Physiology of Peritoneal Dialysis

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Introduction

The history of peritoneal dialysis is a rich one, and echoes the accumulated knowledge across a multitude of medical specialties and disciplines. The earliest known recorded descriptions of the peritoneal cavity are inscribed in the Ebers Papyrus, an Egyptian medical manuscript dating back to 1550 BC. In ancient Rome, Galen, progenitor to the modern physician, noted its anatomy while treating abdominal injuries to gladiators. Centuries of medical stagnation followed, with renewed interest in the peritoneum blossoming during the Industrial Revolution followed with clinical applications during the twentieth century paving the way for modern peritoneal dialysis. It is now the dominant option in home dialysis therapy, and is the modality of choice in many countries, including Canada, Mexico and Australia, used by about 200,000 patients worldwide [1]. Since its establishment as a viable option for ESRD patients in the 1960s, peritoneal dialysis remains an attractive option for patients and physicians who desire a convenient, flexible and low cost alternative to traditional hemodialysis (HD) [2].

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During HD, blood and dialysate interact across a semipermeable membrane, ultimately leading to water removal, solute balance, and toxin clearance. Unlike HD utilizes artificial semi-permeable tubules through which blood passes and is bathed by dialysate, PD harnesses the intrinsic physiologic properties of the peritoneal membrane itself. Additionally, rather than pump-applied pressure gradients in HD, osmotic and solute gradients between dialysate and blood are employed to transport solutes and water via filtration, diffusion and advection in PD.

The Peritoneal Membrane

Central to PD are the properties of the peritoneal membrane – also known as peritoneum – the serous membrane that lines the abdominal cavity. Embryonically derived from layers of mesenchyme, its gross anatomy and cellular constituents were first described in scientific detail in 1862 by the renowned pathologist von Recklinghausen [3].

Anatomy

The peritoneal membrane encompasses a large surface area that roughly, and coincidentally, equals that of the body surface area of an average healthy adult – approximately 1–2 m^2 [4].

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Blood flow through the peritoneum is also an important consideration, and can directly affect a patient's dialyzing capabilities. In normal physiologic conditions, estimated blood flow through the peritoneum is 50–100 ml/min, approximately 1% of a person's cardiac output, however this can vary depending on individual anatomy and inflammatory states [4].

The peritoneum is divided into two components:

1. The visceral peritoneum which lines the gut and associated viscera. This comprises 80% of the entire peritoneum, with blood supply coming from the superior mesenteric artery; drainage is through the portal venous system.
2. The parietal peritoneum lines the walls of the abdominal cavity, and comprises the remainder (20%) of the peritoneum. Blood supply of the parietal peritoneum is derived from the abdominal wall vasculature, and drains directly to the inferior vena cava.

Between the parietal and visceral peritoneum is the peritoneal cavity, the site where dialysate "dwells" during exchanges. The cavity is remarkably pliable; while small in healthy persons and housing less than 100 mL of fluid, during peritoneal dialysis upwards of 3 liters of dwell may be tolerated without significant discomfort [4, 5].

The specific extent and proportions of the peritoneum involved during dialysis remain unknown. Although the visceral peritoneum comprises the majority of the membrane surface area, it is largely adhered to fibrous viscera with poorly exposed to dialysate. Consequently it is thought to not contribute significantly to fluid and solute exchange during PD. This lack of contribution has been demonstrated with eviscerated animal studies.

In contrast, despite its limited size, the parietal peritoneum contributes most to the diffusion and ultrafiltration that defines PD primarily due to the availability of usable vasculature to the peritoneal cavity. The concept of "effective peritoneal surface area" is evoked through this discrepancy; simple surface area does not account for the three dimensional differences in capillary distribution, membrane thickness and dialysate – membrane matching. All things being equal, the perfusion of capillaries within the peritoneal membrane can greatly affect the dialyzing capabilities of each individual person.

Histology

Histologically, the peritoneum is a complex, living and dynamic structure that includes and encompasses interstitial matrix, microvasculature, connective tissue and mesothelial cells [4–6]. In general the following landmarks are noted:

(a) Capillary fluid film covering the endothelium of the capillaries
(b) Capillary wall (endothelium)
(c) Endothelium basement membrane
(d) Interstitium
(e) Mesothelium – layer of squamous epithelial cells
(f) Fluid film that overlies the mesothelium

Simplistically, these six landmarks can be thought of as the six layers of resistances to solute transport. There are two popular concept of peritoneal transport; they are complementary rather than mutually exclusive, and will be discussed below.

