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CKJ Review

CKJ REVIEW

Peritoneal dialysis for acute kidney injury: back on the front-line

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ABSTRACT

Peritoneal dialysis (PD) for acute kidney injury (AKI) has been available for nearly 80 years and has been through periods of use and disuse largely determined by availability of other modalities of kidney replacement therapy and the relative enthusiasm of clinicians. In the past 10 years there has been a resurgence in the use of acute PD globally, facilitated by promotion of PD for AKI in lower resource countries by nephrology organizations effected through the Saving Young Lives program and collaborations with the World Health Organisation, the development of guidelines standardizing prescribing practices and finally the COVID-19 pandemic.

This review highlights the history of PD for AKI and looks at misconceptions about efficacy as well as the available evidence demonstrating that acute PD is a safe and lifesaving therapy with comparable outcomes to other modalities of treatment.

Keywords: acute kidney injury, COVID, dialysis, PD, peritoneal dialysis

HISTORY OF PD FOR AKI

Peritoneal dialysis (PD) has been used to treat acute kidney injury (AKI) since 1946 when Frank, Seligman and Fine successfully treated the first patient until recovery of function. Their series described the early difficulties encountered with access, fluid constituents and infections, as well as the solutions they developed. Their initial treatments used a steel, rubber and glass catheter and sump drain to instil Tyrodes solution supplemented with 1%–1.5% glucose and 1% gelatin [1, 2]. Initially the fluid caused hyperchloraemia and sodium chloride was substituted with sodium bicarbonate or sodium lactate. Concerns that glucose concentrations greater than 1.5% would cause significant irritation of the peritoneum along with the continuation of intravenous fluid replacement in the face of oliguria meant that many patients suffered from and often succumbed to pulmonary oedema. Peritonitis was common and thought due to the open fluid system and bedside mixing of fluids. Developments in peritoneal access further improved outcomes with better flow rates and fewer mechanical complications. Rigid plastic catheters introduced over a sharp stylet were used until very recently, however flexible catheters inserted at the bedside are now considered preferable [3].

PD has been the dominant modality for treating AKI in children, however in adults the proportion of patients has significantly fallen since the advent of pump-driven continuous kidney replacement therapy (CKRT) [4–7]. A study from Canada showed that in the 2 year periods beginning in 1994 and 1999 the reduced number of patients on PD was associated with an increase in CKRT use (9%–26%) [5]. A multicentre study of AKI management in intensive care units (ICU) globally showed that PD was used in only 3.2% patients. It must be noted that all countries except one were in the high-income category and this has a significant bearing on PD utilization [6]. A survey of 560 nephrologists, predominantly from Europe, found that PD for

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AKI was only available in 24% of centres. CKRT was the predominant modality used by intensivists whereas nephrologists were more likely to use intermittent therapies and PD [7]. This highlights the disconnect between those who feel that PD is suitable for treating AKI and those who actually practice it. A survey of nephrologists from three international conferences reported that 50.8% and 36.4% of respondents felt that PD was suitable for treating AKI in the wards and ICU, respectively. In contrast only 15.7% and 22% actually used it in these settings [8]. PD was used in 35% of ICU patients in Asia compared with only 13% and 8.2% in Europe and North America [8]. Most acute PD is practiced in low/low-middle income countries, as in many countries CKRT is prohibitively expensive whereas PD carries a lower cost and requires minimal infrastructure thus can be performed in remote areas without the need for electricity or significant volumes of water. As it is a cardiovascularly stable modality it is used preferentially over intermittent therapies in critically ill patients requiring vasopressor support.

Although there was a fall in use of PD in high income countries (HIC) in lower resource settings there has been growth in part due to the Saving Young Lives (SYL) initiative, the publication of the International Society for Peritoneal Dialysis (ISPD) guidelines for PD in AKI in 2014 and 2020 as well as the International Society of Nephrology (ISN) framework for dialysis recommending PD as the preferential modality in low-resource environments [3, 9–20].

The coronavirus disease 2019 (COVID-19) pandemic has challenged the perception that PD is not suitable for critically ill patients, and many nephrologists in HICs turned to acute PD in preference to CKRT. Reasons included the exceptional clotting of the extracorporeal circuit, reduced nursing staff availibility and haemodialysis machine/consumable demand outstripping supply. Case series from the UK and USA have shown good results in these settings [21–29].

