Peritoneal Dialysis Society of India Peritonitis Guidelines – Consensus statement - 2019

FOR FEEDBACK AND COMMENTS

Abstract

Peritoneal dialysis related peritonitis is a major cause of technique failure, morbidity and mortality in patients on peritoneal dialysis (PD). Its prevention and management is key to success of PD program. Because of variability in practice, microbiological trends and sensitivity towards antibiotics, there is a need for customized guideline for management of PD related peritonitis (PDRP) in India. With this need, Peritoneal Dialysis Society of India (PDSI) organized a structured meeting to discuss various aspects of management of PDRP and formulated a consensus agreement which will help in management of PDRP.

Key Words: Peritoneal dialysis, peritoneal dialysis related peritonitis, guidelines

Introduction

It has been observed that the practice patterns of management of peritoneal dialysis related peritonitis (PDRP) is highly variable in India. Our culture positive rates are also variable and mostly below the recommendations (1). We know that microbiological information is critical in optimal management and is determinant of clinical outcome. A working group with representation from all zones of the country came together to formulate guidelines for treatment of PDRP after review of literature and exhaustive debate on the subject.

The Peritoneal Dialysis Society of India guideline for treatment of peritoneal dialysis related peritonitis is intended to help practitioners in decision making in treatment of PDRP. It does not define a standard of care of PDRP and the group acknowledges the variations in practice based on individual patients' needs, available resources, and limitations faced by clinicians. The working group also acknowledges the lack of high quality evidence on this issue from our country and hence the guideline is based on recommendations of International Society of Peritoneal dialysis (ISPD) (2) with modifications suitable for India.

Nomenclature and Description for rating guideline recommendations

We have used the terminology similar to Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Table 1). In view of paucity of literature from India, further subdivision into A, B, C and D is avoided.

Summary of Recommendations and Suggestions

Peritoneal dialysis related peritonitis (PDRP) is the most important and preventable cause of morbidity and mortality in peritoneal dialysis (PD) patients. High peritonitis rates can be a

severe setback to any PD program (3). Keys to successful PD program are dedicated team, appropriate training of patient or care giver, preventive measures, appropriate culture methods, appropriate empiric antibiotics, preservation of peritoneum and periodic auditing. Selection of patient is also important, as utilization of PD as a last resort after failure of other modalities have compromised outcomes.

This guideline is aimed to serve as a quick recap in the management of PDRP and is based on evidence-based recommendations, International Society of Peritoneal Dialysis guidelines for peritonitis, suggestions and expert consensus statements available in literature.

Overview of the guidelines

Prevention of PDRP

- We recommend that systemic prophylactic antibiotic should be given prior to catheter insertion.
- We recommend that the disconnect system with 'flush before fill' bags should be used for continuous ambulatory peritoneal dialysis (CAPD).
- We recommend that PD training should be conducted by a qualified nurse, preferably at the center, and reviewed for each patient by the nephrologist before certified to be complete.
- We suggest that prophylactic antibiotic should be given to all PD patients before any invasive procedure like dental, gynecological or intestinal.
- We recommend that topical antibiotic cream or ointment should be applied to the catheter exit site daily after bath.

- We recommend that catheter exit site or tunnel infections should be treated adequately so as to prevent subsequent peritonitis.
- We recommend that antifungal prophylaxis should be suggested whenever antibiotics are given to a PD patient to decrease fungal peritonitis.

Initial presentation and management of peritonitis

- We recommend that peritonitis should be diagnosed when at least 2 of the three features are present: clinical features consistent with peritonitis like abdominal pain, cloudy dialysis effluent; dialysis effluent white cell count > 100/μL (after a dwell time of at least 2 hours), with > 50% polymorphonuclear leucocytes; and positive dialysis effluent culture.
- We recommend that all cloudy effluent should be considered peritonitis and treated accordingly till excluded.
- We suggest sending the entire bag to the microbiology laboratory for analysis.
- We recommend that PD effluent, when suspected of peritonitis, should be tested for cell count, differential, Gram stain, and culture.
- We suggest initial testing for bacterial and fungal and if possible, suspected, or in non responding cases for mycobacterial cultures.

Empiric Antibiotic selection

- We recommend that empiric antibiotic should be started as soon as possible when peritonitis is suspected, preferably after sending effluent for testing.

