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section 21 Disorders of the kidney and urinary tract 4874 Macleod AM, et al. (2005). Cellulose, modified cellulose and synthetic membranes in the haemodialysis of patients with end-stage renal disease. Cochrane Database Syst Rev, 3, CD003234. Mostovaya IM, et al. (2014). EUDIAL1—an official ERA-EDTA Working Group. Clinical evidence on hemodiafiltration: a system- atic review and a meta-analysis. Semin Dial, 27, 19–27. Rabindranath KS, et al. (2005). Comparison of hemodialysis, hemofiltration, and acetate free biofiltration for ESRD: systematic review. Am J Kidney Dis, 45, 437–47. Selby NM, McIntyre CW (2006). A systematic review of the clin- ical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant, 21, 1883–98. Clinical practice guidelines in haemodialysis Ashby D, et al. (2019). Clinical practice guideline: haemodialysis, https://renal.org/wp-content/uploads/2019/07/FINAL-HD-Guide line.pdf European Best Practice guidelines on haemodialysis (2007). Nephrol Dial Transplant, 22 Suppl 2, S1–S120. National Institute for Health and Care Excellence (2018). Renal re- placement therapy and conservative management. https://www. nice.org.uk/guidance/ng107/resources/renal-replacement-therapy- and-conservative-management-pdf-66141542991301 National Kidney Foundation (2015). KDOQI clinical practice guide- line for hemodialysis adequacy. Am J Kidney Dis, 66, 884–930. 21.7.2 Peritoneal dialysis Simon Davies ESSENTIALS Peritoneal dialysis is achieved by repeated cycles of instillation and drainage of dialysis fluid within the peritoneal cavity, with the two main functions of dialysis—solute and fluid removal—occurring due to the contact between dialysis fluid and the capillary circulation of the parietal and visceral peritoneum across the peritoneal mem- brane. It can be used to provide renal replacement therapy in acute kidney injury or chronic kidney disease. Practical aspects—choice of peritoneal dialysis as an effective mo- dality for renal replacement in the short to medium term (i.e. sev- eral years) is, for most patients, a lifestyle issue. Typically, a patient on continuous ambulatory peritoneal dialysis will require three or four exchanges of 1.5 to 2.5 litres of dialysate per day. Automated peritoneal dialysis and use of the glucose polymer dialysis solution icodextrin enables flexibility of prescription that can mitigate the ef- fects of membrane function (high solute transport). Peritonitis—this remains the most common complication of peritoneal dialysis, presenting with cloudy dialysis effluent, with or without abdominal pain and/or fever, and confirmed by a leucocyte count greater than 100 cells/μl in the peritoneal fluid. Empirical anti- biotic treatment, either intraperitoneal or systemic, with cover for both Gram-positive and Gram-negative organisms, should be com- menced immediately while awaiting specific cultures and sensitivities. Long-term changes in peritoneal membrane function influ- ence survival on peritoneal dialysis if fluid removal is less efficient (ultrafiltration failure), especially in the absence of residual kidney function. This is the main limitation of treatment, along with avoiding the risk of encapsulating peritoneal sclerosis—a life-threatening complication of peritoneal dialysis, particularly if of long duration (15–20% incidence after 10 years), that is charac- terized by severe inflammatory thickening, especially of the mes- enteric peritoneum, resulting in an encapsulation and progressive obstruction of the bowel. Introduction Peritoneal dialysis, along with haemodialysis and renal transplant- ation, is an effective form of renal replacement therapy. Worldwide it is used for both acute kidney injury and chronic renal failure, al- though patterns of use vary considerably. In the treatment of chronic kidney disease, peritoneal dialysis should be considered as a short- to medium-term (several years) treatment option, to be used in the context of an integrated approach to renal replacement therapy. For example, it is of value both before and after transplantation in a life- time of treatment that might require more than one period on each of the renal replacement modalities. The only absolute contraindica- tion is the lack of a peritoneal cavity. Historical perspective In the 1890s, Henry Starling, while conducting experiments from which he made his seminal observations on the forces that govern transcapillary fluid transport, provided evidence that the peritoneal membrane could be used to remove fluid and solutes—the fundamental requirements of renal replacement therapy. By the 1940s, peritoneal dialysis was established in the treatment of acute kidney injury, and a decade later intermittent treatments, typically twice weekly, were used to maintain pa- tients with chronic kidney disease. Critical to this was the devel- opment in 1968 of the Tenckhoff catheter, a soft silicone-based tube that could create permanent access to the peritoneal mem- brane. In 1978, Popovitch and Moncreif argued that peritoneal dialysis could be performed continuously in ambulant patients with permanent renal failure, coining the term ‘continuous am- bulatory peritoneal dialysis’ (CAPD), following which peritoneal dialysis became established as a renal replacement modality that could be undertaken in the home environment. Modifications of this approach, using a device that delivers multiple exchanges of dialysis fluid overnight, so reducing the number of exchanges required during the daytime, is termed ‘automated peritoneal dialysis’ (APD). In addition to the reduced daytime burden of the treatment, the advantages of this approach are that it can facilitate delivery of care by a parent, partner, or assistant. Assisted peritoneal dialysis is the treatment of choice for elderly frail patients in some countries, notably France, providing a vi- able alternative to centre-based haemodialysis for this patient population.