The ICU at King's College London treated 108 patients with AKI secondary to COVID-19 with 34 treated with acute PD. All patients on PD were mechanically ventilated and 61% required vasopressor support. Despite this, survival was 70.3% with 85% of patients recovering renal function after a median of 12 days [22]. Four separate units in New York who had rapidly implemented acute PD programs during the pandemic published their experiences separately and later combined the data highlighting the success of each, along with the barriers that needed to be overcome [26–28, 30, 31]. Ninety-four patients were included, with 87% requiring mechanical ventilation, with a mean modified Acute Physiology And Chronic Health Evaluation (APACHE II) score of 13. PD was the initial modality in 56 patients, with 32 transferring from intermittent haemodialysis (IHD) and the remainder from CKRT. All PD catheters were placed by either surgeons (85%) or interventional radiologists (16%). Mean PD volumes were 1.5 L, with 86% of prescribed volume being achieved with a mean ultrafiltration of 0.7 L (interquartile range 0.3–1.7). Twenty patients were either switched to or supplemented with IHD/CKRT. The reason for switch was split evenly between mechanical complications, persistent hyperkalaemia or fluid overload. After a median follow-up of 30 days 46% of patients had died, 22% had recovered kidney function, 28% were still in hospital on dialysis and 4% had been discharged on dialysis. There was concern that prone positioning would not be feasible in patients on PD, however in this analysis, 47% required prone positioning during their stay. Being prone did not affect potassium or bicarbonate clearance; although adjustments needed to be made to fluid volumes due to increased leaks, it did not require a switch of modality. Analysis of 11 patients in one centre confirmed that patients ventilated in the prone position while on PD showed no worsening of gas exchange. Certain techniques such as a more lateral exit-site were beneficial [27].

This resurgence in the use of PD for AKI in high-resource countries has sparked new interest in the use of PD for AKI in all settings.

Table 1: Advantages and disadvantages of PD compared with other modalities.

Advantages	Disadvantages
Cost effective	Few nephrologists trained to insert PD catheters
Low infrastructure requirement	PD fluids difficult to source in LMICs
Easier training of staff	Mechanical complications may delay therapy
More rapid recovery of renal function	Ultrafiltration is unreliable
No anticoagulation necessary	Peritonitis more likely
No vascular access required	High glucose exposure[b]
No disequilibrium syndrome[a]	Reduced enteral tolerance[b]
Less bacteraemia	Raised intra-abdominal pressure
Less blood loss[b]	
No myocardial stunning[b]	
No exposure to foreign extracorporeal circuit	

[a]Compared with IHD only.
[b]Unproven.

BENEFITS OF PD

There are a number of demonstrable as well as theoretical benefits of PD over other modalities (Table 1).

- Cost effectiveness is extremely important for LMICs where acute dialysis is often poorly resourced and, in many cases, funded out of pocket. Kilonzo and Cagliari both showed that the cost of acute PD in Africa was significantly cheaper than haemodialysis and fell well within the World Health Organisation's criteria for Choosing Interventions that are Cost-Effective (CHOICE) treatments which are deemed to be highly cost effective per life saved [32–34]. Many LMICs offer haemodialysis for AKI, but only in major centres which may be several days' travel from patients in the rural districts and thus many patients with AKI do not survive. PD does not require machines, water, electricity or highly trained staff, and can easily be delivered in these communities. For these reasons training in PD for AKI is chosen preferentially by the SYL program [9, 12, 15–19, 35, 36].
- Recovery of kidney function occurred on average 3 days earlier in two large randomized trials in critically ill patients [37, 38]. The reason for this is not clear but it is possible that relative cardiovascular stability of PD preserves renal perfusion better than the intermittent hypotension of IHD or CKRT. Another theory is that PD does not expose the patient to an extracorporeal circuit and the resulting pro-inflammatory state. It has been clearly demonstrated that in chronic dialysis preservation of residual kidney function has a significant impact on survival and one wonders whether this might be similar for patients with AKI [39–42].
- The cardiovascular stability mentioned above is an advantage for critically ill patients with hypotension or shock

where CKRT is not available. It has been shown in chronic patients that myocardial stunning does not occur during peritoneal dialysis, whereas this is commonplace in those on IHD [43–45]. A small study of 11 patients was suggestive of stunning in CKRT patients and needs to be confirmed with larger numbers, however considering that patients with AKI in HICs often have cardiovascular comorbidities it is enticing to think that PD may prove to be superior in these settings [46].

