

Evidence-based medicine: An update on treatments for peritoneal dialysis-related peritonitis

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of this manuscript is to review the results of PD peritonitis treatment reported in narrative reviews, systematic reviews, and proportional meta-analyses. Two narrative reviews, the only existing systematic review and its update published between 1991 and 2014 were included. In addition, we reported the results of a proportional meta-analysis published by our group. Results from systematic reviews of randomized control trials (RCT) and quasi-RCT were not able to identify any optimal antimicrobial treatment, but glycopeptide regimens were more likely to achieve a complete cure than a first generation cephalosporin. Compared to urokinase, simultaneous catheter removal and replacement resulted in better outcomes. Continuous and intermittent IP antibiotic use had similar outcomes. Intraperitoneal antibiotics were superior to intravenous antibiotics in reducing treatment failure. In the proportional meta-analysis of RCTs and the case series, the resolution rate (86%) of ceftazidime plus glycopeptide as initial treatment was significantly higher than first generation cephalosporin plus aminoglycosides (66%) and glycopeptides plus aminoglycosides (75%). Other comparisons of regimens used for either initial treatment or treatment of gram-positive rods or gram-negative rods did not show statistically significant differences. The superiority of a combination of a glycopeptide and a third generation cephalosporin was also reported by a narrative review study published in 1991, which reported an 88% resolution rate.

Key words: Peritonitis; Peritoneal dialysis; Antibiotic; Treatment

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Abstract

Peritonitis continues to be a major complication of peritoneal dialysis (PD), and adequate treatment is crucial for a favorable outcome. There is no consensus regarding the optimal therapeutic regimen, and few prospective controlled studies have been published. The objective

Core tip: This manuscript revised the data from narrative and systematic review, as well as those from a proportional meta-analysis study, regarding comparisons between antibiotic regimens used to peritoneal dialysis-related treatment, empathizing protocols for initial treatment.

There is no consensus on the best treatment and the only published systematic review and its recent update have failed to find superiority of any regimen. This type of analysis, commonly excludes several studies, some of them with a great number of cases. Therefore, this review intends to contribute in this issue analyzing the results from different types of reviews.

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INTRODUCTION

Since the introduction of peritoneal dialysis (PD) in routine clinical practice, peritonitis has been the main complication influencing patient mortality. Peritonitis continues to be the most frequent cause of technique failure^[1], despite technological improvement. The choice of initial treatment for PD-related peritonitis remains a challenge to nephrologists who perform PD, particularly because of the lack of evidence to indicate the best therapeutic protocols, beyond temporal changes in the bacterial antibiotic susceptibility profile.

Coagulase negative staphylococci (CNS) are the most common etiological agents of PD-related peritonitis. In most PD centers^[2], these microorganisms cause approximately one-third of the episodes. Over the last two decades, *Staphylococcus aureus* has lost its status as a PD-related peritonitis etiology, possibly because of technological advances in connection systems and the routine use of antibiotic prophylaxis at the catheter exit site^[3]. However, the proportion of cases due to gram-negative bacilli has increased in several centers^[4]. In addition, a gradual increase in the frequency of methicillin-resistant CNS and gram-negative species resistant to commonly used antibiotics has been reported^[5,6].

Historically, the choice of initial antimicrobial regimen for PD-related peritonitis has been based on the recommendations of the International Society for Peritoneal Dialysis (ISPD), which published six documents between 1989 and 2010^[7-12]. According to these guidelines, the initial treatment of peritonitis (prior to the results of microbiological tests) should be based on a combination of drugs for coverage of gram-positive cocci and gram-negative bacilli. The recommendations regarding the class of antimicrobials have varied over time. In general, for coverage of gram-positive cocci, the use of a first generation cephalosporin or vancomycin has been proposed, while for gram-negative bacilli an aminoglycoside or ceftazidime has been recommended. However, based on the available literature there is no consensus regarding the best antimicrobial therapy for the initial treatment of these infections, and few

prospective and controlled studies have been published.

This manuscript intends to review the results from evidence-based medicine, comparing different treatment protocols for PD-related peritonitis in narrative reviews, systematic reviews and proportional meta-analysis.

NARRATIVE REVIEWS

Since the introduction of ambulatory PD as a modality of renal substitutive therapy as part of the clinical routine, several reviews have been published discussing general and specific aspects of this therapy, including peritonitis and its management; however, few of these articles have focused on comparing the therapeutic regimens.