21.7.2 Peritoneal dialysis 4875 The use of peritoneal dialysis in renal replacement Acute kidney injury Peritoneal dialysis is an important component of the International Society of Nephrology’s ‘0by25’ strategy to reduce the global burden of acute kidney injury-related deaths. There is much greater reliance on peritoneal dialysis to treat acute kidney injury in developing coun- tries, the exception to this being in infants and small children in whom it remains the treatment of choice in the developed world. Advantages of peritoneal dialysis in acute kidney injury include lack of reliance on a clean water supply, relatively stable haemodynamics, no need for vascular access, and the avoidance of anticoagulation and its com- plications. The International Society for Peritoneal Dialysis has pub- lished guidelines for peritoneal dialysis in acute kidney injury, freely available at https://ispd.org/ispd-guidelines/; key recommendations include the routine use of tunnelled soft Tenckhoff catheters, anti- biotic prophylaxis, and advice on the constitution of dialysis fluids. Chronic kidney disease The EVEREST study (Explaining the Variation in Epidemiology of RRT through Expert opinion, Secondary data sources and Trends over time) found that 70% of the international variability in the use of peritoneal dialysis to treat chronic kidney disease (the proportion of patients on peritoneal dialysis differs from 4 to 80% by country), is explained by healthcare systems, clinical factors, and macroeco- nomic factors. Independent determinants of lower peritoneal dia- lysis use include a high proportion of incident patients with diabetes as primary renal disease, a higher percentage of GDP per capita spent on healthcare, a larger private-for-profit share of haemodi- alysis facilities, and the high cost of peritoneal dialysis consumables relative to staffing. Currently, the highest growth rates for peritoneal dialysis are seen in the developing world, especially Indo-Asia. Predictors of survival As for all types of renal replacement therapy, the most important fac- tors associated with survival are age, inflammation, and comorbidity, the latter being weighted towards cardiovascular disease. As for haemodialysis patients, the continued presence of residual renal function, a benefit that can be demonstrated with creatinine clear- ances as low as 1 to 2 ml/min, or just 250 ml/day of urinary volume, also improves survival. In addition, there is strong evidence that peritoneal membrane function has an effect. Membranes associated with less efficient fluid removal, due to high solute transport char- acteristics or low ultrafiltration capacity (see 'Monitoring treatment quality'), are associated with worse outcomes. Comparison with haemodialysis Current evidence supports the view that when both haemodialysis and peritoneal dialysis are equally available, the choice between the therapies is largely determined by lifestyle issues (Table 21.7.2.1). The failure to date to perform a randomized controlled trial com- paring modalities lies in the fact that most patients (96%) demon- strate a strong modality preference when the choice is made freely available. Modality comparisons have thus relied on observational studies from registry data, with adjustment for baseline factors. Over the last 20 years, survival has improved dramatically (>50% reduc- tion in mortality), such that early survival (1–3 years) tends to be better on peritoneal dialysis than haemodialysis, with equivalence at 5 years. The early survival advantages, most apparent in nondiabetic patients, are likely to reflect relatively better preservation of residual kidney function, avoidance of central venous catheters, and residual confounding. Technique failure is more likely to occur in peritoneal dialysis than haemodialysis, reflecting the effects of membrane damage associated with infection and long-term exposure to dialysis fluid, as well as changes in a patient's circumstances, such that con- tinuing with home treatment becomes untenable. Taken overall, these patient and technique survival differences are not sufficient to override patient preferences associated with lifestyle choices, provided there is an understanding that modality switching may well be required. APD extends choice to the patient or their carer, so accommodating a variety of lifestyles; it is the preferred dialysis treatment for children. Choosing the right dialysis modality is an im- portant component to preparing for renal replacement therapy and can be facilitated by the use of a dialysis