- PD does not require anticoagulation and is the preferred modality in those with high risk for or ongoing postoperative bleeding, especially those following brain injury or surgery. It also limits blood loss which commonly occurs through clotting in extracorporeal circuits.
- PD is not associated with dialysis disequilibrium syndrome and may be more appropriate for patients with raised intracranial pressure.
- Vascular access is not required for PD and carries a significant advantage in small children where peritoneal catheter insertion is often easier than dialysis catheter insertion.
- Specific to the COVID-19 pandemic, acute PD reduced the time renal nurses were required to be at the bedside, thus reducing personal protective equipment usage as well as reducing spread of infection back into the chronic dialysis unit. Remote patient monitoring allowed optimal care with fewer face to face visits [25]. Concerns about infectivity of PD fluid to staff and other patients are likely unfounded but universal precautions should continue to be used [47].

BARRIERS TO PD

Whilst there are a number of advantages of PD over other modalities, a number of disadvantages and barriers to higher PD uptake exist.

- Clinician perceptions are a significant factor, Gaião *et al.*'s survey showed that 62% of clinicians did not believe PD was suitable for treating AKI in ICU [8]. This is not surprising as, until recently, there was little evidence to support the use of PD and even less to guide prescription thereof. Evidence of equivalent outcomes has accumulated over the past two decades and along with guidelines on prescription there has been an increase in acceptance of PD, especially in low resource countries.
- Timely PD access has been a further stumbling block as it is not universal practice for nephrologists to place PD catheters at the bedside and taking a critically ill patient to a surgical theatre is often not feasible. Training sufficient nephrologists has been challenging especially when PD numbers are small, however programs such as the SYL initiative have used pork-belly models to train over 360 doctors and nurses to place PD catheters at the bedside [12] (Fig. 1). The ISPD guidelines recommend flexible PD catheters, but in many countries, PD is still performed using the rigid nylon catheters introduced over a sharp introducer stylet. Although these catheters are prone to infection and generally have poor flow characteristics, they are simple to insert and do save lives. Assistance of surgeons and interventional radiologists with bedside placement has also improved uptake as was seen in the COVID-19 pandemic [22, 23].
- Obtaining PD fluid supplies in low-resource countries may be extremely troublesome. Most PD fluids are produced in HICs and shipped by sea and then by land, often crossing multiple borders to landlocked countries. The high costs of both shipping fees as well as legal and illicit border charges result in the cost-effectiveness being reduced. There is often unreliable delivery of fluids to remote areas especially when there are small numbers of patients treated. Although the ISPD guidelines recommend commercially produced solutions, in the event of fluid not being available, clinicians are trained to mix their own solutions using the most sterile technique possible. The simplest is the combination of modified Ringers lactate and 50% dextrose. There have been three case series from SYL sites showing this to be safe, with equivalent peritonitis rates to patients using commercial solutions [16, 17, 48].
- There have been concerns that an increased intraperitoneal volume will impact on diaphragmatic movement in critically ill patients and impair gas exchange. This has not been shown to be the case. Studies from Brazil and the USA showed daily improvement in gas exchange rather than worsening. These are observational data and need to be confirmed with comparative studies between PD and extracorporeal therapies [27, 49].
- Mechanical complications are seen in between 5% and 13% of cases [37, 50, 51]. This cannot be predicted and in a patient with life-threatening hyperkalaemia or pulmonary oedema the risk of delays due to a mechanical complication make it safer to place vascular access and perform extracorporeal therapy rather than PD in the first instance.
- Adequate ultrafiltration is essential in critically ill patients to ensure a neutral fluid balance despite high volumes of fluids used for antibiotics, feeding, vasopressors, etc.

