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Management of Peritoneal Dialysis Related Infections

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SUMMARY

Introduction: Patients with end-stage renal disease who start active treatment with peritoneal dialysis have an increased risk of developing infections.
Methods: This paper will present information from relevant professional/scientific sources regarding modern diagnostic and therapeutic modalities for the treatment of infections in patients on peritoneal dialysis.
Topic: Infections associated with peritoneal dialysis are: peritoneal catheter exit site infections, tunnel infections and peritonitis. The symptoms of the mentioned infections vary from mild ones such as erythema and secretion at the exit point of the peritoneal catheter to pronounced symptomatology in the development of peritonitis accompanied by abdominal pain and elevated body temperature. The most common cause of peritonitis is infection of the exit site of the catheter, and the two main causes of infection are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. If the existence of an infection is suspected, it is necessary to sample the dialysate for cytological examination and culture and to take a swab of the exit site of the catheter. Treatment begins with empiric antibiotic therapy, then it is corrected according to the antibiogram, and the exit site is treated locally with an antibiotic. If there is no therapeutic response after five days of intraperitoneal therapy in peritonitis, it is recommended to remove the catheter.
Conclusion: According to the current guidelines of the International Society for Peritoneal Dialysis (ISPD), timely prevention of infections, diagnosis and treatment of peritoneal dialysis-related infections are necessary to prolong patient survival.

Keywords: Peritoneal Dialysis, Peritonitis, Infections, Antibiotics

INTRODUCTION

Patients with end-stage renal disease require treatment with one of the modalities of kidney function replacement (hemodialysis (HD) or peritoneal dialysis (PD) or kidney transplantation [1,2]. Both types of dialysis represent the replacement of kidney function by withdrawing solutes and water, restoring balance of electrolytes and the correction of acidosis. However, unlike HD, which is based on the passage of blood through the extracorporeal circuit and vascular access, in PD, the exchange of dissolved substances and water between the blood in the peritoneal capillaries and the dialysate in the peritoneal cavity is achieved through a catheter, using the peritoneal membrane [1,3].

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Continuous ambulatory peritoneal dialysis (CAPD) is one of the modalities of peritoneal dialysis. In this method, the peritoneal cavity is always filled with a dialysis solution (usually 2L of solution), and this liquid is changed four times a day at a time interval of 4-8 hours. The changes are made manually and occur due to gravity through a system consisting of two bags connected to a catheter. This two-bag system consists of an empty bag that stands on the floor to remove solution from the peritoneal cavity and a bag of dialysis solution that sits on a pedestal above the level of the catheter to be instilled immediately after removal of the saturated solution. When connecting the system to the catheter, the patient first drains the solution that has been in the peritoneal cavity for the previous hours and then infuses a new solution. After infusing the solution, the patient turns off the system and puts it away and is then free to perform activities until the next shift [1]. Automatic Peritoneal Dialysis (APD) is a method that usually involves three to six cycles during the night by an automatic cycler. There are several types of APD: The intermittent night peritoneal dialysis: In this method, the patient makes the changes at night with the cycler, and the peritoneal cavity remains without dialysis fluid during the day. This method is generally indicated for patients who have residual renal function. The Continuous Cycle Peritoneal Dialysis: In addition to performing the appropriate number of cycles during the night, the patient maintains the dialysis solution in the peritoneal cavity during the day and may or may not perform manual changes during the day. This modality is performed by patients who do not have residual renal function [1,4].

The following complications can develop in PD patients: dialysate leakage, catheter malposition, hernias, hydrothorax, edema and ultrafiltration failure, weight gain, hypertriglyceridemia and hyperglycemia, encapsulating peritoneal sclerosis and infectious complications [1]. Knowledge of the pathogenesis of PD-related infections, possible sources and reservoirs of potential causative agents, represent the basis for defining effective protocols and guidelines for the prevention and control of PD-related infections [5,6]. Infections associated with PD can be identified by patients, caregivers, and clinicians [7]. Catheter exit site infection and catheter „tunnel" infection (at the exit site on the skin or subcutaneous tunnel) are the main types of PD-related infections [2]. They can potentially lead to peritonitis, hospitalization, transfer to HD and death. Recommendations on the prevention and treatment of peritoneal catheter-related infections were published together with the recommendations for the treatment of peritonitis by the International Society for Peritoneal Dialysis (ISPD) for the first time in 1983 and revised subsequently to include the latest guidelines for infections related to catheter from 2017 [8]. Current guidelines focus on catheter-related infections, while recommendations related to peritonitis have recently been updated [8,9].

The ISPD recommendations are organized into five sections with a focus on: definitions, monitoring and reporting of peritoneal catheter-related infections, prevention of peritoneal catheter-related infections, treatment of PD catheter-related infections, and future research. These recommendations are based on current evidence. If there are several similar studies on the same topic, the selected committee refers to more recent publications. These recommendations follow the Grades of Recommendation Assessment, Development and Evaluation (GRADE), a system for evaluating the quality and level of evidence in clinical research. Within each recommendation, the strength of the recommendation is indicated as Level 1 (recommend), Level 2 (suggest) or not rated, and the quality of the supporting evidence is shown as A (high certainty), B (moderate certainty), C (low certainty) or D (very low security). Recommendations are not intended to be implemented in every situation, indiscriminately. Each PD department should have its own pattern for infections, causative agents and their antibiotic susceptibilities and adapt protocols to local conditions [8].