- We recommend that the choice of empiric antibiotic should be to cover both Gram positive and negative organism and better guided by local antibiogram.
- We recommend that Gram positive organism should be covered by Vancomycin and Gram negative by Pipracillin-Tazobactam or Aminoglycoside, unless local antibiogram suggest cephalosporin susceptibility.
- We recommend that preferred route of antibiotic administration should be intra-peritoneal (IP), unless there is evidence of severe systemic sepsis.
- We recommend that antibiotic should be deescalated once the antibiotic sensitivity pattern is available.
- We recommend that PD catheter should be removed in cases of refractory peritonitis, defined by failure of the PD effluent to clear up after 5 days of appropriate antibiotics.
- We suggest that coagulase-negative Staphylococci should be treated for 2 weeks with appropriate antibiotics.
- We suggest Enterococcal peritonitis should be treated for 3 weeks. We also suggest adding an Aminoglycosides for severe infection. For Vancomycin Resistant Enterococci (VRE), we suggest 3 weeks of IP Ampicillin if it is sensitive or Linezolid, Daptomycin or Teicoplanin as per sensitivity, if ampicillin resistant.
- We suggest that Streptococcal peritonitis should be treated for 2 weeks.
- We suggest that Staphylococcus aureus peritonitis should be treated for 3 weeks.
- We suggest that Corynebacterial peritonitis should be treated for 3 weeks.
- We suggest that Pseudomonas peritonitis should be treated for 3 weeks with 2 susceptible antibiotics.

- We suggest that non Pseudomonas Gram negative peritonitis should be treated for 3 weeks.
- We suggest that peritonitis associated with exit site and/or tunnel infection should be managed with catheter removal.
- We suggest that polymicrobial Gram negative peritonitis should be managed with surgical evaluation and antibiotics for 3 weeks.
- We suggest that culture negative peritonitis, if responding within 3 days, should be treated assuming CONS, for 2 weeks. If no response, special culture techniques should be resorted to.
- We suggest that catheter should be removal for fungal peritonitis and anti-fungals to be given for 2 weeks.
- We suggest that Tuberculous peritonitis should be treated appropriately with anti-tuberculous drugs and catheter removal may be individualized.

Catheter removal and re-insertion

- We recommend that PD catheter should be removed for refractory, relapsing and fungal peritonitis.
- We suggest that re-insertion of catheter can be considered after 2-4 weeks of bacterial and 4-6 weeks of fungal peritonitis and complete resolution of peritoneal symptoms.
- We recommend that each PD center should have a continuous quality improvement (CQI) program to reduce the rates of peritonitis.

Guidelines for PD related Peritonitis

Prevention of PDRP

- We recommend that systemic prophylactic antibiotic should be given prior to catheter insertion.

Every center should determine the choice of antibiotic as per their spectrum of sensitivity. Three randomized controlled trials (RCTs) showed reduction in early peritonitis with use of perioperative antibiotic (4-6). One trial showed no benefit (7). Systematic review of these trials shows benefit of prophylactic antibiotic (8).

- We recommend that the disconnect system with 'flush before fill' bags should be used for continuous ambulatory peritoneal dialysis (CAPD).

The risk of developing peritonitis is reduced to 1/3rd with the use of Y system (9-10). It also shows that there is no difference between the double bag or the Y system. There are conflicting results of comparison of peritonitis rates between CAPD and APD.

- We recommend that PD training should be conducted by a qualified nurse, preferably at the center, and reviewed for each patient by the nephrologist before certified to be complete.

Training has great influence on incidence of peritonitis (11-22) and it is suggested that retraining should be done periodically and after each episode of peritonitis (17, 19).

- We suggest that prophylactic antibiotic should be given to all PD patients before any invasive procedure like dental, gynecological or intestinal.

Invasive procedure like colonoscopy has been shown to increase the risk of peritonitis (23). Prophylactic antibiotic before an invasive procedure except upper gastroscopy, reduces the risk of peritonitis (24). However, the choice of prophylactic antibiotic has not been studied and is left to the discretion of local physician.

- We recommend that topical antibiotic cream or ointment should be applied to the catheter exit site daily after bath.
- We recommend that catheter exit site or tunnel infections should be treated adequately so as to prevent subsequent peritonitis.

There is an association between exit site infection (ESI) and subsequent peritonitis and hence appropriate management will reduce the risk of peritonitis (25-27). Though one of the systematic review did not show benefit of topical povidone-iodine in reducing peritonitis (28), another meta-analysis showed that topical mupirocin reduced rates of S. aureus infection by 70% and peritonitis by 40% (29). Mupirocin resistance is of concern but is reported particularly with intermittent rather than daily use (30-34).