decision aid, freely available at https://www.kidneyresearchuk.org/kidney-health-information/. Principles of therapy Peritoneal dialysis is achieved by repeated cycles of instillation and drainage of dialysis fluid within the peritoneal cavity. The fluid is heat sterilized, a process that requires an acidic pH; ideally a pH of 2 to 3 should be used, but this requires two or more dialysis bag com- partments to enable reconstitution just prior to infusion. This ap- proach enables a physiological pH solution with low concentrations of glucose degradation products and in some cases substitution of bicarbonate for lactate as the buffer. The benefits of biocompatible solutions include reduced infusion pain, better preservation of re- sidual kidney function, and more stable peritoneal solute transport characteristics. Such solutions are not universally available, how- ever, and most conventional peritoneal dialysis solutions have a pH of 5.2, with 35 to 40 mmol/litre of

lactate as the buffer. Typically, a patient on peritoneal dialysis will require three or more exchanges of 1.5 to 2.5 litres of dialysate per day. CAPD re- gimens usually comprise three 4- to 6-h daytime exchanges and an overnight exchange; APD regimens may use up to six exchanges overnight and a long daytime dwell period. The frequency of over- night exchanges can be further increased by using a 'tidal' pro- gramme, which exchanges a proportion of the intraperitoneal fluid Table 21.7.2.1 Typical reasons for choosing peritoneal dialysis or haemodialysis as renal replacement modality Reasons favouring peritoneal dialysis Reasons favouring haemodialysis No vascular access No peritoneal access Haemodialysis-induced hypotension Multiple comorbidities Preference for home treatment Increasing age Independence Living alone Distant from haemodialysis facility Dependent Family and work commitments Close to haemodialysis facility Dependent, when assisted APD performed
by a carer or parent is available Home haemodialysis option preferred and available APD, automated peritoneal dialysis.

 more rapidly without losing dialysis time due to complete emptying. APD can be further augmented by adding an additional—typically evening—exchange, so increasing the dose of dialysis given. These volumes will be very different for children in whom they are ad- justed according to body surface area. The patient or their carer is trained in the sterile procedure of dia- lysis fluid exchange by a specialist peritoneal dialysis nurse, a process that generally takes a few days and can be achieved by most individ- uals, despite physical and educational disabilities. Peritoneal access In order to drain peritoneal dialysis fluid in and out of the peritoneal cavity, a flexible permanent dialysis catheter is required, and this is also to be preferred when peritoneal dialysis is used for acute kidney injury. Correct insertion and subsequent catheter management is critical for success. Insertion should be performed as a planned procedure by an experienced operator and may be achieved using either the Seldinger technique, open surgery, or with the use of a laparoscope. Catheters usually have two Dacron cuffs, one at each end of the subcutaneous tunnel: the deep cuff is placed at the entry to the peritoneum, whereas the superficial cuff should be situated about 1.5 cm deep to the exit site, which should be positioned on the abdominal wall so that it is visible to the patient. Up-to-date recommendations for peritoneal dialysis catheter insertion (also for the management of peritonitis, see later) are freely available at the International Society for Peritoneal Dialysis website (https://ispd.org). Peritoneal physiology The two main functions of dialysis, solute and fluid removal, occur due to the contact between dialysis fluid and the capillary circulation of the parietal and visceral peritoneum. In a typical adult, approxi- mately 0.5 m2 of the peritoneum is in contact with fluid, representing about one-third of the anatomical membrane. Solute clearance Removal of solute is predominantly by diffusion across the mem- brane and is thus governed by the concentration gradient, the number and density of capillaries in contact with dialysate (often termed effective peritoneal surface area), and the size of the solute in question. Equilibration time for urea is typically within 4 to 5 h, hence removal is limited by the drained dialysate volume rather than length of dwell. Equilibration is more time-limited for larger mol- ecules such as creatinine and glucose, for example, the average di- alysate to plasma ratio of creatinine at 4 h is 0.65, with a range of 0.4 to 0.85 that is normally distributed. This measurement is termed the solute transport rate and is used to measure the diffusive component of membrane function in the 'peritoneal equilibration test'. There is considerable variability between patients, which appears to be re- lated to local production of the inflammatory cytokine interleukin- 6 rather than clinical variables such as body size or comorbidity. Whereas systemic inflammation is an independent predictor of pa- tient