In 1991, Millikin *et al.*^[13] published the first robust review compiling existing data on antimicrobial treatment of PD-related peritonitis. That study reported on studies of antimicrobial treatment for peritonitis published in the medical literature before January 1990. According to the review, the regimens most frequently used for empirical therapy were a combination of two antimicrobial drugs; the majority of the regimens involved an aminoglycoside associated with an antibiotic to gram positive organism coverage. An aminoglycoside with a first-generation cephalosporin was used in 165 episodes, with an overall resolution rate of 83%, while the combination of an aminoglycoside with a glycopeptide resulted in a clinical response in 88% of 286 cases. When a glycopeptide associated with a third generation cephalosporin was used, the resolution rate reached 93% as reported by three studies in a total of 197 peritonitis episodes.

The efficacy of drugs used for treatment of infections due to gram positive cocci was proven in 413 peritonitis episodes. The resolution rate was 90% for a first generation cephalosporin, used in 164 episodes. A similar clinical response was observed whether intraperitoneal (IP) cefazolin was prescribed for intermittent or continuous administration. However, the results from second-generation cephalosporins, used for treatment in 29 episodes, showed a resolution rate of 76%. In turn, the prescription of a glycopeptide, particularly vancomycin, resulted in a resolution rate of 94% in 220 cases.

For gram negative peritonitis episodes, aminoglycoside monotherapy produced a clinical response in 48% of the 58 episodes, while a monobactam (aztreonam) resolved 22 of 27 cases (81%), and a quinolone resolved 13 of 17 cases (76.4%). In 97% of cases involving *pseudomonas* peritonitis, an aminoglycoside was used either as monotherapy or in combination with anti-*pseudomonas* penicillin. When the peritonitis episode was at the exit site or was catheter related ($n = 47$), the response rate was only 32%. *Pseudomonas* peritonitis that was not associated with catheter infection, however, responded to these agents in 73% of 44 cases.

In 2000, our group published a literature review analyzing the therapeutic response from the empirical antimicrobial regimen proposed in the first, second, and third report of the Ad Hoc Committee on Peritonitis

Management of the International Society of Nephrology ("ISPD guidelines"), published between 1985 and 2000^[14].

From 1985 to 1990, covering the period from the first report by The Ad Hoc Committee on Peritonitis Management^[7], a total of six publications with 204 peritonitis episodes, a resolution rate higher than 80% was observed with the combination of a first generation cephalosporin and an aminoglycoside. In 1993, the second report by The Ad Hoc Committee on Peritonitis Management^[8] recommended the initial use of vancomycin plus an aminoglycoside, both by an intermittent IP route, or IP injection of vancomycin combined with a third generation cephalosporin.

Results from the empirical prescription of vancomycin plus an aminoglycoside were reported in 23 publications between 1985 and 2000, corresponding to more than 1300 peritonitis episodes. A clinical response above 80% was reported in almost all of the series. In the series with the largest number of consecutive episodes (241 cases), the authors observed a resolution rate of 86%.

Vancomycin associated with ceftazidime was used in four studies, with a total of 302 episodes, resulting in a resolution rate above 90%. In the study with the largest number of cases (102 episodes) a cure rate of 92% was reported^[15].

The third report of The Ad Hoc Committee on Peritonitis Management was published in 1996^[9]. Based on the emergence of vancomycin-resistant enterococci and the possibility of gene transfer or resistance to *Staphylococcus aureus*, that document recommended the non-use of vancomycin in the empirical treatment of peritonitis. The combination of a first generation cephalosporin with an aminoglycoside again became the recommended empirical treatment for PD-related peritonitis.

Between the publication of the third report of The Ad Hoc Committee on Peritonitis Management and its fourth version in 2000^[10], the results obtained with this protocol were reported in six publications^[14]. In five of these reports, the resolution rate was over 75%. In our center, a study reporting 34 peritonitis episodes demonstrated complete cure in only 55% of the cases^[16].