- We recommend that antifungal prophylaxis should be suggested whenever antibiotics are given to a PD patient to decrease fungal peritonitis. Antifungal prophylaxis should be continued for a week beyond antibiotics.

Fungal peritonitis is increased after antibiotic courses (35-37). Two randomized trial (38-39) and a systematic review (8) showed benefit of prophylactic anti-fungals during antibiotic course in preventing subsequent fungal peritonitis.

Initial presentation and management of peritonitis

- We recommend that peritonitis should be diagnosed when at least 2 of the three features are present: clinical features consistent with peritonitis like abdominal pain, cloudy dialysis effluent; dialysis effluent white cell count > 100/μL (after a dwell time of at least 2 hours), with > 50% polymorphonuclear leucocytes; and positive dialysis effluent culture.
- We recommend that all cloudy effluent should be considered peritonitis and treated accordingly till excluded.
- We recommend that PD effluent, when suspected of peritonitis, should be tested for cell count, differential, Gram stain, and culture.

Cloudy effluent should be treated as peritonitis unless proven otherwise. There are non infectious causes of cloudy effluent which should be considered in non classical presentations (Table 2) (40). Patients presenting with abdominal pain should also be evaluated for peritonitis even when effluent is clear.

When peritonitis is suspected, dialysis effluent should be drained, inspected for cloudiness, and sent for cell count with differential, Gram stain, and culture (41). An effluent cell count with white blood cells (WBC) > 100/µL (after a dwell time of at least 2 hours), with > 50% PMN, is highly suggestive of peritonitis (42). Appropriate antibiotic therapy (see below) should be initiated once the dialysis effluent specimens have been collected for analysis, without waiting for the results of laboratory testing. For patients on APD, percentage of PMN rather than the absolute WBC count should be used to diagnose peritonitis, and a proportion above 50% PMN is strong evidence of peritonitis, even if the absolute WBC count is less than 100/µL (42).

For patients at remote areas, they can keep the effluent bag refrigerated till they bring the bag for analysis and start intra peritoneal antibiotics as soon as possible. If possible, specimen should be processed within 6 hours of collection. Alternatively, they can send the effluent for analysis at local center or, if trained and available can inoculate into blood culture bottles provided to them. The inoculated culture bottles should be incubated at 37°C.

Gram stain of PD effluent should be performed, preferably after centrifugation. Appropriate culture method is a key to positive results. After collection, 50 ml of effluent should be centrifuged at 3000 g for 15 minutes, followed by resuspension of the sediment in 3-5 ml supernatant and inoculation on solid culture media or standard blood culture media. If cultures remain negative after 3-5 days, PD effluent should be sent for repeat cell count, fungal and mycobacterial cultures.

A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis, including leukocyte esterase reagent strips, biomarker assays (matrix metalloproteinase-8 and -9, neutrophil gelatinase-associated lipocalin and procalcitonin),

polymerase chain reaction (PCR) for bacterial-derived DNA fragments, 16S rRNA gene sequencing, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF), and pathogen-specific “immune fingerprints” (43-55). However, none of them has been proved to be superior to conventional culture techniques.

Empiric Antibiotic selection

- We recommend that empiric antibiotic should be started as soon as possible when peritonitis is suspected, preferably after sending effluent for testing.
- We recommend that the choice of empiric antibiotic should be to cover both Gram positive and negative organism and better guided by local antibiogram.
- We recommend that Gram positive organism should be covered by Vancomycin and Gram negative by Pipracillin-Tazobactam or Aminoglycosides unless local antibiogram suggest cephalosporin susceptibility.

In the recent data analysis, gram positive organisms are more commonly encountered across the country but almost close to gram negative organisms (2). However, center wise difference also been noted. It is suggested to start with antibiotics covering for both positive and negative organisms. In a meta analysis (56), the combination of a glycopeptide (vancomycin or teicoplanin) and ceftazidime was superior to other regimens. Cefepime or imipenem/cilastatin can be used as monotherapy. Once the culture results are available, antibiotics can be adjusted and deescalated to avoid future antibiotic resistance.

- We recommend that preferred route of antibiotic administration should be intra-peritoneal (IP), unless there is evidence of severe systemic sepsis.
- We recommend that antibiotic should be deescalated once the antibiotic sensitivity pattern is available.