survival, the local inflammatory response is not, provided ap- propriate dialysis regimens are prescribed. Ultrafiltration Fluid transport across the membrane is governed mainly by pres- sure gradients, including hydrostatic, osmotic, and oncotic, as well as some fluid reabsorption due to lymphatics. Instillation of fluid within the peritoneal cavity creates a positive pressure that is close to capillary pressure, resulting in little net fluid movement by this mechanism unless excessive intraperitoneal pressures are created. Conventional glucose-containing dialysis fluids create an osmotic pressure gradient proportional to glucose concentration (1.5– 4.25%) that results in a peak net ultrafiltration volume between 2 and 4 h, depending on solute transport characteristics of the membrane (Fig. 21.7.2.1). It is by prescription of exchanges containing different glucose concentrations ('weak', 'medium', and 'strong' bags) that the –300 –200 –100 0 100 200 300 400 500 600 700 0 60 120 180 240 300 360 420 480 540 600 660 720 Time (min) Intraperitoneal ultrafiltration volume (ml) Aquaporins Intercellular pores Lymphatics Net fluid Icodextrin
Fig. 21.7.2.1 Pathways of fluid transport across the peritoneal membrane. The net changes in intraperitoneal fluid volume and thus ultrafiltration achieved at each time point when using glucose (3.86%) as the osmotic agent are the result of fluid transport via at least three pathways: aquaporins (water exclusive), small intercellular pores, and lymphatic reabsorption. Fluid is reabsorbed once the intraperitoneal glucose has equilibrated with plasma. By contrast, when using the glucose polymer icodextrin, sustained ultrafiltration occurs for several hours.

 patient's fluid status can be controlled to achieve the target weight specified by their physician. There are two pathways of water trans- port by this mechanism, intercellular and transcellular, each con- tributing about half the fluid removal, the latter being via aquaporins and thus water exclusive. Once the osmotic gradient has dissipated, fluid reabsorption occurs due to a combination of transcapillary oncotic (Starling) forces and lymphatics. Removal of ions such as sodium and calcium is predominantly by convection because the diffusion gradient is small (typical dialysate sodium concentration is 132 mmol/litre). Due to the existence of the aquaporin pathway, there is uncoupling of water and sodium removal, termed sodium sieving, that is most pronounced in the early part of the dwell. As a consequence, peritoneal dialysis is always at risk of removing excess water compared with sodium, and treatment regimens that rely on too many short, hypertonic glucose exchanges are to be avoided. By the same token, lack of sodium sieving is an indicator of poor free- water transport and thus membrane failure. Monitoring treatment quality Solute clearance Residual renal and peritoneal solute clearances are not equivalent in their impact on patient survival. To date, in chronic kidney disease, no randomized study has been able to demonstrate an association between survival and peritoneal clearances, and there are no studies published in acute kidney injury. It is important, therefore, that both residual and peritoneal clearances are measured. Both urea (Kt/ Vurea) and creatinine clearances can be used to monitor treatment, and there is general agreement in international guidelines—based on at least two large randomized trials—on minimum treatment targets. For Kt/Vurea, a combined residual and peritoneal clearance of 1.7 using the Watson formula to calculate V (total body water) should be achieved. Alternatively, a combined creatinine clearance of 50 litres/week per 1.73 m2 can be used. In either case, however, dialysis dose should be increased in the presence of symptoms at- tributable to uraemia. Ultrafiltration Several observational studies have shown that a reduced peritoneal ultrafiltration and by implication sodium removal is associated with reduced survival, especially in