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NEPHROLOGY - REVIEW

Peritoneal dialysis-related infections recommendations: 2016 update. What is new?

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Abstract In 2016, the International Society of Peritoneal Dialysis (ISPD) published guidelines that focus on the importance of both prevention and treatment of peritonitis. For once more, the need for annual reporting of peritonitis rates and recording of peritonitis and exit-site infections, isolated microorganism and antimicrobial susceptibilities as a central component of a quality improvement program is highlighted. Data on new antibiotic regimens, techniques for microorganism isolation and peritoneal dialysis solutions are included. Training of both peritoneal dialysis nurses and patients seems to be crucial, while the modifiable risk factors for peritonitis seem to be of great interest. In this article, we record the changes in the last ISPD (2016) guidelines compared to the previous ones published in 2010.

Keywords Guidelines · Peritoneal dialysis · Peritonitis

Introduction

Peritonitis remains one of the most serious and life-threatening complications of peritoneal dialysis (PD). It is closely related to loss of ultrafiltration and permanent peritoneal membrane damage, as well as to the necessity of catheter removal leading thus to technique failure and conversion to hemodialysis.

The International Society for Peritoneal Dialysis has been publishing guidelines on PD-related infections since 1983. In 2016, ISPD published the "ISPD peritonitis recommendations: 2016 update on prevention and treatment" [1]. The 2005 guidelines focused on prevention [2], while in the 2010 guidelines treatment was covered for the first time in a separate ISPD position statement [3]. The latest guidelines highlight the importance of both prevention and treatment as the title of the statement reveal. The authors of the present article, as have already done in the past [4], aim to compare the recent guidelines to the previous ones published in 2005 and in 2010 in order to record the changes and any new guidelines introduced.

Peritonitis rate

In the present guidelines "reporting of peritonitis" constitutes a separate section similarly to the 2010 guidelines. For once more, the need for annual reporting of peritonitis rates and recording of peritonitis and exit-site infections, isolated microorganism and antimicrobial susceptibilities as a central component of a quality improvement program is highlighted. Several methods have been used for reporting peritonitis rates leading to a certain degree of confusion. Therefore, for practical reasons, the guidelines recommend a specific way of reporting rates, more precisely number of episodes per year, instead of number of patient-month per episode or percentage of peritonitis-free patients that have been also used in the past. Episodes of relapsing peritonitis should be counted as one episode. The Committee gives credit to centers with very low peritonitis rates,

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as low as 0.18–0.20 episodes per year [5], and incites centers to achieve lower peritonitis rates (0.5 episodes per year of risk instead of 0.67 proposed in the 2010 guidelines). Another addition, based on recent publications, is the recommendation for reporting peritonitis episodes that have occurred after the placement of the catheter and before the initiation of PD, separately.

Prevention of peritonitis

The current guidelines are trying to underline the importance of peritonitis prevention by dedicating a significant part similarly to the 2005 guidelines. Prevention of peritonitis and the exit-site and tunnel infections' prevention are covered in separate guidelines [6]. The placement of the catheter constitutes the important first step for the initiation of the method. In the 2005 guidelines, prophylactic use of antibiotics prior to the catheter insertion was suggested. In the present guidelines, the Committee supports this practice based on the results of a systematic review that included four randomized trials [7]. On the other hand, although vancomycin seems to be more effective than first-generation cephalosporins, the Committee does not support its routine use, since vancomycin resistance remains a problem of great concern. Finally, the Committee deals with the handling of nasal colonization of *Staphylococcus aureus*, but is unable to provide a clear suggestion. Regarding the catheter insertion technique, there are not enough data to support laparoscopic or peritoneoscopic catheter insertion over the standard laparotomy procedure. Furthermore, there is no clear benefit of buried catheter techniques.