Intraperitoneal dosing results in high IP drug levels and is preferable to IV administration. Intraperitoneal antibiotics can be given as continuous (in each exchange) or intermittent dosing (once daily) (56-61). In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption. The role of monitoring serum vancomycin levels is controversial (62-63). In general, a dosing interval of every 4 to 5 days would keep serum trough levels above 15 µg/mL, but there is substantial inter-individual variability (64-65). Re-dosing is probably appropriate when serum vancomycin levels are below 15 µg/mL (65-67). There is no firm evidence that monitoring aminoglycoside levels mitigates toxicity risk or enhances efficacy (67).
Antibiotic dosing in APD is of concern because of rapid exchanges. However, intermittent dosing given at long day dwell is effective. Alternatively, if possible, patients may switch to CAPD till completion of treatment. The recommended dosage of antibiotics for the treatment of PD related peritonitis is summarized in Table 3 and 4 (68-122).

- We recommend that PD catheter should be removed in cases of refractory peritonitis, defined by failure of the PD effluent to clear up after 5 days of appropriate antibiotics.

Refractory peritonitis is defined as failure of the PD effluent to clear up after 5 days of appropriate antibiotics. If there is failure to respond to empiric antibiotic in culture negative or to susceptible antibiotic in culture positive peritonitis in 3 days, a trial of higher / susceptible antibiotic is recommended for another 2 days before labelling it as refractory. Catheter removal is indicated in cases of refractory peritonitis. Delay in catheter removal leads to extended hospital stay, peritoneal membrane damage, increased risk of fungal peritonitis and excessive mortality (123). Catheter should also be removed if patient's condition is deteriorating.

- We suggest that coagulase-negative Staphylococci should be treated for 2 weeks with appropriate antibiotics.

CONS is mostly due to touch contamination. Intraperitoneal vancomycin or cephalosporins can be advised for 2 weeks. Relapsing CONS peritonitis suggests colonization and bio-film formation, when catheter removal may be considered.

- We suggest Enterococcal peritonitis should be treated for 3 weeks. We also suggest adding an Aminoglycosides for severe infection. For Vancomycin Resistant Enterococci (VRE), we suggest 3 weeks of IP Ampicillin if it is sensitive or Linezolid, Daptomycin or Teicoplanin as per sensitivity, if ampicillin resistant.

Enterococci infection suggests intra abdominal source of infection. Identification of species is important as many are resistant to penicillins and carbapenems.

- We suggest that Streptococcal peritonitis should be treated for 2 weeks.

Streptococci frequently originate from the mouth (124) although S bovis comes from colon (125). Viridans streptococci are more likely to be refractory.

- We suggest that Staphylococcus aureus peritonitis should be treated for 3 weeks.

S aureus is often secondary to touch contamination, or exit site or tunnel infection. Data suggests 3 weeks treatment (126-127) with appropriate antibiotic. Concomitant exit site or tunnel infection may need catheter removal.

- We suggest that Corynebacterial peritonitis should be treated for 3 weeks.

- We suggest that Pseudomonas peritonitis should be treated for 3 weeks with 2 susceptible antibiotics.

The outcome is reported to be better with 2 anti-pseudomonal antibiotics (128).

- We suggest that non Pseudomonas Gram negative peritonitis should be treated for 3 weeks.

- We suggest that peritonitis associated with exit site and/or tunnel infection should be managed with catheter removal.

- We suggest that polymicrobial Gram negative peritonitis should be managed with surgical evaluation and antibiotics for 3 weeks.

When multiple enteric organisms are isolated, intra-abdominal pathology is a possibility and should be evaluated. The choice of antibiotic becomes metronidazole with vancomycin with cephalosporin or aminoglycoside. Carbapenems or piperacillin/tazobactam are an alternative.

- We suggest that culture negative peritonitis, if responding within 3 days, should be treated assuming CONS, for 2 weeks. If no response, special culture techniques should be resorted to.

Inappropriate culture technique is the commonest cause of 'culture negative' peritonitis. Recent antibiotic usage also leads to culture negative peritonitis. Predominantly, these are due to gram positive organisms and hence, if responded within 3 days, should be managed for 2 weeks (129-131).

- We suggest that catheter should be removal for fungal peritonitis and anti-fungals to be given for 2 weeks.

