Review Article

Peritoneal dialysis associated-peritonitis: a preventable complication

Regina de Miguel-Ibañez[1]*, Carlos Alberto Ramirez-Ramirez[1], Marcos Daniel Sanchez-Gonzalez[1], Angel Cesar Ortiz-Bello[2]

[1]Department of Internal Medicine, [2]Department of Nephrology, Regional General Hospital Institute of Social Security, Queretaro Mexico

*Correspondence:
Regina de Miguel-Ibañez,
E-mail: reginadm94@gmail.com

ABSTRACT

Peritoneal dialysis is useful renal replacement therapy for patients with end-stage chronic kidney disease. Latin America has 30% of the world population in peritoneal dialysis and within these countries Mexico covers 73% of them. In our country, the Mexican institute of social security (IMSS by its Spanish acronym) serves more than half of the Mexican population that requires renal replacement therapy. In 2014 it represented 15% of total annual cost of the institution. Peritonitis in peritoneal dialysis is the main complication seen in this renal replacement therapy with morbidity and mortality from 2 to 6%. The epidemiology of peritonitis associated with peritoneal dialysis varies according to the continent, country and dialysis center. The rate of peritonitis per year of each center reflects their quality of care. The prevention, diagnosis and treatment of peritonitis impact in the quality of life of the patient, the success of renal replacement therapy, public health costs and associated mortality. This review addresses the epidemiology, diagnosis, treatment, and preventive measures of peritonitis, focused on the procedures for improving the standards of care.

Keywords: Peritoneal dialysis, Peritonitis, Risk factors, Quality improvement

INTRODUCTION

Renal replacement therapy includes kidney transplantation or one of the dialysis modalities: hemodialysis (HD) or peritoneal dialysis (PD), both allow renal replacement through the extraction of solutes and water, restoring an electrolyte balance and correcting acid-base disorders, however, unlike HD that uses a vascular access and an extracorporeal system, PD involves an exchange of solutes and water between the peritoneal capillaries and the solution installed in the peritoneal cavity.[1] The different modalities of peritoneal dialysis are chosen based on the individual characteristics of each patient. Continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are the most common methods used.

In CAPD the replacements are carried out manually while in APD an automatic cycler performs 3 to 6 changes during the night as the patient sleeps. The latter is subdivided into intermittent nocturnal peritoneal dialysis (INPD) and continuous cyclic (CCPD), with the difference that the cyclical mode allows the use of manual replacements during the day.[1] Peritonitis associated with peritoneal dialysis is a serious complication it represents one of the main failures in the technique and the main cause of transfer to permanent hemodialysis.[2]

EPIDEMIOLOGY

In 2013, the CKD was the third cause of death in Mexico reported by the world health organization (WHO) and the global burden of disease project, with 9% of all mortality

reported, in addition to contribute to 8.1% of the years of life lost due to premature death and 5.7% of the years of healthy life lost due to disability.[3]

In 2018 it was estimated that 11% of patients on long-term dialysis were managed with peritoneal dialysis, of which more than half of the population in peritoneal dialysis were in countries such as China, Mexico and the United States.[1] Latin America represents 30% of the population on peritoneal dialysis worldwide, with a reported growth of 14% from 2008 to 2010.[4] The countries with the largest population in this modality of renal replacement therapy were Mexico, Brazil, Colombia and El Salvador. Within these, Mexico has 73% of the Latin American population that receives peritoneal dialysis.[5] In our country, the Mexican institute of social security (IMSS by its Spanish acronym) serves approximately 73% of the Mexican population that requires renal replacement therapy. In 2014, it represented 15% of the total annual expenditure of the institution. If access to dialysis were universal in our country, an investment of more than 33,000 million pesos per year would be required, which represents close to 40% of the national budget for health.[3]