SYSTEMATIC REVIEWS

Wiggins *et al.*^[17] published a systematic review of randomized controlled trials (RCTs) on PD-related peritonitis in 2007. The study included 36 trials published from 1985 to 2006. The results indicated that there was no superior antimicrobial agent or regimen, although glycopeptide-based regimens achieved a significantly higher complete cure rate (three studies, 370 episodes) than first-generation cephalosporin-based regimens. Vancomycin and teicoplanin resulted in similar treatment failure and relapse rates (two trials,

178 participants). Equivalent treatment failure rates and risk of relapse were observed between IP intermittent or continuous antibiotic administration (four trials, 338 participants), while one trial with 75 patients showed an advantages of IP antibiotics over intravenous therapy. Based on one trial with 37 patients with relapsing or persistent peritonitis, simultaneous catheter removal/replacement was demonstrated to be superior to urokinase at reducing treatment failure rates. Catheter removal was not decreased by urokinase treatment compared with placebo (two trials, 168 participants). Based on one trial with 36 patients, there was no statistically significant difference in clinical response within a 24-h period of peritoneal lavage when compared to non-lavage.

Recently, Ballinger *et al.*^[18], from the same group of investigators, published an update of this systematic review. The authors included RCTs and quasi-RCTs to assess the treatment of peritonitis in adults and children. In total, there were 42 studies published up to March 5 2014, with 3013 episodes of peritonitis. Their results were similar to the previous analysis; the authors did not identify any optimal antibiotic agent or combination of agents. The advantages of a glycopeptide-based regimen over those based on a first generation cephalosporin regarding complete cure rate were demonstrated (three studies, 370 participants). However, no differences between these regimens have been found when the endpoints were primary treatment failure (two studies, 305 participants), relapse (3 studies, 350 participants), catheter removal (two studies, 305 participants), and microbiological eradication (one study, 45 participants). Similarities between vancomycin and teicoplanin in the treatment failure and relapse were shown, although the authors provided new information, showing that the primary treatment failure rate was lower with teicoplanin than vancomycin (two studies, 138 participants). Similar to the previous systematic review, comparisons between IP intermittent or continuous antibiotic administration showed no difference in the complete cure and relapse rates (four studies, 338 participants). The results were updated for primary treatment failure (five studies, 522 participants) and the catheter removal rate (1 study, 20 participants); no differences between the two forms of antibiotics were found. A preference for IP antibiotics (vancomycin and tobramycin) over intravenous administration was newly stated based on one study with 75 patients. In addition, based on one study, comparisons of the adverse effects of these antibiotic administration routes were included. No significant differences were observed in the incidence of hypotension (76 participants), cutaneous rash (20 participants), and infusion pain (20 participants). The advantage of simultaneous catheter removal/replacement over urokinase at reducing treatment failure rate was rewritten (one study, 37 participants), but the authors presented new information on comparisons between fibrinolytic agents and non-urokinase or

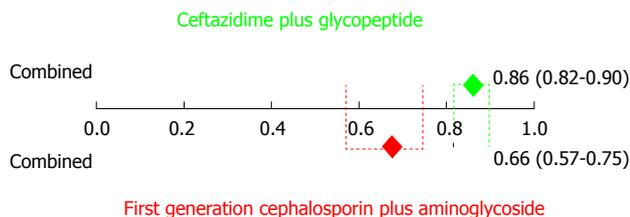


Figure 1 Combined resolution rate and 95%CIs of studies on initial treatment of peritoneal dialysis-related peritonitis with ceftazidime plus a glycopeptide vs a first generation cephalosporin plus an aminoglycoside.

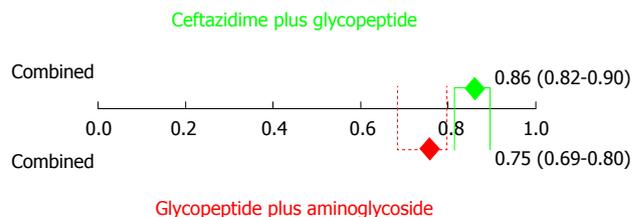


Figure 2 Combined resolution rate and 95%CIs of studies on initial treatment of peritoneal dialysis-related peritonitis with ceftazidime plus a glycopeptide vs a glycopeptide plus an aminoglycoside.

placebo. No significant differences were found in the following outcomes: complete cure rate (one study, 88 participants), primary treatment failure (two studies, 99 participants), relapse in persistent peritonitis (2 studies, 101 patients), relapse when fibrinolytic therapy was initiated at the time peritonitis was diagnosed (one study, 80 participants), catheter removal (2 studies, 116 participants), and all-cause mortality (1 study, 88 participants). Finally, the study found that there is no advantage to a 24-h period of peritoneal lavage compared to non-lavage (one study, 36 participants).