METHODS

This paper will present information from relevant professional/scientific sources regarding modern diagnostic and therapeutic modalities for the treatment of infections in patients on peritoneal dialysis.

TOPIC

Clasificationand manifestation of PD-related infections

PD catheter-related infections can be classi-

fied by type, cause, timing (related to catheter placement and previous episode), and outcomes. It is defined as an episode occurring within 30 days of PD catheter placement [9]. Infections that occur during this time interval are probably related to the placement of the catheter, caused by various microorganisms. According to the latest ISPD recommendations, PD-catheter exit site infection is defined as the presence of a purulent exudate, with or without skin erythema at the catheter epidermal junction. In the absence of a purulent discharge, other signs of inflammation at the exit site of the catheter (erythema, tenderness, swelling, granuloma, or crust formation) are not sufficient for a definitive diagnosis of exit site infection. Catheter tunnel infection is defined by clinical signs of inflammation (erythema, swelling, tenderness, or induration) with or without ultrasound evidence of fluid accumulation anywhere along the catheter tunnel [8]. Significant predictors for the development of infection associated with PD are reductions in blood urea, serum albumin, sodium, and calcium [11]. Other risk factors that influence the development of peritonitis in PD patients are anemia, nutritional status, biological status, and serum iron value. Secondary hyperparathyroidism, increased uric acid value, length of treatment or adequacy of PD did not show a statistically significant effect on the development of peritonitis [2]. A significant factor in PD failure is fungal peritonitis [11]. Although exit site infection and catheter tunnel infection can occur independently, they can also occur simultaneously [8]. Infection of the exit site of the PD catheter can be manifested as peri-catheter erythema without purulent secretion, in the form of an allergic skin reaction to a recently placed catheter or catheter trauma [8,12]. Catheter tunnel infection may manifest as erythema, edema, induration, or increased sensitivity at the exit site or oligosymptomatics with repeated exit site infections. It is diagnosed by ultrasonography examination. If left untreated, it can progress to abscess formation or catheter-peritonitis [8]. The symptomatology of peritonitis is related to the causative agent, as an entity of inflammation and/or disease. The diagnosis of peritonitis is made based on turbidity of the dialysis fluid, abdominal pain, and abdominal tenderness to palpation, high body temperature, vomiting, fever and diarrhea [2].

Diagnostic modalities of PD-related infections

Diagnosis of peritonitis

According to the guidelines for the initial diagnosis of peritonitis, two of the three listed criteria must be met: diffuse sensitivity of the abdominal wall (70%), turbidity of the dialysis fluid with leukocytes >100/mm^3 (granulocytes >50%) and isolation of the causative agent of the dialysate [2,13].

Laboratory diagnostics

Laboratory signs of infections related toperitoneal dialysis in patients on are: leukocytosis 10-15x10^{-9} and elevated C-reactive protein,the number of leukocytes in the dialysate sediment, >100 leukocytes/mm^3 and the dominance of neutrophils (>50%) in peritonitis; predominance of lymphocytes in fungal peritonitis andand less than <100 leukocytes/mm^3 in tunnel infection [2,14].

Microbiological diagnosis of infections associated with PD

After sampling the swab from the exit site of the catheter, the preparation is stained by Gram [8]. Dialysate culture determines the type of microorganism, but empiric intraperitoneal therapy is started until the arrival of the antibiogram, when the therapy is corrected in case of clinical need [3]. Exit site infection with negative cultures is defined when an exit site infection is diagnosed using the criteria already mentioned, without an identified microorganism from the culture of the catheter exit site swab. This type of infection was verified in the mupirocin and polysporin triple randomized controlled trial (MP3 trial) in 11.4% of cases, but was less common than culture-negative peritonitis (19.5%) [8]. Bernardini et al reported an exit site infection rate with negative cultures of 0.06 episodes per year in the mupirocin group and 0.03 episodes per year in the gentamicin group [15]. These infections may occur due to recent antibiotic intake by the patient, inadequate specimen collection or culture, or misclassification of slow-growing atypical organisms (eg, mycobacteria, fungi) [8].

The cause of PD catheter-related infection can be divided by causative agents. The

most frequently isolated microorganisms of catheter exit site infection in the MP3 study were: diphtheroids (20.5%), *Staphylococcus aureus* (13.6%), *Pseudomonas aeruginosa* (13.6%) and fungi (9.1%) [8,16]. Comparing topical mupirocin versus gentamicin, at the exit site, the most common pathogens in the mupirocin group were *S. aureus* (0.06 episodes per year), other gram-positive organisms (0.26 episodes per year), and *Pseudomonas aeruginosa* (0.11 episodes per year). In the gentamicin group, there were more fungal and fewer gram-positive and gram-negative infections. In relation to the above, it is certain that the epidemiology of microorganisms varies depending on the region, the approach to prophylaxis, the use of antibiotics, etc. Classification, monitoring and reporting of catheter-related infections by causative agent will facilitate continuous quality improvement activities as well as inform more tailored treatment recommendations, as with ISPD guidelines over the last decade [8].