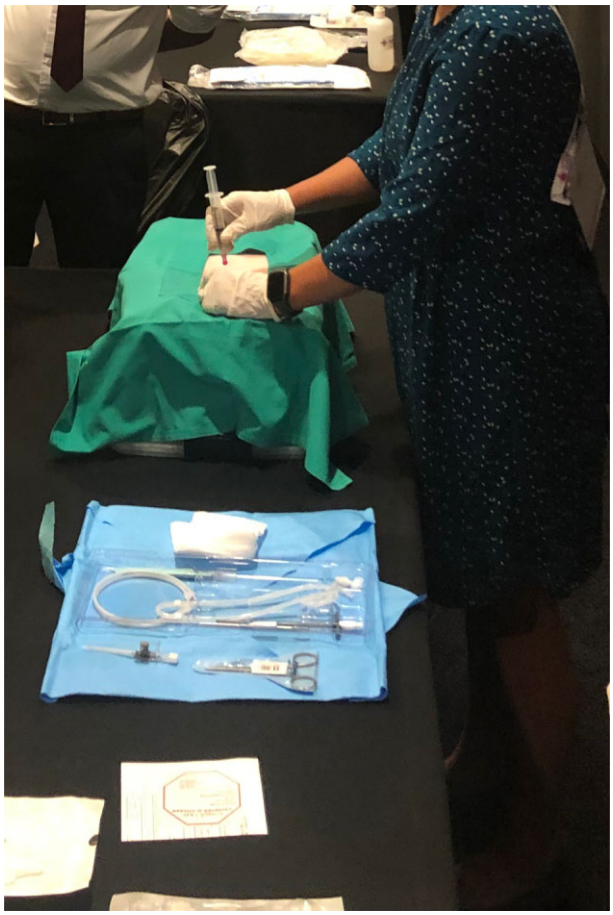


Figure 1: SYL training course using pork-belly model.

Although PD can reliably achieve ultrafiltration rates of 1000–2500 mL/24 h, this may not be sufficient in a profoundly fluid-overloaded patient and here haemofiltration/dialysis may be more effective [38, 50, 52, 53]. Many intensive care specialists are reluctant to use PD as they are unable to reliably dial in an ultrafiltration volume and must adjust glucose concentrations to achieve fluid removal. It must be noted that extracorporeal therapies rely on a stable intravascular volume in order to achieve ultrafiltration without inducing hypotension and clotting. This may not be feasible if there is significant third space loss and low intravascular volumes. PD does not rely on this to such an extent and may occasionally be more effective than extracorporeal methods at removing fluid whilst maintaining perfusion.

- The COVID-19 experience highlighted the difficulties in rapidly setting up a functional acute PD team [31]. There needs to be preparation and procurement of supplies, training of nursing and medical staff, and communication between clinicians (nephrologists, surgeons, intensivists and radiologists) prior to implementation. Collaboration with other acute PD units for advice and support will enhance the program.

ACCESS FOR PD

When deciding on the optimal access options consider the flow rate (much higher than chronic PD), ease of insertion and training, cost and complication risk. The ISPD guidelines recommend a flexible catheter as optimal, but acknowledge that rigid and other makeshift catheters will indeed save lives. In many low resource countries where flexible catheters are not available for cost or logistical reasons, clinicians have no option but to use alternatives such as intercostal drains, nasogastric tubes, haemodialysis catheters and in children, central venous catheters [9, 15, 16, 35, 54]. Flexible catheters have the advantage of larger lumens and side holes and are less prone to blockage. In children they are associated with better patency and lower incidence of malfunction, infection and organ damage compared with rigid catheters [55, 56]. Catheters can be placed at the bedside using a modified Seldinger technique, thus allowing more rapid initiation of PD, and have the advantage that they can be tunnelled under the skin to allow easier nursing and less risk of leak.

ADEQUACY AND SURVIVAL OUTCOMES OF PD FOR AKI

A common cause of hesitancy amongst clinicians to use PD is based on the misconception that PD is unable to achieve the same clearance seen with extra-corporeal therapies. Those who practice acute PD are often perplexed by the excellent outcomes despite what at first glance appear to be suboptimal clearances, which begs the question what is the adequate clearance required for acute PD?

There are many case series and randomized trials of PD in AKI which demonstrate rapid correction of hyperkalaemia, acidosis and fluid overload usually returning to normal levels within 24–48 h [37, 38, 50, 57]. As these still remain the indications for starting acute dialysis it is clear that acute PD is adequate for saving lives by rapidly correcting these parameters.

There is much debate in critical care nephrology about the impact that dialysis/filtration has on modulating the inflammatory milleu and although it makes theoretical sense that removing cytokines and other larger molecules might improve outcomes, this has never conclusively been shown to impact on survival or recovery of renal function [58, 59]. As a result, the lower middle-molecule clearance seen with PD compared with CKRT may not be relevant when comparing modalities.