The epidemiology of peritonitis associated with peritoneal dialysis varies according to the continent, country and dialysis center analyzed. The epidemiological analysis within the same region has determined different peritonitis-year rates because each center has different characteristics in their quality of care, even though international recommendations have been established to unify criteria by the International society for peritoneal dialysis (ISPD).[6] The reported mortality ranges from 2 to 6%.[7] In a study by Sipahioglu et al an 87% increase in the risk of associated mortality was reported for each 1 increase in the patient-year peritonitis rate.[8] The variation in the incidence of peritonitis between centers depends on the degree of adherence to the recommendations proposed to improve the care of patients on peritoneal dialysis according to the guidelines of the ISPD. The centers that follow these recommendations had better performance with lower peritonitis-year rates, lower transfer to hemodialysis and lower mortality.[9] The annual incidence of peritonitis should be reported as the rate of peritonitis per patient-year, in order to make comparisons between centers and establish the causality between the most prevalent etiological agents and the route of transmission. The ISPD suggests the use of a universal language under the term patient-year peritonitis rate calculated as an absolute rate.[2]

In the results of the various studies on the incidence of peritonitis associated with peritoneal dialysis, rates of peritonitis as low as 0.06 patient-years and as high as 1.66 in Israel have been reported, with a proposed rate of 0.36 episodes of patient-year peritonitis.[10,11] However, the overall suggested maximum peritonitis rate should not exceed 0.5 patient-year episodes regardless of the peritoneal dialysis modality used.[2]

PERITONITIS ASSOCIATED WITH PERITO-NEAL DIALYSIS

Peritonitis is defined by the presence of two of the following elements: abdominal pain, which is usually diffuse, general malaise and sometimes fever, with cloudy characteristics in the dialysis fluid; leukocyte count of the effluent ≥ 100 cells with$> 50\%$ polymorphonuclear cells (PMN), with at least two hours of stay in the cavity; isolation of the causative agent. Patients in APD can be diagnosed with peritonitis by presenting 50% PMN without the need for cytology with more than 100 cells associated with the rapid changes performed by the cycler with a short stay in the cavity.[2]

Peritonitis is the main cause of transfer to permanent hemodialysis, the cost of hemodialysis therapy in external centers, with surrogate service, is 4.8 times greater than the cost per patient at year in CAPD, and 3.2 times more expensive hemodialysis compared to APD.[12] Based on this, peritoneal dialysis centers should focus attention on preventive measures applying programs to seek continuous quality improvement, identifying the sources of contamination since the etiological agents of peritonitis reveal where the problem may be. Retraining the staff and patients, change of equipment, application of new protocols and improving the precipitating condition found, since these measures achieve a reduction in the rate of peritonitis, upgrading the patients quality of life.[13,14]

RISK FACTORS AND PREVENTIVE MEASURES

There are modifiable and non-modifiable risk factors associated with the development of peritonitis listed in (Table 1).[2,15] Unfortunately, in our country the low socioeconomic status and the average study degree per person being8 years, represents one of the main risk factors for the development of peritonitis with no much to do at this basis, being a burden for the public health.[16] Exit site and catheter tract infections represent one of the main predisposing factors for the development of peritonitis associated with peritoneal dialysis, so prompt diagnosis and treatment of these infections is crucial.[2]

TREATMENT

Once the diagnosis of peritonitis has been made, it is essential to cultivate the fluid sample in order to isolate the infecting microorganism and perform the Gram stain. Inoculating the peritoneal fluid into blood culture bottles, being the currently recommended technique, needing only 5-10 ml of sample, and preferably seeking for both aerobic and anaerobic bacteria.[17] Once the culture samples have been taken, the administration of empirical antibiotic treatment, including spectrum for gram-positive bacteria and gram negative, with a first-generation

cephalosporin or vancomycin, should be promptly initiated, the latter would be the main choice if methicillin-resistant *Staphylococcus aureus* (MRSA) is more prevalent in the center. For the coverage of gram-negative bacteria, a third-generation cephalosporin such as ceftazidime, cefepime or anaminoglycoside must be added.[2] The treatment should be administered intraperitoneal since it gets into direct contact with the infection site and has an adequate systemic absorption, with subsequent diffusion back to the peritoneum.[18] This facilitates the outpatient management of patients to complete the treatment regimens, since the duration should be 14 days for gram-positive coagulase-negative cocci, and 21 days for *S. aureus* and gram-negative bacteria. Intravenous administration of treatment is reserved in those patients who present with septic shock secondary to the episode of peritonitis.[2]

