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Evolving Strategies in Peritoneal Dialysis

Edited by Edward T. Zawada Jr.

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Meet the editor

Edward T. Zawada Jr. graduated *summa cum laude* from Loyola University in 1969 and *summa cum laude* from Loyola-Stritch School of Medicine in 1973. He trained at the University of California at Los Angeles (UCLA) from 1973 to 1978. His faculty positions include UCLA, University of Utah, Medical College of Virginia, and University of South Dakota. Other positions include professor and chairman emeritus, Department of Internal Medicine, University of South Dakota, Sanford School of Medicine; Bush Foundation of Minnesota Sabbatical Fellowship in Critical Care, Department of Anesthesiology at the University of Iowa in 2009; and board certified by the American Board of Internal Medicine in Internal Medicine, Nephrology, Geriatrics, Critical Care Medicine. Other board certifications include Nutrition and Clinical Pharmacology. He is a Master of the American College of Physicians and Fellow of the American College of Critical Care Medicine, the American Society of Nephrology, the American Society of Hypertension, the American College of Chest Physicians, the American College of Clinical Pharmacology, the American College of Nutrition, and the American Heart Association.

Contents

Preface

In my 47 years of nephrology experience, peritoneal dialysis has had two peaks in usefulness. Initially, it was the most cost-effective and easily available form of life support for patients with acute renal failure. Now, it is being targeted as a way to provide maximum patient independence and autonomy and the most sustained fluid balance, with the least number of missed treatments and the least number of hospitalizations. It is also the cheapest form of end-stage renal disease management, because the patient and his or her caregiver provide the treatments, not a paid cadre of technicians and nurses. Changes in catheter design, packaging of peritoneal dialysis solutions, and the emergence of cycling machines allow safe, mostly nocturnal, treatment, relatively less expensively than chronic hemodialysis. I am fortunate to have worked side by side or at least collaborated with many of the pioneering innovators in peritoneal dialysis, including Drs. Morton Maxwell, Charles Kleeman, Todd Ing, John Daugirdas, Allen Nissenson, and of course Willhelm Kolff. I wish to thank my chapter contributors for their reviews of current practices and suggestions for future improvements in this most common form of home dialysis. I also wish to thank my current home dialysis team, Shaun Kittrell, Misty Reeder, Janice West, Michael Skinner, and Michelle Brouillard, in Redding, California.

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Chapter 1

Introductory Chapter: Peritoneal Dialysis, Overview and Current Concepts

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Additional information is available at the end of the chapter

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1. Historical perspective

Understanding the evolution of the peritoneal dialysis technique we use today is useful in enhancing the successes and reducing the failures we still face with this most common form of home dialysis empowering the patient to be in control of his own end-stage renal disease management. This chapter cannot mention all the early heroes who advanced this technology. I have had the good fortune of working with several of these individuals in my 48 years of study and practice of nephrology. I present this review emphasizing those with whom I worked or shared their experience at conferences and seminars.

The first clinical reports of a technique which we would recognize today as peritoneal dialysis was based on the care provided by George Carter in Germany in 1923 [1]. He instilled 1–3 L of sterile electrolyte-containing fluid with dextrose added for fluid removal into the abdomen by a needle. He drained it by a rubber hose into bottles. He had sterilized his tubing and bottles by boiling water. He used a 30-min dwell and demonstrated improved blood chemistries.

In 1936, the first patient who survived acute obstructive renal failure by peritoneal dialysis until recovery was described by Wear et al. [2]. The first series of patients reported success in the peritoneal dialysis of 10 of 21 patients by Kolff [3]. I had the honor of working side by side with Dr. Kolff years later at the University of Utah where he had established an Artificial Organs Institute. They used a glass catheter, rubber tubing, and porcelain containers all of which were able to be sterilized for repeat usage. Morton Maxwell reported the successful dialysis of patients using a flexible polyethylene catheter with side holes for drainage. He instilled 2 L into the peritoneum, let it dwell for 30 min, and then drained it back to the same bottles by gravity using the kind of tubing we recognize today [4]. This system was found to be simple to initiate in any patient, had the fewest numbers of connections to have periodically changed, and became quickly commercially available.

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The problem with early peritoneal dialysis was that the tube was semirigid and required direct percutaneous placement with a trochar. If a patient was conscious, was normal in size and nutritional status, and could cooperate by tensing the rectus muscles, the trochar could be placed more easily. If the patient was small, thin, or malnourished, the indentation of the abdominal wall by the trochar risked penetration or perforation of intraabdominal structures. Thus, establishing the access to the peritoneal cavity was the first problem we encountered in using peritoneal dialysis as much as we did in the 1960s and 1970s due to the lack of wide availability of hemodialysis equipment and trained staff. Other uses of peritoneal catheters besides dialysis soon followed, including treatment of hypothermia [5] and diagnostic peritoneal lavage for intraabdominal bleeding or for proof of peritonitis.

The placement of the catheter became easier and more accurate with several modifications in technique. Instead of direct puncture through the intact skin, it became clear that a small scalpel incision in the midline raphe and limited blunt dissection to the parietal peritoneal membrane made the insertion less of a risk of intraabdominal penetrations. Then, Ash popularized a small peritoneal scope over which the catheter was placed to guide it internally into a paracolic space that was free of adhesions. Initially, it was used for acute renal failure with the more rigid catheters, but later its use included placing the more flexible catheters used for long-term dialysis to be described below [6, 7]. Finally, the use of a guidewire and dilator before the catheter was placed with the trochar or scope made the process safer and easier to establish acute peritoneal access with a high probability of effective flow and drainage.

Tenckhoff and Schechter [8] contributed to the development and widespread use of a double-cuffed very pliable catheter which launched the ability of patients to have a catheter in place indefinitely with low risk of infection. The cuffs allowed tissue growth into the mesh to create a seal. The pliability made the catheter conform to the paracolic gutter so as to bend with the patient allowing the patient to be comfortable and mobile. Today, chronic catheters are most often placed by surgeons during conventional laparoscopy, but some still do open procedures. These techniques will be reviewed in a subsequent chapter in this book. There still are problems with pain after catheter insertion due to migration from the original location, plugging of the drainage ports by omentum, and discomfort depending on the location of the exit site in relation to the umbilicus or belt line. Catheter extensions can be used to allow the exit sites to be moved more superiorly. Such a strategy is often helpful if a large pannus is present.

Popovich et al. [9] expanded the use of peritoneal dialysis as it morphed into the most convenient form of home dialysis. They were among the earliest to report the largest number of patients being maintained on chronic home peritoneal dialysis, often continuous ambulatory peritoneal dialysis (CAPD). Later, improved automation of the delivery, dwell, and drainage of solutions by what has become known as a "cycler" has now become the preferred technique of home peritoneal dialysis at least in part due to the need for only one connection per day at night and one disconnection in the morning. The reduction of manipulation of the catheter reduces contamination and infection and is less time-consuming to the patient. The development of the "cycler" has been attributed to a variety of pioneers including Lasker [9].

Solute removal and ultrafiltration assessment are mandated to be measured periodically to assess the quality of care delivered by home peritoneal dialysis. Twardowdki has been credited

with assisting in the development of the peritoneal equilibration test (PET) to assess transport characteristics of a patient's peritoneal membrane [10]. Briefly, the PET test assists in managing fluid removal strategies of a patient by manipulating dwell time. Survival of patients with end-stage renal disease has been shown to be better associated with effective ultrafiltration rather than solute removal [11].

While in training, I noticed that fluid removal by acute peritoneal dialysis was always less efficient at the time of initiation compared to hours later after many repetitions of hourly cycles of instillation, dwell, and then the drainage of the fluid. Negative fluid balance with more out than in per cycle got easier as the cycles accumulated. Later, it became clear to me that the difference lays in the osmotic gradient of dextrose vs. the osmotic effect of nitrogenous toxins which decreased over time as their concentration reduced over time due to diffusion during each successive cycle. For chronic peritoneal dialysis, the efficiency or ultrafiltration is a function of using different concentrations of dextrose alone or in combination over the period of consecutive cycles. Using 1.5, 2.5, and 4.5% dextrose solutions to fill the peritoneal cavity with a usual amount of 2000 cc, progressively more fluid returns are usually seen. The difference represents the net ultrafiltration. One common and annoying problem occurs when drainage is unexpectedly low. The impact is that the patient's net dialysis and ultrafiltration will be impaired. To solve the problem, evaluation of the location and function of the catheter, health of the peritoneal membrane, and hemodynamic and volume status of the patient are needed. If the patient is hypovolemic or hypotensive, blood may be shunted from the viscera leading to reduced membrane function transport.

Icodextrin was developed to assist with problem cases of inadequate ultrafiltration in some patients. It is nonabsorbable carbohydrate which exerts a long duration osmotic effect. It is added as an afternoon long swell exchange [12]. This intervention is useful when the membrane is not functioning normally, when patients have very low urine volumes, need more dialytic fluid removal, or cannot tolerate the glucose load of the usual peritoneal dialysis solutions.

Oreopoulos is credited with simplifying peritoneal dialysis by the introduction of lightweight bags of solutions, y-tubing, and automated cycling. He put it all together and reported on a growing cohort of patients performing chronic peritoneal dialysis at home. He therefore suggested the idea that this strategy be considered as the first choice in initiating end-stage renal disease management [13].

Ultrafiltration efforts are monitored monthly by dialysis centers. The PET referenced above tests the speed of diffusion of glucose from the peritoneal solutions to the patient. In this way patients are described as fast transporters or slow transporters. Since the glucose determines the osmotic gradient for ultrafiltration, the dwell time has to be tailored to the individual patient depending on their transport characteristics. Short dwell times preserve the osmotic gradient in the fast transporters but shorten the time for other nitrogenous substances to be removed. More cycles are needed in some cases to meet these needs in a fast transporter. Slow transporters maintain ultrafiltration gradients throughout a long dwell but may need fewer exchanges because the prolonged dwell allows more nitrogenous solute diffusion. **Table 1** illustrates the variety of prescription adjustments depending upon PET results. Because of changes in the transport characteristics of the peritoneal membrane over time and after

Very fast transport	Excellent ultrafiltration	Poor solute diffusion	Short dwells	More cycles
Fast transport	Good ultrafiltration	Fair solute diffusion	Medium dwells	Variable cycles
Slow transport	Fair ultrafiltration	Good solute diffusion	Variable dwells	Medium cycles
Very slow transport	Poor ultrafiltration	Excellent solute removal	Long dwells	Less cycles

Table 1. PET test results.

1. Twenty-four-hour urine volume is needed—200 cc/24 hours
2. Measure the urine urea concentration—22.5 mg/dL
3. Measure the serum urea concentration—75 mg/dL
4. V is the total body water—60 kg × 60% water = 36 L
5. kT/V for residual renal function therefore is 22.5 × 2 (convert ml to dL)/75 = 0.533 mL/min × 1440 min/day 0.767 L/day divided by 36 L = 0.02 L per day of kT/V × 7 days = 0.14 total kT/V from residual function
6. Twenty-four-hour collection of peritoneal drainage is needed—10 L
7. Measure the peritoneal urea concentration—70 mg/dL
8. The fluid/plasma urea (D/P ratio) is calculated—70/75 = .93. The kT of urea is .93 × 10 L of drainage = 9.3.
9. V is the total body water—36 L
10. kT/V per day for dialysis therefore is 9.3/36 = .258 per day. kT/V per week from dialysis is .258 × 7 = 1.8
11. Total kT/V is that for dialysis plus residual renal function—1.8 + 0.14
12. Total kT/V therefore is 1.94
13. The goal is total kT/V per week >1.7

Table 2. Calculation of kT/V in 60 kg women.

episodes of peritonitis, it is recommended that peritoneal equilibration testing (PET) be repeated periodically in a given patient.

Solute removal adequacy is monitored closely by centers for home dialysis. Adequacy is assessed by the term kT/V which was first developed by Gotch to assess urea kinetics in hemodialysis patients but later applied to patients receiving peritoneal dialysis [14]. Total kT/V is determined from the peritoneal dialysis urea clearance per week plus the contribution of the patient's own renal function. **Table 2** illustrates the calculation of kT/V in a 60 kg patient. Total and dialytic kT/V is monitored monthly by dialysis centers, and the dialysis prescription is adjusted accordingly if necessary. If there is a high residual renal function, the kT/V of the dialysis can be reduced, for example. As time progresses, it can be adjusted upwards.

Tidal dialysis [15] was developed as an additional strategy for additional solute removal with a comfortable small amount of peritoneal fluid after the evening cycles are completed. It has also been used to allow a volume to serve as an aqueous cushion to keep the catheter from abutting on internal structures to cause irritation and pain. I mention it here only for completeness in the historical evolution of the concepts used by centers in managing home peritoneal dialysis patients.

Infections remain a constant threat to the long-term success of home peritoneal dialysis [16]. Infections have been found to fall into three categories: initial, relapsing, and recurrent. Peritonitis vs. tunneled infections are the two possible locations for the brunt of consequences. The problem of managing various types of infections in peritoneal dialysis patients will be reviewed in a separate chapter in this book.

2. Future possibilities

In my observations as a nephrologist for nearly 50 years, I have witnessed the overwhelming trend in the evolution of dialysis technology to miniaturization and increased efficiency. The large tanks of dialysate have been replaced by efficient pumps of water sources either from pipes or bags. The large parallel plates of dialyzers have been replaced by small cylinders of hollow fibers. In some cases, sorbsystems allowed recirculation of small volumes of dialysate. So with peritoneal dialysis, the future will likely continue in this fashion. There will be continued miniaturization of products to increase efficiency. I envision smaller volumes of solution mixed with sorbents to allow more efficient diffusion and ultrafiltration driven internally by much smaller pumps approaching the size of insulin pumps or pacemakers running on long-term atomic batteries. Likely, the solutions will need to be refreshed much less often, perhaps once a week or even longer. The portals into the body will become smaller and smaller, perhaps ultimately the size of medium-gauged needles.

3. Summary

My first recollection of the problems faced with peritoneal dialysis included placing the catheter in the first place. Secondly, I felt we faced problem with drainage. Thirdly, we faced infections. Finally, we faced adequacy and fluid balance problems. These initial problems have continued as ongoing problems today. In addition they form the basis for monthly reporting of quality measures, although additional measures are also being monitored today. In this book the chapters address current issues which not surprisingly mirror the problems faced in the evolution of peritoneal dialysis and home dialysis.

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Chapter 2

Techniques for Peritoneal Dialysis Catheter Placement

Stephen Akau Kache, Danjuma Sale and
Jerry Godfrey Makama

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Abstract

This chapter describes the peritoneal dialysis (PD) catheter implantation techniques. It will also discuss the merits and demerits of each technique, catheter types as well as the PD catheter-related complications. Several techniques and modifications have been described for the insertion of the catheter into the abdominal cavity. We will describe the currently available catheter designs which come in a variety of shapes (straight, pigtail-curled, swan-neck), length and number of Dacron cuffs for optimal ingrowth and fixation and insertion techniques with its early and late complications. These techniques include open surgical, laparoscopic and percutaneous techniques. The strategy for an optimal catheter implantation together with the preventive and therapeutic means for complicated treatment will be discussed.

Keywords: technique, peritoneal dialysis, catheter placement

1. Introduction

A well-placed and functioning peritoneal dialysis (PD) catheter is central to the success of peritoneal dialysis (PD) as a renal replacement therapy, therefore, knowledge of best practices in catheter insertion can minimise the risk of catheter complications that leads to peritoneal dialysis failure [1]. The first successful PD was done in 1959 by Richard Ruben, his patient survived for 6 months, by 1964, Fred Boen from the Netherlands used a machine he developed a year earlier to treat two patients with end-stage renal disease for 2 years [2, 3]. These initial successes with the PD were soon followed by descriptions of several techniques and modifications for catheter placement ranging from open surgical techniques, through percutaneous placement to later laparoscopic placement [2, 4–8].

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Several advantages of PD over haemodialysis (HD) have been described, including the quality of life due to superior patient mobility and independence, its simplicity in use, along with the clinical advantages like the maintenance of residual renal function and lower mortality in the first years after the beginning of PD. A significant disadvantage is the poor blood pressure control due to fluid overload [9].

The aim of this chapter is to describe the currently available catheter types and insertion techniques.

2. Technique for peritoneal dialysis catheter insertion

2.1. Types of peritoneal dialysis catheters

Peritoneal dialysis catheters come in various shapes (straight, pigtail-curled, swan-neck), lengths and numbers of Dacron cuffs (**Figure 1**). The peritoneal dialysis catheter is composed of a flexible silicone tube with an open-end port and several side holes to provide optimal drainage and absorption of the dialysate [2, 10].

The extraperitoneal component of the catheter has either one or two Dacron cuffs. The Dacron cuffs are for optimal growth and fixation. In adults, a double-cuff catheter is typically used. With the double-cuff peritoneal dialysis catheter, the proximal cuff is positioned in the preperitoneal space and the distal cuff in the subcutaneous tissue [2, 10]. The pubic symphysis

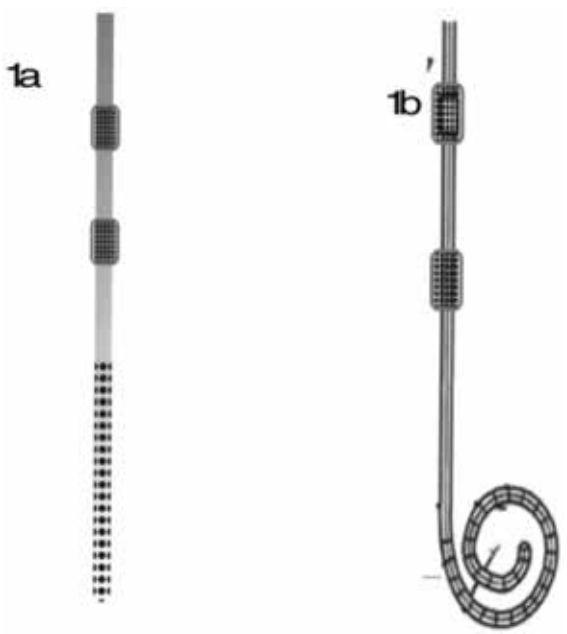

Figure 1. (a) Straight and (b) coiled PD catheters.

has been recommended as a reliable marker for the ideal location of the catheter tip in the true pelvis [2] (**Figure 2**).

The proximal cuff holds the catheter in place while the distal cuff acts as a barrier to infection. The type of catheter selected is usually based on the surgeon's preference.

2.1.1. Characteristic of an ideal peritoneal dialysis catheter

An ideal PD catheter should allow for optimal inflow and outflow and should be kink resistant; it should have no effect on physiology of abdominal tissues, should be resistant to infection with good surgical handling and should be affordable [10].

2.2. Techniques for insertion

There are several techniques used for the introduction of the PD catheter into the abdominal cavity. Open surgical and laparoscopic techniques are preferred because of their safety and good initial results [2]. The laparoscopic technique is becoming more popular because of its advantage in performing partial omentectomy, omentopexy or adhesionlysis during

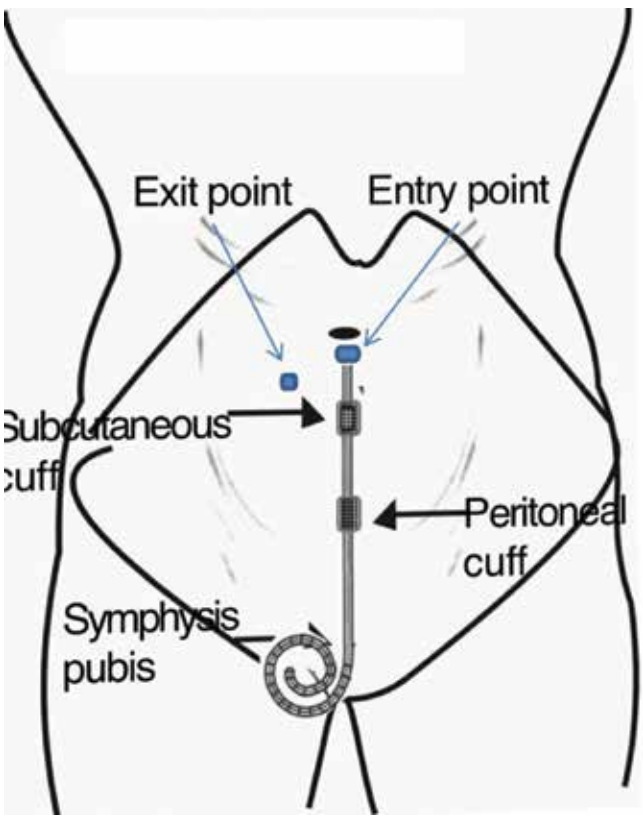

Figure 2. Exit and entry point of PD catheter with final position of the catheter tip.

the initial catheter placement [2, 11–14]. Percutaneous (radiological) catheter insertion may be less invasive but bears the risk of unsatisfactory catheter placement and danger of bowel perforation [2, 8].