Fungal peritonitis is associated with higher rates of hospitalization, catheter removal, transfer to hemodialysis, and death (132-135). Catheter removal is suggested once diagnosis is confirmed to reduce mortality and preserve the peritoneum. Anti-fungal agents are

continued for 2 weeks after catheter removal. The choice of anti-fungals are a combination of amphotericin B and flucytosine. However, IP amphotericin causes chemical peritonitis and IV has poor peritoneal bioavailability. Flucytosine is not widely available. Other agents include fluconazole (for Candida and cryptococcus), echinocandin (for Aspergillus and non albicans Candida), posconazole, and voriconazole (for filamentous fungi).

- We suggest that Tuberculous peritonitis should be treated appropriately with anti-tuberculous drugs and catheter removal may be individualized.

Patient with refractory or relapsing peritonitis with negative bacterial cultures should be suspected of tuberculous peritonitis. Routine testing for tuberculosis like Ziehl Neelsen stain or conventional culture are not sufficiently sensitive. Culture in fluid medium like MGIT or BactAlert or mycobacterial DNA PCR (Gene Xpert) can be better in diagnosing tuberculous peritonitis. Laproscopic peritoneal or omental biopsy can be diagnostic in suspicious cases (136). Catheter removal is not mandatory and is individualized if patient is sick or non responding.

Catheter removal and re-insertion

- We recommend that PD catheter should be removed for refractory, relapsing and fungal peritonitis.
- We suggest that re-insertion of catheter can be considered after 2-4 weeks of bacterial and 4-6 weeks of fungal peritonitis and complete resolution of peritoneal symptoms.

- We recommend that each PD center should have a continuous quality improvement (CQI) program to reduce the rates of peritonitis. Satellite centers may strengthen the patient management and the PD program.

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Table 1. Nomenclature of guideline statements

Statement	Implication for patients	Implications for clinicians
“We recommend”	Most people in this situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action
“We suggest”	The majority of people in this situation would want the suggested course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with their values and preferences

Table 2. Differential diagnosis of cloudy effluent.

Culture positive peritonitis
Culture negative infectious peritonitis
Chemical peritonitis
Calcium channel blockers
Eosinophilia of the peritoneum
Hemoperitoneum
Malignancy (rare)
Chylous effluent (rare)
Specimen taken from ‘dry abdomen’

Adapted and modified from Li PKT et al. Perit Dial Int 2016; 36(5): 481-508

Table 3. Intraperitoneal Antibiotic Dosing Recommendations for Treatment of Peritonitis

	Intermittent (1 exchange daily)	Continuous (all exchanges)
Aminoglycosides		
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	1,000 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	500–1,000 mg daily	no data
Ceftazidime	1,000–1,500 mg daily	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1,000 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 gm/1 gm every 12 hours	LD 750–100 mg/L, MD 100 mg/L
Piperacillin/Tazobactam	no data	LD 4 gm/0.5 gm, MD 1 gm/0.125 gm
Others		
Aztreonam	2 gm daily	LD 1,000 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
Meropenem	1 gm daily	125 mg/L (case report)
Teicoplanin	15 mg/kg every 5 days	LD 400 mg/bag, MD 20 mg/bag

Vancomycin	15–30 mg/kg every 5–7 days (Supplement doses for APD patients)	LD 30 mg/kg, MD 1.5 mg/kg/bag
Antifungals		
Fluconazole	IP 200 mg every 24 to 48 hours	no data
Voriconazole	IP 2.5 mg/kg daily	no data

LD = loading dose in mg; MD = maintenance dose in mg; IP = intraperitoneal; APD = automated peritoneal dialysis. Adapted and modified from Li PKT et al. Perit Dial Int 2016; 36(5): 481-508.

Table 4. Systemic Antibiotic Dosing Recommendations for Treatment of Peritonitis

Drug	Dosing
Anti-bacterials	
Ciprofloxacin	Oral 250 mg BD (500 mg BD, if residual renal function > 5 ml/min)
Colistin	IV 300 mg loading, then 150–200 mg daily (expressed as Colistin Base Activity, CBA)
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
Anti-fungals	
Amphotericin	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 hours; increased to target dose 0.75 1.0 mg/kg/day over 4 days
Caspofungin	IV 70 mg loading, then 50 mg daily
Fluconazole	Oral 200 mg loading, then 50–100 mg daily
Posaconazole	IV 400 mg every 12 hours
Voriconazole	Oral 200 mg every 12 hours

BD = twice a day; IV = intravenous; BW = body weight. Adapted and modified from Li PKT et al. Perit Dial Int 2016; 36(5): 481-508.