Models of Transport

The two most popular models of peritoneal transport emphasize the importance of peritoneal vasculature and interstitium. They are the "three pore model" which helped explain how solutes of varying sizes, as well as water are transported and the "distributed model", which has been used to develop the concept of effective peritoneal surface area.

Three Pore Model

This model emphasizes peritoneal capillary endothelium as the critical barrier to the peritoneal transport. Transports of solutes and water movement across these capillaries are mediated by pores of different sizes. The fluid films and the

mesothelium – layers a, e and f above are thought to offer only trivial resistance to transport [7, 8].

Ultrapores – the smallest of the pores, these are transcellular with a radius of only 2–5 Å. They also constitute only 2% total pore surface area. These are responsible for the transport of water only and have been experimentally found to correspond to aquaporins (AQP-1) channels, which are known to be the present in the endothelial cell membrane of the peritoneal capillaries. Because of the water selective properties of the ultrapores, sodium is unable to pass through which leads to the initial drop in sodium concentration in dwell fluid (with corresponding increase in sodium concentration in plasma) accounting for the phenomena of "sodium sieving".

Small pores – Pores with radius of 40–50 Å and represent small intercellular defects between endothelial cells. Small pores are large enough to allow transport of both water and solutes, and thus contribute to both diffusion and ultrafiltration. These are the most numerous of the three pore model, comprising over 90% of the total pore surface area and are the dominant site of small solute transportation

Large pores – intercellular pores that constitute radius of 200–300 Å which correspond to large clefts in the endothelium. These are the least abundant and contribute to less than 0.1% of the total effective pore area and macromolecules such as protein are transported by convection through these pores [7–9].

Distributed Model

The distributed model emphasizes the importance of the distribution of capillaries in the peritoneal membrane and the distance water and solutes have to travel from the capillaries across the interstitium to the mesothelium. Transport is dependent on the surface area of the peritoneal capillaries rather than on the total peritoneal surface area [9, 10]. Additionally, the distance of each capillary from the mesothelium determines the relative contribution. The cumulative contribution of all the peritoneal capillaries determines the effective surface area and the resistance of properties of the membrane. From the distributed model, the concept of "effective peritoneal surface area" has arisen [9–11].

Therefore, two patients with the same peritoneal surface area may have markedly different peritoneal vascularity and so also have different effective peritoneal surface areas. Similarly, a patient's effective peritoneal surface area may vary in different circumstances, for example increasing in peritonitis as the inflammation will increase the vascularity.

Peritoneal Dialysis Transport Physiology

At the heart of PD is transport physiology. It is important to remember that the peritoneal membrane maintains bidirectionality throughout dialysis; however, there is no singular component of the membrane that is the definitive measure for fluid transport (ultrafiltration) or solute transport. Dialysate molecules such as dextrose and water in the peritoneal cavity are subject to the same physiologic principles as are waste products in the blood stream and can cross the membrane into plasma if conditions are favorable.

Ultrafiltration

Ultrafiltration refers to the osmotic flow of water across a dialyzing membrane. It occurs as a consequence of the osmotic gradient between the hypertonic dialysis solution and the relatively hypotonic peritoneal capillary membrane. The movement of fluids across the peritoneal membrane is primarily determined by ultrapores and small pores mechanism and depends on the following:

(a) Concentration gradient for the osmotic agent i.e. glucose. This is maximum at the start of PD dwell and decreases with time due to dilution of the glucose by ultrafiltration and from diffusion of the glucose from the dialysis solution into the blood. The gradient can be maximized by using a higher concentration of the dextrose, or by doing more frequent exchanges [5, 9, 12, 13].