anuric patients. Several reasons for this association have been proposed, but there is little doubt that a failure to remove adequate fluid due to membrane characteristics that result in less good ultrafiltration or excessive fluid reabsorption are important. The simplest way to monitor membrane function is to perform a regular peritoneal equilibration test that measures solute transport rate and net ultrafiltration capacity in a standard- ized 4-h dwell. A membrane that results in less than 400 ml ultra- filtration using 3.86% or less than 100 ml using 2.27% glucose is unlikely to achieve adequate fluid removal once the patient becomes anuric. If this is associated with a fast rate of solute transport (4- h dialysate:plasma creatinine ratio above 0.65), and thus early loss of the glucose gradient and more rapid fluid reabsorption, then a combination of APD delivering shorter exchanges overnight and icodextrin (a polydispersed glucose polymer derived from starch) in the long exchange will result in adequate fluid removal in most cases. Use of APD in this situation is associated with better patient survival, mitigating the observed increased mortality seen in patients with rapid transport membranes when using CAPD. Icodextrin achieves sustained ultrafiltration in the long dwell as it acts rather like a colloidal agent, thus counterbalancing Starling forces. It has been shown to improve fluid status, reduce peritoneal glucose exposure, and enhance diabetic control, and it represents a major advance in peritoneal dialysis therapy. Note, however, that icodextrin metab- olites in blood can interfere with estimation of blood glucose by monitors that use glucose dehydrogenase, such that there is a risk of failing to diagnose hypoglycaemia. Complications and their management Peritonitis Peritonitis is the most common and potentially serious complica- tion of peritoneal dialysis, resulting in up to 50% of technique fail- ures. With enhanced training, patients can be expected to have one episode of peritonitis for every 3 years of treatment. Presentation is with cloudy dialysis effluent, with or without abdominal pain and/ or fever, and the diagnosis is confirmed if the leucocyte count is above 100/μl in the peritoneal fluid. Clinical assessment should in- clude examination of the exit site and tunnel for infection, and the abdomen for signs of intraabdominal pathology. At least 20 ml of freshly drained dialysate should be sent for culture by appropriate methods, which are absolutely crucial. The technique recommended by the International Society for Peritoneal Dialysis (freely accessible at https://ispd.org) is for 50 ml of peritoneal effluent to be centri- fuged at 3000 g for 15 min, followed by resuspension of the sediment in 3 to 5 ml of sterile saline and inoculation of material on both solid culture media and into a standard blood culture medium. With this method, fewer than 5% of cases should be culture negative. Empirical antibiotic treatment, either intraperitoneal or systemic, with cover for both Gram-positive and Gram-negative organisms should be commenced immediately while awaiting specific cultures and sensitivities. The reader is again directed to the International Society for Peritoneal Dialysis website for detailed up-to-date guidelines on management, but most typically Gram-positive or- ganisms will be covered by vancomycin or a cephalosporin, and Gram-negative infections by a third-generation cephalosporin, aminoglycoside, or (if local sensitivities support such use) quin- olone, with the regimen adjusted as and when results of culture and sensitivity of peritoneal fluid are available. A mixed bacterial growth, especially associated with anaerobes, should dictate early surgical assessment, catheter removal, and laparotomy. Catheter removal is also likely to be necessary if there is an associated catheter-tunnel infection or a failure to respond to antibiotics within a few days. Exit-site infection A simple scoring system has been devised to assess the exit site (Table 21.7.2.2). Mechanical failure Mechanical failure is common in the early stages of a patient’s career on peritoneal dialysis, and can be due either to catheter displace- ment (outflow affected), wrapping of the catheter by the omentum