Regarding the catheter design, still the Committee cannot provide safe guidelines. It seems that there is no difference in peritonitis rate between straight and coiled catheters or between swan-neck and traditional Tenckhoff catheters [8]. Even the use of double-cuffed catheters instead of single-cuffed ones remains controversial [9], and there are also not enough data to support the downward direction of the tunnel [10]. Regarding the connection methods, the Committee recommends, as in the 2005 guidelines, the use of "flush before fill" disconnection systems for continuous ambulatory PD. Two systematic reviews support this disconnection system [11], while the results of three systematic reviews regarding the use of the double bag instead of the Y system are conflicting [11]. Finally, the Committee has not enough data on the difference of peritonitis rate between continuous ambulatory peritoneal dialysis (CAPD) and machine-assisted automated PD.

Although ISPD has already published separate recommendations for PD training, this subject is covered in the present guidelines, as well. The role of the PD training nurses is crucial and remains central; so much effort must be spared on their education and on the update of their skills [12]. The home visit is still supported, even though a retrospective study did not manage to prove its significance [13]. The use of specific protocols, as well as the further testing of each patient as soon as his/her education has been completed, is suggested. Finally, retraining seems to be of great importance and a table of the indications for retraining is included. Two uncontrolled [14] studies support its use [15], while the results of the only randomized controlled trial on the field have not been yet published [16]. Moreover, the Committee cannot suggest the use of specific dialysis solutions for prevention of peritonitis because the results of randomized controlled studies [17] and a subsequent meta-analysis are controversial [18].

The exit-site care is a new chapter on the 2016 ISPD guidelines of great importance because exit-site infection is closely related to peritonitis [19]. The Committee suggests the daily topical use of antibiotics in order to prevent exit-site infections and peritonitis. Hand hygiene remains important, the use of face-mask is considered optional and the use of povidone-iodine does not seem to be superior to simple soap and water use [20]. Mupirocin and gentamicin are the most studied topical antibiotics. The daily use of mupirocin seems to reduce *S. aureus* exit-site infection and peritonitis significantly [21], is cost-effective [22] and in conjunction with sodium hypochlorite solution can be more drastic in reducing peritonitis rate [23], but the issue of mupirocin resistance deserves more research [24]. Intranasal prophylactic use of mupirocin although effective [25] is not universally proposed because it seems that is not well tolerated by patients [26]. The use of prophylactic agents against *S. aureus* has been related to increased incidence of exit-site infections related to Pseudomonas species. On the other hand, gentamycin cream or ointment is considered as effective as mupirocin in exit-site infection prevention, but in observational studies its use has been related to increased infection rate by Enterobacteriaceae, Pseudomonas species, and probably non-tuberculous mycobacteria [27]. Gentamicin should be considered as an alternative to mupirocin, but still gentamicin resistance remains an issue. Antibacterial honey [28], topical triple ointment [29], ciprofloxacin otologic solution and oral rifampicin have been successfully tested but cannot be integrated in a routine exit-site care. In particular, rifampicin, due to high rates of resistance occurrence, adverse effects and interactions with other drugs, must be used with caution.

In the current guidelines, a comment is made regarding invasive interventional procedures, such as colonoscopy and gynecologic procedures that have been related to increased peritonitis incidence. The Committee supports the prophylactic use of antibiotics prior to those procedures [30]. In the 2005 guidelines, ampicillin with or without metronidazole and removal of fluid from the abdomen prior

to the procedure were suggested. In the present guidelines, data are considered to be inconclusive in order the Committee to suggest the implementation of those methods and each PD center is advised to choose the prophylactic antibiotics of its preference. A further comment about constipation and enteritis that remain important problems in preventing peritonitis is included in the guidelines [31], while hypokalemia is introduced as a new parameter related to enteric peritonitis [32]. Finally, lactulose use is mentioned as a reducing peritonitis agent although its use is supported only by observational data [33].

The Committee in the 2016 guidelines included a table with the modifiable risk factors for peritonitis that are social or environmental, medical, dialysis related and infection related. Gynecological and dental procedures are considered risk factors for peritonitis, and the Committee suggests, especially in the latter case, the prophylactic use of ampicillin, even as a single dose [34]. For wet contamination on the other hand, no standard protocol is suggested, although prophylactic antibiotics seem to be necessary. Hypoalbuminemia, depression, loss of motivation [35], domestic animals presence [36, 37] and vitamin D deficiency [38, 39] are considered to be related to peritonitis, but more studies are needed to provide safe data on their role and the way that PD centers must deal with them.