(b) Effective peritoneal surface area, as discussed above under the distributed model.
(c) Reflection coefficient of the osmotic agent (i.e., glucose). This is a measure of how effectively the osmotic agent diffuses out of the dialysis solution into the peritoneal capillaries. It is ranges between 0 and 1. The lower the value the faster the osmotic gradient is lost across a pore and leading to correspondingly less sustained ultrafiltration. Lower numbers are thus not ideal for osmotic agents. Glucose has a reflection coefficient of 0.3 whereas icodextrin is close to 1 [14–16].
(d) Hydrostatic pressure gradient. The hydrostatic pressure is higher in the capillary than the peritoneum and this favors ultrafiltration. This hydrostatic pressure is higher in volume-overloaded ambulatory patients and lower in recumbent or volume depleted patients.
(e) Resorption. Also known as 'fluid loss', and 'wrong way flow', resorption is the reclamation of peritoneal fluid back into circulation. The majority of fluid is resorbed through the membrane itself via hydrostatic convection back through tissue. This occurs among the vasculature in the parietal peritoneum lining the abdominal wall. The remainder is accomplished through the lymphatic system, with the main drainage site being the sub-diaphragmatic lymphatic stomata. Hydrostatic increases in peritoneal cavity pressure, particularly with larger dwell volumes and correspondingly larger pressures, can thus ultimately cause a decrease in net ultrafiltration [4, 17].
(f) Oncotic pressure gradient. A subset of osmotic pressure due to colloids (proteins), this acts to keep fluid in the blood, thereby resisting ultrafiltration [17].

Solute Transportation

Transportation of solutes from the bloodstream to the dialysate fluid depends on two concurrent processes:

(a) Diffusion is the dominant method of small solute transportation in PD, which includes electrolytes, simple sugars and uremic solutes. By definition, diffusion is dependent on concentration gradients of individual solutes between dialysate and blood across the semipermeable peritoneum to facilitate transfer. As in ultrafiltration, the gradient between the dialysate and plasma decreases over time, with the greatest potency occurring in the first hour of a dwell. Numerous other secondary factors will also affect net transport. These include the size of the effective peritoneal surface area, volume of the dialysate, molecular size of the solute, and amount of peritoneal blood flow. Each given solute has its own intrinsic property determining rate of diffusion, and is determined by its molecular weight [4, 5, 9, 13].
(b) Convection – or, more accurately, advection – is clearance of solutes which depends neither on the properties of the solute itself nor the concentration gradient of the solute but, rather, on its relation with the flow of fluid. Solvent drag occurs with the bulk movement of ultrafiltrate across the peritoneum due to osmotic gradients, bringing with it solutes. The amount of solutes carried by the ultrafiltrate is limited by components of peritoneum that allow passage of fluid but not solute. This is seen in with aquaporin channels. This phenomenon is known as 'sieving', and is most commonly observed with sodium when utilizing low molecular weight osmotic molecules for dialysate. In the clinical setting, sodium sieving is an important parameter in assessing the adequacy of free water transport in PD patients, and can become a significant issue during rapid dialysate cycling [14].

Dialysis Solutions

In 1923, Gantar injected normal saline into the peritoneal cavity of uremic guinea pigs, thereby performing the first known attempt at peritoneal dialysis in animals. A failed attempt in PD on a uremic woman soon followed, again using normal saline. The importance of PD fluid hyperosmolarity in inducing fluid removal became apparent, with Heusser first adding dextrose to PD solutions in 1927 [3].

Modern PD solutions are varied, however they share important distinguishing features: a primary osmotic agent, electrolytes and buffers. Given that the average PD patient uses 7–10 *tons* per year of dialysate, certain considerations are important in determining an ideal solution, namely expense, safety and efficacy.

Osmotic Agents

As mentioned earlier, hydrostatic gradients are the primary engine of ultrafiltration in hemodialysis. Due to inherent limitations of anatomy, however, utilizing pressure gradients in PD is close to impossible. Fluid transport in PD is thus reliant on osmotic differences between dialysate and plasma to move water.