Intraperitoneal treatment can be administered continuously or intermittently, the latter must be kept in the cavity for at least 6 hours. In CAPD, the continuous administration of first-generation cephalosporins presented slight superiority over intermittent doses, while aminoglycosides are preferred in intermittent doses, since there is an increase in ototoxicity associated with continuous doses due to increased peritoneal absorption in the event of peritonitis.[2] In patients with APD, the efficacy of providing antibiotic treatment with each replacement has been questioned. It is believed that there could be an under dosing because the rapid changes carried out by the cycler without reaching the minimum inhibitory concentration in intermittent schedules; as an alternative, the ISPD proposes to add the antibiotic regimen in each replacement or to change temporarily to DPCA while treating the infection.[2] However, in a study published by Ruger et al they retrospectively investigated 508 patients with peritonitis associated with peritoneal dialysis in a period of 10 years, the results showed that there is no difference in the rate of cure, relapse, catheter removal or mortality between patients treated under CAPD and APD.[19] Therefore, changing the patient during the episode of peritonitis to CAPD is unnecessary and has been associated with increases in technique failure and fluid overload.[20] Therefore, the placement of intraperitoneal antibiotics during the day in patients with APD is a favorable option with comparable success rates.[13]

There is a direct correlation between the development of fungal peritonitis after antibiotic treatment of any kind, given in a patient with peritoneal dialysis.[21-23] Therefore, the use of nystatin or oral fluconazole as antifungal prophylaxis is recommended. Nystatin shows a good safety profile, low associated adverse effects and availability in our country, compared with several pharmacological interactions, increased resistance and adverse effects associated with use of fluconazole.[2]

After 48-72 hours of initiation of empirical treatment, clinical improvement and decreased cellularity should be observed in cytology. The decrease in the cell count will be evaluated after 3 days of appropriate treatment and a total clearance should be presented in the cytology after 5 days of receiving effective antibiotics. A count greater than or equal to 1,090 cells on the third day after the start of treatment confers a data of poor prognosis, demonstrated by a cohort of 217 patients as a predictor of treatment failure with a sensitivity of 75% and specificity of 74% (relative risk 9. 03; 95% confidence interval: 4.40 to 18.6; p<0.0001).[24] Failure in the cellular clearance of dialysis fluid on the third day of appropriate therapy is associated with infection by gram negative bacteria, or infection of unusual microorganisms such as Mycobacteria, Nocardia, Legionella, filamentous fungi and other fastidious growth bacteria.[2]

Once the causative agent is isolated, we must adjust the treatment based on the sensitivity shown in the antibiogram and complete 14 days in coagulase-negative cocci and fungi, while *S. aureus* and gram-negative bacteria require 21 days of treatment. In the case of presenting Mycobacterium tuberculosis infection, it is suggested to complete antifungal treatment for 12 to 18 months.[2]

Refractory peritonitis is defined as failure in the clearance of dialysis fluid after 5 days of appropriate antibiotic treatment, relapsing is the presence of a new episode of peritonitis within 4 weeks after the end of treatment with the same microorganism or a negative culture. Recurrence is the presence of a new episode of peritonitis within 4 weeks after the end of treatment with a different microorganism and repeat is the presence of a new episode of peritonitis that occurs more than 4 weeks of completing treatment of a prior episode with the same infecting microorganism.[2]