2.2.1. Open surgical technique

With the patient placed in supine position under general anaesthesia, we routinely use an infraumbilical (two finger breaths) curvilinear incision on skin and subcutaneous tissue and a midline incision is then made on the fascia to gain access to the peritoneal cavity. However, Peppelenbosch et al. [2] described a technique in which a vertical incision of ~5 cm is made in the midline, 2–3 cm below the umbilicus. The subcutaneous layer is then dissected, till the sheath of the rectal abdominal muscle is reached. The anterior rectus sheath is opened and the muscle fibres are bluntly dissected. Subsequently, the posterior sheath is cut to 3–4 cm and the abdominal cavity is opened after dissecting the peritoneum. The abdominal wall is inspected for adhesions. After this, a retractor is used to lift the anterior abdominal wall. If the adhesions are present close to the abdominal wall, they are dissected. The patient is placed in a Trendelenburg position and the catheter is placed over a stylet and advanced into the peritoneal cavity. The intraperitoneal segment is slid off the stylet and the cuff is advanced to the preperitoneal space. The peritoneum and rectus sheaths (posterior and anterior) are closed carefully with absorbable sutures, ensuring not to obstruct the catheter and to prevent dialysate leakage. A tunnel is created to the preferred exit site using a needle and care should be taken to ensure that the exit site is facing downwards. The distal cuff is placed subcutaneously, 2 cm from the exit site. The exit site is usually lateral and caudal to the entrance site (**Figure 2**). Haemostasis is secured, and the incision is closed and the catheter itself is not fixated with a suture. The functioning of the catheter is tested by filling the abdomen with 100 ml of saline and the entrance site is checked for leakage. The saline is allowed to drain and is inspected for evidence of haemoperitoneum and faecal contamination.

2.2.2. Percutaneous

Placement of PD catheters with a guide wire and peel-away sheath is performed using a Seldinger technique. The procedure can be performed under local or general anaesthesia with prophylactic antibiotics. A small incision is created above the entrance site, usually in the midline with blunt dissection of the abdominal rectus sheath. The peritoneal cavity is cannulated with an 18-gauge needle and filled with either air or 500 ml of saline. With proper needle placement, the patient should not experience pain or resistance to fill the cavity with fluid. A 0.035-inch guide wire is advanced into the abdomen and the introduction needle is removed. A dilator and the peel-away sheath are advanced over the wire into the abdominal cavity. The wire and the dilator are removed and the catheter is placed on the stylet, advanced through the sheath. The intraperitoneal segment is advanced until the proximal cuff is located in the preperitoneal space. The peel-away sheath and stylet are removed and the catheter position is checked. A tunnel is created to the selected exit site with the placement of the distal cuff subcutaneously, 2 cm from the exit site. The entrance site is closed. The abdomen is filled with 500 ml of saline and drained [2].

2.2.3. Laparoscopic technique

The patient is placed in the supine position. General anaesthesia is inducted and intravenous antibiotics are administered. It is preferable to create a pneumoperitoneum with an open procedure. A small subumbilical incision is made (2–3 cm) and the umbilical cord is grasped with forceps and lifted. Subsequently, the subcutaneous layer is transected. The anterior rectus sheath is opened and a suture is placed to lift the anterior sheath. The posterior sheath and subsequently the peritoneum are digitally opened. If adhesions are present close to the abdominal wall, they are transected. A 5 mm trocar or a screw trocar is inserted into the abdomen and insufflated with CO_2 gas to create a pneumoperitoneum of 12–14 mmHg. A Veress needle technique can also be adopted. Several methods have been described. One is to place the needle in the upper-left quadrant of the abdomen. Another way is to open the anterior sheath as explained in the open procedure, but the Veress needle is used for the last one or two steps (the posterior sheath or the peritoneum). After the needle is in place, its correct position is tested by the water drop test, which should disappear into the abdomen through the needle and by insufflating and aspirating the 10 ml saline. After creating a pneumoperitoneum, a 5 mm trocar is inserted in the subumbilical position. After the 5 mm trocar is in place, the patient is placed in a Trendelenburg position and a diagnostic laparoscopy is performed with a 5 mm 0° scoop. In case the Veress needle is placed in the left-upper quadrant of the abdomen, its position is checked and the needle is removed. An extra 5 mm trocar is inserted under direct vision at the site of the planned exit-site position of the PD catheter (paraumbilical left or right 2–3 cm below the umbilicus). This trocar is introduced through the anterior and posterior rectus sheaths but not through the peritoneum. Under direct vision, the trocar is directed in the preperitoneal space, 2–4 cm downwards and to the midline of the abdomen. If adhesions are present, the trocar is introduced into the peritoneal cavity. Adhesions close to the abdominal wall are ligated with electrocoagulation or with the ligature device (US Surgical). A double-cuffed curled-tip PD catheter is then introduced through the paraumbilical port, ensuring no torsion has occurred, and is placed with the curled tip into the cavum douglasi. If no adhesions are present, then the second trocar is not introduced into the peritoneal cavity but is left in the preperitoneal space. Now, the stiff stylet is used to introduce the catheter into the peritoneal cavity. If the placement is troublesome, an extra 5 mm trocar is used, which can be inserted under the direct vision to grasp the catheter for proper positioning. The distal cuff of the PD catheter should be outside the peritoneum (in the preperitoneal space or between both the rectus sheaths). The paraumbilical trocar is removed and the catheter is now directed to its exit-site position. A needle is used to create the subcutaneous tunnel to the left or the right abdomen. The proximal cuff should be in this tunnel. The catheter is tested and then the abdomen is desufflated, with the camera still in position to check on the location of the catheter. The trocar is removed and the rectus sheaths are closed carefully with resorbable sutures. The wounds are closed with a resorbable monofilament suture, intracutaneously [2].

2.2.4. Alternative techniques

The Moncrief-Popovich catheter and technique involves subcutaneous burial of the external segment of the peritoneal dialysis catheter to prevent colonisation of the catheter by skin

bacteria and to promote attachment of the cuff to the tissue prior to exteriorization. A reduction in the rate of peritonitis and colonisation of bacterial biofilms in the catheter segments between the two cuffs was noted with the Moncrief-Popovich catheter [15]; however, a controlled randomised study failed to confirm these results [16].

2.2.5. Extended dialysis catheters

Longer dialysis catheters have been developed to allow placement of the exit site in remote places such as the presternal area [17]. Such extended catheters may be useful in obese patients and in those with an abdominal stoma [18].

2.3. Complications

Complications after PD catheter placement are defined as those occurring early (<30 days) or late (>30 days), after surgery [2].

2.3.1. Early complications

2.3.1.1. Bowel perforation

The risk of bowel perforation is less than 1%, and it usually occurs during entry into the abdominal cavity or when the catheter and stylet are advanced into the abdomen. Surgical exploration is necessary with repair of the perforation and removal of the catheter [2].

2.3.1.2. Bleeding

Bleeding is rarely a significant problem after peritoneal dialysis catheter placement. When bleeding occurs, it is usually at the exit site.

2.3.1.3. Wound infection

Wound infection is uncommon and often can be treated with antibiotics when it is superficial. If the wound is deeper, then it may need to be drained.

Outflow failure may be due to

1. Clots or fibrin in the catheter: an attempt to irrigate the catheter forcefully with saline or urokinase can be tried or a stiff wire can be inserted into the catheter under fluoroscopy.
2. A kink in the subcutaneous tunnel: an incision is made directly over the kink and the catheter is repositioned.
3. Placement of the catheter in the omentum.
4. Occlusion from omentum or adhesions.
5. Malpositioning of the catheter into the upper abdomen.

Laparoscopy is useful for identification and treatment of obstruction due to omentum or adhesions as well as for repositioning and fixation in the case of a malpositioned catheter [19]. The position of the catheter may also be identified on plain film or under fluoroscopy with the injection of contrast into the catheter and may be repositioned with a stiff guide wire or forceps [20].

Leakage of the dialysate may be identified by the presence of drainage at the exit site or the appearance of a bulge underneath the entrance site. Leaks may occur due to

1. hernia at the entrance site
2. positioning of the proximal cuff on the rectus muscle
3. trauma

Withholding use of the peritoneal dialysis catheter for several weeks may solve the problem [21]. The use of a modified technique of peritoneal dialysis catheter insertion with fibrin glue has been shown to prevent pericatheter leakage [18, 22].

Peritonitis may occur early and manifests as abdominal pain associated with cloudy peritoneal fluid. The fluid should be cultured, and appropriate antibiotics should be administered [18].

2.3.2. Late complications

Late complications include exit-site infection, tunnel infection, cuff protrusion, outflow failure and dialysate leaks or hernias [2, 18].

2.3.2.1. Cuff extrusion or infection

Cuff extrusion or infection can occur when the exit site is placed directly beneath the belt line. Superficial cuffs placed close to the skin may extrude or become infected. In such situations, the catheter should be exchanged and a new exit site selected [2, 18].

2.3.2.2. Outflow failure

Outflow failure beyond 30 days may occur due to constipation and can be treated with laxatives.

2.3.2.3. Peritonitis

Peritonitis is often the result of contamination with skin bacteria, but it may also be due to gram-negative bacteria associated with diarrhoea or diverticulitis. Systemic or intraperitoneal antibiotics are administered, and the exchange volumes decrease. Usually, a peritoneal dialysis catheter-related peritonitis will resolve with proper antibiotic therapy. If the infection persists, catheter removal and use of haemodialysis for 4–6 weeks is sufficient for

resolution of the peritonitis [18, 22]. There is a strong association between exit-site infections and subsequent peritonitis, with an increased risk up to 60 days after initial diagnosis [18, 23].

3. Conclusion

The success of PD as a renal replacement therapy is dependent on the proper placement of the permanent PD catheters. A good knowledge of the implantation techniques and complications is very essential for a good outcome.

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Chapter 3

Assisted Peritoneal Dialysis

Mark Dominik Alscher

Additional information is available at the end of the chapter

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Abstract

The number of patients depending on dialysis therapies increases worldwide. The home-based dialysis modalities offer some advantages especially for elderly patients. In the case of peritoneal dialysis (PD), the life quality is superior compared to in-center hemodialysis (HD), and other advantages are existent. Due to the effect that a lot of elderly PD patients are frail, a concept covering the different modalities of PD must include the assistance at home or the living environment (assisted PD) for the bag exchanges that often cannot be performed reliably by elderly and frail patients by themselves. Nowadays, we have enough data to safely offer assisted peritoneal dialysis (aPD) in a cost-saving manner. Putting all these aspects together, aPD is a safe and in some countries widely used modality. The issue of reimbursement and education of home nurse staff must be solved. However, for elderly and frail patients, aPD offers a change to use the advantages of PD for these population, and on a local level, the provider should seek ways to establish aPD programs.

Keywords: dialysis, peritoneal dialysis, assisted, home care, assisted peritoneal dialysis

1. Introduction

The number of patients depending on dialysis therapies increases worldwide. The estimations now are 284 patients per million population (pmp) for 2010 [1, 2]. This increasing numbers are due to the effect of aging and the demographic shift with increasing incidences of diabetes and hypertension, besides a better access to dialysis in the Third World [3]. The home-based dialysis modalities offer some advantages especially for elderly patients. In the case of peritoneal dialysis (PD), the life quality is superior compared to in-center hemodialysis (HD), and other advantages have to be taken into account (**Tables 1** and **2**) [4]. However, a lot of elderly PD patients are frail [5, 6]. Therefore, a concept covering the different modalities of PD must include the assistance at home or the living environment (assisted PD) for the bag exchanges

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Advantages	Practice consequence
Home-based treatment	• Patients stay in their environment • Less medication of the disease • More independence • Fewer hospital visits
No need for vascular access	• Less surgical procedures required • No use of central venous catheter and reduced risk of related infection
Better hemodynamic tolerance	• Less hypotensive episodes with less associated ischemic complications (myocardial stunning, ischemic brain injury, gut hypoperfusion, and bacterial translocation) • No need for post-dialysis recovery time
No need for transportation	• Less time required for treatment
Better residual renal function preservation	• Flexibility of dialysis prescription, allowing incremental peritoneal dialysis
Possibility of providing assistance for non-self sufficient patients	• Increase in peritoneal dialysis eligibility • Less burden of disease

Table 1. Advantages of peritoneal dialysis in elderly patients [4].

Hemodialysis advantages	Peritoneal dialysis advantages
Others take the burden of therapy	Independence
Social contacts	Roles can be fulfilled
Regular medical consultations	Less need to show up at the dialysis center
Better monitoring	Higher mobility
	No need for access to major vessels

Table 2. Comparison of HD versus PD for elderly patients [7].

that often cannot be performed reliably by elderly and frail patients by themselves. The different dialysis modalities have additionally pros and cons. Therefore, some colleagues additionally are asking "Peritoneal or hemodialysis for the frail elderly patient, the choice of 2 evils?" In the cited article, the authors conclude that aPD could be first modality even in elderly and frail patients [7]: "Elderly patients often have complex medical conditions and wide-ranging priorities for their care. With multifaceted assessments of care, physicians should be able to give these individuals the ability to select and continue to make the best decisions for their care."

2. Assisted peritoneal dialysis (aPD)

The use of peritoneal dialysis (PD) offers advantages for the elderly patient [4]. Elderly dialysis-dependent patients on HD stay almost 50% of the remaining lifetime in hospitals. PD offers more time in the home environment of the patients [8]. One contributing point is that PD

is better tolerated (hemodynamic) and there is no need for a vascular access [9]. Additionally, the need for regularly transports into the center for HD is cost-saving and often means better life quality [10]. A better preservation of residual renal function by PD must not only be mentioned as a major factor to life quality but also reduced mortality at the beginning of PD [11–13]. To make all these advantages accessible for the elderly and frail patient with end-stage renal disease (ESRD), PD has to be part of the decision regarding the modality selection [14]. However, all these logical arguments lead not to a robust use of PD in elderly patients in different countries. With assisted PD (aPD), some obstacles of a self-treatment can be answered; however, the community of nephrologists has some skepticisms. On an international level, we found an extreme heterogeneous picture regarding the use of assisted peritoneal dialysis (aPD) [4]. Therefore, the facts have to be discussed further. In a summary about the evidences regarding elderly patients on dialysis, the authors found 14 studies with more than 100,000 PD and fare more HD patients [15]. Regarding mortality, in six studies there were no differences between HD and PD, and in five studies, HD was better and in three PD. Most of the experiences came from France. Other authors summarized the experiences with home-based assistance in case of chronic kidney diseases (CKD) [16]. They were able to collect 14 studies about aPD. In aPD studies with comparators, outcomes such as peritonitis rate and technique and patient survival constituted the main areas of focus. The probability of technique failure following an episode of peritonitis was similar between home-assisted aPD, self-care PD, and family aPD patients. They found that in general studies using information from France the technique failure/transfer to HD was lower among home-care (nurse) aPD patients when in self-care PD patients only. Together, aPD is a modality that can be offered evidence-based in a safe manner.

The French experiences, which further were summarized in a report from the French peritoneal dialysis registry (RDPLF), were very positive and gave a lot of support for discussions in other countries [17]. They observed 1613 patients older than 75 years who started PD between January 2000 and December 2005. The conclusion was that "PD is a suitable method for elderly patients. In order to increase the rate of PD utilization in elderly patients, the need for the funding of aPD has to be taken into account."

What we learn from the French data and have to keep in mind is the topic of reimbursement of the assistance. This is an issue in a lot of countries. Without reimbursement, the home care could not be delivered. In countries such as France, a correct reimbursement is established, and the aPD is used in wide areas.

From an economic point of view, we additionally have to discuss the modality of aPD: we can use data from Dutch and Canada in that discussion that put all aspects into the account: aPD in the long term is offering cost-savings (especially because you do not need transportation thrice per week to a center HD) [18, 19].

Besides the issue of reimbursement, the problem of teaching the home-care nurses in the technique of PD has to be solved. In different countries (Brazil, Canada, China, Denmark, France, Italy), the use of standardized teaching programs is often established [4]. The time for these programs is going from 2 up to 20 hours. From my experience, the nurse staff of home care loves to provide aPD.

What about the life quality of patients on aPD? An analysis from Canada provides us with data about this topic [20]. In a direct comparison between aPD and HD in elderly patients, they found a significant tendency to more depressions in aPD; however, the other scales were not significantly different. Another study looked directly to aPD versus self-PD [21]. It comes to no surprise that with aPD the role model of independence was reduced.

One of the most pressing issues with home-based dialysis is the rate of hospitalizations. In a study patients on HD (n = 198) were matched to aPD patients (n = 203) and then compared [22]. The median in both groups were 1 hospital visit spanning 4 days.

Following the arguments, a nephrologist should be eager to start such an aPD program. Most important at the beginning is the decision, who is taking the task of assistance. In some healthcare systems, a network of home-care services by nurses is available; then, they should be trained, and reimbursement must be guaranteed. In other systems, a nursing home-based program could be the only solution that is available and achievable. My personal recommendation is that the single specialist could contact the national kidney society for further support, since often only the national level can bundle the often-spare experiences in a national health system regarding this topic. What is extremely important is the backbone of an existing successful PD program at the local kidney center. Bringing all these aspects together, enthusiasm of the staff together with the doctor should be the fundament to start a program of aPD. The patients will gain the most.

3. Conclusion(s)

Putting all these aspects together, then aPD is a safe and in some countries widely used modality. The issue of reimbursement and education of home nurse staff must be solved. However, for elderly and frail patients, aPD offers a change to use the advantages of PD for these population, and on a local level, the provider should seek ways to establish aPD programs.

Conflict of interest

There is no “conflict of interest” declaration necessary.

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Chapter 4

Centre Effects in Peritoneal Dialysis

Samantha Ng, Yeoungjee Cho, Htay Htay and David W. Johnson

Additional information is available at the end of the chapter

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Abstract

Peritoneal dialysis (PD)-related complications and outcomes have been shown to be influenced by both patient- and centre-level factors. There is a significant variability in outcomes across different centres, which is not explained by patient factors alone. This chapter aims to evaluate those modifiable centre-level factors that have been shown to impact PD outcomes, focussing specifically on peritonitis and technique failure, and the evidence that addressing these centre effects may lead to appreciable improvements in PD patient outcomes. Peritonitis rates have been shown to be related to a centre's degree of automated PD (APD) use, extent of icodextrin use, performance of home visits prior to PD commencement, the presence of a specialised PD nurse and duration of PD training. Better peritonitis outcomes have been shown to be associated with larger centre size, greater share of PD patients among dialysis cohorts and treatment of peritonitis with comprehensive empiric antimicrobial therapy. PD technique failure has been shown to be related to centre size and degree of PD experience. Although there is little evidence currently available to demonstrate that prospectively modifying centre factors improves PD outcomes, an Australian continuous quality improvement initiative has been associated with progressively improved peritonitis and technique failure outcomes.

Keywords: ambulatory care facilities/organisation and administration, centre effects, centre size, health facility size, kidney failure, outcomes, peritoneal dialysis, peritonitis, predictors, registries, technique failure

1. Introduction

Peritoneal dialysis (PD) is an important dialysis modality that offers key benefits compared with haemodialysis, including better preservation of residual renal function, superior quality of life and patient satisfaction and possibly an early survival advantage in the first few years

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[1]. The major pitfalls associated with PD are peritonitis and relatively high technique failure rates [1]. Recent studies have demonstrated up to 10-fold variation in the frequencies of peritonitis and technique failure between different PD centres within the same country [2–5]. This between-centre variability is greater than between-country variability and appears to be predominantly driven by centre-related factors ('centre effects') rather than by patient-related factors ('casemix') [6–9]. This chapter aims to review the evidence for centre effects in PD patient outcomes (focusing on peritonitis and technique failure), the modifiable centre-related factors that may contribute to these centre effects and the evidence that addressing these centre effects may lead to appreciable improvements in PD patient outcomes.

2. Peritonitis rates

Rates of PD peritonitis vary considerably between centres and between countries. Reported rates vary from as low as 0.06 episodes per year in a Taiwanese programme to as high as 1.66 episodes per year in Israel [10]. In addition to variable peritonitis rates between countries, peritonitis rates vary significantly between centres within countries. For example, a 2011 analysis of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) demonstrated 10-fold variation in peritonitis rates across 72 Australian centres (6639 patients (2003–2008)), which was not correlated with centre size [3]. In another registry analysis of all 10 PD units in Scotland between 1999 and 2002, Kavanagh et al. [5] reported significant differences in peritonitis rates across centres that did not correlate with centre size or mix of modality (automated peritoneal dialysis [APD] versus continuous ambulatory peritoneal dialysis [CAPD]). Similarly, Davenport et al. [4] analysed data from 12 PD units treating over 800 PD patients in the Thames area over 2002–2003 and demonstrated approximately sevenfold variation in peritonitis rates with no significant correlation with unit size or PD modality. More recently, Nadeau-Fredette et al. [6] reported on peritonitis outcomes from 8711 patients from 51 PD centres in Australia (2003–2013). They described wide variability in peritonitis rates across centres, ranging from 0.17 (95% confidence interval [CI], 0.04–0.50) episodes per patient-year to 1.74 (95% CI, 1.40–2.13) episodes per patient-year. This centre variation was reduced by 16% after adjusting for patient characteristics and by 34% after adjusting for centre characteristics. In this study, peritonitis rates were evaluated using a mixed-effects negative binomial regression model with a random intercept for dialysis centres. Patient-level effects (e.g. age, gender, primary kidney disease, race and comorbidities) and centre-level effects (e.g. centre size, PD proportion and proportion of APD) were analysed as fixed effects. The final model included age, gender, race, diabetes, body mass index, cardiovascular disease, PD as the first renal replacement therapy (RRT) modality, centre size, PD proportion, APD exposure, icodextrin exposure, PET use, hospitalisation and antifungal prophylaxis at time of peritonitis [6]. Finally, Bechade et al. [8] examined rates of the first episode of peritonitis among 5017 incident PD patients across 127 PD centres in France over 4 years (2008–2012). They reported significant variability between centres (variance of random effect 0.11) with only a 9% reduction in variance when adjusted for patient-level characteristics and a significantly higher 35% reduction of variance of random effect when adjusting for PD centre characteristics. In this study, the investigators used bivariate analysis with a Cox model to explore the association

between each patient-level and centre-level covariate. These studies therefore suggest that centre effects rather than patient characteristics (casemix) are the major driver for centre variation in peritonitis rates. A number of centre characteristics have been linked to these observed centre effects [7].