Prior to standardization of PD dosing proposed in the ISPD guidelines there were marked variations in dialysis prescriptions with fluid volumes ranging from 13 to 70 L per day [33, 37, 50, 52, 57, 60–62].

The intensive care nephrology literature for extracorporeal therapies, especially CKRT, focus on clearance of small molecules (Kt/V urea) or effluent volumes. Small molecule clearance is easy to measure and has outcome evidence in chronic dialysis patients [63]. AKI is a completely different disease, especially in the ICU where it is a component of multiple organ dysfunction and there is little evidence that small solute clearance targets have an impact on survival. Effluent rates of CKRT are a surrogate measure of clearance of small and larger molecules and are currently the target in most ICUs. These effluent rates are based on randomized studies which have suggested a lower threshold of 22 mL/kg/h, above which there is no survival benefit even in sepsis [64–66]. One study compared CKRT (at 22 mL/kg/h) with alternate day dialysis with a Kt/V urea of 1.2 per session and found no difference in survival [64]. If this is converted to a weekly Kt/V urea (a clearance target used in studies on acute PD) the target would be a weekly Kt/V urea of ~2.2. Acute PD has been shown to achieve these clearances easily with weekly Kt/Vs in excess of 4.1 being achieved in some cases using high volume automated PD (APD) [37, 50, 52, 53, 57]. It must be noted though that rapid cycling in PD will often achieve good urea clearances, but larger molecule clearances which are dependent on dwell time and convection may be suboptimal as rapid cycling increases the time spent draining fluid in and out and reduces overall dwell time. For this reason, it may be more appropriate to target larger molecule clearance such as creatinine or others in future studies [62]. A randomized trial of acute PD versus daily IHD in critically ill patients showed no difference in survival when a weekly Kt/V of 3.5 was achieved [37]. The same group then randomized patients to higher targets and achieved weekly Kt/Vs of 3 and 4.13, respectively. There was no difference in survival between these groups suggesting a threshold effect with dosing as is seen in CKRT [64–66]. It was based on this data that the ISPD guidelines in 2015 recommended a target weekly Kt/V of 3.5 as the optimal, however it was the feeling of many of the authors that a lower dose may be suitable after extrapolation from the CKRT literature. For this reason, a minimum standard, weekly Kt/V of 2.1 was suggested [10]. Parapiboon *et al*. performed a randomized trial using these two targets in 75 critically ill patients, 88% of whom were on mechanical ventilation with an average APACHE 2 score of 26.3. They achieved weekly Kt/Vs of 2.26 and 3.3 in the conservative and intensive groups, respectively. There was no difference in survival between the groups. It must be noted that ultrafiltration was higher in the intensive group [53].