Within the previously mentioned definitions, relapsing is associated with more cases of ultrafiltration failure, a lower cure rate and a greater reason for failure in the technique, while recurrent peritonitis represents a worse prognosis for the patient. Both relapsing and recurrent episodes suggest colonization of the catheter by biofilm-producing bacteria, such as *S. aureus* and *P. aeruginosa*. Catheter removal is mandatory in patients with refractory peritonitis, exit site infection or tunnel infection with concomitant peritonitis and fungal peritonitis, being necessary to continue with treatment for at least 2 weeks after removal.[2] There are other conditions in which removal of the catheter is not mandatory but there is a high recommendation to do so, such as recurrent peritonitis, Pseudomonas sp peritonitis, tuberculous peritonitis and that caused by multiple enteric microorganisms.

Table 1: Peritonitis risk factors.

Modifiable risk factors.[2, 15]	Non-modifiable risk factors.[15]
Obesity	
Depression	
Smoking	Advanced age
Living far away from peritoneal dialysis unit	Female gender
Wet contamination	Low socioeconomic status
Hypoalbuminemia	Afro-American or indigenous racial origin
Hypokalemia	Decreased residual kidney function
Absence of vitamin D supplement	Diabetes Mellitus
Nasal carrier of S. aureus	Arterial hypertension
Dialysis against the will of the patient	Coronary heart disease
Previous exit site infection	Chronic obstructive pulmonary disease
History of hemodialysis	
Invasive interventions (e.g. colonoscopy)	

PERITONITIS WITH NEGATIVE CULTURE

Peritonitis associated with peritoneal dialysis with a negative culture is an indicator of the quality of care at the dialysis center, since it encompasses both the technique used for taking the sample and processing the culture.[28]

A point of good practice is considered a having less than 15% of negative cultures.[2]However, there are associated medical issues that prevent the growth of the microorganism in vitro, such as the initiation of the antibiotic prior to taking the culture sample, the administration of antibiotics in the 30 days prior to the moment of culture, or the presence of microorganisms that need special nutrients for growth.[29] If after 3 days of incubation of the culture, there is no growth neither cellularity clearance, it is suggested to try to isolate unusual microorganisms such as mycobacteria, nocardia, legionella, filamentous fungi, and other fastidious bacteria. If improvement at 3 days after the start of treatment, with clearance in cellularity, it is acceptable to discontinue coverage for gram negative bacteria and continue only coverage for gram positive bacteria completing 14 days.[2]

RECOMMENDATIONS FOR IMPROVEMENT IN CARE

Each dialysis center must have knowledge of their peritonitis rate per-year and establishing appropriate protocols to standardize clinical practice and achieving the best possible results, making the necessary adjustments in the biases observed.[30] Retraining of both the patient and the staff has been proposed according to the peritonitis rate and main etiology, since it is one of the major actions to reduce the transmission.[30] Periodic retraining (every 6 months) includes re-education of the procedure, hand washing technique, connection circuits, infection control, contamination risks and application of skin antibiotics around the catheter insertion.[31] Those

patients with episodes of peritonitis or infection at the exit site benefit from new retraining.[2,6,13]

Regarding the placement of the catheter there is no difference in terms of dysfunction rate, catheter half-life, and infection rate when comparing the different insertion techniques: percutaneous guide, image-mediated, open surgical dissection and laparoscopy.[30] The use of topical gentamicin has equivalent effectiveness to topical mupirocin, however an increase in the incidence of infections at the catheter exit site caused by *P. aeruginosa* and fungi was observed in those patients who alternate the use of gentamicin and mupirocin. Therefore, using the same prophylactic topical antibiotic reduces the risk of infections by these microorganisms.[32,33] There are established measures to reduce the risk of peritonitis, such as the use of prophylactic antibiotics prior to insertion of the peritoneal dialysis catheter with coverage for gram-positive cocci. The use of vancomycin compared to a first-generation cephalosporin shows superiority in reducing the risk of developing postsurgical peritonitis.[34]