Refractory catheter exit site infection should raise suspicion for atypical organisms such as nontuberculous mycobacterium, which may be misidentified as diphtheroid species or *Corinebacterium*, leading to delayed diagnosis. When in doubt, testing for acid-fast bacilli should be performed using Ziehl–Neelsen staining and culture on specific media [8]. The most common species is *Mycobacterium fortuitum*, followed by *M. abscessus* and *M. chelonae* [17]. It is necessary to differentiate isolates identified as „*M. chelonae/abscessus*", since therapy for *M. abscessus* is more demanding [18].

There is no consensus as to whether catheter exit site culture is necessary for sampling 1-2 weeks after completion of antibiotic treatment. However, monitoring the culture after treatment showed that sometimes persistent colonization was detected even after the exit site infection was cured, which was associated with a higher risk of peritonitis and conversion to HD [19,20].

When it comes to peritonitis, the most common causes of peritonitis are Gram-positive microorganisms in 50% of cases: *Staphylococcus* coagulase negative, *Staphylococcus aureus*, *Streptococcus sp.*, *Neisseria sp.* Other potential gram negative microorganisms are (15%): *Pseudomonas sp.*, *Enterococcus*, *Klebsiella sp.*, *Proteus sp.*, *Acinetobacter sp.* Gram-positive and/or Gram-negative microorganisms are represented by 1-4%, while fungal infections are rarer <2% of cases [2,21,22]. Microbiological diagnosis of peritonitis implies the following: dialysate culture should be taken before the clinical manifestation of peritonitis, and the first cloudy dialysate is the best sample (50 ml of dialysate). Staining of a gram-negative sample of dialysate proves the presence of microorganisms in 20-30% of cases. Microbiological cultivation of dialysate is important for determining the causative agent and its sensitivity to antibiotic therapy [2].

Ultrasound diagnostics

Ultrasound examination is recommended to detect catheter tunnel infection. Additional information on hypervascularity, which indicates an inflammatory process, is provided by additional diagnostics with color Doppler ultrasound [8,23,24]. The research results so far show the auxiliary role of ultrasound in evaluating the response to therapy. Namely, a hypoechoic zone more than 1 mm thick around the outer cuff 1 week after the end of antibiotic treatment could be a predictor of a poor clinical outcome [8].

Principles of treatment and prognosis

Selection and dosage of antibiotics

Avoiding nephrotoxic drugs is the most important principle that we must follow in patients with chronic kidney diseases. If the administration of nephrotoxic drugs is necessary, regular control of the strength of glomerular filtration is required, as well as the concentration of electrolytes and drugs in the serum, if possible. Dosage of drugs in patients with chronic kidney failure requires careful prescribing of the initial dose and then the maintenance dose. For most drugs, there are recommendations from the Agency for Drugs and Medical Devices of the Republic of Serbia on how to correct the dose of the drug in chronic kidney failure. Drug clearance during peritoneal dialysis (PD) is lower and it is considered that PD patients can be dosed in the same way as those with a glomerular filtration rate below 15 mL/min/1.73 m^2. There is not much work on drug dosing for patients with automatic PD (APD), which is more effective in removing drugs than continuous ambulatory PD (CAPD) [25].

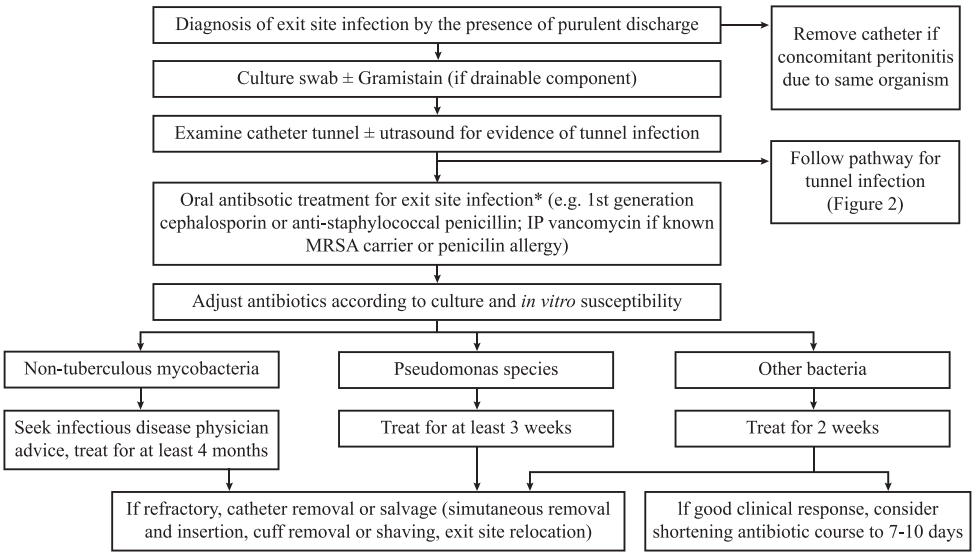

Figure 1. Management of catheter exit site infections in peritoneal dialysis patients [8]