2.1. Centre size

Centre size has been variably associated with peritonitis risk in the literature. Several studies have found no association between centre size and peritonitis rate [3, 6, 8, 11–13]. However, a study by the Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD) group [13] looking specifically at training methods and peritonitis risk noted a significant relationship between smaller centre size (<61 patients versus ≥61 patients) and shorter time to the first episode of peritonitis (subhazard ratio [SHR] 0.75; 95% CI, 0.62–0.90). In contrast, Nadeau-Fredette et al. [6] reported that smaller centre size, defined as less than 235 cumulative patient-years of PD exposure over the 10-year study period, was associated with *lower* peritonitis risk after adjustment for patient-level factors (incidence rate ratio [IRR] 0.78; 95% CI, 0.69–0.90, $p < 0.001$). They postulated that this seemingly paradoxical finding may have represented more favourable nurse:patient ratios or residual confounding related to PD patient selection. Overall, the association between centre size and centre peritonitis rates remains uncertain at this time.

2.2. PD experience

In addition to centre size, share of PD patients has been associated with lower peritonitis rate in a single study. Nadeau-Fredette et al. [6] reported that centres with a higher proportion of PD patients (>30%) were associated with lower peritonitis count (IRR 0.87; 95% CI, 0.77–0.99).

2.3. APD exposure

Centre APD exposure has been variably described as a risk factor for peritonitis [4–6]. Davenport et al. described no association between centre peritonitis rates and dialysis modality [4]. This was replicated in Kavanagh et al.'s study, which demonstrated variable results across centres with regard to peritonitis rates and dialysis modality but no clear association between APD and peritonitis rate. In contrast, in their Australian study, Nadeau-Fredette et al. [6] found that higher peritonitis rates were associated with centres with the lower use of APD compared with centres with average or higher than average APD exposure (<45% APD use compared to between 45 and 78% use or higher than 78% APD use). The lower use of APD at a centre level may have been associated with a higher peritonitis rate for several reasons. It has been hypothesised that APD offers fewer opportunities for contamination during connecting and disconnecting bags (with less overall connections taking place) or may represent unit management practices influenced by economic factors or flexibility with PD prescriptions.

2.4. PD management practices

PD centre practices, such as providing specialised PD nurses and home visits prior to PD commencement, have been shown to correlate with lower rates of peritonitis. In the French

study by Bechade et al. [8], 86 (68%) of 127 PD centres undertook home visits prior to PD commencement, and 24% offered specialised PD nurses. Centres undertaking home visits had a statistically significant 13% lower risk of peritonitis, while centres with specialised PD nurses had a 25% lower hazard of peritonitis. Furthermore, Chow et al. [14] observed an association between nurse experience among PD trainers and peritonitis rates, whereby the cohort of patients trained by the least experienced PD trainers (lowest tertile <3 years' time in practice) exhibited the lowest subsequent peritonitis rates. This somewhat surprising finding may have represented a failure to maintain contemporaneous learning for more experienced PD trainers. Alternatively, the finding may have been confounded by indication bias, whereby higher risk patients were more likely to be assigned to more experienced nurses for training. In keeping with the latter possibility, a single-centre, Chinese observational cohort study of 305 incident PD patients observed that increasing duration of nursing experience among PD trainers was associated with lower risks of Gram-positive peritonitis [15].

Training practices and their association with peritonitis rates have also been examined. Figueiredo et al. [13] undertook a prospective analysis of 2243 patients from 122 centres enrolled in the BRAZPD II cohort. The investigators reported significant differences both for cumulative amount of training received and timing of training with regard to catheter insertion and peritonitis rates. Establishing that the median amount of training across centres was 15 hours, they reported that centres providing >15 hours of training demonstrated significantly lower peritonitis rates compared to centres providing less than 15 hours of training (0.32 episodes per patient-year compared with 0.26 episodes per patient-year, respectively, $p = 0.01$). Peritonitis rates also significantly decreased with the amount of training provided per day, with centres providing <1 hour per day demonstrating a higher rate of peritonitis (0.35 episodes per patient-year) compared with centres providing >2 hours per day (0.27 episodes per patient-year, $p = 0.02$). Lastly, timing of training with regard to catheter insertion was also found to be associated with peritonitis rate. Patients trained within 10 days of catheter insertion had higher rates of peritonitis compared to those trained after 10 days or those trained before catheter insertion.

Another aspect of PD management is PD prescription practices, which have been examined by looking at icodextrin use. Nadeau-Fredette et al. [6] found that centres with a higher icodextrin exposure (>65% of patients) were associated with a higher peritonitis count (IRR 1.26; 95% CI, 1.10–1.44, $p = 0.001$). While icodextrin use has not been shown to represent a risk for peritonitis at the patient level [16], centre icodextrin exposure may be associated with higher peritonitis incidence by reflecting less flexible or personalised PD prescription practices (e.g. a 'one-size-fits-all' approach), or as Nadeau-Fredette et al. have hypothesised, it may reflect residual unmeasured differences in centre practices. For example, icodextrin use may have been used to extend the duration of PD treatment for a patient who might otherwise have been converted to haemodialysis [6].

2.5. Centre adherence to guidelines

Adherence to evidence-based best-practice guidelines has been postulated to correlate with better peritonitis-related outcomes but has been poorly studied outside of Australia.

Nadeau-Fredette et al. studied peritoneal equilibration test (PET) performance at PD commencement as a surrogate measure of centre compliance with best-practice guideline recommendations and postulated that higher PET use (and therefore better PET guideline compliance) would correlate with lower peritonitis rates. However, they found that the lower use of PET was associated with lower rates of peritonitis. While the reasons for this observation remain unclear, the authors speculated that centre adherence to guidelines might not be consistent across the board, such that some centres may have prioritised compliance with peritonitis prevention guidelines at the expense of complying with other guidelines (such as monitoring peritoneal solute transport rate). Other Australian investigators have reported higher peritonitis rates in centres that frequently deviated from the International Society for Peritoneal Dialysis (ISPD) guideline recommendations for peritonitis prevention, such as the use of antibiotic and antifungal prophylaxis [17]. The relationship between centre adherences to ISPD peritonitis prevention guidelines will be examined in detail by the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [18].

2.6. Evidence that modifying centre practices leads to better peritonitis rates

Continuous quality improvement programmes have been shown to be associated with improved peritonitis outcomes at national levels [19, 20]. Strong evidence for this can be seen in the Australian and New Zealand approach, as reported by Nataatmadja et al. [19], which was characterised by the creation of a national peritonitis registry to monitor peritonitis incidence and identify risk factors for peritonitis (ANZDATA) and a commitment to ongoing cycles of data analysis and feedback to PD centres with a national PD peritonitis key performance indicator (KPI) project. This was supported by additional state-level initiatives and teaching programmes. Following these initiatives, peritonitis rates decreased by approximately one third, and between-centre variations in peritonitis rates decreased by 50%. These findings were supported by those of a PD CQI programme in Colombia [20] in which introducing six key programme elements (improved PD nurse:patient ratios, the use of an exit-site care protocol, standardisation of PD guidelines and protocols, nurse certification and continuing education, home visits and systematic follow-up and actioning clinic results) resulted in a reduction in peritonitis rates from 0.57 episodes per patient-year in 2006 to 0.20 episodes per patient-year in 2014. Similar improvements in PD peritonitis rates at the individual centre level have been reported by Yu et al. in China [21] and Qamar et al. in the United States [22].

3. Peritonitis outcomes

Centre-level characteristics have been shown to be associated with key peritonitis outcomes, such as peritonitis cure, PD catheter removal, transfer to haemodialysis, relapse or recurrence, hospitalisation and mortality. In their national registry analysis, Htay et al. [23] studied all incident PD patients in Australia who developed peritonitis between 2004 and 2014. They found that peritonitis cure rates for individual centres varied between 38 and 86%. The investigators explored the association between patient- and centre-related characteristics and peritonitis

outcomes by conducting multilevel mixed-effects logistic regression models, whereby patient- and centre-level characteristics were applied as fixed effects and patient and centres as random effects. This allowed for nesting of outcomes within patients and patients within each centre to allow analysis of clustered data. Covariates with *P*-values less than 0.2 on univariate analyses were included in the multivariate models. In addition, the era of PD commencement was also fitted as a fixed-effects covariate in the final model to adjust for era effect. Several patient-related covariates (e.g. gender, primary renal disease, late nephrology referral, initial modality of PD) and centre characteristic-related covariates (e.g. transplanting centre, exposure to APD, icodextrin, PET practice) were excluded during the model building process. The final model included era of PD commencement (2004–2009 versus 2010–2014), age, race, BMI, smoking status, diabetes mellitus, cardiovascular disease, chronic lung disease, causative microorganisms for peritonitis, PD as initial modality of RRT, socio-economic position (reported as Index of Relative Socio-economic Advantage and Disadvantage) and centre-level characteristics, including centre size, proportion of PD patients in a centre and the proportion of patients receiving complete empiric antibiotics covering Gram-positive and Gram-negative organism during peritonitis. The centre characteristics significantly associated with achievement of cure were higher share of PD patients (>29% PD patients, adjusted odds ratio [OR] 1.21; 95% CI, 1.04–1.40) and higher proportion of peritonitis episodes receiving complete antibiotic cover (as defined by receiving antimicrobial cover for both Gram-positive and Gram-negative organisms at presentation) (OR 1.22; 95% CI, 1.06–1.42). Similarly, centres with a larger share of PD patients were associated with lower odds of peritonitis-related catheter removal (>29% PD patients; OR 0.78; 95% CI, 0.62–0.97) and lower odds of HD transfer (>29% PD patients; OR 0.78; 95% CI, 0.62–0.97). Peritonitis relapse or recurrence was less common in centres with higher or lower PD patient share as compared to average PD patient share (>29% PD patients; OR 0.68; 95% CI, 0.48–0.98 and <18% PD patients; OR 0.68; 95% CI, 0.51–0.90). Finally, the authors reported significant improvements in peritonitis outcomes over time. Compared with the earlier study period, the contemporary period (2010–2014) was associated with significantly higher odds of achieving peritonitis cure (OR 1.17; 95% CI, 1.04–1.30) and lower odds of relapsed or recurrent peritonitis (OR 0.66; 95% CI, 0.55–0.80), likely reflecting the implementation of national quality improvement programmes and evidence-based best-practice guidelines.

4. Technique failure

Several studies have identified significant variability in technique failure rates between different PD centres [9, 24–27]. Technique failure was variably defined as transfer to haemodialysis (HD) for ≥30 days or death (including death within 30 days of transfer to HD) [9], death-censored transfer to HD for ≥60 days within the first 6 months of PD [25] or death-censored transfer to HD for ≥90 days [24]. One of the studies [26] did not define technique failure in their study. All studies were based on registry data, and patients who met systematic registry definitions of technique failure were included in the analyses.

Huisman [24] et al. examined data from RENINE, the Netherlands national dialysis registry, and observed that average annual technique failure rates varied between 10 and 59% across

the 43 centres reporting to the registry. Schaubel et al. [26] examined data from 86 renal centres contributing to the Canadian Organ Replacement Register and found significant differences in technique failure and mortality across different centres when stratified for size and casemix, suggesting that centre-level factors were strong predictors of outcomes in PD patients. The key role played by centre effects in technique failure was further reinforced by the findings of Guillouet et al. [25], who analysed outcomes for 5406 incident PD patients based on data from the French Language Peritoneal Dialysis Registry using a multilevel mixed-effects logistic regression model with centre as a random effect and all patient characteristics (level 1) and all centre characteristics (level 2) as fixed effects [25]. The patient-level characteristics examined in the study were gender, comorbidities (classified by Charlson comorbidity scores), diabetes mellitus, cause of renal failure, initial PD modality, assisted PD (family assistance, nurse assistance), initial modality of renal replacement therapy (RRT) and suboptimal PD initiation (defined by a time spent on HD before PD of less than 1 month). The centre-level characteristics examined in the study included the presence of a full-time nurse (nurses dedicated only to PD) versus a part-time nurse, number of nephrologists specialised in PD, number and types of home visits by PD nurses, centre size (defined as <10 versus ≥10 incident PD patients in centre per year) and types of centres (categorised by academic centre, community centre, non-profit centre and private centre). Looking specifically at early technique failure (defined as transfer to HD for >2 months within the first 6 months of PD, regardless of PD duration with censored renal transplantation and death during the first 6 months on PD), they reported a 52% difference in variation of outcomes between PD centres after adjustment for patient characteristics and centre experience.

This variability above and beyond patient-level characteristics was similarly observed by Htay et al. [9], who used Cox proportional regression with shared frailty models to account for clustering of patients within the centre and reported a sevenfold variation in technique failure rates across centres in their Australian registry-based study. This variation was reduced by 28% after accounting for patient-related characteristics and by a further 53% after accounting for centre-related characteristics. Technique failure in the study was defined as transfer to haemodialysis (HD) for ≥30 days or death (including death within 30 days of transferring to HD). The detailed statistical methods are available elsewhere [9]. All patient-level characteristics with p-values <0.2 in univariable Cox-shared frailty model were included as fixed effects in the first model. The patient-level characteristics in the first model and all centre-level characteristics with p-values <0.2 in the univariable Cox-shared frailty model were included in the final model. The era of PD commencement was also fitted as a fixed-effects covariate in the final model to adjust for era effect. The likelihood ratio test was used to compare the first and final models. The final model included era of PD commencement (2004–2009 versus 2010–2014), age, gender, race, BMI, smoking status, diabetes mellitus, cardiovascular disease, chronic lung disease, primary renal disease, late referral, initial modality of RRT, initial PD modality, socio-economic position (reported as Index of Relative Socio-economic Advantage and Disadvantage) and centre-level characteristics, including centre size, proportion of PD patients in a centre, APD exposure in a centre, proportion of patients on icodextrin in a centre, proportion of patients achieving baseline target phosphate level in a centre and proportion of patients on antifungal prophylaxis during peritonitis.

These studies therefore suggest that there is a large and unacceptable variation in PD technique failure rates between centres, which appears to be largely driven by centre characteristics. However, the precise centre characteristics underpinning these centre effects have received only limited study to date.

4.1. Centre size

Of all the centre characteristics that have been linked with PD technique failure, the relationship between smaller centre size and higher rates of technique failure has been the most robustly described [9, 12, 24–27]. Afolalu et al. [27] examined technique failure over the first 2 years of PD treatment in 5003 PD patients from 105 PD units in the United States. Defining smaller centre size as units with ≤25 patients and larger centre size as units with >25 patients, they reported significantly higher rates of technique failure in the smaller centre size group for both the first and second years of treatment (OR 1.36, $p < 0.005$ and OR 1.35, $p = 0.03$, respectively). These findings have been replicated in other large registry-based studies, including from the Netherlands [24], Canada [26] and Australia [9]. This 'volume-outcome' [11] relationship has also been confirmed in a systematic review by Pieper et al. [11], despite heterogeneity in definitions of centre size (ranging from greater than or less than 20 patients to greater than or less than 400 patients).

One of the problems with evaluating the relationship between technique failure and centre size based on the number of prevalent PD patients is that centres with higher technique failure rates will experience falls in the number of prevalent PD patients (i.e. the outcome reciprocally affects the predictor). This issue has been mitigated in some studies by examining the number of incident PD patients treated by a PD centre. For example, Guillouet [25] reported that centres treating more than 10 new patients per year had a lower risk of early PD failure (OR 0.71; 95% CI, 0.58–0.88). Similarly, in a study of Australian registry data between 2004 and 2014, Htay et al. reported higher rates of technique failure in centres with <16 new patients per year (HR 1.10; 95% CI, 1.00–1.21) [9]. Consequently, regardless of how centre size is defined, there appears to be a clear inverse association between PD centre size and technique failure rate.

4.2. PD experience

It has been hypothesised that total unit experience with PD provision and management would positively impact technique failure rates. Assessing this factor has been approached variably in the literature. Schaubel et al. [26] examined data from the Canadian Organ Replacement Register on 17,900 patients across 86 centres and defined 'PD experience' as the cumulative number of PD patients treated. After dividing centres into tranches of 100 with <99 patients treated with PD as the 'least experienced' and >500 as the 'most experienced', they observed a reduction in technique failure with increasing cumulative PD patient experience, which became statistically significant when the cumulative number of PD patients treated exceeded 200 (200–299 adjusted rate ratio [aRR] 0.89; 95% CI 0.80–0.99; 300–399 aRR 0.81, 95% CI 0.71–0.91; 400–499 aRR 0.82, 95% CI 0.72–0.94; ≥500 aRR 0.83, 95% CI 0.73–0.95; ≤99 reference).

The percentage of patients treated with PD within dialysis cohorts has also been studied to reflect a centre's 'degree of specialisation' towards PD. Schaubel et al. [26] reported a significant correlation between a lower percentage of patients initiating dialysis with PD at a centre and higher technique failure rates, which became statistically significant when the percentage of patients initiating dialysis on PD at a centre fell below 60%. Huisman et al. [24] also observed an inverse correlation between the fraction of dialysis patients on PD and annual technique failure rate ($r = -0.410$, $p = 0.006$). Finally, Htay et al. found that both technique failure and death-censored technique failure were significantly less likely when the proportion of dialysis patients treated with PD exceeded 29% [9].

4.3. Centre PD practices

Few studies have examined other centre characteristics that may affect PD technique survival. Htay et al. [9] hypothesised that PD centre practices, including prescription practices (such as APD exposure and icodextrin use) and management practices (such as proportion of patients who had had a PET within 6 months of PD commencement or target serum phosphate achievement), would correlate with technique failure outcomes. However, they found that none of these more specific centre-related factors was associated with death-censored technique failure.

4.4. Transplanting status/academic status

Schaubel [26] classified centres into academic or nonacademic centres based on affiliations with a medical school and did not find any association with technique failure rates. Similarly, Htay et al. [9] found no relationship between technique failure outcomes and whether or not the centre was a superspecialised service providing kidney transplantation.

4.5. Evidence that modifying centre factors leads to better technique failure outcomes

Although centre-based factors have demonstrable effects on technique failure outcomes for PD patients, there is currently little evidence prospectively examining the hypothesis that modifying centre factors improves technique failure outcomes in PD. An epidemiological study from France by Evans et al. [28] sought to hypothetically model interventions to improve technique failure outcomes for patients by constructing a probability-based model 'moving' PD patients from smaller centres to larger ones and by modelling outcomes based on a hypothetical 'PD first' initiative. Although entirely theoretical, the study found that lower technique failure rates could be expected by undertaking such initiatives. The quality improvement initiative in Australia described previously has also been associated with progressive improvements in national PD technique failure rates [19].

5. Conclusions

In conclusion, studies have demonstrated significant variability in both PD peritonitis rates and outcomes and in technique failure outcomes across different PD centres. This variation has

been shown to be driven in a significant part by PD centre-level characteristics, such as unit size, degree of PD specialisation and PD prescription, and management factors such as APD exposure, use of icodextrin and centre adherence to evidence-based best-practice guidelines. Focussing further study on characterising these centre-level factors thus represents an important opportunity to improve patient outcomes. Centre-level factors may be a more practical and efficient target for future intervention than focussing on patient-level factors.

6. Future directions

Studies on centre-level effects on PD outcomes have been limited by the challenge of collecting data at the multicentre level. Further work is needed to examine in more granular detail those centre practices that impact PD outcomes and to inform and prospectively evaluate quality improvement measures. It is hoped that further insights will be gained from the forthcoming Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [18], which is an international research initiative to better understand and improve PD practice and outcomes for PD patients. It was launched in October 2013, and active data collection is in process involving over 4000 patients across 180 PD units from Canada, the United States, Japan, Australia, New Zealand, the United Kingdom and Thailand.

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Chapter 5

The Bone and Mineral Disorder in Patients Undergoing Chronic Peritoneal Dialysis

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Additional information is available at the end of the chapter

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Abstract

Disorders of mineral metabolism and bone disease are common complications in CKD patients. They are very complex and involve a number of feedback loops between the kidney, bone, intestine, and the vasculature associated with an increased morbidity and mortality and decreased quality of life of the patients. The work group of the kidney disease: Improving Global Outcomes (KDIGO) recommended in 2006 the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe a systemic disorder that incorporates these abnormalities. Compared to hemodialysis (HD), patients undergoing peritoneal dialysis (PD) appear to have an increased prevalence of low turnover bone disease defined as adynamic bone disease (ABD). The most important risk factors for ABD are age, oversuppression of parathyroid hormone (PTH) with vitamin D, diabetes, circulating antagonist PTH fragments, and frequent presence of a positive calcium balance, which may result in an oversuppression of PTH. PTH levels and bone phosphatase alkaline (bALP) should be assessed among such patients as the earliest markers of abnormal mineral and bone metabolism. Treatments considered are interventions to treat hyperphosphatemia, hyperparathyroidism, and bone disease. The optimal management of chronic kidney disease-mineral and bone disorder (CKD-MBD) includes the prevention of vascular calcifications.