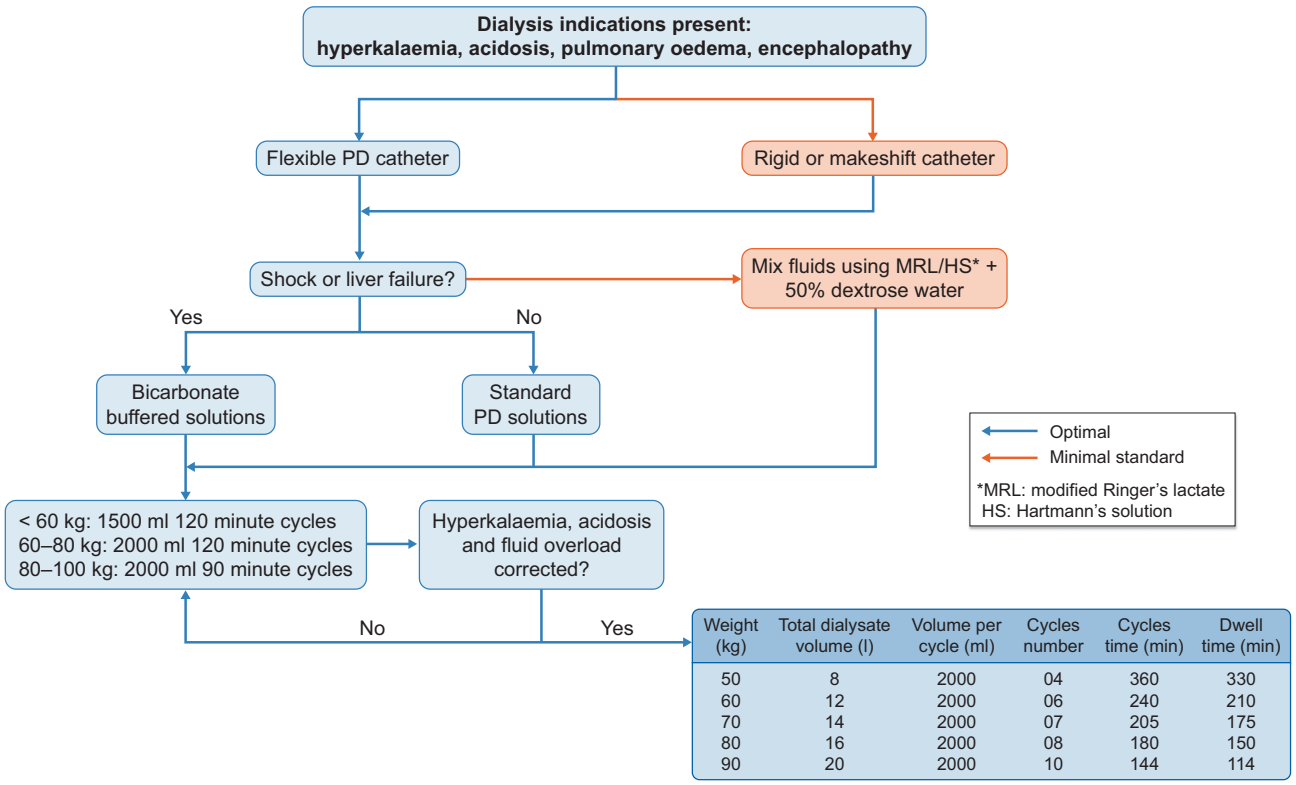
Based on the above findings and expert opinion, the most recent ISPD guidelines have set a recommended weekly Kt/V target of 2.2 [3].

Al-Hwiesh *et al*. adopted a different approach to delivery of acute PD—rather than focussing on Kt/V and its inherent shortfalls, they report on using tidal APD and a fixed volume of 25 L of fluid per 24 h. This was compared with CKRT with an achieved effluent volume of 23 mL/kg/h. Tidal APD may be beneficial in that there is always a residual volume of fluid in the abdomen and this may improve larger molecule clearance [38, 67].

Table 2: Randomized trials of acute PD performed in ICU.

Study	Ponce 2013 [69]	Gabriel 2008 [37]	Al-Hwiesh 2018 [38]	Ponce 2011 [52]	Parapiboon 2017 [53]
	High volume PD vs daily EHD	High volume PD vs daily HD	Tidal APD vs CVVHDF	Higher vs lower intensity	Intensive vs minimal standard
Number of patients	63 vs 201	60 vs 60	63 vs 62	31 vs 30	41 vs 39
Dosage	Weekly Kt/V 3.6 vs 4.1	Weekly Kt/V 3.6 vs 4.7	25 L 70% tidal vs CVVHDF effluent 23 mL/kg/h	Weekly Kt/V 4.13 vs 3.0	Weekly Kt/V 3.3 vs 2.26
Ventilated	83.6% vs 86.6%	68% vs 75%	62% vs 69%	68% vs 72%	87% vs 89%
APACHE II score	27.5 vs 26.7	26.9 vs 24.1	22.1 vs 21.3	26.4 vs 24.8	26.9 vs 25.7
Ultrafiltration (L)	0.6 vs 1.4	2.1 vs 2.4	0.95 vs 1.39	2.4 vs 2.1	1.5 vs 0.5 (day 1), 2.1 vs 0.9 (day 2)
Mortality	63.9% vs 63.4% ($P = .94$)	58% vs 53% ($P = .48$)	30.2 vs 53.2 ($P = .002$)	55 vs 53% ($P = .42$)	79% vs 63% ($P = .13$)
Limitations	Single centre, significantly different baseline characteristics	Single centre, patients not surviving 24 h excluded, underpowered for mortality	Single centre, adequate effluent rates on CKRT, however creatinine levels remained higher than expected for the dose achieved	Single centre	Single centre, small body surface area of patients

EHD, extended haemodialysis; CVVHDF, continuous veno-veno haemodiafiltration.