(a) Low Molecular Weight Agents – Inexpensive, easy to produce, and relatively safe, sugar based agents are the dominant osmotic agents even today, though their structural components may differ. Dextrose (D-glucose) remains the most commonly used agent, with solutions containing variable concentrations standardized into 1.5%, 2.5% and 4.5%. Fluid osmolality ranges between 346 and 485 mOsm/kg; higher concentrations lead to greater ultrafiltration. Due to their low reflection coefficients, they are readily diffusible through the peritoneal membrane into plasma [14, 18]. With their passage several phenomena can be noted. First, the osmotic potency of the dialysate diminishes overtime, reducing ultrafiltration. Second, unsurprisingly hyperglycemia and hyperinsulinemia can ensue. With diabetes being the leading cause of end stage renal disease worldwide this can become a significant issue. A consideration when using small molecular weight sugar based osmotic agents is their susceptibility to forming cytotoxic glucose degradation products (GDP) during fluid sterilization processes. These can further react with native proteins forming advanced glycation end products (AGE) [19]. Long term exposure to these components leads to superoxide radicals, mesothelial necrosis and fibrosis which raises concern for association with PD failure [5, 6, 19–21].

(b) High Molecular Weight Agents – High molecular weight agents such as glucose polymers, dextran polypeptides and the like, range in weight from 10 k to 350 k Daltons. The most commonly utilized polymer is icodextrin at 7.5%, a glucagon isomer that averages roughly 16 k Daltons. Icodextrin circumvents many of the issues that plague lower molecular weight sugars. Due to its high reflection coefficient, it remains in dialysate much longer – its diffusion into the bloodstream is limited to lymphatic resorption and consequently maintains ultrafiltration capabilities for a longer time period. They are removed from dialysate either through lymphatic absorption or through endothelial large pores. This property allows icodextrin solutions to also have much less osmolarity than dextrose-based solutions – 282 mOsm/kg compared to 346 mOsm/kg for a 1.5% dextrose solution. The smaller osmolarity of icodextrin solutions are supplemented by osmotic pull of electrolytes that have diffused from plasma to the dialysate [16, 18, 22].

Electrolytes

Electrolyte additives in PD dialysate generally run low to better facilitate diffusion, clearance, and ultimately removal during exchanges. Potassium, for example, is usually not added to dialysate, and any deficiencies can easily be corrected with oral supplementation. Sodium sieving can cause an abrupt hypernatremia within the first hour of PD exchanges whilst using dextrose based dialysate due to increased isolated ultrafiltration of water. Due to the tendency of PD patients towards hypernatremia, sodium in dialysate tend to run lower than plasma levels to encourage diffusion of sodium out of plasma. Commercial solutions range between 130 and 137 mmol/L internationally.

Calcium levels have a tendency to be low in renal patients due to failure to synthesize calcitriol. Supplementation can be added to solutions, though with caution as patients tend to be on calcium containing phosphate binders or vitamin D supplementation.

Buffers

Buffering components mixed into dialysis fluids have been used control acidosis in PD since Dr. Boen used bicarbonate in the 1960s [3]. However its propensity to precipitate calcium and magnesium led to its replacement with lactate and similar containing solutions.

Today, lactate is the most commonly used buffer due to its efficacy, and compatibility. Lactate is metabolized to bicarbonate in the liver though its acidic nature is thought to possibly contribute to cellular death. Lactate based solutions also have an unfortunate tendency to cause inflow pain as well as abdominal discomfort. Bicarbonate solutions have stubbornly continued to be a suitable alternative for buffering; it is particularly useful for patients wishing to avoid infusion pain provided that they are separated from calcium or magnesium solutions [18]. Realistically this can be a cumbersome experience for patients and caregivers alike.

Assessment of Membrane Transport Status

Measurements of membrane transport status is critical in both predicting an individual patient's physiologic response to dialysis as well as assessing and evaluating their current status to adjust needed prescriptions.

Peritoneal Equilibration Test (PET)

Described in 1987 by Twardowski and colleagues, this was the first and still most utilized standardized evaluation of patient response to peritoneal dialysis [23, 24]. By checking the levels of a given solute in the dialysate and plasma, nephrologists can determine the dialyzing capabilities of a patient and estimate adequacy. The initial body of work emphasized categorizing peritoneal membrane solute transport characteristics amongst four distinct patient types: high, high-average, low-average, and low depending on their rate of solute transport. The test is typically performed as an in-office visit four to 6 weeks after initiation of PD to allow for membrane stabilization. The test requires complete drainage of the overnight dwell, with reinfusion of a standardized fluid (2 L of 2.5% dextrose).