Another guideline to reduce the appearance of peritonitis is the use of "y" systems for manual connection of CAPD patients, the use of antifungal prophylaxis when administering an antibiotic treatment scheme, and the use of antibiotic prophylaxis for invasive procedures, such as colonoscopy, hysteroscopy, endodontic procedures that cause gum bleeding or if the catheter administration set was open for a long period.[2]

CONCLUSION

Among the complications associated with this modality of renal replacement, peritonitis associated with peritoneal dialysis represents an impact on the morbidity and mortality of the patient, affects the expenses of the center and indicates, according to the type of microorganism, the potential causes that trigger the infection. It is imperative that each center have knowledge of their patient-year peritonitis rate on an

annual basis since it reveals several indicators in the quality of care, as well as preventable and modifiable causes that can be implemented in order to improve the quality of life of each patient in peritoneal dialysis.

REFERENCES

1. Andreoli MCC, Totoli C. Peritoneal dialysis. Rev Assoc Med Bras. 2020;66:s37-44.
2. Li PK, Szeto CC, Piraino B, de Arteaga J, Fan S, Figueiredo AE, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2016;36(5):481-508.
3. Prevention, diagnosis and treatment of chronic kidney disease. evidence and recommendations guide: clinical practice guide. Mexico; Cenetec: 2019.
4. Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, et al. Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol. 2017;13(2):90-103.
5. Rosa-Diez G. Renal replacement therapy in Latin American end-stage renal disease. Clin Kidney J. 2014;7:431-6.
6. Piraino B, Bernardini J, Brown E, Figueiredo A, Johnson DW, Lye WC, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int. 2011;31(6):614-30.
7. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The Current state of peritoneal dialysis. J Am Soc Nephrol. 2016;27(11):3238-52.
8. Sipahioglu MH, Aybal A, Unal A, Tokgoz B, Oymak O, Utas C. Patient and technique survival and factors affecting mortality on peritoneal dialysis in Turkey: 12 years' experience in a single center. Perit Dial Int. 2008;28(3):238-45.
9. Htay H, Cho Y, Pascoe EM, Darssan D, Nadeau-Fredette AC, Hawley C, et al. Center effects and peritoneal dialysis peritonitis outcomes: analysis of a national registry. Am J Kidney Dis. 2018;71(6):814-21.
10. Chen TW, Li SY, Chen JY, Yang WC. Training of peritoneal dialysis patients Taiwan's experiences. Perit Dial Int. 2008;28(3):S72-5.
11. Cleper R, Davidovits M, Kovalski Y, Samsonov D, Amir J, Krause I. Peritonitis in a pediatric dialysis unit: local profile and implications. Isr Med Assoc J. 2010;12:348-52.
12. Méndez-Durán A, Ignorosa-Luna MH, Pérez-Aguilar G, Rivera-Rodríguez FJ, González-Izquierdo JJ, Dávila-Torres J. Estado actual de las terapias sustitutivas de la función renal en el Instituto Mexicano del Seguro Social. Rev Med Inst Mex Seguro Soc. 2016;54(5):588-93.
13. Fang W, Ni Z, Qian J. Key factors for a high-quality peritoneal dialysis program--the role of the PD team and continuous quality improvement. Perit Dial Int. 2014;34(2):S35-42.
14. Qamar M, Sheth H, Bender FH, Piraino B. Clinical outcomes in peritoneal dialysis: impact of continuous quality improvement initiatives. Adv Perit Dial. 2009; 25:76-9.
15. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving evidence, practices, and outcomes. Am J Kidney Dis. 2014;64(2):278-89.
16. Paniagua R, Ramos A, Fabian R, Lagunas J, Amato D. Chronic Kid- ney Disease and Dialysis in Mexico. Perit Dial Int. 2007;27:405-9.
17. Azap OK, Timurkaynak F, Sezer S, Cag'ir U, Yapar G, Arslan H, et al. Value of automatized blood culture systems in the diagnosis of continuous ambulatory peritoneal dialysis peritonitis. Transplant Proc. 2006; 38:411-2.
18. Salzer WL. Peritoneal dialysis-related peritonitis: challenges and solutions. Int J Nephrol Renovasc Dis. 2018;11:173-86.
19. Rüger W, van Ittersum FJ, Comazzetto LF, Hoeks SE, ter Wee PM. Similar peritonitis outcome in CAPD and APD patients with dialysis modality continuation during peritonitis. Perit Dial Int. 2011;31(1):39-47.
20. de Moraes TP, Olandoski M, Caramori JC, Martin LC, Fernandes N, Divino- Filho JC, et al. Novel predictors of peritonitis-related outcomes in the BRAZPD cohort. Perit Dial Int 2014;34:179-87.
21. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev. 2004;4:CD004679.
22. Kumar KV, Mallikarjuna HM, Gokulnath, Jayanthi S. Fungal peritonitis in continuous ambulatory peritoneal dialysis: The impact of antifungal prophylaxis on patient and technique outcomes. Indian J Nephrol. 2014;24(5):297-301.
23. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. Kidney Int. 2006;70(103): S44-54.
24. Chow KM, Szeto CC, Cheung KK, Leung CB, Wong SS, Law MC. Predictive value of dialysate cell counts in peritonitis complicating peritoneal dialysis. Clin J Am Soc Nephrol. 2006;1(4):768-73.
25. Nouwen J, Schouten J, Schneebergen P, Snijders S, Maaskant J, Koolen M, et al. Staphylococcus aureus carriage patterns and the risk of infections associated with continuous peritoneal dialysis. J Clin Microbiol. 2006;44(6):2233.
26. Whitty R, Bargman JM, Kiss A, Dresser L, Lui P. Residual kidney function and peritoneal dialysis-associated peritonitis treatment outcomes. Clin J Am Soc Nephrol. 2017;12(12):2016.
27. Iñigo M, Del P. Infecciones por bacilos Gram negativos no fermentadores: Pseudomona-