Keywords: peritoneal dialysis, phosphate, calcium, adynamic bone disease, hyperparathyroidism

1. Introduction

Chronic kidney disease (CKD) is a global public health problem affecting 5–10% of the world population [1]. Disorders of bone and mineral metabolism and vascular calcification have been

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identified as major risk factors for cardiovascular morbidity and mortality in patients with CKD. In the course of CKD appears a reduction in the ability of the kidney to excrete an adequate load of phosphate which leads to hyperphosphatemia. At the same stages of CKD in which phosphorus retention appears to occur, we are faced with calcium retention too. The main hormones and factors that contribute to the kidney regulation of phosphorus and calcium include parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), klotho and 1,25-dihydroxyvitamin D (1,25(OH)2D). It is now accepted that the increase in FGF-23 is an early event in the pathogenesis of mineral disorders in CKD. FGF-23 levels increase early in CKD, and may reflect an increased phosphorus load. This adaptive change favors the reduction of kidney 1-alpha-hydroxylase, which in turn results in lower levels of the active form of vitamin D 1,25(OH)2D3, decreasing intestinal calcium absorption and allowing a decrease in serum calcium. These changes allow increased PTH synthesis and its release. High level of PTH increases bone turnover and bone resorption, stimulates 1-alpha-hydroxylase, and increases phosphorus removal through reducing its kidney tubular resorption. Although FGF-23 and PTH having synergic effects regarding phosphorus removal, they have opposite effects on 1,25(OH)2D3 synthesis by inhibiting or stimulating 1-alpha-hydroxylase, respectively. During late Stage 4 CKD and into end-stage renal disease (ESRD), all these mechanisms become insufficient and most patients show hyperphosphatemia, high PTH, marked elevations of FGF-23, and reductions of klotho and 1,25(OH)2D3 [2–4]. All these changes together are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling) [5]. High serum phosphorus was considered the most important uremia-related, non-traditional cardiovascular risk factor so controlling hyperphosphatemia was considered one of the most important goals in managing bone disorders in CKD patients [1].

Effective dietary phosphate restriction has resulted difficult in clinical practice so the use of phosphate binders has become the mainstay of efforts to decrease phosphate absorption from the intestine. The generalized usage in the past of aluminum-containing phosphate binders and calcium-containing phosphate binders was reported to be associated with increased incidence of adynamic bone disease (ABD) [6]. The mineral and hormonal changes in CKD patients go beyond bone alterations and are responsible for systemic consequences such as vascular calcification [1]. These changes have a major impact on morbidity and mortality [7] and consequently their control is of great importance in CKD patients. This chapter is a review that briefly discusses etiology, pathophysiology diagnosis of mineral bone disorders in chronic kidney disease patients on treatment with peritoneal dialysis and therapeutic options.

2. Overview on bone disease and mineral metabolism disorders in peritoneal dialysis patients

2.1. Etiology and pathogenesis

Disorders of mineral metabolism and bone disease are common complications in CKD patients. They are very complex and involve a number of feedback loops between the kidney, bone, intestine, and the vasculature. These are associated with numerous adverse clinical outcomes, in particular cardiovascular disease and increased fracture risk [8] which contributes in an increased morbidity and mortality and decreased quality of life of the patients [3].

The work group of the kidney disease: Improving Global Outcomes (KDIGO) recommended in 2006 the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe a systemic disorder that incorporates these abnormalities [9]. These systemic disturbances may manifest themselves by the presence of any one or a combination of the following three conditions: (1) laboratory abnormalities of calcium, inorganic phosphorus, PTH or vitamin D; (2) bone abnormalities in turnover, mineralization, volume, linear growth or strength, and (3) calcification of the vasculature or other soft tissues [8].

The work group recommended that the traditional term "renal osteodystrophy" be exclusively used to define alterations in bone morphology associated with CKD and stated that definitive diagnosis of renal osteodystrophy can only be made by bone biopsy [1].

It is well known that the traditional types of renal osteodystrophy have been defined on the basis of turnover and mineralization, with substantial differences in pathophysiology and treatment.

- Bone turnover and bone volume may both be classified as high, normal or low.
- Bone mineralization may be categorized as normal or abnormal.

In this way, it was suggested that bone biopsies in patients with CKD should be characterized by determining bone turnover (T), mineralization (M), and volume (V) (the TMV system) [9].

Six types of bone disorder are distinguished in the CKD-MBD complex [9]: hyperparathyroid bone disease (high turnover, normal mineralization, and any bone volume); mixed bone disease (high turnover with mineralization defect and normal bone volume); osteomalacia (low turnover with abnormal mineralization and low-to-medium bone volume); ABD (low turnover with normal mineralization and low or normal bone volume); and two distinct disorders due to specific causative agents, namely, amyloid bone disease and aluminum bone disease [10].

While the majority of studies focusing on CKD-MBD in dialysis patients involved hemodialysis (HD) patients, relatively few studies involving peritoneal dialysis (PD) patients have been published [1, 10]. It has been argued that features of CKD-MBD differ between patients undergoing PD and HD, secondary hyperparathyroidism remains the most common pattern in HD patients, and adynamic bone disease was more frequent in patients on PD [1]. This is based on a systematic review which analyzed studies carried out between 1983 and 2006 (**Table 1**). These findings strengthened the worldwide belief that PD is an important risk factor for ABD development.

ABD was first described in association with aluminum overload, being in the past the major cause of this bone lesion [11]. Aluminum deposition along the calcification fronts prevents the mineralization process and also inhibits the deposition of osteoid by directly damaging the osteoblasts [12].

Although there is a large difference between current and past clinical practice and patient characteristics regarding PD treatment (common use of aluminum- and calcium-based phosphate (P) binders, or PD modality mainly for elderly patients), in recent studies, bone histomorphometry persists to reveal lower turn-over parameters and worst mineralization in peritoneal dialysis patients when compared to hemodialysis ones [13, 14].

	PD	HD
Adynamic bone disease	50%	19%
Mild disease	20%	3%
Osteitis fibrosa	18%	34%
Mixed bone disease	5%	32%
Osteomalacia	5%	10%
Normal bone histology	2%	2%

Table 1. Prevalence of types of bone disease as determined by bone biopsy in patients with CKD-MBD.

Over time, it became apparent that adynamic bone or low bone formation exists without aluminum overload and became associated with abnormal calcium balance, the low levels of 1.25 dihydroxyvitamin D, metabolic acidosis, in addition to low levels of estrogen and progesterone, and systemic inflammation. It is referred to be linked with calcific arteriolopathy and cardiovascular disease (CVD) [15, 16].

There are a lot of specific factors which are reported to contribute in the pathogenesis of ABD in peritoneal dialysis:

- Accumulation of advanced glycation end products (AGEs) proteins reported in diabetes was also observed in PD patients. This happens during heat sterilization of PD conventional fluids, where glucose is degraded into products that include reactive carbonyl compounds [17]. Serum from uremic patients was also shown to contain high levels of these compounds derived not only from carbohydrates but also from lipids. The generation of high quantities of AGEs and advanced lipid end products modify bone matrix and participate in the processes which lead to the development of ABD [18]. In addition of elevated AGEs, PD patients have impaired glucose tolerance and high glucose levels during explosion to high glucose concentrations. High glucose levels were reported to inhibit bone mineralization in vitro by preventing calcium uptake by bone cells [19], a finding that could further support the altered bone structure in diabetic patients.
- High levels of calcium and magnesium found in dialysate. High magnesium concentrations may inhibit parathyroid hormone secretion just as high calcium concentrations do [20], being involved in the pathogenesis of adynamic bone in PD patients [21].
- Sclerostin is another factor with impact on ABD in PD patients. Sclerostin is a glycoprotein (22 kDa) product of the SOST gene in osteocytes, which leads to a negative regulation of bone formation by inhibiting differentiation and proliferation of osteoblasts. Recent investigations, demonstrated that increased plasma levels of sclerostin, were found to be associated with reduced bone turnover and osteoblast proportion in dialysis patients [14, 22].
- In PD patients, we are faced with high prevalence of hypoalbuminemia which came as a result of loss through the peritoneal membrane or malnutrition. It is reported that low level of albumin contributes to the development of ABD by reducing the plasma level of PTH. Serum intact PTH has been shown to positively correlate with serum albumin in PD patients [23].

The relationship between low PTH level, ABD, increased fracture risk [24], and vascular calcifications may at least partially explain the association of ABD with increased mortality rates. To achieve optimal bone and cardiovascular health, attention should be focused not only on classic control of secondary hyperparathyroidism but also on prevention of ABD, especially in the steadily growing proportions of diabetic, white, and elderly patients in PD [25].

2.2. Phosphate retention and hyperphosphatemia

It is generally accepted that the accumulation of phosphorus appears to begin in CKD Stage 3b and contributes to secondary hyperparathyroidism [3]. Persistent stimulation of the parathyroid glands by elevated extracellular phosphorus concentrations, especially when is accompanied by decreased extracellular ionized calcium concentrations, and markedly reduced serum calcitriol levels leads to increased parathyroid hormone (PTH) production [26]. This promotes diffuse polyclonal hyperplasia followed by monoclonal nodular hyperplasia, decreases the levels of calcium-sensing receptor and vitamin D receptor, lowering the activity of 1-alpha-hydroxylase and consequently decreases serum 1,25(OH)2D3 levels [27].

In severe hyperparathyroidism, hyperphosphatemia may be worsening via phosphorus efflux from the skeleton compromising its phosphorus reserve capacity. On the other side, in low bone turnover, the size of the exchangeable calcium and phosphorus pool is reduced and also is drastically reduced the buffer capacity of the skeleton for the excess of phosphorus. In this way, hyperphosphatemia links vascular calcification with low bone turnover.

Phosphate excess also has reported to be linked with endothelial dysfunction [28] and elevated FGF23, which contributes to left ventricular hypertrophy [29], being so an independent risk factor for mortality in ESRD [2].

Phosphate enters the body by intestinal absorption and is excreted through stools and dialysis fluids (plus urine output in patients with residual renal function). In dialysis patients, elimination of the inorganic phosphate by dialysis is a cornerstone of the management of hyperphosphatemia. The elimination characteristics of phosphate in HD and PD are unlike the urea and other low molecular weight toxins much more similar to those of typical middle molecules although the molecule is only 96D. This is explained with its negative charge, the aqueous cover that increases its effective molecular weight, and the slow intra/extracellular solute transfer rate [30].

In the case of daily dialysis or long nocturnal dialysis, P mass removal is usually large enough to reduce the need of dietary restrictions and the use of P binders. It does not happen in the case of well-nourished patients on standard three-times-a-week dialysis schedule, where to achieve a good P balance is needed an optimal dialysis removal, careful use of phosphate binders, and dietary P control [31].

Some studies suggest that continuous PD may be better in controlling hyperphosphatemia than intermittent hemodialysis [32–35]. This observation supports thesis that PD provides better phosphorus clearance through better preservation of renal failure and its continuous nature.

At the start of PD therapy, residual renal function (RRF) may contribute up to 65% of total phosphate clearance [30, 35]. Urinary phosphate excretion is found to highly correlate with

residual renal function and also a strong correlation between RRF and serum phosphate concentration on PD has been reported [32, 35]. It is well known that RRF declines with time on PD and the effect of this decline on phosphate homeostasis has been described in a few observational studies [34, 36, 37]. Phosphate removal is shown to correlate strongly with residual renal function, but it is dissociated from peritoneal Kt/V urea, creatinine clearance, and net ultrafiltration. Peritoneal creatinine transporter status and creatinine clearance cannot be used as surrogate markers of peritoneal phosphate transport and clearance. Prescription of high volume of dialysate is one of the strategies recommended to increase P removal in anuric patients [30]. Hyperphosphatemia is more frequent in patients with low transporter status, so they may achieve higher peritoneal P clearance under continuous ambulatory peritoneal dialysis (CAPD) regimens. In automated peritoneal dialysis (APD), hyperphosphatemia has been significantly associated with a lower number of automated peritoneal dialysis (APD) cycles and a shorter duration of nocturnal treatment, with insufficient dwell time. Here, recommended strategies to improve P management are increasing dwell times or transfer to CAPD [37]. Recently, Van Biesen et al., confirmed that for slow transporters, longer dwells resulted in higher peritoneal phosphate clearances, whereas for high transporters, shorter dwells were more optimal [38].

2.3. Fibroblast growth factor 23

FGF23 is a circulating peptide that plays a key role in the control of serum phosphate concentrations [4, 39]. It is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, PTH, and calcium [40, 41]. In CKD patients, we are faced with high level of FGF23 due to its decreased clearance too [4]. FGF23's primary function is to maintain normal serum phosphate concentration by reducing renal phosphate reabsorption and indirectly by decreased calcitriol production [42]. FGF23 inhibits the proximal tubular expression of 1-alpha-hydroxylase enzyme, leading to decreased calcitriol synthesis [43]. The net effect of both hormonal actions is to lower serum phosphate concentration. Increased FGF23 is considered as one of the earliest detectable biomarkers of CKD-MBD [44]. Is important to underline that treatments used to control CKD-MBD, such as vitamin D analogs and calcium-based phosphate binders, stimulate FGF23 production.

FGF23 also suppresses PTH secretion by the parathyroid gland [45]. Klotho expression declines progressively with decreasing GFR. Moreover, the decrease in klotho expression on hyperplastic parathyroid glands may contribute to the resistance and impaired parathyroid suppression by FGF23 [46].

In the PD patient population, data on FGF-23 are scarce. In a study by Isakova et al., the authors reported that longer dialysis vintage ($R = 0.31$), lesser RRF ($R = -0.37$), and lower renal phosphate clearance ($R = -0.38$) were associated with higher levels of serum FGF-23 [47]. Golembiewska et al. in her study highlights the strong positive association between serum phosphorus and FGF-23 in patients at the start of PD therapy independently from RRF [48]. It is suggested that FGF23 is a more stable marker of phosphate metabolism than PTH or phosphate itself, which could help explain its stronger association with outcomes and support the further development of FGF23 testing for clinical practice [47].

FGF23 levels are associated with increased risk of cardiovascular disease and mortality in patients with CKD [47]. Clinical and experimental studies have shown that FGF23 has a direct

pathogenic effect causing left ventricular hypertrophy [29]. However, FGF23 does not seem to promote cardiovascular calcification [49].

2.4. Calcitriol

Peritoneal dialysis (PD) patients have a high risk of developing vitamin D deficiency as 25(OH) vitamin D and the precursor of active vitamin D is lost during dialysis, apart from low exposure to sunlight and reduced dermal synthesis.

Plasma calcitriol concentrations generally fall below normal when the GFR is <60 mL/min/1.73 m^2 [8]. This initially happens due to the increase in FGF23 concentration rather than the loss of functioning renal mass [50]. However, further with the advanced CKD, hyperphosphatemia in addition to increased FGF23 levels contribute to the decline of calcitriol synthesis.

FGF23 decreases the synthesis of calcitriol by suppressing the activity of 1-alpha-hydroxylase, which converts 25-hydroxyvitamin D into calcitriol, and by stimulating the 24-hydroxylase enzyme, which converts calcitriol (1,25-dihydroxyvitamin D3) into inactive metabolites in the proximal tubule [43, 51]. Phosphate retention (or perhaps increased phosphate concentrations in the proximal tubule) can directly suppress the renal synthesis of calcitriol by inhibiting 1-alpha-hydroxylase activity [52]. Increased dietary phosphate load and increased calcitriol stimulate the secretion of FGF23 predominantly by bone osteocytes.

Low calcitriol concentrations increase PTH secretion by indirect and direct mechanisms:

- Indirect effects on PTH are achieved through decreased intestinal absorption of calcium and calcium release from bone, both of which promote the development of hypocalcemia, and hypocalcemia stimulates PTH secretion.
- Calcitriol normally acts on the Vitamin D Receptor (VDR) in the parathyroid gland to suppress PTH transcription but not PTH secretion. A decrease in calcitriol concentrations lowers the number of VDRs in the parathyroid cells. This is reported that can be corrected by taking supplementation with calcitriol [53]. The lack of calcitriol and the decreased number of receptors may promote both parathyroid cell hyperplasia and nodule formation. At a later stage of CKD, we have also the contribution of retained uremic toxins, by decreasing both receptor synthesis and the ability of the active hormone-receptor complex to bind to vitamin D response elements in the nucleus [54].

2.5. Skeletal resistance to PTH

In CKD, the skeletal resistance to the calcemic action of parathyroid hormone (PTH) is reported to contribute to the pathology of secondary hyperparathyroidism [55] due to down-regulation of PTH receptors induced by the high circulating PTH concentrations; calcitriol deficiency and hyperphosphatemia [3, 56].

2.6. Disorders of calcium balance

Studies have suggested that disorders of calcium balance due to CKD-MBD may play a role in the high cardiovascular mortality in patients with CKD.

A positive calcium balance may arise, because the intestinal absorption of calcium overcomes the capacity of the diseased kidney for its excretion. The absorbed calcium enters in the extracellular space and is distributed in three compartments: blood, soft tissue, and bone. Bone contains 99% of total calcium being the major compartment of body calcium. It includes mineralized bone sites suggested to be partly mediated by PTH and a rapidly exchangeable calcium pool. The regulation of this exchangeable calcium pool might be altered in CKD.

The assessment of calcium balance in dialysis patients (including PD patients) becomes extremely complex. It has to take into account not only dietary calcium intake, but also calcium supplement dose, intake of vitamin D analogs (which increase intestinal calcium absorption), calcium uptake by soft tissue, stool calcium output, urinary calcium excretion, continuous calcium flux from the rapidly exchangeable calcium bone pool, and net bone remodeling or turnover, also influx from PD fluid across the peritoneum membrane if a high-calcium dialysate is used as a result of the concentration gradient or efflux of it when is used lower dialysate calcium [57].

Both hypocalcemia and hypercalcemia are associated with increased mortality in patients with CKD [7, 58].

Hypocalcemia is common among CKD patients and may be associated with increased PTH secretion and abnormal bone remodeling. Ca is a major regulator of PTH secretion. Minute changes in the serum ionized Ca are sensed by a specific Ca membrane receptor (CaSR), which is highly expressed on the surface of the chief cells of the parathyroid glands [59]. Changes in PTH secretion in response to serum Ca are tightly regulated by the CaSR. The fall in serum Ca concentration in CKD, as sensed by the CaSR, is a potent stimulus to the release of PTH. When Ca level goes persistently low, it appears to directly increase PTH mRNA concentrations via posttranscriptional actions and stimulates the proliferation of parathyroid cells over days or weeks [60].

A positive calcium balance, hypercalcemia, inhibits the secretion of PTH and stimulates the development of adynamic bone disease in patients undergoing PD. The risk of protein energy wasting (PEW), often referred as malnutrition, is higher especially in the elderly PD patients. This is associated with reduced bone mass [61] and increase fracture risk in this population [1, 62]. In addition, hypercalcemia has been implicated in the pathogenesis of extraskeletal calcification and is evaluated as an important factor in progression of calcification.

2.7. Vascular calcifications

In the last decades, although the number of peritoneal dialysis (PD) patients is increased, most of the studies related to vascular calcification development are mainly focused on HD population. The prevalence of cardiac valvular calcification is reported to be high in both modalities, ranges from 32–47% in PD patients [1, 63] to 19–84% in hemodialysis patients [64, 65] and greatly contribute on high cardiovascular mortality in this population [2, 66–68].

Recent studies suggest that vascular calcification is a process that involves more than simple precipitation of calcium and phosphate. A complex series of events causes predisposed vascular smooth muscle cells to differentiate into osteoblasts or bone forming cells. Chronic

Uremic toxins
Older age
ABD
Hyperphosphatemia
Higher dose of Vit D analogs
Higher dose of calcium-based phosphate binder
Hypercalcemia
Hypomagnesemia
Diabetes
Malnutrition, inflammation
High level of sclerostin
Low levels of fetuin-A

Table 2. Contributing factors to vascular/valve calcification in PD patients.

inflammation is one of the predisposing factors too. Serum fetuin-A, which is a potent inhibitor of extraskeletal calcification, is reduced in CKD patients with severe vascular calcification. A list of contributing factors in vascular/valve calcifications in PD is present in (**Table 2**).

The increased prevalence of risk factors for atherosclerosis [69], disordered mineral metabolism with a high calcium load and/or uncontrolled phosphate resulting in poor calcium-phosphate balance, as well as the loss of inhibitors of calcifications are considered largely responsible for the higher prevalence of valve and vascular calcification in dialysis patients [70] compared to age- and sex-matched individuals without the evidence of renal disease [71].

The treat-to-goal study revealed that after 3 years in dialysis, 83% of patients had vascular calcifications underlining the importance of the evaluation and control of all the parameters of CKD-MBD [68].

3. Diagnostic workup for disorders of bone and mineral metabolism in patients under peritoneal dialysis treatment

As stated above, regarding bone metabolism and morphology, differences may exist between chronic hemodialysis and peritoneal dialysis treatment. These differences apart from preservation of renal function are mainly linked to deficiency of vitamin D, which is lost in peritoneal fluid and to and poor adherence to oral vitamin D therapy in PD [72]. The latest guideline with new recommendations was provided by KDIGO in 2017, in order to better reflect the complex interaction between CKD-MBD laboratory parameters [73]. It is important to emphasize that there are no separate or different recommendations for diagnostic workup in PD.