Table 1. First-line of empiric oral antibiotic therapy in catheter-associated infections in peritoneal dialysis patients [8]

Oral antibiotic therapy	Dose
Amoxicillin/Clavulanate	500mg/125mg or 250mg/125mg BD
Cephalexin	250-500mg BD
Cloxacillin or Dicloxacillin	500mg QID

BD - two times per day
QID - four times per day

Principles of management of peritoneal dialysis catheter-related infections

Oral antibiotic therapy is often used empirically primarily to cover S. aureus (Figure 1). Dosing recommendations for commonly used oral antibiotics are shown in Tables 1 and 2 [8,26]. In accordance with the updated 2022 ISPD guidelines on the prevention and treatment of peritonitis, it is recommended that concomitant antifungal prophylaxis should be prescribed whenever patients receive antibiotics for any reason, in order to reduce the risk of fungal peritonitis [9]. Patients should be examined in within 1 week after treatment (Figure 1). It is important to examine the sensitivity of the applied drug to the infectious agent. The currently recommended first-line oral antibiotics shown in Table 1 may not be effective against the organisms, given the increasing resistance of microorganisms to antibiotics [8,2].

Two weeks of antibiotic therapy is recommended for most PD catheter-related infections, except for those caused by *Pseudomonas*, for which three weeks of therapy is recommended [8]. Although the previous 2017 guidelines recommended at least 2 weeks of antibiotic therapy for catheter exit site infection, there is a lack of high-quality evidence for mandatory treatment of 2 weeks. The Infectious Diseases Society of America (IDSA) guidelines suggest seven-day therapy for su-

Table 2. Alternative oral antibiotic therapy in catheter-associated infections in peritoneal dialysis patients [8]

Oral antibiotic therapy	Dose
Ciprofloxacin	500-700mg/24h
Clarithromycin	500mg loading, then 250mg BD
Clindamycin	300-450mg TID to QID
Levofloxacin	250mg/24h or 500mg/48h
Linezolid	600mg BD for 48h, then 300mg BD 600mg/24h if used for NTM infection
Moxifloxacin	400mg/24h
Rifampicin	450mg/24h (for BW <50kg) 600mg/24h (for BW >50kg)
Trimethoprim/Sulfamethoxazole	80mg/400mg (one single-strength tablet)/24h or BD 160mg/800mg (one single-strength tablet)/24h

BD - two times per day
BW - body weight
QID - four times per day
TID - three times per day
***** rifampicin is used for treating *S. Aureus* synergistically with other antibiotics and should not be given as single-agent therapy

perficial streptococcal and staphylococcal infections [8,22]. Since there are no biomarkers that would accurately determine the discontinuation of antibiotic treatment of an exit site infection, definitive antimicrobial treatment and its duration are determined by clinical response and, when available, wound culture and antibiogram results [8]. Recommendations are to consider clinical response aimed at balancing the risk of prolonged antibiotic therapy. It should be noted that many observational studies in patients with fungal peritonitis confirmed the risk factor of antibiotic use within 1 month of the onset of peritonitis [8,27,28]. Because there is insufficient data to support a fixed biweekly treatment protocol, it is considered reasonable to prescribe antibiotics for a period of 7-10 days (Figure 1), which is the time required to resolve an uncomplicated acute infection. Prolongation of antibiotic therapy is necessary when there are complications such as catheter tunnel infection (Figure 2) or with virulent organisms such as *Pseudomonas species* [8].

Infection with nontuberculous mycobacteria requires treatment with two agents with in vitro activity against the clinical isolate for at least 4 months of therapy. There is no standardized recommendation for the treatment of this infection, but guidelines emphasize the need to remove any foreign body to ensure a high probability of cure, especially for *M. abscessus* [8].

In the literature, refractory tunnel infection is defined as failure to heal within 4 weeks. Catheter-related infections that fail to resolve completely after recommended antibiotic therapy can be defined as refractory catheter-related infections, requiring surgical intervention or catheter removal [8,29].

Principles of treatment in peritonitis

Regardless of the sterile conditions when changing the dialysate, there is a possibility of infection - peritonitis, which should be diagnosed in time and antibiotic therapy started before the results of the dialysate culture arrive. Recommendations advise which antibiotics should be used to start the treatment of peritonitis and how they should be adjusted, according to the causative agent, after obtaining a dialysate culture [25]. Peritonitis can be treated with intraperitoneal (IP) or systemic antibiotics for 14 to 28 days, depending on the causative agent, with doses adjusted for renal function. Intraperitoneal administration of drugs is preferred. Repeated infections of the peritoneal cavity lead to a reduction in the replacement area of the peritoneal membrane, with a consequent reduction in the effectiveness of dialysis treatment. The ISPD recommends that the choice of antibiotic be made taking into account the history of local sensitivity to the agents. Thus, a first-generation cephalosporin or vancomycin (gram-positive coverage) can be prescribed in combination with a third-generation cephalosporin or aminoglycoside (gram-negative coverage). Antibiotics administered by the IP route can