In the current guidelines, a new concept is introduced, the continuous quality improvement program [40]. It is a program that involves a multidisciplinary team that reviews each centers performance in a regular basis identifying problems and developing solutions, including patients' retraining, catheter removal and reinsertion. Finally, antifungal prophylaxis for patients receiving antibiotics that was discussed in the 2005 guidelines and very briefly mentioned in the subsequent 2010 guidelines is now in the 2016 guidelines supported as an effective method for secondary prevention of peritonitis. Two randomized controlled trials and one systematic review proved the efficacy of both oral nystatin and fluconazole [7], but problems regarding the availability of nystatin and interactions with other drugs and resistance for fluconazole must be taken into account.

Initial presentation and management of peritonitis

Clinical presentation and diagnosis of peritonitis represent a chapter in the 2016 ISPD guidelines that has very few changes compared to the 2010 guidelines. There is an addition of calcium channel blockers in the differential diagnosis of cloudy effluent. Another important section of the guidelines is the specimen processing and identification of causative organism. In the new version of the guidelines, the Committee suggests an even lower acceptable rate of culture-negative peritonitis episodes (less than 15% compared to the less than 20% in 2010) and describes how data support the effectiveness of lysis techniques beyond the blood-culture bottle and the centrifuging technique [41]. Although some new techniques for the early diagnosis of peritonitis have been described in 2010 and 2016 guidelines, their use cannot be described as superior to the ones that are already being widely used. Finally, when it comes to the empiric antibiotic selection, vancomycin or a first-generation cephalosporin plus a third-generation cephalosporin or an aminoglycoside remains the recommended combination in order to cover for both gram-positive and gram-negative organisms, although a recently published proportional meta-analysis supports the combination of vancomycin or teicoplanin with ceftazidime as more effective than other combinations [42].

Dosing of antibiotics is another chapter of great interest in the 2016 guidelines. The Committee continuously supports the intraperitoneal (IP) route for the administration of antibiotics instead of the intravenous (IV) route, while specific recommendations for the IP administration of aminoglycosides, vancomycin and cephalosporin are provided. The guidelines include an updated table with the IP antibiotic dosing with some corrections from the previous guidelines [14] and a new table with the systemic (IV) antibiotic dosing. Of interest is the recommendation that vancomycin should preferably be administered intermittently (in one exchange every 5–7 days) and not continuously (in every exchange). Moreover, the Committee confirms the lack of data regarding the stability of various new antibiotics and the possible effect of new peritoneal dialysis solutions, such as icodextrin. Special consideration is given in the administration of antibiotics in patients under automated peritoneal dialysis (APD), as rapid exchanges seem to interfere with the antibiotics concentration. Conversion to CAPD, longer exchange cycles and intermitted administration of vancomycin are recommended, but still more studies are needed to provide sufficient data. Only one retrospective single-center observational cohort study has been conducted on this issue that showed no significant difference between the two modalities [43].

The 2016 ISPD guidelines include a chapter with the adjunctive treatments to the typical antibiotic treatment in peritonitis. As in the past guidelines antifungal treatment, heparin and analgesics use, peritoneal lavage and use of IP urokinase are being mentioned. Regarding IP use of urokinase data do not seem to support its routine use, while the IP use of immunoglobulin mentioned in the past guidelines is omitted in the present ones. The Committee for the first time highlights the need of using hypertonic solutions or icodextrin [44] and short duration dwells in order to address the encountered problem of low ultrafiltration and hypervolemia during peritonitis episodes. Moreover, better glycemic control in diabetic patients and screening

for signs of malnutrition due to increased protein loss as a result of inflammation and enhanced permeability of the peritoneum are being also suggested.