3.1. Biochemical components: Ca, P, PTH, ALP, bALP, 25(OH)D

In the above mentioned guidelines in CKD Grade 5 in Dialysis (G5D) [73], it is stated with a nongraded level of recommendation, that it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH in the presence and magnitude of abnormalities. Guideline evaluated as reasonable measurement of serum calcium and phosphate every 1–3 months, PTH every 3–6 months, and alkaline phosphatase activity every 12 months or more frequently in the presence of elevated PTH. The guideline also had a very weak (2D level) suggestion that instead of calcium-phosphate (CaxP) product, values of serum calcium and phosphate, evaluated together should be used in clinical practice.

PTH is a hormone with high biological variation because of feedback control and its short half-life. For instance, 26 blood samples are required in hemodialysis patients to determine the individual homeostatic set-point (within 10%) [74]. In PD patients, it is confirmed the U-shaped curve association between mortality and PTH concentration [75].

Alkaline phosphatase. The use of total alkaline phosphatase (ALP) as a biomarker in CKD-MBD is considered limited by its nonspecificity for bone disease, as only approx. 50% of blood activity is attributable to bone ALP. In contrast to the U-shaped curve for mortality and time-averaged PTH confirmed in PD patients [76], higher ALP activity (even within high-normal ranges) was found to be more linearly and independently associated with increased all cause and cardiovascular mortality in this population [77, 78]. In studies reporting a relationship between ALP and mortality in hemodialysis patients, it has been implied that the relationship is driven by vascular calcification mediated by the bone fraction of ALP [79].

Bone ALP is strongly and independently related to BMD, not accumulated with declining GFR and its concentration reflects directly osteoblastic activity [80], providing a "living biopsy" of bone activity. Most importantly, its biological variation is almost half that of PTH [81]. It is shown that higher b-ALP is an independent predictor of all-cause mortality in male HD patients [82] and high activities of b-ALP are strongly associated with cardiovascular mortality in dialysis patients, including PD population [83].

25(OH)D. Peritoneal dialysis (PD) patients have a high risk of developing vitamin D deficiency as 25(OH) vitamin D (the precursor of active vitamin D), is lost during dialysis. Vitamin D (25(OH) vitamin D) is measured to detect deficiency/insufficiency status. Defects of mineralization are presumably because of osteomalacia and hip fractures that associate its low levels [84]. Increase in mortality and hospitalization for patients on dialysis with severe 25-OH vitamin D deficiency was found [85] in a prospective cohort study. 2017 KDIGO guideline suggests (2C) in G5D patients, that 25(OH)D (calcidiol) levels might be measured, and repeated testing might be performed, determined by baseline values and therapeutic interventions.

In order to facilitate the appropriate interpretation of biochemistry data, it is moderately strongly recommended (1B) that clinical laboratories inform clinicians of the assay method or any change in method used, sample source (plasma or serum), or any specific relevant information [73]. It is also recommended (1C) that therapeutic decisions to be based on trends rather than on a single laboratory value and to take into account all available CKD-MBD parameters [73].

3.2. Biomarkers and tests for diagnosis of bone abnormalities in peritoneal dialysis

Parathyroid hormone (PTH) and total bone specific alkaline phosphatase (b-ALP) are biomarkers currently used in clinical practice despite some assay limitations. They may reflect bone turnover and bone formation. In an individual patient, no single biomarker or in combination is sufficient to diagnose low, normal, and high bone turnover although whole PTH, iPTH, and b-ALP levels are found associated with bone turnover. This was the conclusion of a recent cross-sectional retrospective diagnostic study of biomarkers and bone biopsies in 492 dialysis patients, with the objective to determine the predictive value of PTH [both intact PTH (iPTH) and total PTH], bone-specific alkaline phosphatase (b-ALP), and amino-terminal propeptide of type 1 procollagen (P1NP) as markers of bone turnover [86]. Rather than simple measurement of PTH, the continued use of trends in PTH is encouraged to guide therapy [73].

BMD testing. Identifying biomarkers and imaging test for non-invasive evaluation of patients at fracture risk is very important in dialysis patients, which in their 40s have a relative risk of hip fracture 80-fold that of age and sex-matched controls [87]. Multiple new prospective studies conducted in patients with CKD G3a-G5D demonstrated that lower dual-energy X-ray absorptiometry bone densitometry (DXA BMD) predicts incident fractures and the associations are comparable to the ones seen in the absence of CKD [76–79, 88]. In the light of these studies, in patients with G5D with the evidence of CKD-MBD and/or risk factors for osteoporosis, KDIGO guideline has a moderately strong suggestion for performing BMD testing to assess fracture risk, if results will impact treatment decisions (2B level) [73]. A DXA BMD result might also impact the decision to perform a bone biopsy [73].

Bone biopsy. In many centers, experience in performing and evaluating bone biopsies is limited [89]. In one side, DXA BMD does not distinguish among types of renal osteodystrophy. On the other side, (considering the short half-lives of the circulating biomarkers and the long (3–6 months) bone remodeling cycle), it is not surprising that cross-sectional studies have shown conflicting and non-conclusive data on the biomarkers use to predict underlying bone histology [89]. Biomarkers resulted of limited diagnostic use because of poor sensitivity and specificity. Although they correlate with some histomorphometric measurements in bone biopsy, studies have shown only modest positive predictive value of circulating PTH or bone-specific alkaline phosphatase levels for detection of states of high and low bone turnover, especially for adynamic bone disease [90–94].

Bone biopsy is the gold standard for the assessment of renal osteodystrophy, which is a component of the bone abnormalities of CKD-MBD. Its goals are to determine high- or low-turnover disease, identify a mineralization defect (both influencing treatment decisions), and rule out atypical or unexpected bone pathology. When trends in PTH are inconsistent, or in patients with progressively decreased BMD despite standard therapy, with unexplained fractures, refractory hypercalcemia, suspicion of osteomalacia or an atypical response to standard therapies for elevated PTH, a bone biopsy should be considered [73]. In the recent KDIGO guideline, it is stated that it is reasonable to perform a bone biopsy, if knowledge of the type of renal osteodystrophy will impact treatment decisions [73]. The bone biopsy is undertaken with a trocar preferably in the iliac crest. Double labeling with tetracycline according to a protocol is required to assess the turnover.

Bone turnover markers. During skeletal metabolic activity, bone turnover biomarkers are released into circulation and can be measured in the serum.

- **Serum marker of bone resorption** in which levels are not dependent in GFR (not renally cleared) is serum tartrate-resistant acid phosphatase (TRAP5b). Renally cleared markers of bone resorption are serum amino-terminal cross-linking telopeptide of type 1 collagen (s-NTX), serum carboxy-terminal cross-linking telopeptide of type 1 collagen (s-CTX), and carboxy-terminal crosslinking telopeptide of type 1 collagen (s-ICTP or CTX-MMP).
- **Serum markers of bone formation.** Serum alkaline phosphatase, bone specific alkaline phosphatase, and procollagen type IN propeptide (s-PINP) are not dependent in GFR and serum osteocalcin, procollagen type IC propeptide (s-PICP) are renally cleared [95]. 2017 guideline suggests not to routinely measure bone-derived turnover markers of collagen synthesis and breakdown (2C) [73]. Keeping in consideration their renal and dialytic elimination, those biomarkers and circulating fragments need to be studied and re-evaluated prospectively in CKD and ESRD population [95].
- **FGF23. FGF23 may be a more stabl**e marker of phosphate metabolism in ESRD compared to PTH or serum phosphate. Differently from parathyroid hormone (PTH), which fluctuates diurnally, acutely in response to changes in serum calcium and postprandially, FGF23 levels show minimal circadian and postprandial fluctuations in CKD [96, 97]. Despite no consensus about the ideal FGF23 assay, FGF23 showed significantly less within-subject variability compared to PTH and phosphate (measured contemporaneously). A single measurement of FGF23 could more accurately assess the phosphate metabolism disorder compared to markers actually in use. Prospective studies found elevated FGF23 to independently associate with mortality in incident hemodialysis patients [2, 98]. Accounting together these data further support usage of FGF23 testing.

3.3. Diagnosis of vascular abnormalities of CKD-MBD

An increasing number of data have shown the very high prevalence of cardiovascular calcification in dialysis patient population, including patients receiving long-term peritoneal dialysis treatment [63–69, 99]. Electron beam computerized tomography (EBCT) or multi-slice computerized tomography (MSCT) can measure coronary artery and valvular calcifications, but other more widely available tests as lateral abdominal X-ray and echocardiography also can measure calcifications. Vascular and valvular calcifications are important factors for determining the prognosis of patients on CAPD [100] and patients with confirmed vascular or valvular calcifications are at highest cardiovascular risk [68, 101]. This is the rationale of the use of vascular and valvular calcification information to guide the management of CKD-MBD. Despite the long and ongoing debate [102–105] about screening of ESRD population, according to 2017 KDIGO guideline, based on low quality of evidence (2C), a lateral abdominal radiograph and an echocardiogram can, respectively, be used (as alternatives to CT-based imaging) to detect the presence of vascular/valvular calcification in patients with G5D [73].

4. Treatment of CKD-MBD in patients on peritoneal dialysis

4.1. Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium

4.1.1. Control of phosphorus and calcium in peritoneal dialysis patients

As outlined above, the risk of hyperphosphatemia has been clearly shown for population treated with both hemodialysis and peritoneal dialysis [31, 38, 106]. The role of hyperphosphatemia as a principle actor in the development and progression of vascular calcification has been well documented in this population [70].

Vascular calcifications are predictive of higher morbidity and mortality in dialysis patients. The main target of pharmacological research in the field has moved from bone toward the cardiovascular apparatus [107]. The control of serum phosphorus at all stages of CKD is considered one of the more important aspects to improve clinical outcomes in CKD-MBD.

On the other side, the complex relationship between abnormal CKD-MBD parameters suggests the need of optimal control of all CKD-MBD parameters in order to modify the mortality risk among PD patients and improve clinical outcomes.

Phosphate balance in dialysis patients depends on phosphate intake, absorption (minus phosphate binding), and dialysis removal. KDIGO guidelines in 2017 suggest lowering elevated phosphate levels toward the normal range in dialysis patients [73].

- Dietary restriction of phosphorus is an important part of phosphate control treatment in all dialysis modalities. The impact of phosphorus intake on patients is clear: higher levels of dietary phosphorus intake and a higher ratio of dietary phosphorus to protein are associated with an increased risk of death [3, 28, 108]. But because of other important risk factors for patient mortality and morbidity, such as malnutrition and hypoalbuminemia, dietary restriction may not be successful alone and cannot be effective without the help of other treatment measures, mainly the use of phosphate binders.
- Type of dialysis may also be an important factor in the adequacy of phosphorus control in dialysis patients [109, 110]. Chronic PD as a continuous dialysis modality has an expected theoretical superiority over intermittent hemodialysis [32–35].

Compared to hemodialysis (HD), patients undergoing PD appear to have an increased prevalence of low turnover bone disease defined as adynamic bone disease (ABD) [16–23, 111]. In PD, as discussed above, calcium transfer across the peritoneum is regulated by two different mechanisms known like diffusion and convection. These processes depend on serum calcium levels, calcium concentration in the dialysate, and dialysis dextrose concentration [8].

Moraes et al. reported that in patients with PTH < 150 pg/mL conversion to low calcium solutions (2.5 mEq/L) appears to be a simple and effective strategy to bring PTH levels to the

range determined by current guidelines when compared with 3.5 mEq/L calcium PD solutions [112]. This supports the finding of Spasovski et al. in HD patients where the lower dialysate calcium (1.25 mmol/l [2.5 mEq/l]) was found to improve bone and mineral parameters compared with the higher concentration of 1.75 mmol/l (3.5 mEq/l) in patients with adinamic bone disease [113].

There is no data on Ca balance in PD patients, so the safety limit for an elemental calcium dose in PD patients is currently uncertain but based on the opinion of Wang the maximal additional elemental calcium given daily in the form of calcium-containing phosphate binder should be kept to not more than 800 mg to avoid calcium overload [114]. Patients with a negative dialysate calcium balance may show an overall positive calcium balance, if they are concomitantly treated with calcium-containing phosphate binders, especially when coupled with vitamin D [114].

It is important to emphasize that the KDIGO 2009 guidelines recommend a 1.25–1.50 calcium dialysate for both HD and PD and this is an additional consideration that should be taken into account when choosing a phosphate binder [1].

Without phosphate-binding therapy, all patients undergoing PD are in a positive phosphorus balance, unless they are severely malnourished. As mentioned before, the reduction of oral phosphate intake, an adequate dialysis schedule and the use of intestinal phosphate binders are three strategies used to manage hyperphosphatemia in dialysis patients [114]. Inevitably, in the long term, patients rarely observe rigid dietary phosphate restriction, especially in the context of PD where a higher number of patients are prescribed a less restrictive diet with a higher content of dietary protein [115].

Phosphate binders are essential in control of phosphate overload and in the improvement of outcomes in peritoneal dialysis patients. Phosphate binders are used for their binding actions to reduce the absorption of phosphorus by the gastrointestinal lumen. First, it should be stressed that patient compliance is fundamental not only in limiting dietary intake of phosphorus but also in adhering to the prescribed protocol of phosphate binder administration, frequently linked to the number of pills the patient is required to take and the degree of gastric tolerance of the product prescribed.

There is insufficient evidence that any specific phosphate binder significantly impacts patient-level survival. The decision to use a phosphate binder should be followed by consideration of which currently available phosphate-binding agent is suitable for the patient. Ideally, a phosphate binder should effectively bind dietary phosphate regardless of pH have minimal systemic absorption, few side effects, good palatability, a low pill burden, and be available at a low cost [116]. Traditionally, phosphate binders are classified into calcium-containing phosphate binders and calcium-free phosphate binders.

4.1.2. Calcium-containing phosphate binders

Calcium-containing phosphate binders are available in two formulations: calcium carbonate and calcium acetate. Efficacy of calcium-based phosphate binders is known to be clinically satisfactory, especially when combined with adequate dialysis and dietary measures. Nowadays, calcium salts are considered not free of side effects. Great concern has been expressed about

their effect on raising serum calcium levels, especially when used in association with vitamin D or high calcium dialyzing solutions.

High calcium balance may over suppress PTH, exiting in a state of adynamic bone disease (ABD), which is as dangerous as a high bone turnover state [114]. Furthermore, the excess of calcium may lead to tissue and vascular calcifications, increasing cardiovascular mortality. Regarding the use of calcium-based phosphate binders in PD patients, there are limited data available. The majority of studies comparing calcium salts and sevelamer are performed in hemodialysis patients. These studies confirm the efficacy of calcium salts as phosphate binders and the potential role of them in developing calcifications.

Calcium salts should be administered carefully, considering the clinical status of each patient. KDIGO guidelines suggest restricting the dose of calcium salts in the presence of arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low [1].

4.1.3. Calcium-free phosphate binders

Aluminum salts were largely used as calcium-free phosphate binders, but this treatment was abandoned when cases of systemic aluminum toxicity were reported [117].

Sevelamer is a calcium- and aluminum-free phosphate binder, developed for hyperphosphatemia management in dialysis patients. There are also few data regarding sevelamer administration in PD patients. A study comparing the efficacy of sevelamer and calcium acetate showed the same efficiency of both treatments in control of serum phosphorus and PTH [118]. This study also evaluated the association between sevelamer administration and risk of peritonitis in PD patients, because it has been thought that a higher rate of diarrhea and constipation induced by sevelamer might increase the risk of peritonitis caused by Gram-negative microorganisms due to trans-mural migration of bacteria. Although peritonitis occurred in 11% of the patients in the sevelamer group and in 4% of the patients on calcium-containing phosphate binders, no significant increase in the risk of peritonitis was found [118]. Another study performed in PD patients in Canada showed the efficacy of sevelamer in ameliorating CKD-MBD parameters [119].

Lanthanum carbonate is another nonaluminum- and noncalcium-containing phosphate binder that has more recently become available for the management of hyperphosphatemia in dialysis patients. Unfortunately, less evidence and studies are available for patients undergoing PD [114]. An open, noncomparative study in patients with hyperphosphatemia undergoing continuous ambulatory PD evaluated safety and efficacy of lanthanum carbonate to reduce serum phosphate levels [120]. This study showed that lanthanum carbonate was generally well tolerated. Furthermore, majority of the patients reached the therapeutic target level in 2 months at doses between 750 and 2250 mg, suggesting that the efficacy dose was lower than that for HD patients.

A novel noncalcium iron-based phosphate binder, sucroferric oxyhydroxide is introduced for the management of hyperphosphatemia in dialysis patients. It is formulated as a chewable tablet containing 500 mg iron. Long-term efficacy and tolerability of the iron-based phosphate binder, sucroferric oxyhydroxide, was compared with that of sevelamer carbonate in an open-label Phase III extension study [121]. A representative proportion (9.3%) of patients receiving peritoneal dialysis was included in this long-term analysis of phosphate binders. Extension

study data demonstrate that the efficacy of sucroferric oxyhydroxide for controlling serum phosphorus concentration was robust, maintained over the long-term (1 year) and similar to that of sevelamer. Sucroferric oxyhydroxide was generally well tolerated over 1 year. The pill burden over 1 year of treatment was 62% lower with sucroferric oxyhydroxide than with sevelamer [121].

4.2. Treatment of secondary hyperparathyroidism in PD patients

Though the prevalence of secondary hyperparathyroidism (SHP) and the related mineral metabolism changes have been reported at almost the same rate in peritoneal dialysis as in hemodialysis patients, PD patients have a higher prevalence of adynamic bone disease suggesting that their bone is less sensitive for a given level of PTH [122].

It has also been widely reported that PD patients have lower vitamin D levels as compared with the HD patients [123]. Among the multiple causes which might explain the higher prevalence of vitamin D deficiency in PD patients, the peritoneal loss of vitamin D binding protein probably plays an overwhelming role.

It is suggested to correct vitamin D deficiency, using low doses of either cholecalciferol or calcifediol (800–100 UI/day), by adding calcitriol or paricalcitol only when, after the first two described steps, the PTH levels are stable at 450–500 pg/mL or show a clear increasing trend in the absence of relatively high calcium (>10.0 mg/dl) and/or phosphorus (>5.5 mg/dl) levels [122]. In these latter cases, it is suggested to start treatment with cinacalcet.

Most of studies on administration of calcimimetics in dialysis are performed in hemodialysis patients. Few studies that are PD have a very limited number of patients. So, most of the recommendations for peritoneal dialysis patients are simply transferred from the HD experiences. The calcimimetic cinacalcet was approved by the US Food and Drug Administration in 2004 and by European Committee for Medical Products for Human Use in 2005 to treat secondary hyperparathyroidism in patients on dialysis.

Cinacalcet acts directly upon the parathyroid cell calcium-sensing receptor (CaR). Upon binding CaR, cinacalcet allosterically increases its sensitivity to extracellular calcium thus suppressing PTH secretion without increasing serum calcium and phosphate levels [124]. A retrospective study was performed at a single PD unit based on 27 patients with moderate to severe SHPT (PTHi > 500 pg/mL with normal or elevated serum calcium levels) who were treated with cinacalcet. Cinacalcet was started due to the lack of response with conventional treatment: diet, phosphate binders, and vitamin D or inability to treat with vitamin D due to hyperphosphatemia >5.5 mg/dL or hypercalcemia >10.5 mg/dL [125]. This study showed that cinacalcet was a safe but not effective therapy in moderate to severe SHPT in PD patients. The gastrointestinal adverse factors made impossible the prescription of higher doses of cinacalcet and an eventual benefit of this therapy at higher doses in SHPT was impossible to evaluate.

On contrary with these conclusions were results of another study performed by Portoles et al. in PD patients. They evaluated efficiency and safety of cinacalcet in eighteen patients undergoing more than 4 months on PD with a severe SHPT (PTH > 500 pg/mL) resistant to conventional treatment with diet, chelants and vitamin D, in a prospective open-label study

[126]. The authors concluded that the addition of cinacalcet to conventional treatment in PD patients with resistant SHPT has improved the achievement of targets of K/DOQI guidelines and has been reasonably safe.

Lindberg et al. [127] evaluated a total of 395 patients on dialysis (349 on HD and 46 on PD). Two hundred and ninetyfour patients (260 HD and 34 PD) were treated with once-daily oral cinacalcet (titrated from 30 to 180 mg/day), while the remaining 101 patients (89 HD, 12 PD) were on placebo in addition to the ongoing standard therapy. This study confirmed that cinacalcet induced a more pronounced reduction of PTH in a larger percentage of patients as compared with standard therapy, with no major difference in the percentage of patients on HD and on PD treatment achieving a PTH level lower than 250 pg/mL (39 and 38%, respectively).

Cinacalcet treatment was associated with a slight, but significant, decrease in both calcium and phosphorus concentrations as compared with patients treated with the standard therapy only. Gastrointestinal symptoms were reported to be the most frequent adverse effects. However, no difference was observed between HD and PD patients in the incidence or type of the reported side events. A severe form of SHP is an unusual finding in PD patients. Furthermore, the control of phosphate is usually better in PD than in HD patients, at least until the residual diuresis is maintained. Another specific characteristic of patients treated with PD is the higher tendency to status of vitamin D deficiency which might make these patients more prone to hypo rather than hypercalcemia. For all these reasons, it is possible to predict that the need for the use of the most recent and potent drugs which are nowadays available for the control of SHP, including cinacalcet, might be lower in PD than in HD patients [122].