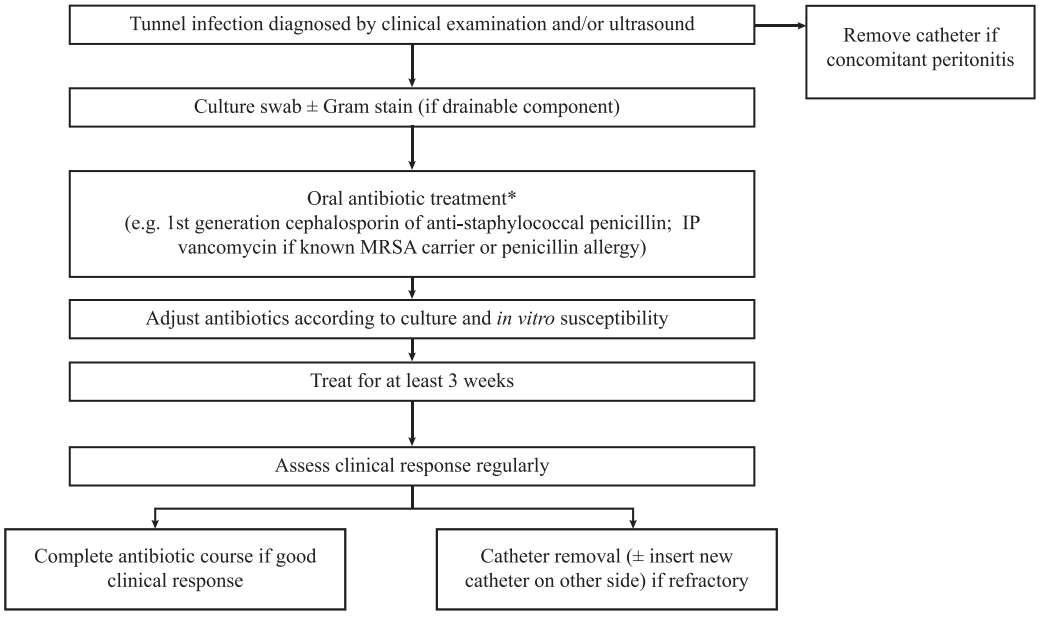

Figure 2. Management of catheter tunnel infection in peritoneal dialysis patients [8]

Table 3. Intraperitoneal dosing of antibiotics and antimycotics in the treatment of peritonitis in CAPD patients [25]

LD - loading dose
MD – maintenance dose
IV – intravenous
IP - intraperitoneal

Antibiotics	Intermittently (1x6h/24h)	Continuously (all shifts)
Aminoglycosides		
Amikacin	2mg/kg/24h	Avoid
Gentamicin	0,6mg/kg/24h	Avoid
Netilmicin	0,6mg/kg/24h	Avoid
Tobramycin	0,6mg/kg/24h	Avoid
Cephalosporins		
Cephazolin	15-20mg/kg/24h	LD 500mg/L, MD 125mg/L
Cefepime	1000mg/24h	LD 500mg/L, MD 125mg/L
Cefotaxime	500-1000mg/24h	No data
Ceftazidime	1000-1500mg (20mg/kg)	LD 500mg/L, MD 125mg/L
Ceftriaxone	1000mg/24h	No data
Cephalosporins		
Penicilin G	4g/24h	LD 50000IU/L, MD 25000IU/L
Amoxicillin		MD 150mg/L
Ampicillin		MD 125mg/L
Ampicillin/Sulbactam		LD 1000mg/500mg, MD 133,3mg/66,7mg/L
Piperacillin/Tazobactam		LD 4/0,5g, MD 1/0,125g
Ticarcillin/Clavulanic acid		LD 3/0,2g, MD 300/20mg/L
Other antibiotics		
Aztreonam	2g/24h	LD 500, MD 250mg/L
Ciprofloxacin		MD 50mg/L
Clindamycin		MD 600mg/in the bag
Daptomycin	300mg/24h	LD 100mg/L, MD 20mg/L
Fosfomycin	4g/24h	
Imipenem/Cisplatin	500mg/every second shift	LD 250mg/L, MD 50mg/L
Ofloxacin		LD 200mg/L, MD 25mg/L
Polymyxin B		MD 300 000IU (30mg)/shift
Qinupristin/Dalfopristin	25mg/ every second shift	
Meropenem	500 (APD); 1000mg (CAPD)	MD 125mg/L
Teicoplanin	15mg/kg/5days	LD 400mg/shift, MD 20mg/L
Vancomycin	15-30mg/kg/5-7days 15mg/kg/4days (APD)	LD 20-25mg/kg, MD 25mg/L
Antimycotics		
Fluconazole	IP 150-200mg/24-48h	
Voriconazole	IP 2,5mg/kg	

be given continuously (at all dialysis changes) or intermittently (once a day; in this case, the antibiotic bag should remain in the cavity for at least 6 hours) [1]. Table 3 shows the doses of antibiotics and antimycotics administered IP for the treatment of peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD) [30], while table 4 shows the doses of antibiotics with systemic administration in the treatment of peritonitis in patients on PD [9,25].