Subsequent management of peritonitis

Refractory, recurrent, relapsing and repeat peritonitis are four different types of peritonitis with different prognosis [45]. In the present guidelines, two new methods for early prediction of relapsing or refractory peritonitis are mentioned. The measurement of bacterial DNA fragments levels in the PD effluent 5 days before and upon the completion of the treatment [46] and the effluent white cell count and leukocyte strip test upon the completion of the treatment [47] seem to predict relapse or recurrent episodes of peritonitis. Their clinical utility, however, remains yet to be proven.

Gram-positive peritonitis

Coagulase-negative *Staphylococcus* and especially *S. epidermidis* is a common cause of peritonitis. IP cephalosporins or vancomycin are considered effective antibiotic regimens for *Staphylococcus* peritonitis. Important problem that still has to be faced is methicillin resistance [48]. The Committee suggests continuous IP administration instead of intermittent in order to avoid the growth of resistant strains. As in the past guidelines, IP urokinase and oral rifampicin are proposed as a method for catheter salvage in cases of *Staphylococcus* peritonitis, although more studies are needed to support this approach.

Enterococcus and *Streptococcus* peritonitis are being separately discussed in the present guidelines and not as one entity as in 2010. More precisely, new data regarding the treatment of *Enterococcus* peritonitis have been derived from recent studies and modified the therapeutic protocols. IP vancomycin for 3 weeks is considered the first antibiotic choice when it comes to *Enterococcus* peritonitis, while first-generation cephalosporins should be avoided because of high prevalence of resistance [49]. In case of peritonitis with severe clinical presentation and high suspicion of *Enterococcus* origin, aminoglycosides should be added. In cases of vancomycin resistance, daptomycin is now considered the best antibiotic choice [50]. In streptococcal peritonitis, IP ampicillin is still the preferred regimen [51]. The species of *Streptococcus* seems to play an important role in the clinical outcome of peritonitis episodes. *Streptococcus viridans* is closely related to refractory episodes of peritonitis [52].

The ISPD in the 2016 guidelines focuses on the duration of the treatment for *S. aureus* peritonitis that should be 3 weeks with proper antibiotic regimen [53]. Based on recent data, first-generation cephalosporins are the first choice antibiotics, while IP vancomycin and teicoplanin or daptomycin can be used in case of methicillin resistance [54]. Rifampicin remains a useful adjuvant antibiotic, but its enzyme-inducing effect and the risk of development of resistant tuberculosis strains should be taken into consideration.

When it comes to peritonitis episodes due to Corynebacterium the 2016 ISPD guidelines do not include new data derived from new studies. However, because its rate has increased over the past few years and it is closely related to repeat and relapsing peritonitis, hospitalization, permanent catheter loss, transfer to hemodialysis and even death, the Committee suggests that it should be treated with proper antibiotics for 3 weeks as in *S. aureus* peritonitis.

Gram-negative peritonitis

Pseudomonas species usually cause severe peritonitis. Although the 2016 ISPD guidelines do not refer to new studies regarding this type of peritonitis, they suggest that the treatment should last for 3 weeks and include two differently acting antibiotics. The recommended antibiotic combination is IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime, while carbapenems could be an option and moxifloxacin should be avoided. Finally, for once more the Committee suggests prompt catheter removal when Pseudomonas peritonitis and exit-site or tunnel infection coexist.

Other gram-negative peritonitis is a type of peritonitis that has increasingly caught the attention of experts over the past few years. In the present guidelines, the duration of the recommended treatment is 3 weeks, but full eradication remains a problem. Extended-spectrum beta-lactamases and carbapenem-resistant Enterobacteriaceae are two mechanism of accumulated resistance to antibiotics that can influence the progress of each peritonitis episode [55]. The lower sensitivity of the organisms in a biofilm compared to that in laboratory is a problem related to the high prevalence of treatment failure. Finally, regarding Stenotrophomonas peritonitis, the Committee still considers that prior antibiotic treatment could be responsible and that treatment should last for 3–4 weeks including two different antibiotics. Besides trimethoprim/sulfamethoxazole that should be initially included in the treatment, the Committee suggests the use of tigecycline, polymyxin B and for the first time colistin.