saeruginosa, Acinetobacterspp. Y Stenotropho-monasmaltophilia. 2018;12(50):2931-40.

28. Borrajo M, Pérez C. Tuberculous peritonitis in peritoneal dialysis. Soc Esp Nefrología. 2009;29(2): 95-184.

29. Kocyigit I, Unal A, Karademir D. Improvement in culture-negative peritoneal dialysis-related peritonitis: a single center's experience. Perit Dial Int. 2012; 32(4):476-8.

30. Cullis B, Goh BL, Briggs VR, Brown EA, Dor FJMF. Creating and maintaining optimal peritoneal dialysis access in the adult patient. Perit Dial Int. 2019;39(5): 414-36.

31. Sastre LA, Linares FB, Aguilera FA, Prieto VM. EL reentrenamiento programado reduce la tasa de peritonitis en diálisis peritoneal. Nefrología. 2020; 40(5):810-1.

32. Chu KH, Choy WY, Cheung CC, Fung KS, Tang HL, Lee W, et al. A prospective study of the efficacy of local application of gentamicin versus mupirocin in the prevention of peritoneal dialysis catheter-related infections. Perit Dial Int. 2008;28(5):505-8.

33. Szeto CC, Li PK, Johnson DW, Bernardini J, Dong J, Figueiredo AE, et al. ISPD catheter-related infection recommendations. Perit Dial Int. 2017;37(2):141-54.

34. Gadallah MF, Ramdeen G, Mignone J, Patel D, Mitchell L, Tatro S. Role of preoperative antibiotic prophylaxis in preventing postoperative peritonitis in newly placed peritoneal dialysis catheters. Am J Kidney Dis. 2000;36(5):1014-9.