5. Nomenclature

The recommendation on diagnosis and management of CKD-MBD presented in this chapter are based on KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD).

The level of recommendations presented in these guidelines are:

Level 1—we recommend; Level 2—we suggest; the ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Quality of evidence presented in these guidelines:

Meaning A High: we are confident that the true effect lies close to that of the estimate of the effect.

B Moderate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

C Low: The true effect may be substantially different from the estimate of the effect.

D Very low: The estimate of effect is very uncertain and often will be far from the truth.

Conflict of interest

None to declare.

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Chapter 6

Diagnosis, Prevention, and Treatment of Protein-Energy Wasting in Peritoneal Dialysis

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Abstract

Protein-energy wasting (PEW) is highly prevalent in peritoneal dialysis (PD) patients and is associated with mortality. Reduced protein and energy intake, comorbidity conditions, endocrine disorders, increased inflammatory cytokines, uremic toxins, metabolic acidosis, oxidative stress, nutrient losses into dialysate, continuous absorption of glucose from PD solutions, abdominal fullness induced by the dialysate, and peritonitis contribute to PEW. Assessment of nutritional status for the detection and management of PEW includes the PEW definition criteria, subjective global assessment (SGA), malnutrition-inflammation score (MIS), and geriatric nutritional risk index (GNRI). Diverse factors can affect nutritional and metabolic status in these patients so multiple strategies may be required to prevent or reverse PEW. Preventive measures include continuous nutritional counseling, optimizing dietary nutrient intake, and managing comorbidities. To treat PEW, the following may be used: administration of oral, intraperitoneal, enteral, or parenteral nutritional supplementation and adjunct therapies such as anabolic agents, appetite stimulants, anti-inflammatory interventions, and exercise. Diagnosis, prevention, and treatment of PEW in PD patients may favorably impact the prognosis and course of the disease.

Keywords: protein-energy wasting, peritoneal dialysis, nutritional assessment, protein-energy wasting definition criteria, subjective global assessment, malnutrition-inflammation score, geriatric nutritional risk index

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1. Introduction

End-stage renal disease (ESRD) represents a serious public health problem in Mexico. It has been reported among the ten primary causes of death in the country with an annual mortality of 12.3 deaths per 100,000 people and is the second cause of years of life lost. The annual incidence is 421 persons per million population (pmp) with a prevalence of 1568 pmp. It is estimated that 8.5% of the Mexican population has chronic kidney disease (CKD) and almost 65,000 patients undergo dialysis. Peritoneal dialysis (PD) was introduced in Mexico in the early 1980s, and it became the renal replacement therapy of choice that rapidly extended to the population with social security coverage, as well as the uninsured population: the use of PD is the first choice in treatment when there is inadequate access to other methods like hemodialysis and renal transplant, and so the number of PD patients continues to rise [1, 2]. Despite the progressive rise in the use of hemodialysis in Mexico for some years now [1], when compared to other countries, Mexico continues to be one of the countries in the world where more PD is used [2, 3]. One of the most serious complications of CKD is protein-energy wasting (PEW), and this has an important therapeutic challenge because of its frequency in patients with ESRD who receive dialysis [4]. Therefore, from an integrated standpoint, this chapter reviews the diagnosis, prevention, and treatment of PEW in PD patients.

2. Protein-energy wasting

A variety of terms and definitions have been used to describe the conditions associated with loss of the muscle and fat tissue, malnutrition, and inflammation in patients with CKD, which have been denominated: uremic malnutrition, uremic (renal) cachexia, protein-energy malnutrition, malnutrition-inflammation-atherosclerosis syndrome, or malnutrition-inflammation complex (or cachexia) syndrome. The use of nonuniform and ill-defined terminologies may lead to both conceptual errors and malinterpretation of the data [5]. Therefore, the panel of experts of the International Society of Renal Nutrition and Metabolism (ISRNM) proposed the term "protein-energy wasting" as the state in which a decline in the body stores of protein

1. Decreased protein and energy intake

- **a.** Anorexia
  - **i.** Dysregulation in circulating appetite mediators
  - **ii.** Hypothalamic amino acid sensing
  - **iii.** Nitrogen-based uremic toxins
- **b.** Dietary restrictions
- **c.** Alterations in organs involved in nutrient intake
- **d.** Depression
- **e.** Inability to obtain or prepare food

2. Hypermetabolism

- **a.** Increased energy expenditure
  - **i.** Inflammation
  - **ii.** Increased circulating proinflammatory cytokines
  - **iii.** Insulin resistance secondary to obesity
  - **iv.** Altered adiponectin and resistin metabolism
- **b.** Hormonal disorders
  - **i.** Insulin resistance of CKD
  - **ii.** Increased glucocorticoid activity

3. Metabolic acidosis

4. Decreased physical activity

5. Decreased anabolism

- **a.** Decreased nutrient intake
- **b.** Resistance to growth hormone/insulin-like growth factor-1
- **c.** Testosterone deficiency
- **d.** Low thyroid hormone levels

6. Comorbidities and lifestyle

- **a.** Comorbidities (diabetes mellitus, congestive heart failure, depression, coronary artery disease, peripheral vascular disease)

7. Dialysis

- **a.** Nutrient losses into dialysate
- **b.** Dialysis-related inflammation
- **c.** Dialysis-related hypermetabolism
- **d.** Loss of residual renal function

Table 1. Causes of PEW in CKD patients.

and energy fuels (i.e., body protein and fat masses) presents due to the multiple nutritional and catabolic alterations that occur in CKD [5, 6]. These alterations include a decrease in the protein and energy intake, comorbidity conditions, endocrine disorders, an increase in the production of inflammatory cytokines, uremic toxins, metabolic acidosis, oxidative stress, and the nutrient losses into dialysate, among others (**Table 1**) [5, 6]. PD itself can lead to PEW due to the continuous absorption of glucose from PD solutions, the abdominal fullness induced by the dialysate, and peritonitis that can suppress the appetite [7]. Cachexia occurs infrequently in kidney disease, and it is the most severe form of PEW since the latter can refer to mild degrees of depleted protein and energy mass [5].

3. Prevalence of protein-energy wasting

PEW has been reported in PD patients in a wide range that goes from 23 to 90%, and the prevalence of PEW varies depending on the definitions used and the origin of the population [8–15]. In Mexico, the prevalence fluctuates between 49 and 92% in the prevalent as well as the incidental population in distinct PD programs [16]. This is a serious problem since PEW is associated with mortality in these patients [8].

4. Assessment of protein-energy wasting

Assessment and monitoring of the nutritional status is important to diagnose, prevent, and treat PEW [17]. Nutritional tools like the PEW definition criteria, subjective global assessment (SGA), malnutrition-inflammation score (MIS), and geriatric nutritional risk index (GNRI) have been widely recommended [18].

4.1. Protein-energy wasting definition criteria

The expert panel of the ISRNM has recommended diagnostic criteria for PEW that include (1) serum chemistry (albumin, prealbumin, cholesterol), (2) body mass (body mass index-BMI), unintentional weight loss, total body fat percentage), (3) muscle mass (muscle wasting, reduced mid-arm muscle circumference-MAMC, creatinine appearance), and (4) dietary intake (low protein or energy intake) (**Table 2**). At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart [5].

4.1.1. Serum chemistry

The reduction in serum albumin levels is a strong predictor of mortality in PD patients [8, 19, 20]. Also, it is one of the most used biochemical criteria in the diagnosis of PEW [21]. However, as a nutritional parameter, it should be interpreted with caution because its half-life is approximately 20 days and can be affected by inflammation, losses into dialysate, and the volume state [7]. Our research group has reported that serum albumin levels are not associated between patients with and without incidents of PEW in PD [21]. On the other hand, the half-life of approximately 2 days makes the prealbumin or transthyretin a more sensitive marker for nutritional status than serum albumin [7]. The levels of prealbumin of <30 mg/dL have been observed to increase the risk of mortality [22, 23]. The value of the prealbumin as a nutritional biochemical predictor of greater survival has been confirmed [22–24]. Another proposed biochemical marker is cholesterol. Low levels of cholesterol have been associated with worse results in this population [25, 26], and this diagnostic criterion is among the most controversial for PEW because the low level as a result of diet and exercise might not reflect PEW [27].

4.1.2. Body mass

Among the indicators of body mass, the BMI is the most commonly used measurement of weight-for-height and can be applied to assess PEW. However, this can be influenced by diet,

Criteria
Serum chemistry
Serum albumin (<3.8 g/dL (bromocresol green)[a])
Serum prealbumin (transthyretin) (<30 mg/dL (for maintenance dialysis)[a])
Serum cholesterol (<100 mg/dL[a])
Body mass
BMI (<23[b])
Unintentional weight loss over time (5% over 3 months or 10% over 6 months)
Total body fat percentage (<10%)
Muscle mass
Muscle wasting: reduced muscle mass (5% over 3 months or 10% over 6 months)
Reduced MAMC[c] (reduction >10% in relation to 50th percentile of reference population)
Creatinine appearance[d]
Dietary intake
Unintentional low dietary protein intake (<0.80 g/kg/day for at least 2 months[e] for dialysis patients)
Unintentional low dietary energy intake (<25 kcal/kg/day for at least 2 months[e])

At least three out of the four listed categories (and at least one test in each of the selected categories) must be satisfied for the diagnosis of kidney disease-related PEW.

Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.

[a]Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines.

[b]A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass.

[c]Measurement must be performed by a trained anthropometrist.

[d]Creatinine appearance is influenced by both muscle mass and meat intake.

[e]Can be assessed by dietary diaries and interviews or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.

Table 2. Criteria for the clinical diagnosis of PEW in CKD.

exercise, fat mass, and hydration status and may not be pathological in certain racial-ethnic groups [5, 27]. In a recent meta-analysis, it was confirmed that patients with PD who presented with low weight compared to the ranges of overweight and obesity had an increased risk of mortality [28]. The expert panel also recommends that the unintentional loss of 5% of non-edematous weight within 3 months or an unintentional loss of 10% of non-edematous weight over the past 6 months should be considered an indicator of PEW [5]. Even still, the majority of PD patient cases experience a significant gain in body weight [29]. The presence of weight loss in the first year is associated with adverse results [30, 31]. One limitation for the assessment of this parameter is the fluid gain that can mask weight loss [27]. The third measure that can be considered for the diagnosis of PEW is a low percentage of body fat, but the specificity of this criterion is questionable in persons who are very muscular and athletic [5, 27].

4.1.3. Muscle mass

The reduction of muscle mass appears to be the most valid criterion for the presence of PEW [5]. Methods like the dual-energy X-ray absorptiometry and bioelectrical impedance analysis have

been used to assess the loss of muscle mass in PD patients [32–34]. The increase in risk of mortality has been observed with the loss of muscle mass assessed through these types of methods [35, 36]. The reduction in MAMC is another recommended criterion for the diagnosis of PEW [5], and the anthropometric parameters, including the MAMC, have been demonstrated to identify low muscle mass in these patients [37]. However, this method can be insensitive since it is associated with a substantial interobserver error and the volume state [7]. Equations based on the MAMC and handgrip strength have been favorably correlated with muscle mass [38].

4.1.4. Dietary intake

A decrease in appetite (anorexia) can be associated with PEW. Therefore, the unintentional reduction of protein intake <0.80 g per kg of body weight per day and an unintentional reduction in energy intake of <25 kcal per kg of body weight per day for at least 2 months have been proposed as an indicator of PEW [5]. Dietary intake can be assessed by dietary diaries and interviews or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements [5]. One important aspect to consider is the obligatory absorption of glucose with PD, since it can result in an absorption of carbohydrates on average of approximately 400 kcal of energy intake every day, and so estimating the total daily energy intake derived from the sum of the diet and the dialysate could be adequate for the diagnosis of PEW [39].

4.2. Subjective global assessment

The SGA is a tool that is used to assess the nutritional status, and it has been validated for use in PD patients [18, 40–42]. The increase in risk of mortality has been confirmed with the presence of PEW assessed by this tool [12, 43]. The SGA is composed of a medical history and a physical examination (**Figure 1**). In each component a score is assigned based on a scale from 1 to 7, with lower values representing worse nutritional status. The medical history includes weight change (the last 2 weeks, as well as the previous 6 months), dietary intake, gastrointestinal symptoms, functional capacity, and the disease state and comorbidities. The physical exam includes the loss of subcutaneous fat (below the eye, triceps, biceps, chest), muscle wasting (temple, clavicle, scapula, ribs, quadriceps, calf, knee, interosseous), and edema. When this examination has been completed, an overall SGA rating is assigned to the patient and ranges from a rating of 1–2 for severe PEW, 3–5 for mild-moderate PEW, and 6–7 for very mild PEW to well-nourished [17, 40].

4.3. Malnutrition-inflammation score

Upon recognizing the role that inflammation plays in the pathogenesis of PEW, a more comprehensive, quantitative scoring system was created called the MIS, which utilizes a revised form of the SGA scoring system and adds BMI, serum albumin, and the binding capacity of iron or transferrin [17, 18, 44]. The MIS has 10 components, each one with four levels of severity, from 0 (normal) to 3 (severely abnormal) (**Figure 2**). The sum of all 10 MIS components ranges from 0 (normal) to 30 (severe PEW); a higher score reflects a more severe degree of PEW and inflammation [44]. The MIS assessment has been identified as a predictor of morbidity and mortality in PD patients [45, 46]. Also, diverse authors have observed a reasonable correlation of the MIS with the SGA in this population [47, 48].

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SUBJECTIVE GLOBAL ASSESSMENT RATING FORM

Patient Name: **ID #:** **Date:**

HISTORY **Rate 1-7**

WEIGHT/WEIGHT CHANGE: ***(Included in K/DOQI SGA)***

1. Baseline Wt: _____ (Dry weight from 6 months ago)
Current Wt: _____ (Dry weight today)
Actual Wt loss/past 6 mo: _____ **% loss:** _____ (actual loss from baseline or last SGA)

2. Weight change over past two weeks: _____ No change _____ Increase _____ Decrease

DIETARY INTAKE No Change _____ (Adequate) No Change _____ (Inadequate)
1. Change: Sub optimal Intake: _____ Protein _____ Kcal _____ Duration _____
Full Liquid: _____ Hypocaloric Liquid _____ Starvation _____

GASTROINTESTINAL SYMPTOMS ***(included in K/DOQI SGA-anorexia or causes of anorexia)***

Symptom:	**Frequency:***	**Duration:***
_____ None	_____	_____
_____ Anorexia	_____	_____
_____ Nausea	_____	_____
_____ Vomiting	_____	_____
_____ Diarrhea	_____	_____
	Never, daily, 2-3 times/wk, 1-2 times/wk	>2 weeks, <2 weeks

FUNCTIONAL CAPACITY **b**

Description	**Duration:**
_____ No dysfunction	_____
_____ Change in function	_____
_____ Difficulty with ambulation	_____
_____ Difficulty with activity (patient specific "normal")	_____
_____ Light activity	_____
_____ Bed/chair ridden with little or no activity	_____
_____ Improvement in function	_____

DISEASE STATE/COMORBIDITIES AS RELATED TO NUTRITIONAL NEEDS
Primary Diagnosis _____ Comorbidities _____
Normal requirements _____ Increased requirements _____ Decreased requirements _____
Acute Metabolic Stress ____ None ____ Low ____ Moderate ____ High

PHYSICAL EXAM

_____ Loss of subcutaneous fat (Below eye, triceps, biceps, chest) ***(Included in K/DOQI SGA)*** _____ Some areas _____ All areas
_____ Muscle wasting (Temple, clavicle, scapula, ribs, quadriceps, calf, knee, interosseous) ***(incluided in K/DOQI SGA)*** _____ Some areas _____ All areas
_____ Edema (Related to undernutrition/use to assess weight change)

OVERALL SGA RATING

Very mild risk to well-nourished= 6 or 7 most categories or significant, continued improvement.
Mild-moderate= 3, 4, or 5 ratings. No clear sign of normal status or severe malnutrition.
Severely Malnourished= 1 or 2 ratings in most categories/significant physical signs of malnutrition.

Figure 1. Seven-point scale SGA.

4.4. Geriatric nutritional risk index

The GNRI was proposed using the argument that because current methods of nutritional assessment use several subjective assessments and judgments, assessment by a well-trained staff is necessary to obtain consistent results between the different examiners and institutions. Furthermore,

(A) Patients´ related medical history:			
1- Change in end dialysis dry weight (overall change in past 3–6 months):			
0	1	2	3
No decrease in dry weight or weight loss < 0.5 kg	Minor weight loss (≥ 0.5 kg but < 1 kg)	Weight loss more than one kg but < 5%	Weight loss > 5%
2- Dietary intake:			
0	1	2	3
Good appetite and no deterioration of the dietary intake pattern	Somewhat sub-optimal solid diet intake	Moderate overall decrease to full liquid diet	Hypo-caloric liquid to starvation
3- Gastrointestinal (GI) symptoms:			
0	1	2	3
No symptoms with good appetite	Mild symptoms, poor appetite or nauseated occasionally	Occasional vomiting or moderate GI symptoms	Frequent diarrea or vomiting or severe anorexia
4- Functional capacity (nutritionally related functional impairment):			
0	1	2	3
Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation, or feeling tired frequently	Difficulty with otherwise independent activities (e.g. going to bathroom)	Bed/chair-ridden, or little to no physical activity
5- Co-morbidity including number of years on dialysis:			
0	1	2	3
On dialysis less than one year and healthy otherwise	Dialyzed for 1–4 years, or mild co-morbidity (excluding MCC*)	Dialyzed > 4 years, or moderate co-morbidity (including one MCC*)	Any severe, multiple co-morbidity (2 or more MCC*)
(B) Physical Exam (according to SGA criteria):			
6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, chest):			
0	1	2	3
Normal (no change)	Mild	Moderate	Severe
7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):			
0	1	2	3
Normal (no change)	Mild	Moderate	Severe
(C) Body mass index:			
8- Body mass index: BMI = Wt(kg) / Ht^2(m)			
0	1	2	3
BMI ≥ 20 kg/m^2	BMI: 18–19.99 kg/m^2	BMI: 16–17.99 kg/m^2	BMI: < 16 kg/m^2
(D) Laboratory parameters:			
9- Serum albumin:			
0	1	2	3
Albumin ≥ 4.0 g/dL	Albumin: 3.5–3.9 g/dL	Albumin: 3.0–3.4 g/dL	Albumin: < 3.0 g/dL
10- Serum TIBC (total Iron Binding Capacity): ♣			
0	1	2	3
TIBC ≥ 250 mg/dL	TIBC: 200–249 mg/dL	TIBC: 150–199 mg/dL	TIBC: < 150 mg/dL
Total Score = sum of above 10 components (0–30):			

*MCC (Major Comorbid Conditions) include hearth failure class III or IV, full blown AIDS, severe coronary artery disease, moderate to severe chronic obstructive pulmonary disease, major neurological sequelae, and metastatic malignancies or s/p recent chemotherapy.
♣Suggested equivalent increments for serum transferrin are: > 200 (0), 170–200 (1), 140–169 (2), and < 140 mg/dL.

Figure 2. Components of the malnutrition-inflammation score (MIS).

these methods are somewhat time-consuming and cumbersome. The GNRI was developed with the intention of being the simpler method to assess nutritional status in which only three objective parameters are used: body weight, height, and serum albumin levels (**Table 3**) [18]. It has been observed that the GNRI is related to diverse nutritional parameters including the MIS, SGA,

Formula
GNRI = [14.89 × albumin (g/dL)] + [41.7 × (body weight/ideal body weight)]

Table 3. Geriatric nutritional risk index (GNRI).

BMI, creatinine, albumin, arm circumference, and fat mass index, as well as being associated with greater mortality in PD patients [9, 49]. This makes the GNRI a simple method to predict nutritional status and the clinical results in these patients [49].

4.5. Clinical scenario for the diagnosis of protein-energy wasting in peritoneal dialysis

4.5.1. Case 1

A 27-year-old male with PD for 36 months who attending to the nephrology service in order to perform a peritoneal equilibrium test, wich results in a low-average transport.

Baseline weight 64.5 kg, current weight 64.5 kg, height 1.75 m, BMI 21.06 kg/m^2, ideal body weight 70.5 kg, MAMC 21.51 cm (reduction >10%), percentage of body fat 13.52, energy intake 742 kcal (10.52 kcal/kg per day), and protein intake 28 g (0.39 g/kg per day).

Laboratory measurements: hemoglobin 7.64 g/dL, total lymphocyte count 900 cells/mm^3, glucose 85 mg/dL, creatinine 18.75 mg/dL, BUN 79.80 mg/dL, P 8.10 mg/dL, Ca 8.7 mg/dL, Cl 100 mmol/L, K 4.90 mmol/L, Na 140 mmol/L, Mg 3.30 mg/dL, albumin 3.00 g/dL, total proteins 5.7 g/dL, cholesterol 139 mg/dL, and transferrin 256.5 mg/dL.

Based on these data, which of the following diagnostic criteria meet for PEW (**Table 2**)?

(A) Cholesterol, percentage of body fat, and MAMC

(B) Albumin, BMI, and MAMC or protein/energy intake

(C) Albumin, unintentional weight loss, and percentage of body fat

4.5.2. Case 2

An 18-year-old male with PD for 13 months who is hospitalized in our service for the presence of abdominal pain at the time of the replacement dialysis solutions is diagnosed with peritonitis and *Pseudomonas aeruginosa*, which were isolated.