In addition to CAPD, there is also APD, which is mainly performed at night using the device, with a possible combination with one day shift. Treatment of peritonitis in these patients is a little more complicated. These patients are advised to switch to four-shift CAPD, which is easier to treat and administer antibiotics in each dialysis bag. If they remain on APD, they can be given occasional

Drug	Dose
Antibiotics	
Amoxicillin	Orally 500mg/8h
Ciprofloxacin	Orally 500-750mg/24h Orally 750mg/12h for CAPD
Clarithromycin	Orally 250mg/12h
Colistin	LD IV 300mg, MD 60-200mg/24h
Daptomycin	IV 4-6mg/kg/48h
Ertapenem	IV 500mg/24h
Levofloxacin	Orally 250mg/24h or 500mg/48h
Linezolid	IV or Orally 600mg BD/ 48h, 300mg BD/24h
Moxifloxacin	Orally 400mg/24h
Rifampicin	IV or Orally 450mg/24h for BW <50kg, 600mg/24h for BW >50kg
Ticarcillin/clavulanic acid	IV 3mg/0,2mg/12h
Tigecycline	LD IV 100mg, MD 50mg/12h
Trimetoprim/Sulfamethoxazole	Orally 160mg/800mg BD/24h
Antibiotics	
Amphotericin B deoxycholate	IV 0,75-1mg/kg/24h for 4-6h
Amphotericin B (liposomal)	IV 3-5mg/kg/24h
Anidulafungin	LD IV 200mg, MD 100mg/24h
Caspofungin	LD IV 70mg, MD 50mg/24 h
Fluconazole	LD Orally 200mg, MD 100mg/24h
Isavuconazole	LD Orally or IV 200mg/8h 6doses (48h) MD 200mg/24h
Micafungin	IV 100g/24h
Posaconazole	LD Orally 300mg/12h, MD 300mg/24h
Voriconazole	IP 2,5mg/kg

Table 4. Systemic dosing of antibiotics and antimycotics during the treatment of peritonitis in CAPD patients [25]

BD - two times per day
BW - body weight
LD - loading dose
MD - maintenance dose
IV - intravenous
IP - intraperitoneal

first-generation cephalosporins only during the day shift, but the antibiotic concentration is low during the night. Therefore, it is recommended to administer cephalosporins in each shift. Vancomycin can be used occasionally in adults. Oral ciprofloxacin can achieve an adequate dose in the peritoneum in patients on automatic peritoneal dialysis. Dosing of antibiotics in patients on automatic peritoneal dialysis is shown in the table 5 [25].

In cases of peritonitis caused by *Staphylococcus aureus* (*S. aureus*), treatment for 21 days is suggested; for cases of *Pseudomonas aeruginosa* (*P. aeruginosa*) peritonitis, oral administration of ciprofloxacin, aminoglycosides, or ceftazidimeintraperitoneally is suggested. In such cases, treatment should last 21 to 28 days [31]. If a patient develops fungal peritonitis, discontinuation of PD therapy, removal of the peritoneal catheter, and transfer of the patient to HD are recommended. Antimycotics are then given intravenously for at least two weeks after catheter removal [25,31]. After catheter removal due to infection and subsequent conversion to HD, a minimum of two to three weeks should elapse before reinsertion of a new PD catheter [31].

Recommendations for the surgical treatment

Many authors have evaluated the role of various catheter insertion techniques in order to reduce the risk of peritonitis in patients [2,32]. Indications for removing the catheter are: refractory peritonitis, relapsed peritonitis, peritonitis associated with infection of the exit site of the catheter, so-called. „tunnel" infection; fungal peritonitis, recurrent peritonitis caused by mycobacteria or multiple enteric microorganisms [2,33]. The ISPD recommendations are as follows:

1. Removal of the PD catheter is recommended in patients with an exit site or tunnel infection that progresses, or occurs concurrently

Table 4. Dosing of antibiotics and antimycotics during the treatment of peritonitis in patients on APD [25]

Drug	Intraperitoneal dose
Cephazolin	IP 20mg/kg every second day in the second daily shift
Cefepime	IP 1g in one daily shift
Fluconazole	IP 200mg every 24/48h
Tobramycin	LD 1,5mg/kg IP in the long shift, then 0,5mg/kg IP in the second dialysate shift
Vancomycin	LD 30mg/kg IP in the second dialysate shift, repeat 15mg/kg IP in the second daily shift every 3-5days

APD – automatic peritoneal dialysis
LD - loading dose
IP - intraperitoneal

with peritonitis, caused by the same microorganism;
2. It is suggested to simultaneously remove and replace the PD catheter with a new exit site under antibiotic coverage in case of infection from the exit site or tunnel when the infection is not effectively resolved by antibiotic therapy;
3. It is suggested to avoid simultaneous removal and re-placement of a new catheter when there is peritonitis;
4. Simultaneous antifungal prophylaxis is recommended for PD patients;
5. It is suggested to consider relocating the exit site of the PD catheter in case of antibiotic-resistant catheter exit site infection [8].