Peritonitis due to multiple organisms

Peritonitis due to multiple organisms is an entity related with severe clinical presentation and outcome when gram-negative organisms are present and with more favorable

prognosis when only gram-positive organisms are present [56]. In the case of gram-negative organisms, surgical evaluation and special antibiotic treatment are required. As in the past guidelines, the Committee suggests the use of three antibiotics (metronidazole, IP vancomycin and IP aminoglucoside or IP ceftazidime) for at least 3 weeks. Similarly, 3-week duration of antibiotic treatment is now suggested for multiple gram-positive organisms as well.

Culture-negative peritonitis

Culture-negative peritonitis is an important problem that the peritoneal dialysis centers have to face and a special section is included in the present guidelines. It is suggested that if the culture remains negative after day 3, new effluent WBC count with differential should be obtained and in the case of ongoing inflammation special culture techniques should be used in order to isolate unusual microorganisms. Regarding antibiotic therapy, if peritonitis is resolving then initial therapy should be continued, but aminoglycosides could be discontinued in rapidly resolving (within the first 3 days) episodes.

Fungal peritonitis

Fungal peritonitis on the other hand requires prompt catheter removal and continuation of antifungal therapy for at least 2 weeks after the removal [57]. It is considered to be a severe type of peritonitis and according to recent data only one-third of the patients will be able to return to the method after the resolution of peritonitis [58]. As in the past guidelines, amphotericin B, flucytosine, fluconazole, echinocandins, posaconazole and voriconazole are described as effective antifungal treatment options. Still, the Committee highlights that the use of fluconazole could lead to azole resistance [59].

Tuberculous peritonitis

Mycobacteriae are still considered to be a rare cause of peritonitis. If tuberculous peritonitis is suspected, then Ziehl-Neelsen stain, a combination of conventional solid (Löwenstein–Jensen agar) and fluid medium cultures and mycobacterial DNA PCR in the effluent can be used in order to isolate mycobacteriae. Even the performance of laparoscopy with biopsy has been proposed for rapid diagnosis. The treatment protocol has not changed over time. Rifampicin, isoniazid, pyrazinamide and ofloxacin are the four drugs used. The Committee in the present guidelines has reduced the duration of pyrazinamide and ofloxacin treatment to two months instead of three months suggested in the past guidelines. Still pyridoxine, streptomycin and ethambutol are related to high rate of adverse effects. In particular, for ethambutol the committee suggests a dose of 15 mg/kg every 48 h or three times per week for up to two months [60]. New studies confirmed previous ones that the anti-tuberculous therapy could be carried through without removal of the catheter [61].

Non-tuberculous mycobacterial peritonitis

Non-tuberculous mycobacterial peritonitis is a type of peritonitis that was mentioned in the 2010 guidelines. During the past few years, many new studies have been published bringing to light important information [62–64]. It is now known that many of the non-tuberculous mycobacteria are rapidly grown and can be easily confused with gram-positive microorganisms [65]. On the other hand, gentamycin remains an important risk factor for the induction of this type of peritonitis. Still the Committee cannot suggest a proper antibiotic regimen, and catheter removal is very common.

Catheter removal and reinsertion

In the 2016b guidelines, the Committee included a table with the indications for catheter removal. Moreover, new data are included and the Committee gives information regarding the catheter reinsertion after a peritonitis episode, the proper duration of therapy before the reinsertion of the catheter, the indicated method for the reinsertion and patients' prognosis after reinsertion of the catheter [66–68].

Conclusion

The 2016 guidelines provide new data on peritonitis, one of the major complications of PD. The focus is now balanced between both preventing and treating peritonitis. The studies conducted over the past 6 years have been studied and analyzed in order new data on microorganisms, their isolation and their handling to be exported and presented. Still the Committee recognizes the need for more studies so that new antibiotics, new techniques for microorganisms isolation and new PD solutions to be analyzed and incorporated in the everyday clinical practice.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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