Weight (kg)	Total dialysate volume (l)	Volume per cycle (ml)	Cycles number	Cycles time (min)	Dwell time (min)
50	8	2000	04	360	330
60	12	2000	06	240	210
70	14	2000	07	205	175
80	16	2000	08	180	150
90	20	2000	10	144	114

Figure 2: ISPD guidelines for PD in AKI recommended dosing schedule (reproduced with permission) [3].

Certainly, acute PD is appropriate for use in critically ill patients with good outcomes, this is demonstrated in the studies in Table 2.

Figure 2 shows the suggested initial dosing schedule as recommended in the ISPD guidelines [3].

With all the shortfalls of dosing and clearance targets mentioned above, it is important that clinically relevant outcome measures are assessed when comparing therapies. Chionh *et al.* performed a systematic review and meta-analysis of all observational studies and found no difference in survival between PD

and extracorporeal therapy [68]. Six randomized controlled trials have compared acute PD with extracorporeal therapy, four of which have significant flaws in methodology; the final two are single-centre studies but of a slightly higher quality [37, 38, 60, 61, 69, 70].

- A randomized trial from Vietnam comparing acute PD using rigid catheters, acetate-based solutions and rapid cycling with CKRT in patients with sepsis and malaria. It was stopped early, after 35 patients were recruited in each arm, due to a higher mortality in the PD group. Not only was the study underpowered, the mortality in the CKRT arm was unusually low for this group of patients compared with other international studies of AKI in sepsis and suggested a type 1 error [6, 60].
- George *et al*. in India compared PD with CKRT but the trial was stopped early due to poor recruitment and thus was underpowered. It showed mortality was lower in the PD group, however the CKRT effluent dose was suboptimal [61].
- Arogundade *et al*. randomized patients with acute and chronic kidney disease to PD or IHD. There were only four patients in each arm with AKI and therefore could not be analysed [70].
- Ponce *et al*. from Brazil compared acute PD with extended daily dialysis and found no difference in mortality; however, the randomization resulted in significant differences in baseline characteristics [69].
- Gabriel *et al*. further randomized 60 patients to either high volume acute PD or daily haemodialysis. There was no significant difference in mortality although it was not powered to detect this. There was however recovery of renal function 3 days earlier in the PD group [37].
- Al-Hwiesh *et al*. compared tidal APD using biocompatible solutions with CKRT. The effluent dose achieved in the CKRT group was appropriate. The patients on APD had a better survival than those on CKRT (69.8% versus 46.8% $P < .01$) and recovery of renal function was again 3 days earlier [38].

A Cochrane review of PD versus extracorporeal therapies concluded that based on moderate level of evidence there appeared to be little or no difference in mortality or recovery of renal function between the two groups [71]. The ISPD guidelines have given a 1B recommendation in adults and 1C in paediatrics that PD is suitable for treating AKI in all settings [3, 10, 13].

FUTURE DIRECTIONS FOR PD IN AKI

As with CKD patients, PD appears to be equivalent to other modalities for treating AKI in all settings. Although the study from Al-Hwiesh does suggest improved outcomes compared with CKRT, unless there is a multicentre randomized trial confirming this, there will remain reluctance for its use in adults in high resource countries. Certainly, the evidence is sufficient to justify its preferential use in low resource settings and paediatrics where there are significant benefits over other therapies, which is why it is recommended by the SYL program and ISN.

Suggested areas for research which may bring PD into the mainstream if results are confirmed include:

- Assessing the comparative stimulation of the inflammatory cascade between PD (using the bodies biocompatible membrane) and extracorporeal circuits.
- Tidal APD and the effect on outcomes including larger molecule clearance.
- The use of biocompatible, bicarbonate containing solutions as well as newer solutions being trialled for liver failure and hepatorenal syndrome.
- The comparative incidence of myocardial and gut hypoperfusion in extracorporeal therapies and PD.

CONCLUSION

The recent COVID-19 pandemic has led to a renewed interest in PD in high-resource countries. There is sufficient evidence of comparable outcomes between PD and extracorporeal therapies even in critically ill ICU patients. The benefits of cost effectiveness, ease of training, and reduced need for electricity and water make it the optimal form of therapy for low-resource environments. Standardization of practice through the ISPD guidelines will hopefully improve outcomes for patients across the globe.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

B.C. has received lecture fees and honoraria from Baxter Healthcare and Adcock Ingram Critical Care. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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