PROPORTIONAL META-ANALYSIS

One limitation of systematic review studies is the exclusion of a large number of publications with a large number of patients and episodes of peritonitis. Most of these excluded studies were case series. In turn, their authors have noted the inclusion of many trials with small patient numbers as a limitation^[17,18]. In an attempt to overcome these limitations, our center is employing an alternative methodology: the proportional meta-analysis to examine possible differences among therapeutic protocols. This method has been used in other clinical settings^[19,20], and it is possible to perform a meta-analysis of results from case series. Accordingly, a review of case series and RCTs concerning the treatment of PD-related peritonitis has been developed, focusing on comparing peritonitis resolution with antibiotics or antibiotic combinations more frequently recommended by the ISPD guidelines for empirical treatment of peritonitis and peritonitis due to gram positive or gram negative bacteria^[21].

Studies were obtained between 1966 and January 2013, using the following sources: United States National Library of Medicine, Excerpta Medica database, and Literatura Latino-Americana e do Caribe em Ciências da Saúde. Peritonitis was defined according to the authors in accordance with the contemporary ISPD guidelines^[7-12]. The criterion for peritonitis resolution was based on definitions used by authors and can vary greatly; the outcome resolution rate was treated as a dichotomous variable (peritonitis resolution vs non-resolution).

For first generation cephalosporins, we included the following: cefazolin, cephalotin, and cephaloridine. The only third generation cephalosporin we analyzed

was ceftazidime. For aminoglycosides, we included gentamicin, amikacin, netilmicin and tobramycin. Vancomycin and teicoplanin were considered in the analysis as glycopeptides. Finally, ciprofloxacin, levofloxacin and ofloxacin were the fluoroquinolones included.

After screening by title and abstract, we obtained full paper copies of 140 eligible studies reporting antibiotic therapy for PD-related peritonitis. However, after applying the inclusion and exclusion criteria, only 43 studies (26 case series and 17 RCT) were acceptable for a proportional meta-analysis.

Initial treatment with ceftazidime plus a glycopeptide was used in five^[15,22-25] studies with a total of 443 episodes; the pooled resolution rate was 86% (95%CI: 0.82-0.89). This resolution rate was significantly higher than initial treatment with a first generation cephalosporin plus aminoglycosides (pooled proportion of 66%, 95%CI: 0.57-0.75) from 14 studies^[25-38] with a total of 1438 total episodes (Figure 1). Initial treatment with ceftazidime plus a glycopeptide also showed a higher resolution rate than a glycopeptide plus aminoglycosides (pooled proportion of 75%, 95%CI: 0.69-0.80), which was used in 16 studies^[29-31,38-50] with a total of 574 episodes (Figure 2).

The following comparisons showed no statistically significant differences because their CIs overlapped: a first generation cephalosporin plus aminoglycosides [resolution rate (RR) = 66%, 95%CI: 0.57-0.75] vs glycopeptides plus aminoglycosides (RR = 75%, 95%CI: 0.69-0.80); a first generation cephalosporin plus aminoglycosides (RR = 66%, 95%CI: 0.57-0.75) vs a first generation cephalosporin plus ceftazidime (RR = 59%, 95%CI: 0.32-0.83); glycopeptides plus aminoglycosides (RR = 75%, 95%CI: 0.69-0.80) vs first generation cephalosporin plus ceftazidime (RR = 59%, 95%CI: 0.32-0.83), and a first generation cephalosporin plus ceftazidime (RR = 59%, 95%CI: 0.32-0.83) vs ceftazidime plus a glycopeptide (RR = 86%, 95%CI: 0.82-0.89).

For treatment of episodes due to gram-positive rods, the pooled resolution rate from 13^[23,39,40,48,49,51-58] studies with a total of 917 episodes was 78% (95%CI: 0.66-0.88) for a glycopeptide, while the rates from five studies^[26,37,53,58,59] with a total of 532 episodes for a first generation cephalosporin were 73% (95%CI: 0.55-0.88). There were no significant differences

Table 1 Recommendations for antibiotics choice in peritoneal dialysis-related peritonitis