section 21 Disorders of the kidney and urinary tract 4878 (in- and outflow), or leakage. The latter can occur at the deep cuff or at any hernia site and may present as genital swelling. Diagnosis is either obvious or requires appropriate imaging, usually a CT scan with contrast introduced into the catheter. Ultrafiltration failure Changes can occur in membrane function with time on peritoneal dialysis that result in less good ultrafiltration. Drivers of this change appear to be early loss of residual renal function and use of more hypertonic glucose dialysis solutions. Most frequently, this is due to a progressive increase in solute transport that can be addressed using APD and icodextrin (discussed previously). In some patients, however, more serious membrane damage occurs which results in reduced osmotic conductance (efficiency) of the membrane for a given osmotic gradient due to progressive membrane fibrosis. These patients require transfer to haemodialysis. Encapsulating peritoneal sclerosis Encapsulating peritoneal sclerosis (EPS) is a relatively uncommon but life-threatening complication of peritoneal dialysis, character- ized by severe inflammatory thickening, especially of the visceral peritoneum, resulting in an encapsulation and progressive obstruc- tion of the bowel. Diagnosis is made from CT scan or laparotomy confirmation of bowel obstruction due to macroscopic appearances of thickened membrane, with cocoon-like encapsulation of the entire intestine in severe cases. Risk factors identified include prolonged time on treatment (incidence 15–20% after 10 years), severe and protracted peritonitis, and acquired, severe ultrafiltration failure characterized by loss of membrane efficiency and in particular reduced free water transport. EPS may resolve slowly after stopping peritoneal dialysis, but often continues to progress and presents after modality transfer, including after renal transplantation. Corticosteroids and immuno- suppressants (both anti-inflammatory) and tamoxifen (antifibrotic) have been used as treatments, but without convincing evidence of benefit. Management includes nutritional support, parenteral feeding in the presence of vomiting, and in severe cases— especially with life-threatening obstruction—extensive surgical enterolysis. This should be performed in specialized centres which report good primary cure rates when the treatment is planned, although recur- rence can require repeat procedures. Emergency surgery, especially following bowel perforation or infarction, has a very high mortality. EPS is an awful disease: case series report overall mortality of 26 to 58%, although many deaths within such series were not from the EPS itself. Because of the risk of the condition, there has been much discussion in the renal community as to whether patients should be advised against remaining on peritoneal dialysis for more than a particular number of years. However, the risk of developing EPS is extremely low in patients who have been on peritoneal dialysis for less than 5 years, most long-term peritoneal dialysis patients are not affected, and the risks of EPS must be balanced against those of any alternative renal replacement therapy for the individual patient. Furthermore, there are no prospective data supporting a benefit of pre-emptively transferring long-term peritoneal dialysis patients to haemodialysis.

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Dis, 43, 891–9. Johnson DW, et al. (2012). Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol, 23, 1097–107. Lambie M, et al. (2013). Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. J Am Soc Nephrol, 24, 2071–80. Li PK, et al. (2016). ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int, 36, 481–508. Mehta R, et al. (2015). International Society of Nephrology’s 0by25 ini- tiative for acute kidney injury: a human rights case for nephrology. Lancet, 385, 2616–43. Paniagua R, et al. (2002). Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, ran- domized, controlled trial. J Am Soc Nephrol, 13, 1307–20. Szeto C-C, et al. (2017). ISPD catheter-related infection recommenda- tions: 2017 update. Perit Dial Int, 37, 141–54. Rippe B, et al. (2004). Fluid and electrolyte transport across the peri- toneal membrane during CAPD according to the three-pore model. Perit Dial Int, 24, 10–27. Table 21.7.2.2 Classification and treatment of exit-site infections Symptom Points awarded 0 1 2 Swelling Absent <0.5 cm

> 0.5 cm or includes tunnel Crust Absent <0.5 cm 0.5 cm Redness Absent <0.5 cm 0.5 cm Pain Absent Slight Severe Drainage Absent Serous Purulent An exit site with a score of 4 or greater, or a purulent discharge, should be treated with empirical antibiotics that cover coagulase-positive staphylococcus and pseudomonas until sensitivities are available.

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