Baseline weight 55 kg, current weight 44.7 kg, height 1.60 m, BMI 17.46 kg/m^2, ideal body weight 59 kg, MAMC 19.61 cm, and percentage of body fat 8.3. The medical history shows an unintentional weight loss of 18.73% in the last 6 months, as well as an inadequate calorie intake of 1075 kcal (18.22 kcal/kg per day) and a protein intake of 56.5 (0.95 g/kg per day). Anorexia, nausea, vomiting, and diarrhea were not present. In terms of functional capacity with loss, rarely gets out of bed and does so with help for <2 weeks and in the state of the disease and comorbidities, presents an increase in nutritional requirements and high metabolic stress due to the presence of peritonitis. The physical exam shows a severe loss of subcutaneous fat and muscle wasting in all areas, without the presence of edema.

Laboratory measurements: hemoglobin 6.48 g/dL, total lymphocyte count 670 cells/mm^3, glucose 65 mg/dL, creatinine 9.91 mg/dL, BUN 53.30 mg/dL, P 3.90 mg/dL, Ca 9.92 mg/dL, Cl 92 mmol/L, K 3.90 mmol/L, Na 132 mmol/L, Mg 1.90 mg/dL, albumin 2.10 g/dL, total proteins 4.7 g/dL, cholesterol 115 mg/dL, and transferrin 98.4 mg/dL.

Based on these data, what overall SGA rating presents this patient (**Figure 1**)?

(A) 6–7 Very mild PEW to well-nourished

(B) 3–5 Mild–moderate PEW

(C) 1–2 Severe PEW

4.5.3. Case 3

A 36-year-old female with PD for 60 months who is hospitalized for the presence of abdominal pain, constipation, nausea and vomiting is diagnosed with peritonitis and *Staphylococcus haemolyticus*, which were isolated.

Baseline weight 62 kg, current weight 51.2 kg, height 1.55 m, ideal body weight 55 kg, MAMC 21.95 cm, and percentage of body fat 21.39.

In the medical history component, there is evidence of an unintentional weight loss of 17.42% in the last 6 months, as well as an inadequate calorie intake of 630 kcal (11.45 kcal/kg per day) and a protein intake of 21.1 gr (0.38 g/kg per day). Also presenting gastrointestinal symptoms like nausea every day >2 weeks and vomiting every day <2 weeks. In the functional capacity, presents difficulty with independent activities, and as the only comorbidity, the time in dialysis of 5 years. The physical exam shows a moderate loss of subcutaneous fat in the triceps and biceps, as well as a moderate muscle wasting in the interosseous, temples, clavicles, and quadriceps. With a calculated BMI of 21.31 kg/m^2 and laboratory parameters with albumin 2.00 g/dL and transferrin 128 mg/dL.

Other laboratory measurements: hemoglobin 9.41 g/dL, total lymphocyte count 670 cells/mm^3, glucose 78 mg/dL, creatinine 9.41 mg/dL, BUN 27.57 mg/dL, P 4.60 mg/dL, Ca 9.42 mg/dL, Cl 91 mmol/L, K 3.50 mmol/L, Na 130 mmol/L, Mg 1.60 mg/dL, total proteins 5.1 g/dL, and cholesterol 152 mg/dL.

Based on the 10 components of the MIS, what score does this patient present (**Figure 2**)?

(A) 22

(B) 29

(C) 15

4.5.4. Case 4

A 32-year-old male with PD for 74 months who attending to the nephrology service in order to perform a peritoneal equilibrium test, wich results in a high-average transport.

Baseline weight 55 kg, current weight 55 kg, height 1.62 m, BMI 20.95 kg/m^2, ideal body weight 60.5 kg (ideal body weight = ([BMI = 23 kg/m^2] x height^2), MAMC 19.68 cm, percentage of body

fat 21.07, energy intake 1380 kcal (22.80 kcal/kg per day), and protein intake 52 g (0.85 g/kg per day).

Laboratory measurements: hemoglobin 7.63 g/dL, total lymphocyte count 1460 cells/mm^3, glucose 97 mg/dL, creatinine 10.27 mg/dL, BUN 40.90 mg/dL, P 3.30 mg/dL, Ca 8.7 mg/dL, Cl 101 mmol/L, K 4.40 mmol/L, Na 139 mmol/L, Mg 1.90 mg/dL, albumin 2.00 g/dL, total proteins 5.6 g/dL, cholesterol 135 mg/dL, and transferrin 138.1 mg/dL.

Based on this data, which of the following ranges of IRNG does this patient present (**Table 3**)?

(A) 92.91

(B) 67.68

(C) 72.93

5. Prevention of protein-energy wasting

Diverse factors can affect the nutritional and metabolic status of patients with CKD, for which they require interventions to prevent or reverse protein and energy depletion. Preventive measures include continuous nutritional counseling, optimizing dietary nutrient intake, renal replacement therapy, and management of the different comorbidities (metabolic acidosis, diabetes mellitus, congestive heart failure, depression) [50].

5.1. Nutritional counseling

Nutritional counseling can be a useful tool in PD patients in order to improve compliance with nutritional recommendations [51]. The minimum recommendations in order to prevent inadequate nutrient intake in these patients is presented in **Table 4** [50]. In a prospective study with 258 PD patients, individualized nutritional counseling significantly improved calorie and protein intake, the BMI, and the PEW [14]. However, despite this type of intervention, it has been observed that not all patients achieve an optimal nutrient intake [14, 52]. In our population, although nutritional counseling has been shown to not significantly improve all of the nutritional parameters, it is capable of maintaining the nutritional status despite the decrease in residual kidney function and the presence of systemic inflammation [53]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines recommend that nutritional counseling should be intensive initially and provided thereafter every 1 or 2 months and more frequently if inadequate nutrient intake or PEW is present or if adverse events or illnesses occur that may cause deterioration in nutritional status [54].

5.2. Optimize dietary nutrient intake

Optimizing the dietary nutrient intake is one strategy that can improve calorie and protein intake [50]. The suggestion of individualized menus and the list of interchangeable foods in equivalent quantities have been demonstrated to improve the achievement of protein intake in PD patients [55]. The increased protein requirement (>1.2 g/kg/day) in these patients makes them subject to a higher phosphorus load; thus, the reduced intake of

Protein	>1.2 g/kg/day Peritonitis >1.5 g/kg/day
Energy	30–35[a] kcal/kg/day including kcal from dialysate
Sodium	80–100 mmol/day
Potassium	Not usually an issue
Phosphorus	800–1000 mg and binders if elevated

Greater than 50% of high biological value protein (i.e., complete protein sources, containing the full spectrum of essential amino acids) is recommended.[a]Based on the physical activity level. In sedentary elderly adults, recommended energy intake is 30 kcal/kg/day.
All recommendations are based on ideal body weight. Regular follow-up supports compliance.

Table 4. Recommended minimum protein, energy, and mineral intakes for peritoneal dialysis patients by the ISRNM.

phosphorus without depriving protein intake should be centered in food choices with a lower quantity of phosphorus per gram of protein (e.g., egg whites) and in those choices that have lower intestinal absorption (vegetables) [56]. The reduction in sodium intake is another commonly prescribed strategy to maintain volume state [57]. It has been observed that patients with a low sodium intake are associated with nutrient deficits, poor muscle protein stores, and worse results [58]. Therefore, measures to reduce dietary sodium through the use of flavor enhancers, and preparing a diet with 2 g of sodium (88 mM NaCl) adding 1/3 teaspoon of salt to each meal throughout the day, could help to avoid nutritional deficits [57, 59].

5.3. Renal replacement therapy

The dialysis adequacy has long been considered a measure for the prevention and treatment of PEW in patients who undergo maintenance dialysis, and a minimum dose of dialysis has been recommended to maintain optimal dietary nutrient intake [50]. A 25% increase in PD volume has been shown to improve calorie intake and stabilize the mid-arm circumference, protein nitrogen appearance, and SGA in PEW patients [60]. However, in the ADEMEX study, significant differences were not observed between the nutritional markers (nPNA, body weight, prealbumin) with the increase in the dose of PD to 60 l/week [61]. Therefore, it can be concluded that what is actually considered an adequate dialysis in different guidelines is sufficient to preserve the nutritional status [50].

5.4. Comorbidities

Diverse comorbidities associated with ESRD contribute to a catabolic milieu and the development of PEW [6]. Metabolic acidosis increases muscle protein catabolism via suppression of the insulin/insulin growth factor-1 signaling and the activation of the ubiquitin-proteasome system [50]. In PD patients, correction of the serum level of bicarbonate has demonstrated downregulation of branched-chain amino acid degradation and muscle proteolysis [62].

Other studies have reported an improvement in the nutritional status with the correction of the metabolic acidosis through an increase in the body weight, mid-arm circumference, SGA score, and the nPNA [63, 64]. Diabetes mellitus is one of the most frequent comorbidities in patients with CKD [6], and PEW is more prevalent in diabetic PD patients compared to nondiabetics [65, 66]. The degree of insulin resistance and/or insulin deprivation seems to develop this condition [50]. Therefore, the adequate management of diabetes and insulin resistance is important in preventing further loss of lean body mass in patients undergoing maintenance dialysis. This is especially relevant for PD patients because of the exposure to around 80–330 g of additional glucose from the dialysate [50]. Inflammation is frequent in PD patients and is associated with PEW, peritoneal membrane dysfunction, and cardiovascular events [67]. The increase in systemic concentrations of proinflammatory cytokines is thought to play an integral role in the muscle catabolism of patients with ESRD. Interleukin-6 causes an increase in muscle proteolysis, and the tumor necrosis factor-alpha can cause anorexia through its effects on the satiety center in the central nervous system [68]. Strategies that can reduce inflammation include the control of infectious processes, optimizing the prescription of PD (improving the volume state, biocompatible solutions), pharmacological interventions (statins, angiotensin-converting enzyme inhibitors, sevelamer), and nutritional interventions (antioxidants) [69]. Another common comorbidity is congestive heart failure [6]. In these patients the circulatory congestion has been associated with a reduction in the protein and calorie intake, greater inflammation, PEW, and the increase in resting energy expenditure [70]. Other disorders like uncontrolled hyperparathyroidism and cardiac cachexia are associated with systemic inflammation and the increase in energy expenditure [50]. The symptoms of depression, which are common in ESRD patients, are related to fatigue, the lack of appetite, and weight loss. Early recognition and treatment are important components in the prevention of PEW [68].

6. Treatment of protein-energy wasting

For patients in whom the standard preventative measures are unable to diminish the loss of protein and energy stores, nutritional supplementation should be initiated through oral, intraperitoneal, enteral, or parenteral routes. Anabolic agents, appetite stimulants, anti-inflammatory interventions, and exercise can be utilized as adjuvant therapies [50].

6.1. Oral nutritional supplementation

Oral supplementation can provide an additional 7–10 kcal/kg per day of energy and 0.3–0.4 g/kg per day of protein. This requires a minimum spontaneous dietary intake of 20 kcal/kg per day of energy and 0.4–0.8 g/kg per day of protein in order to meet the recommended dietary energy intake and dietary protein intake targets [50, 68]. Oral nutritional supplements have been shown to improve protein-calorie intake and the nutritional status (body weight, prealbumin, SGA score) in PD patients [71, 72]. However, a high rate of non-compliance and intolerance has been reported with the long-term use of these types of supplements [73]. Other

studies have demonstrated that supplementation with calcium caseinate and egg albumin increases levels of serum albumin and nutrient intake [74, 75]. When considering the use of these supplements, in addition to the type and quantity to use, one must also take into consideration the baseline nutritional status, dietary intake, patient preference, acceptance, willingness to use and to purchase the supplements, tolerance and contraindications, and duration of use in the care plan [76].

6.2. Intraperitoneal nutritional supplementation

PD patients lose 3–4 g/day of amino acids (AAs) and 4–15 g/day of proteins [77, 78]. One exchange with a 1.1% AA dialysis solution has been demonstrated to be sufficient to compensate for these losses [78]. In patients with PEW, the treatment with AA in the nitrogen balance dialysate became significantly positive, and there was a significant increase in net protein anabolism, the fasting morning plasma amino acid pattern became more normal, and serum total protein and transferrin concentrations rose [79]. In another long-term study, improvements in some nutritional parameters including the nPNA, lean body mass, and handgrip strength have been observed [80]. In general, it is recommended to use one bag of AA dialysate in place of one glucose-based dialysate. Using more than one bag during a 24-h period runs the risk of increasing the level of urea nitrogen and decreasing levels of bicarbonate [39]. Overall, AA dialysate remains a viable option in PD patients with PEW who cannot tolerate or are not suitable for PO (per oral) and other enteral supplements [50].

6.3. Enteral nutritional supplementation

Enteral nutrition has been poorly investigated in PD patients [81]. Considerations for its use include the lack of improvement in nutritional status despite the use of oral nutritional supplements, the presence of severe PEW, spontaneous intake of <20 kcal/day, or conditions of stress [82]. Enteral nutrition can be administered via nasogastric feeding [51]. The use of percutaneous endoscopic gastrostomy or percutaneous endoscopic jejunostomy has been contraindicated in these patients due to the increase in the incidence of peritonitis [81]. However, there have been some reports of cases where the percutaneous endoscopic gastrostomy can be an effective nutritional strategy [83–85]. The feeding formulas with a higher protein but lower carbohydrate content are to be preferred. Products rich in proteins should be used as oral nutritional supplements [81].

6.4. Parenteral nutritional supplementation

Parenteral nutrition has also been poorly investigated in PD patients [82]. It has been suggested that its initiation should be limited to patients with PEW and those who are stressed, or in patients with severe encapsulating peritonitis, when the nutritional requirements cannot be ensured through oral or enteral routes [82]. Early parenteral nutrition has been shown to maintain a positive nitrogen balance in peritonitis [86]. As well, in patients with encapsulating

peritoneal sclerosis, the parenteral nutritional support seems to be better than enteral nutrition [87, 88]. During parenteral nutrition the energy supply should combine carbohydrate and lipid. The use of specific formulas for parenteral mixtures is not yet supported by controlled data [82].

7. Adjuvant therapies

Diverse adjunctive therapies can be used to treat PEW in these patients. The use of anabolic hormones results in a positive nitrogen balance, an increase in lean body mass, and improvement in the anthropometric parameters [89–91]. Appetite stimulants can have favorable effects on body weight, appetite, and calorie intake [92, 93]. When comorbidities and potential dialysis-related causes of inflammation have been assessed and appropriately treated, other anti-inflammatory treatment strategies such as anti-oxidative and/or bioecologic strategies or targeted anti-cytokine therapies could be considered in patients who are persistently inflamed [68]. On the other hand, PD patients have low levels of physical activity, which can be associated with PEW [94, 95]. Progressive resistance exercise induces skeletal muscle hypertrophy, increases muscular strength, and improves the health-related quality of life [96]. This is important since exercise interventions can prevent or reverse PEW [97].

8. Conclusions

PEW is very frequent in PD patients and is associated with mortality. Assessment and monitoring of the nutritional status are important to diagnose, prevent, and treat PEW. Large-scale clinical trials and international collaborations that refer to the effects of nutritional interventions on PEW are necessary in order to advance on this subject. Meanwhile, individualizing the different interventions for prevention and treatment of PEW proposed in this chapter should be employed in PD patients.

Clinical scenario responses for the diagnosis of protein-energy wasting in peritoneal dialysis:

Case 1 = (B) Albumin, BMI, and MAMC or protein/energy intake.

Case 2 = (C) 1–2 Severe PEW.

Case 3 = (A) 22.

Case 4 = (B) 67.68.

Conflict of interest

There are no conflicts of interest to report.

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Chapter 7

Peritonitis in Peritoneal Dialysis

Sohail Abdul Salim and Tibor Fülöp

Additional information is available at the end of the chapter

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Abstract

Peritoneal dialysis (PD) involves solute and water transport across a semipermeable membrane that separates fluid compartments. Peritonitis is a serious complication of peritoneal dialysis that results in considerable morbidity and health care costs. It also significantly distorts the normal anatomy of the peritoneal membrane causing transient and long-term adverse events. Bacterial as well as fungal organisms can cause peritonitis and sometimes cultures can be negative. As much as 5–16% of deaths occur in PD even though the rate of infections has been in decline in last few years. Below we will be reviewing risk factors, host's immune defenses, prevention, diagnosis and evidence-based treatment, types of peritonitis with a role of prophylactic antibiotics for PD peritonitis.

Keywords: bacteria, abdominal pain, leukocytosis, treatment, antibiotics

1. Introduction

Peritoneal dialysis is one of two principal modalities for renal replacement therapy and has been utilized extensively in many countries including Hong-Kong, Mexico, Thailand, Canada, the Netherlands, Australia and Denmark. One of the commonest complications of peritoneal dialysis is peritonitis, which leads to increased health care costs, hospitalizations, catheter removal, malnutrition and peritoneal membrane damage. Survival on PD continues to improve in the United States, with overall survival as good as for similar patients during in-center hemodialysis (HD). Nonetheless, approximately 20% of patients undergo a modality switch to HD during their first year on PD due to modality or access-related infections. Repeated episodes of bacterial peritonitis are a major factor leading to the loss of peritoneal function and resulting in failure of PD [1, 2]. PD peritonitis seldom evolves into systemic bacteremia or fungemia and the infection remains as a rule confined to the peritoneal cavity. With increased

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peritoneal permeability during peritonitis, a reduction in ultrafiltration occurs, which would lead to fluid accumulation and potential symptomatic volume overload.

2. Relative immunosuppression in end-stage renal disease

Peritoneal leucocytes are predominant players in combating bacteria in the peritoneal cavity. Most dialysate solutions have an unphysiological pH of 5, which might inhibit the phagocytic ability of these leucocytes. End-stage renal disease (ESRD) impairs both innate and adaptive immune responses. Decreased endocytosis and impaired maturation of monocytes and dendritic cells are demonstrated in the uremic state, contributing to an increased susceptibility to infections [3, 4]. Impaired maturation of thymic lymphocytes and impaired functions of toll-like receptors (which provide protection against infections) also increase the susceptibility to infections.

3. Strategies for prevention of peritonitis

Peritonitis with automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) are not different. All PD programs in the United States monitor the incidence of peritonitis (rates should be no higher than 0.5 episodes per year), which helps programs target interventions when rates go high. The Baxter database of 35 US centers reports 3111 episodes of peritonitis with an overall peritonitis rate of 1 per 33 patient months, while the overall exit site infection (ESI) rate is 1 per 65 patient months. Reported causes of peritonitis include contamination during treatments, untreated PD catheter tunnel or exit point infections, transmural migration of organisms from the gut due to diverticulitis, systemic infections and procedural instrumentation (gynecologic, dental or post-colonoscopy). Touch contamination is the most common source followed by ESI and tunneled catheter infections. Jassal reported an association between a treated ESI and subsequent PD peritonitis [5]. One of the earliest multi-center randomized clinical trials comparing the Y connector disinfectant system to standard systems showed superiority and decreased infections with Y connectors using "flush before fill" techniques [6]. The practice has become widespread since. Appropriate interventions including educating and teaching patients' strict aseptic precautions (including hand hygiene) during exchanges along with intensive retraining and reinforcement of sterile techniques might have led to a decrease in infections.

In the last 2 decades we have realized that exit site and tunneled infections contribute extensively to peritonitis risk in the days immediately following the diagnosis. Treatment of an exit site infections are especially critical as the peritonitis risk is increased >10-fold in the first 15 days with a progressive decrease but continuous presence up to 2–3 months [5]. These observations resulted in the practice of daily topical application for prophylactic antibiotic (mupirocin or gentamicin) creams or ointments to the catheter exit sites and prompt treatment of ESI worldwide. A double-blind randomized trial showed that the daily application of gentamicin cream on the exit site resulted in a 57%-reduction in ESI and a 35%-reduction in peritonitis compared with mupirocin. Gentamycin, a bactericide, also prevented infections with

Social/environmental
• Smoking
• Living distantly from PD unit
• Pets
Medical
• Obesity
• Depression
• Hypokalemia
• Hypoalbuminemia
• Absence of vitamin D supplementation
• Invasive interventions (e.g. colonoscopy)
Dialysis-related
• Prior hemodialysis
• PD against patient's choice
• Training
• Bioincompatible fluids
• Wet contamination
Infection-related
• Nasal *Staphylococcus aureus* carrier status
• Previous exit site infection

Adapted from Cho [19] and ISPD 2016 guidelines [20].

Table 1. Modifiable risk factors of peritonitis.

Staphylococcus aureus and *Pseudomonas aeruginosa* [7]. At least 3 trials have shown that topical exit site disinfection with povidone-iodine did not reduce the risk of peritonitis compared to soap and water or no treatment [8, 9]. Randomized controlled trial (RCT) of mupirocin to a "triple-antibiotic" combination (bacitracin, gramicidin and polymyxin B) showed non-superiority to mupirocin and concern for fungal colonization of exit site with triple-antibiotic use. Further, exit site trauma should be treated with antibiotic prophylaxis. High levels of soluble C5b-9 in the dialysate predict poor prognosis during peritonitis [10]. Antifungal prophylaxis with oral fluconazole (200 mg orally on day one, then 100 mg/day for 1 week after completion of treatment) or nystatin (500,000 IU orally three times a day while on antibiotics) can be considered with concurrent antibiotic use, while treating peritonitis to prevent fungal peritonitis. There is uncertainty regarding fluconazole for prophylaxis against fungal peritonitis but one RCT supported the use of nystatin [11].