Monitoring the etiologies and antimicrobial resistance profile		
	Yes	No
Initial (empirical) protocol	Start intraperitoneal antibiotics to cover gram-positive and gram rods, according to local microbiologic profile	Start a glycopeptide (gram-positive coverage) plus ceftazidime (gram-negative coverage), both by intraperitoneal route ¹
After results of culture and <i>in vitro</i> susceptibility tests	Culture positive: adjust the treatment according to bacterial susceptibility. If <i>Pseudomonas spp</i> on culture, add a second anti- <i>pseudomonas</i> drug acting in different ways that organism is sensitive to ² Culture negative: continue initial antibiotics	Culture positive: adjust the treatment according to bacterial susceptibility. If <i>Pseudomonas spp</i> on culture, add a second anti- <i>pseudomonas</i> drug acting in different ways that organism is sensitive to ² Culture negative: Continue initial antibiotics
Therapy duration	<i>Pseudomonas spp</i> , <i>Enterococcus/Streptococcus spp</i> = 21 d Non- <i>pseudomonas</i> single gram-negative = 14-21 d Culture negative, coagulase negative staphylococcus, other gram-positive rods = 14 d	

¹Evidence-based medicine; ²*E.g.*, quinolone, ceftazidime, cefepime, amglycoside, piperacillin.

between the schemes.

Comparisons of episodes due to gram-negative rods showed that the pooled proportion resolution rate from nine studies^[39,40,49,57,60-63] with a total of 138 episodes was 68% (95%CI: 0.50-0.85) for a quinolone. For ceftazidime, the resolution rate was 61% (95%CI: 0.53-0.70) from three studies^[33,63,64] with a total of 117 episodes, and for aminoglycosides the resolution rate was 65% (95%CI: 0.51-0.77) from nine studies^[23,26,31,39,40,49,55,60,61] with a total of 211 episodes. There were no significant differences among these antibiotics.

LIMITATIONS

The limitations of narrative reviews are those inherent to this type of publication, which include the use of different types of studies, such as RCTs, case series, and others without a statistical tool for comparisons among the treatments. Moreover, they refer to data published many years ago and may be influenced by an era effect.

Regarding the systematic reviews, their authors emphasize inadequate randomization and concealment methods. In addition, the definitions of peritonitis, successful treatment, and relapse varied among trials^[17]. Finally, many trials had small patient numbers, which reduces their statistical power.

The most important limitation of our proportional meta-analysis is the low evidence level of case series included with the RCTs. In addition, there is significant heterogeneity among the studies, which differed considerably in their patient selection, baseline renal disease, number of subjects, antibiotic administration routes, and definition of peritonitis and resolution.

CONCLUSION

According to the results of the systematic reviews, there is no superior antimicrobial agent to treat PD-related peritonitis, although glycopeptide-based

regimens achieved a significantly higher complete cure rate. Similar treatment failure rates were found with vancomycin and teicoplanin, while the primary treatment failure rate was lower with teicoplanin. Intermittent or continuous IP antibiotic administration had similar complete cure, primary treatment failure, relapse, and catheter removal rates. The advantages of IP antibiotics over intravenous therapy were reported. In cases of persistent or relapsing peritonitis, catheter removal is associated with better outcomes than with IP urokinase. Finally, no advantages were found to be associated with adjunctive therapies, such as fibrinolytic drugs and peritoneal lavage.

A narrative review of antimicrobial treatment for patients with PD-related peritonitis published in 1991^[13] concluded that the optimal empirical treatment was weekly vancomycin and ceftazidime.

Our proportional meta-analysis^[21] was able to identify that the combination of a glycopeptide plus ceftazidime in the initial treatment of PD-related peritonitis was superior to a glycopeptide plus an aminoglycoside or the combination of a first generation cephalosporin plus an aminoglycoside. This result strongly suggests that the differences found may be related to better coverage of gram-negative bacilli with third generation cephalosporins than with aminoglycosides. Bacterial resistance of gram-negative bacilli, particularly *Pseudomonas* species, to commonly prescribed antimicrobials has been reported in recent years^[6]; this finding may explain the superiority of the protocols employing ceftazidime. This review showed that a treatment regimen with a glycopeptide plus ceftazidime could be a promising initial therapy in patients with PD-related peritonitis. However, this result should be carefully analyzed, because this treatment was only used in four cases series^[15,22-24] and one RCT^[25] for a total of 443 peritonitis episodes. Moreover, an emphasis should be placed on the necessity of monitoring the local microbiologic profile in each dialysis center to determine the initial therapeutic protocol. Recommendations for antibiotics choice in peritoneal dialysis-related peritonitis are expressed in the Table 1.

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