Prophylaxis and recommendations according to current ISPD guidelines

According to the updated 2022 ISPD guidelines on the prevention and treatment of peritonitis, it is recommended that systemic prophylactic antibiotics be administered immediately before catheter placement to reduce the risk of peritonitis associated with PD catheter placement [9]. In a Cochrane systematic review and meta-analysis of antimicrobial agents for infection prevention in PD patients compared with placebo, pre- or perioperative antibiotic prophylaxis had uncertain effects on the rate of catheter-related infections (4 studies, 379 participants; vancomycin risk ratio (RR) 0.36, 95% confidence interval 0.10-1.32, cefazolin RR 0.74, 95% confidence interval 0.27-2.05, gentamicin RR 0.07, 95% confidence interval 0-1, 06, cefazolin gentamicin RR 0.86, 95% confidence interval 0.34-2.19, cefuroxime not estimable) [8].

Choice of antibiotics

There are insufficient data available to inform the preferred choice of intravenous antibiotics due to the low methodological quality of the studies conducted on this topic. No significant difference in the rate of catheter-related infection was observed between vancomycin 1000 mg intravenously administered 12 hours before PD catheter placement and cefazolin 1000 mg intravenously administered 3 hours before PD catheter insertion [8,34].

Use of nasal antibiotic prophylaxis

The use of nasal antibiotic prophylaxis had uncertain effects on the risk of catheter exit site infections and tunnel infections, but there was evidence of a significant reduction in the incidence of catheter-related infections among patients carrying nasal *S. aureus* treated with mupirocin ointment [8,34]. Systematic and meta-analyses showed that treatment of patients with *S. aureus* nasal infection with mupirocin was associated with a 74% lower likelihood of PD catheter exit site skin infection caused by *S. aureus* compared to controls [8].

Catheter placement techniques

Studies examining the impact of catheter placement technique on catheter-related infections were few and of variable methodological quality at risk of imprecision. Laparoscopic placement compared with laparotomy has been noted to have little or no significant difference in the incidence of catheter-related infections [8]. More recently, a systematic review and meta-analysis including observational (non-randomized) studies found that, according to low-certainty evidence, percutaneous PD catheter placement may be associated with lower risks of early catheter exit site infection (within 1 month), but little or no difference in the incidence of tunnel infection compared to surgical (open and laparoscopic) PD catheter placement [35].

Before placing the catheter, it is recommended to carefully identify the optimal location of the exit site of the PD catheter, which will allow the patient adequate visibility of the exit site of the catheter, an adequate toilet and the avoidance of unintentional trauma-

tization. An alternative peritoneal catheter exit site (e.g., upper abdominal, pre-sternal) may be particularly important for patients with obesity, intestinal stoma, or urinary or fecal incontinence. Placement of the catheter should be in accordance with post-surgical care, the place of placement should be allowed to heal the wound „per primam". Dressing the exit site is best for 7 days, in case of non-sterility, immobilize the new catheter and thus reduce the risk of infection. Cytotoxic agents, such as povidone-iodine or hydrogen peroxide, should be avoided. In general, PD is recommended to be initiated at least 2 weeks after catheter placement. Earlier initiation of dialysis has been shown to increase the risk of dialysate leakage [8, 36].

Catheter design

The risk of infection associated with a PD catheter is not influenced by the type of catheter (straight vs. coiled). However, the studies conducted had different characteristics in terms of study duration and catheter types (double cuff versus single cuff; Tenckhoff versus swan neck catheter) [32]. In a retrospective observational study involving 4247 PD patients from Canada, the use of a double-cuffed PD catheter was shown to reduce the risk of peritonitis, particularly due to *S. aureus*. However, the effectiveness of double-cuffed catheters in reducing the risk of catheter-related infection has not been clearly demonstrated. Alternative catheter designs to reduce bacterial colonization, such as silver-implanted or antimicrobial-impregnated catheters, due to limited clinical experience, have not demonstrated consistent efficacy to inform their use in the routine setting [8].

Patient training and the adequacy of peritoneal dialysis

PD programs should use ISPD guidelines to implement standardized training for their trainers and patients in the PD unit [37]. However, there is currently no clear evidence for the best way to deliver training in terms of site, person or approach conditions, including the optimal nurse-patient ratio. PD training has been shown to play a vital role in reducing the risk of catheter-related infections. A single-center, retrospective observational study from the United Kingdom noted a tenfold reduction in PD catheter exit site infections after implementing a prevention program focusing on nurse and patient training, improving operative aseptic technique, and reducing the presence of *S. aureus* germs in the patient's nose [8]. Adequate chronic peritoneal dialysis implies a precisely prescribed dialysis procedure to ensure a good patient quality of life similar to that of healthy populations, as well as a reduction in morbidity and mortality. According to the recommendations of the American National Initiative, the most frequently used parameter for the quality of the outcome of kidney dialysis in patients on CAPD is the minimum acceptable weekly values of Kt/V 1.7 L, i.e. creatinine clearance 60 L/1.73 m^2. For patients on continuous cyclic peritoneal dialysis and nocturnal intermittent peritoneal dialysis, given their intermittentcharacter, the mentioned values are even higher and amount to 2.0 L or 2.2 L, and for creatinine clearance 63 or 66 L/1.73 m^2 [2].

