining 982 reports and finally analyzing 24 studies.[32] Pooled mortality was 39.3% in the 13 studies (n = 597) that reported PD only as RRT with wide range in reported mortality rates (1.1%–100%) for individual studies. Although detailed analysis for such large variation was not performed, the authors did highlight severity of illness as reflected by sepsis as a major discriminating factor. Among the 11 studies (n = 959) that compared PD with ECBP therapies, a total of 392 patients underwent PD and 567 were treated with ECBP. The pooled mortality rate was comparable for PD (58%) and ECBP (56.1%), in combined

analysis as well as when separated into the studies reporting observation cohorts findings and those reporting the results of RCT. Vast heterogeneity between the studies precluded further dissection of the factors affecting mortality.

When considering prospects of renal recovery, PD is hemodynamically more physiologic and less inflammatory, leading many to believe that it may allow better chance of recovery of renal function in patients with AKI. In fact disease-specific favorable outcomes for renal recovery have been reported for some forms of AKI that are characterized by a prolonged recovery phase (e.g., atheroembolic renal disease[33]) and thrombotic microangiopathy.[34] However, such benefits on a larger scale have been difficult to replicate.[35,36] Gabriel Ponce et al., in their series of AKI, have shown that when censored for death, nearly half of those surviving recover renal function and come off RRT.[13] These rates were similar to those achieved with their ECBP cohorts, although an advantage for PD in terms of rapidity of renal recovery was suggested in one of their RCTs comparing PD with dHD.[23] In summary, although attractive as a hypothesis, this assertion awaits formal testing through rigorous clinical studies.

Overall, though the criteria for selection of the RRT modality was not available, the longitudinal cohort analysis from Brazil suggests that a quarter of all dialysis-requiring AKI can be well managed with PD.[13] Investigators from other parts of world have taken a different approach and shown a much wider application of PD, although again the true denominator has been difficult to ascertain.[19–21] Unfortunately at the present time the practice of RRT for AKI in most healthcare settings has deviated largely toward the ECBP procedures, and results of large epidemiologic databases show the use of PD limited to less than 5% among all patients with AKI, and close to none in most Western nations.

In the end it is important to discuss the administrative feasibility of an acute PD program. Although PD provides an improved feasibility for RRT around the world, similar assumptions may not be true for many of the Western medical infrastructures. Since the decline in the practice of PD for ESRD and for AKI, the available expertise and infrastructure for PD have declined significantly.[2] This poses logistic concerns for institutes interested in offering PD for AKI but lacks available expertise, either in terms of catheter insertion or the practices of PD. In today's environment with ever-increasing cost for medical services, PD provides a relatively simple and economical, yet effective alternative to a more technologically advanced, labor intensive, and expensive therapies such as CRRT. As the Brazilian report suggests, there may be a learning curve to developing an acute PD program.[13]

CONCLUSION

In summary, PD, despite its contraindication in a small number of patients, is largely feasible and likely adequate for a majority of patients with AKI for their metabolic and fluid clearance needs. Furthermore, the hard outcome data with PD are comparable to ECBP therapies, and there appears to be little evidence-based rationale for the decline in PD use for AKI in recent decades. We recommend greater consideration to provide PD as an option in all healthcare infrastructures, especially considering its simple, noninterfering, and yet effective nature, cost savings, and the possibility of comparably beneficial effects on renal recovery. Such changes require institutional as well as healthcare system initiatives and likely will have their own learning curves in those individual units. Clinical studies, if interwoven within these developments, can provide simultaneous, evidence-based learning and the opportunity to improve patient care for all patients with AKI.

Key Points

1. Based on the cause, severity, and duration of illness, acute kidney injury (AKI) has differing requirements for clearance of solute, volume, and electrolytes in individual subjects; a unified definition of the adequacy of dialysis in AKI is difficult to achieve.
2. Urea kinetics conventionally used in the measurement of the dose and the adequacy of dialysis has significant limitations in patients with AKI, primarily because of the unique and unstable nature of hemodynamics and solute generation.
3. The available cohort and clinical trial data, although suboptimal in quality and quantity, provide evidence that peritoneal dialysis in AKI, especially when performed using modern PD technology, can provide adequate and equivalent small solute clearance, and fluid, electrolyte, and acid-base control, when compared with the extracorporeal therapies.
4. The available pragmatic data, especially the long-term cohort data from South America, show that peritoneal dialysis is a feasible and adequate form of renal replacement therapy for a significant fraction of AKI in modern critical care illness.
5. Together, these considerations argue for a greater role for PD use for patients with AKI, in all healthcare infrastructures, and to evaluate its true place in the management of AKI.

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