Table 2.1 An example of D/P ratio categorization for creatinine levels

$D/P_{creatinine}$ ratio at 4 h	Transporter type
$D/P_{creatinine}$ 0.81–1.03	High
$D/P_{creatinine}$ 0.65–0.81	High average
$D/P_{creatinine}$ 0.50–0.65	Low average
$D/P_{creatinine}$ 0.34–0.5	Low

Modified from Twardowski [23]

The dialysate is sampled as soon as infusion is completed, and repeated at 2 and 4 h intervals. Dwell urea, creatinine, sodium, and glucose levels are checked. A concurrent blood (plasma) sample is checked at the same intervals, and compared with dialysate characteristics. These are presented as D/P (D for dwell, P for plasma) and are termed equilibration ratios. The equilibration ratios between the urea, creatinine, sodium and glucose should be compared with each other to ensure concordance of measurement (Table 2.1).

Higher transporters achieve the most rapid and complete equilibrium for solutes creatinine and urea because they have a relatively large effective peritoneal surface area or low membrane resistance. However high transporters rapidly lose their osmotic gradient for ultrafiltration because the dialysate glucose diffuses into the blood through the highly permeable membrane. They also have higher dialysate protein losses and so tend to have lower serum albumin levels.

Conversely, despite the slow movement of solutes in low transporters and need for longer dwell times, lack of ultrafiltration is rarely an issue due to longer maintenance of the osmotic gradient. High average and low average transporters have intermediate values for these ratios and for ultrafiltration and protein losses (Fig. 2.1). In practice, high transporters do best on PD regimens that involve frequent short duration dwells, so that ultrafiltration is optimized while the low transporters do best on regimens based on long high volume dwell times so that diffusion is maximized.

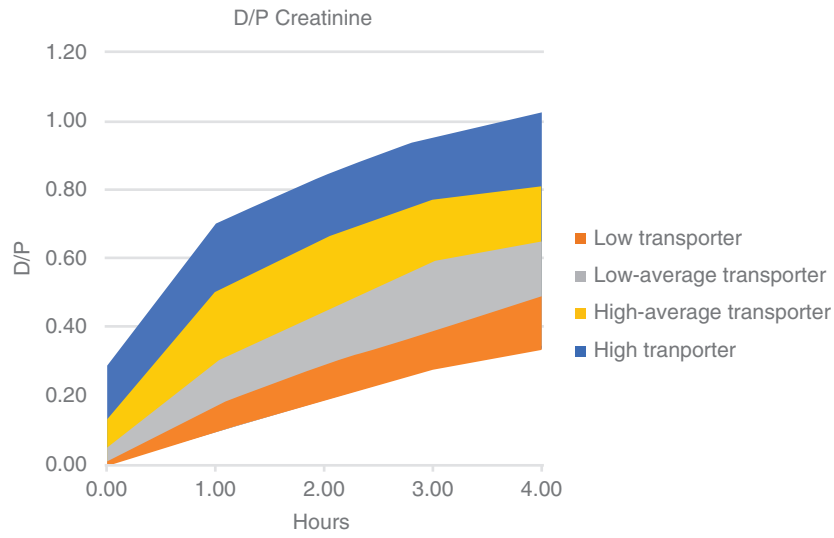

Fig. 2.1 Dialysate to plasma ratio for creatinine (Adapted from Zbylut et al. [24])

Other testing modalities include the Fast PET, an abbreviated test which only samples dwell and plasma creatinine and glucose at the 5 h mark and the Modified PET, which evaluates ultrafiltration failure using an osmotic challenge by utilizing a more concentrated dextrose solution (4.25% 2 L dextrose). Ultrafiltration less than 400 mL during a Modified PET is diagnostic for peritoneal membrane failure [4, 23, 24].

Adequacy of Dialysis

In the broadest sense, adequacy is the overall assessment of the efficacy of dialysis and is an expression of the overall gestalt of a patient's well-being [25, 26]. Ultimately the goal of dialysis is to maintain a patient's subjective quality of life. In practice this is difficult to quantify.

While being secondary goals, outcomes such as solute clearance, acid base maintenance, maintenance of electrolyte equilibrium, and mineral bone disease prevention, are objective and easier to quantify. Urea and its clearance became the most commonly used markers for adequacy after 1981, when a study performed by the National Cooperative Dialysis Study noted that significantly better outcomes were noted in patients with lower BUN levels for patients undergoing hemodialysis [27].