PD-catheter exit site care

Daily administration of mupirocin at the exit site of PD catheters has been shown to be a cost-effective strategy for reducing the risk of infection caused by *S. aureus*, according to the results of various studies. Administration of mupirocin has been reported to reduce the risk of PD catheter exit site infections in 62% of patients. Daily administration is less likely to cause resistance to mupirocin compared to intermittent administration, while the use of long-term therapy remains uncertain [8]. In summary, the available evidence suggests that topical mupirocin prophylaxis may reduce the risk of catheter-related infections. An alternative topical antibacterial prophylactic agent is gentamicin. Daily application of gentamicin to the exit site of the catheter has been shown to be very effective in preventing the spread of infection caused by *Pseudomonas species*, as topical mupirocin has been shown to reduce infections caused by *S. aureus*. Other investigated prophylactic strategies include the use of medicated antibacterial honey at the exit site of the catheter, which has been shown to have a similar risk of infection in patients treated with intranasal mupirocin. However, honey increased the risk of catheter-related infection and peritonitis in patients with diabetes, thus precluding its use in this patient group. It should also be noted that contact between the ointment/cream and the PD catheter should

be minimized. There are reports that the polyethylene glycol base in mupirocin can damage polyurethane catheters and that gentamicin cream can damage silicone catheters [8,38]. It is recommended to care for the exit site of the PD catheter at least twice a week and each time after water contamination or intense exercise, to keep it clean and dry [39].

Guidelines on physical activity of patients

The 2022 ISPD guidelines on physical activity in PD patients suggest that swimming or other water sports should take place in either seawater or well-maintained swimming pools to limit exposure to waterborne pathogens [8,39].

CONCLUSION

The paper presents information from relevant professional and scientific sources about modern diagnostic and therapeutic modalities for the treatment of infections in patients on peritoneal dialysis. Despite the automatic peritoneal dialysis and solutions for peritoneal dialysis, better patient education, introduction of preventive measures, peritonitis remains the leading complication of peritoneal dialysis. The most frequently isolated microorganisms of catheter exit site infection are diphtheroids, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, while the most common causes of peritonitis are *Staphylococcus* coagulase negative, *Staphylococcus aureus*, *Streptococcus sp*. and *Neisseria sp*. In accordance with the updated 2022 ISPD guidelines on the prevention and treatment of peritonitis, it is recommended that concomitant antifungal prophylaxis should be prescribed whenever patients receive antibiotics for any reason, in order to reduce the risk of fungal peritonitis. First-line of empiric oral antibiotic therapy in catheter-associated infections in peritoneal dialysis patients are reccomended to be Amoxicillin / Clavulanate, Cephalexin, Cloxacillin or Dicloxacillin, for two weeks of therapy, except for those caused by *Pseudomonas*, for which three weeks of therapy is recommended. Peritonitis can be treated with intraperitoneal (IP) or systemic antibiotics for 14 to 28 days, depending on the causative agent. Many authors have evaluated the role of surgical removal of the catheter, and the indications such as refractory peritonitis, relapsed peritonitis, peritonitis associated with infection of the exit site of the catheter, so-called. „tunnel" infection; fungal peritonitis and recurrent peritonitis caused by mycobacteria or multiple enteric microorganisms.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Preporuke za dijagnostički i terapijski pristup infekcija povezanih sa peritonealnom dijalizom

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KRATAK SADRŽAJ

Uvod: Bolesnici u terminalnoj bubrežnoj insuficijenciji koji započinju aktivno lečenje peritoneumskom dijalizom imaju povišen rizik za nastanak infekcija.
Metodologija: U ovom radu biće predstavljene informacije iz relevantnih stručnih/naučnih izvora u vezi sa savremenim dijagnostičkim i terapijskim modalitetima lečenja infekcija kod pacijenata na peritoneumskoj dijalizi.
Tema: Infekcije povezane sa peritonealnom dijalizom su: infekcije izlaznog mesta peritoneumskog katetera, infekcija tunela i peritonitis. Simptomi navedenih infekcija variraju od blagih kao što su eritem i sekrecija na izlaznom mestu peritoneumskog katetera do izražene simptomatologije kod razvoja peritontisa praćenih bolom u trbuhu i povišenom telesnom temperaturom. Najčešći uzrok peritonitisa je infekcija izlaznog mesta katetera, a dva glavna uzročnika infekcija su *Staphylococcus aureus* i *Pseudomonas aeruginosa*. Ukoliko se postavi sumnja na postojanje infekcije, neophodno je uzorkovati dijalizat za citološki pregled i kulturu i uzeti bris izlaznog mesta katetera. Lečenje se počinje empirijskom antibiotskom terapijom, potom se koriguje prema antibiogramu, a izlazno mesto se lokalno tretira antibiotikom. Ako izostane terapijski odgovora petog dana od početka intraperitoneumske terapije kod peritonitisa, preporučuje se uklanjanje katetera.
Zaključak: Prema aktuelnim smernicama *International Society for Peritoneal Dialysis* (ISPD), neophodna je prevencija infekcija, pravovremena dijagnoza i terapija infekcija povezanih sa peritonealnom dijalizom kako bi se produžilo preživljavanje pacijenta.

Ključne reči: peritoneumska dijaliza, peritonitis, infekcije, antibiotici

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