Antimicrobial actions of peritoneal macrophages are enhanced by both calcium and vitamin D. Kerschbaum reported that calcitriol decreased the risk of peritonitis and improved survival [12]. Even though there were initial reports of low peritonitis rates with low glucose-degradation-product (GDP) solutions, a subsequent meta-analysis of 6 randomized controlled trials concludes uncertainty at this time [13, 14]. Gastroenteritis and hypokalemia

have been linked to peritonitis risk, though there is no evidence that treating these would decrease said risk. **Table 1** lists modifiable risk factors for peritonitis. For hypokalemia management and prophylaxis, potassium-sparing diuretics are effective even in PD patients [15–17]. Most nephrologists agree on the importance of avoiding constipation to prevent peritonitis and monitoring peritonitis rates and trends in their programs with intensive retraining in patients with frequent episodes of peritonitis. The International Society of Peritoneal Dialysis (ISPD) recommends prophylactic systemic antibiotics immediately prior to catheter insertion on the basis of 4 RCT. Placement of PD catheters with a downward-facing exit site decreases risk. Nevertheless, the 2017 ISPD guidelines concluded that none of the catheter placement techniques are superior in the prevention of any catheter-related infection [18]. The use of topical mupirocin in patients with colonization of nares is recommended before PD catheter insertion. The role of prophylactic antibiotics in preventing peritonitis is discussed in detail below.

4. Role of prophylactic antibiotics prior to procedures

Invasive interventional procedures like colonoscopy, hysteroscopy, sigmoidoscopy, cystoscopy, cholecystectomy or dental procedures show a significant risk of progressing to peritonitis; hence the ISPD recommendation of preprocedural antibiotics in such cases. Even though 2005 ISPD guidelines recommended prophylaxis with minimal evidence, Yip et al. [21] in 2007 conducted a single-center study in which peritonitis occurred in 6.3% of 79 colonoscopies performed without antibiotic prophylaxis and none performed with antibiotic prophylaxis. Since then, most programs have been implementing preprocedural antibiotics. Gadallah's study of 221 patients concludes that single-dose vancomycin is superior to single-dose cefazolin and reduces peritonitis prior to PD catheter insertion [22]. **Table 2** lists appropriate antibiotics before procedures, which are purely opinion-based.

- Exit site care with topical mupirocin or gentamycin in all patients
- Dental procedures
  - Amoxicillin 2.0 g 2 h before
- Colonoscopy or GYN procedures:
  - Aminoglycoside overnight + oral metronidazole or ampicillin 1 g PO
  - Fluconazole added in GYN procedures
  - Perform procedures with dry abdomen and for a day afterwards
- Antifungals when on systemic antibiotics to prevent secondary peritonitis

Adapted from ISPD [18].

Table 2. Preprocedural antibiotic prophylaxis to prevent peritonitis.

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5. Presentation, diagnosis and management of peritonitis

Peritoneal dialysis patients have catheter embedded in their abdomen all the way to peritoneum. Infection can occur anywhere between the exit site of catheter, the tunneled area and the peritoneum. PD-related peritonitis is a local infection and only 20% of patients with peritonitis end up hospitalized. Catheters can get colonized with organisms, which sometimes form a biofilm. Mild trauma to the exit site may also cause peritonitis when conditions are favorable, as is the case with colonization and depressed immunity. Exit site infections could progress to tunneled infections and peritonitis if left untreated in most cases. Since most programs use antimicrobial prophylaxis, exit site infections are on the decline. ISPD 2017 recommends that the rate of catheter-related infections should be presented as numbers of episodes per year. Patients usually present with abdominal symptoms including abdominal pain, discomfort, vomiting or cloudy effluent. Fever with tachycardia and florid sepsis is seldom present. Patients should be asked about contamination during exchanges, signs of exit site infection, constipation, recent procedures, hospitalizations and recent antibiotic use for other systemic infections. A physical exam could reveal abdominal tenderness, redness at the exit site and should look for evidence of hernias.

Once peritonitis is suspected, empiric antibiotics should be started as soon as possible after drawing dialysate for cell count, culture and Gram stain. ISPD recommends collecting cultures of 5–10 mL of effluent in blood culture bottles. Peripheral blood cultures are taken only if the patient looks toxic and septic. Diagnosis requires that cell count be >100 cells/mm^3 with appropriate symptoms. If >50% of WBCs are polymorph mononuclear leucocytes (PML), it is very likely that the patient has bacterial peritonitis even if the total cell count is <100 cells/mm^3. It is recommended in APD to collect PD fluid after a dwell time of at least 2 h. One should be able to read a newspaper when effluent bag is laid over, which is a simple inexpensive test to see whether dialysate is cloudy, or not. Only cell count with appropriate cultures can confirm diagnosis though. Conditions that lead to cloudy effluent are listed in **Table 3** and criteria for diagnosis of peritonitis are listed in **Table 4**.

Most PD-related infectious peritonitis will have amylase levels of <50 IU/L in effluent and pancreatitis or other intra-abdominal pathology showing >50 IU/L, but one needs to note that icodextrin interferes with amylase assay and is not reliable. Systemic antibiotics are usually not needed since infection is local. Antibiotics via dialysate can be given intermittently every few days or continuously with every bag; programs may differ in their approaches. Nevertheless, if the patient is unresponsive to the intermittent approach for 3–4 days, a continuous approach is recommended. The decision to admit to inpatient service is generally dictated by the patient's general condition and degree of illness, rather than the underlying diagnosis of suspected PD-associated peritonitis. Most of these events will be treated in outpatient care.

Initial therapy with broad spectrum antibiotics is recommended as soon as possible for covering both Gram-positive and -negative organisms until culture results are available. For

Infectious peritonitis
Pancreatitis
Chemical peritonitis (medications, e.g., dihydropyridine calcium channel blockers [nifedipine, lercanidipine]))
Malignant ascites
Effluent eosinophilia
Sclerosing peritonitis
Chylous ascites
Specimen from dry abdomen

Table 3. Differential diagnosis of cloudy effluents.

1. Clinical, i.e. abdominal pain with our without cloudy dialysate
2. Effluent white cell count >100/μL or >0.1 × 10^9/L (dwell time of at least 2 h), and >50% polymorphs
3. Culture positive dialysate
Adapted from ISPD [20]. At least 2 of the above should be positive to diagnose peritonitis.

Table 4. Diagnosis of peritonitis.

Gram-positive organisms, vancomycin (with history of MRSA) or cephalosporins are recommended, as well as and ciprofloxacin, ceftazidime, cefepime or aminoglycosides tailored depending on whether the patient has significant residual renal function. Barretti conducted a proportionate meta-analysis and found that vancomycin and teicoplanin with ceftazidime were found to be superior to other regimens [23]. One needs to keep in mind sensitivities, common resistance patterns locally, the patient's residual renal function and a history of peritonitis. The opacity of the fluid is expected to change from cloudy to clear in around 48–72 h. **Figure 1** lists the initial approach to peritonitis. In most cases, culture positivity can be established within 3 days. When the causative organism has been identified, subsequent cultures may be performed for monitoring, but when cultures remain negative after 3–5 days of incubation, cell count and differential, fungal, and mycobacterial cultures are to be repeated. Every organism's interaction with the immune system is unique. Lin's study of 52 patients provide evidence that local "immune fingerprints," representative of specific organisms, are evident in said patients and differentiate between culture-negatives, Gram-positives or -negatives [24]. These immunologic biomarkers seem promising even though point of care tests have not yet been used widely.

Even though vancomycin is the preferred empiric therapy in methicillin-resistant *Staphylococcus aureus* (MRSA), there is no difference in cure rates for vancomycin and cefazolin when an appropriate cephalosporin dose is used in the context of methicillin-sensitive *Staphylococcus aureus*. It has been speculated that local (compartmental) antibiotic concentration with IP administration will greatly exceed concentrations serum concentrations, on which the general

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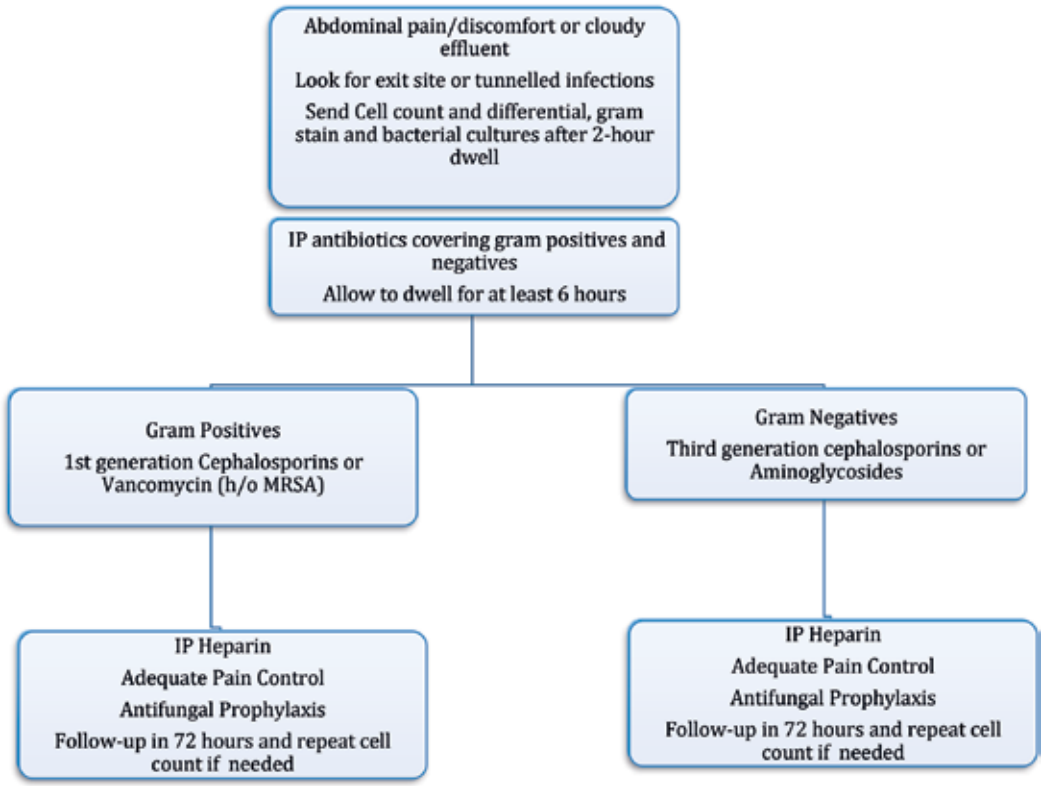

Figure 1. Initial approach to peritonitis.

concept of sensitivity is based upon. Ceftazidime, cefepime, aminoglycosides (e.g. gentamicin or netilmicin) or a carbapenem cover Gram-negatives adequately. Fluoroquinolones could be used if cultures show sensitivity, but there is an increased risk of Achilles tendon rupture in renal failure with fluoroquinolones. In patients allergic to cephalosporin, aztreonam could be used. Aminoglycosides demonstrate excellent Gram-negative activity and could be used in resource-poor nations where cost would be a barrier, as there is no evidence that short courses of aminoglycosides accelerate the loss of residual renal function [25] unless used for more than 3 weeks. Systemic absorption with a prolonged use of IP gentamycin can cause toxicity and might not correlate with systemic levels.

ISPD recommendations regarding the dosing of intraperitoneal (IP) antibiotics are listed in **Table 5**. These antibiotics should be administered using sterile techniques and IP use results in high local drug levels and is preferable to IV administration as peritonitis is mostly local and antibiotics are delivered at high concentration to the infected compartment, including to ensure the penetration of infected biofilms on peritoneal catheters [26]. Intermittent dosing should be dwelled for at least 6 h to allow for adequate absorption. IP vancomycin is dosed every 4–5 days, keeping serum trough levels above 15 μg/mL even though most programs do not check systemic levels. For patients on APD, intermittent doses of IP can be administered,

Aminoglycosides	Intermittent (1 exchange daily)	Continuous (all exchanges)
Amikacin	2 mg/kg daily	LD 25 mg/L, MD 12 mg/L
Gentamicin	0.6 mg/kg daily	LD 8 mg/L, MD 4 mg/L
Netilmicin	0.6 mg/kg daily	MD 10 mg/L
Tobramycin	0.6 mg/kg daily	LD 3 mg/kg, MD 0.3 mg/kg
Cephalosporins		
Cefazolin	15–20 mg/kg daily	LD 500 mg/L, MD 125 mg/L
Cefepime	1000 mg daily	LD 250–500 mg/L, MD 100–125 mg/L
Cefoperazone	No data	LD 500 mg/L, MD 62.5–125 mg/L
Cefotaxime	500–1000 mg	no data on daily dosage
Ceftazidime	1000–1500 mg daily	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1000 mg daily	No data
Penicillins		
Penicillin G	No data	LD 50,000 unit/L, MD 25,000 unit/L
Amoxicillin	No data	MD 150 mg/L
Ampicillin	No data	MD 125 mg/L
Ampicillin/sulbactam	2 g/1 g every 12 h	LD 750–100 mg/L, MD 100 mg/L
Piperacillin/tazobactam	No data	LD 4 g/0.5 g, MD 1 g/0.125 g
Others		
Aztreonam	2 g daily	LD 1000 mg/L, MD 250 mg/L
Ciprofloxacin	No data	MD 50 mg/L
Clindamycin	No data	MD 600 mg/bag
Daptomycin	No data	LD 100 mg/L, MD 20 mg/L
Imipenem/cilastatin	500 mg in alternate exchange	LD 250 mg/L, MD 50 mg/L
Ofloxacin	No data	LD 200 mg, MD 25 mg/L
Polymyxin B	No data	MD 300,000 unit (30 mg)/bag
Quinupristin/dalfopristin	25 mg/L in alternate exchange[a]	No data
Meropenem	1 g daily	No data
Teicoplanin	15 mg/kg every 5 days	LD 400 mg/bag, MD 20 mg/bag
Vancomycin	15–30 mg/kg every 5–7 days[b]	LD 30 mg/kg, MD 1.5 mg/kg/bag
Antifungals		
Fluconazole	IP 200 mg every 24–48 h	No data
Voriconazole	IP 2.5 mg/kg daily	No data

Courtesy of ISPD 2016 [20].

[a]Given in conjunction with 500 mg intravenous twice daily.

[b]Supplemental doses may be needed for APD patients.

Table 5. Intraperitoneal antibiotic dosing recommendations for treatment of peritonitis.

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Drug	Dosing
Anti-bacterials	
Ciprofloxacin	Oral 250 mg BD
Colistin	IV 300 mg loading, then 150–200 mg daily
Ertapenem	IV 500 mg daily
Levofloxacin	Oral 250 mg daily
Linezolid	IV or oral 600 mg BD
Moxifloxacin	Oral 400 mg daily
Rifampicin	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg
Trimethoprim/sulfamethoxazole	Oral 160 mg/800 mg BD
Antifungals	
Amphotericin	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 h; target dose 0.75–1.0 mg/kg/day
Caspofungin	IV 70 mg loading, then 50 mg daily
Fluconazole	Oral 200 mg loading, then 50–100 mg daily
Flucytosine	oral 1 g/day
Posaconazole	IV 400 mg every 12 h
Voriconazole	Oral 200 mg every 12 h

Adapted from ISPD 2016 [20]. BD, twice a day; IV, intravenous; BW, body weight.

Table 6. Systemic antibiotic dosing recommendations for the treatment of peritonitis.

Organism	Duration of treatment
Coagulate negative *Staphylococcus aureus*	2 Weeks
Staphylococcus aureus	3 weeks
Streptococcus	2 weeks
Enterococcus	3 weeks
Most Gram-negative bacilli	3–4 weeks
Stenotrophomonas species	3–4 weeks
Pseudomonas	3–4 weeks
Mixed Gram-positive and Gram-negative organisms	3 weeks
Multiple Gram-positive organisms	3 weeks
Fungal organisms (immediate catheter removal)	2–3 weeks post catheter removal
Corynebacterium species	3 weeks

Table 7. Duration of treatment of PD peritonitis by organism type.

Fungal peritonitis
Failed treatment for mycobacterial and polymicrobial infections
Refractory peritonitis
Relapsing peritonitis
Refractory exit site and tunneled infections

Table 8. Indications for catheter removal.

utilizing a day dwell of APD, or alternatively, a temporary change to CAPD might become necessary. Heparin at a dose of 500 units/L may be added to the PD fluid to decrease fibrin formation. In patients with biofilm in the catheter, the administration of oral rifampicin and IP urokinase to disrupt the catheter-associated biofilm resulted in catheter salvage in 64% of cases [27]. Chow analyzed outcomes of 565 consecutive episodes of peritonitis in relation to dialysate cell counts and concluded that effluent WBC count ≥1090/mm^3 on day 3 was an independent prognostic marker for treatment failure [28]. The dosing of systemic antibiotics per ISPD recommendation is listed in **Table 6**. After empiric initial treatment, antibiotics are tailored depending on culture results with a duration of treatment determined by the type of organism affected (**Table 7**).

Mycobacterial infections are rare but present a challenge to diagnosis and should therefore be considered in the appropriate patients (living in third world or developed countries with endemic areas or history of travel) with persistent symptoms despite optimal periods of time on antibiotics. When effluent cultures are negative by day 3 (culture-negative peritonitis), cell count with differential should be repeated; if symptoms persist, effluent should be tested for tuberculous and nontuberculous mycobacteria in conjunction with a continuation of antibiotics for Gram-positive organisms. Aminoglycoside antibiotics should be discontinued if the patient remains asymptomatic with negative cultures. Native kidneys can clear antibiotics and there is higher risk of treatment failure in patients with significant residual renal function especially in Gram-positive and culture-negative patients [29]. Guidelines for the removal of catheters are listed in **Table 8**.

6. Standard definition with types of peritonitis (not based on type of organism)

6.1. Recurrent

Occurs within 4 weeks of completed therapy of previous episode with new organism. Carries worse prognosis than relapsing and repeat peritonitis. If polymicrobial or enteral organisms are seen, would need surgical evaluation and appropriate imaging of abdomen. Catheter removal should be considered.

6.2. Relapsing

Occurs within 4 weeks of completion of therapy of previous episode with the same organism. Lower rate of cure reported and catheter removal should be considered, especially if there is a suspected bacterial colonization of catheter. Sonography of catheter tunnel is also recommended.

6.3. Repeat

Occurs more than 4 weeks post-therapy of a prior episode with the same organism. Risk is highest 3 months after an episode and remains high for next 24 months [19]. Revaluate antibiotic dosage and optimal duration of treatment. Further management depends on antibiotic sensitivity and might consider adding a second antibiotic for synergy although no evidence exists for this recommendation. Catheter removal could be considered depending on clinical status of patient.

6.4. Refractory

Effluent fails to clear after 5 days of appropriate therapy. Treatment includes immediate removal of PD catheter and intravenous antibiotics.

6.5. Catheter-related peritonitis

Exit site or tunnel infection progressing to peritonitis with the same organism. Sonogram of catheter tunnel if no signs of tunneled infection. Exit site infections that do not progress to peritonitis can be treated with oral antibiotics. If refractory exit site or tunneled infection is diagnosed, one should consider removal of the PD catheter.

6.6. Eosinophilic peritonitis

Cloudy effluent with >15% eosinophils. Could be seen in parasitic, tuberculous or fungal infections, or during recovery from bacterial peritonitis. Also seen with allergy to components of dialysate or catheter material and is usually self-limited needing no treatment, except with severe symptoms where treatments including steroids have been tried.

7. Summary

Peritoneal dialysis can cause infectious and noninfectious complications and peritonitis is one of the most common infectious complications. Peritonitis causes alteration of membrane transport characteristics leading to ultrafiltration failure and, with repeated episodes, will evolve into encapsulating peritoneal sclerosis. Multiple hospitalizations, transfer to hemodialysis and malnutrition-related complications could result in increasing health care costs in an era where pay for performance is advocated. There has been an increasing trend in

Gram-negative infections and decrease in Gram-positive infections [30, 31]. Intensive quality improvement projects, root cause analysis of adverse events, aggressive retraining and other prevention strategies discussed above should be implemented to decrease a potentially preventable adverse event and achieve improved outcomes.

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Evolving Strategies in Peritoneal Dialysis is intended as a concise compilation of articles designed to understand the basics of the current practice of the most cost-effective form of life support for patients with end-stage renal disease who require dialysis. Current strategies are understood best with a review of the historical development of catheter materials, solution packaging, and simplified machinery, which allow safe and effective nocturnal treatments. Quantitation of the efficacy of peritoneal dialysis is also reviewed because such calculations were also developed by the pioneers of nephrology to ensure adequacy of dialysis and daily fluid balance, which are responsible for the best chance for long-term patient survival. Comparison of methods for catheter placement is presented as well as the role that a dialysis center plays in the health and success of this form of end-stage renal disease patient care. The novel concept of assisted peritoneal dialysis for the infirm or institutionalized patients is probably the next direction needed to make available this treatment to many more patients than are currently eligible to receive it. This concept is explored in a separate chapter. Finally, professional dialysis staff must monthly assess individuals' nutritional status, bone health, and infection prevention and treatment to ensure the greatest functional status for these patients. This book concludes with a review of each of these topics to expand the mandatory monthly surveillance performed by dialysis centers for each patient who receives home peritoneal dialysis therapy.

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