In the clinical setting, urea clearance is normalized to body water levels (Kt/V_{urea}) and is measured at 1 month after starting PD concurrently with the PET then subsequently every 4 months thereafter [23, 24]. Urea clearance is comprised of clearance from peritoneal dialysis itself and clearance from any residual kidney function and have to be individually calculated, and then added together.

The components of Kt/V_{urea} are as follows:

K – This is the *daily* clearance of urea, and can be obtained by the D/P_{urea} ratio multiplied by the total volume of dialysate (dwell plus ultrafiltrate) for the PD portion. For assessing urea clearance of the kidneys, D (dialysate) is substituted by U (urine). Correspondingly this is multiplied by the volume of urine produced rather than dialysate volume.

t – This is time, in days. Standard measurements of Kt/V_{urea} is expressed as a weekly value, so this number is typically 7.

V – This is the volume of distribution of urea, and can be obtained by the Watson formula which is available online. It is roughly 60% of a patient's ideal body weight.

Survival on PD has documented associations with maintaining higher Kt/V levels. Initial studies recommended maintaining weekly Kt/V levels of

greater than 2.0 though this has since relaxed. The most recent guidelines from KDOQI committee recommends maintaining the total Kt/V_{urea} (peritoneal and urinary clearance) above 1.7 [25].

Peritoneal Dialysis Modalities

Peritoneal dialysis is divided into two main modalities: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). The choice of peritoneal dialysis to use depends on numerous factors including transport phenotype; however, by and large patient and caregiver preference is the main determinant. There is no difference in survival outcomes between CAPD and APD.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

Developed and refined by Drs. Popovich, Moncrief and Nolph in the 1970s, CAPD was the dominant modality worldwide for a number of years though automated peritoneal dialysis (APD) has since caught up [1, 15, 28]. CAPD requires a continued dwell throughout the day, with exchanges between used dialysate and fresh solutions performed four times per day. Fluid volume per exchange is 2 L. Residual kidney function, patient size, and transport characteristics of the patient will influence subsequent fluid volumes, exchange frequency as well as solution types though these changes are typically made after formal PET and adequacy measurements are performed a month after PD has started.

CAPD offers the advantage of portability, and longer dwell times to facilitate better solute clearance and ultrafiltration. In patients whose residual kidney function is terminal or are low transporters with poor ultrafiltration, CAPD may be the only feasible peritoneal dialysis option. The main disadvantages is the inconvenience of performing exchanges throughout the day, as well as higher rates of peritonitis due to persistent fluid in the peritoneal cavity.

Automatic Peritoneal Dialysis (APD)

The use of cyclers became more mainstream in the early 1980s. APD is now the most common form of PD in the United States. The cycler attempts to compress a patient's dialysis during their least active part of the day – during sleep. This is an especially attractive option in patients who have active schedules, or who require help from persons whose time is limited.

Unsurprisingly, exchanges are performed more frequently and more rapidly compared to CAPD, and the dwell is completely drained once the patient detaches from the cycler in the morning. While high transporters benefit from faster exchanges to limit excessive ultrafiltration, in low transporters this can be problematic and lead to inadequate fluid removal and solute clearance. Using icodextrin in APD is difficult as well, as it typically requires longer dwell periods to realize its full effects.

Fortunately, automated peritoneal dialysis itself is flexible enough to be subdivided into distinct modalities which can help circumvent the problems described above; however, they all share the same characteristic of using a cycler overnight. Several of the more common variables are described below.

(a) Nightly intermittent peritoneal dialysis (NIPD) – "Dry APD", this is the purest form of automated peritoneal dialysis as there are no exchanges performed during the day. The only time a patient undergoes dialysis is when they are asleep.
(b) Continuous cycling peritoneal dialysis (CCPD) – also known as "wet" APD, an additional exchange (or two) is performed during the day in addition to nightly cycling.
(c) Tidal peritoneal dialysis – a common modality in Europe, TPD addresses the problem of reduced dwell time with serial exchanges by instead maintaining a constant dwell throughout the night to allow for more UF and diffusion. Overfilling can be a problem with these patients.
(d) Intermittent peritoneal dialysis – infrequent dialysis over the course of several days [4, 15, 28].

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