

Empirical therapy with cefazolin and ceftazidime in peritoneal dialysis-related peritonitis

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ABSTRACT

Introduction: The best empirical therapy in peritoneal dialysis-related peritonitis is still a matter of debate. The recommendation of first generation cephalosporin as first option treatment is difficult to accept due to the emergence of resistant microorganisms. We describe our 8 years' experience with intraperitoneal cefazolin and ceftazidime as empirical treatment.

Patients and Methods: Peritoneal dialysis-related peritonitis was treated with intraperitoneal cefazolin and ceftazidime 15mg/kg daily in a 6-hour dwell. The duration of therapy was usually 14 days, except in cases of *Staphylococcus aureus*, when it was extended to 21 days. Antibiotic therapy was adjusted in cases of antibiotic resistance or unsuccessful clinical outcome. The protocol was considered efficacious when there was a sterilisation of the dialysate and no relapse within 4 weeks after removal of antibiotics.

Results: We analysed 41 episodes of peritonitis in 32 patients. In 32 episodes (78%) the cultures were positive, with 28 Gram-positive (68%), 3 Gram-negative (7%) and 1 multiorganisms isolated. No organism was identified in 9 peritonitis episodes. Half of the Gram-positive agents were coagulase-negative *Staphylococci* (CoNS). 21% of the CoNS were resistant to cefazolin but all of them were susceptible to vancomycin. No methicillin-resistant staphylococci were identified. All the Gram-negative bacilli were susceptible to ceftazidime. The global cure rate with this antibiotic regimen was 78%, including 68% at first intention and 10% after

changing the antibiotic. In 22% of the peritonitis episodes the protocol was unsuccessful due to persistent (n=2) or relapsing infections (n=6) and to patient death in one case.

Conclusions: Combining intraperitoneal cefazolin and ceftazidime as empirical therapy for peritoneal dialysis-related peritonitis proved to be effective. As there is an absence of methicillin-resistant microorganisms and low resistance to first generation cephalosporins in our unit, vancomycin should not be used as a first choice for empirical initial treatment. Monitoring of the bacterial profile and sensitivities to antibiotics is essential in order to apply the most rational therapy in each unit.

Key-Words:

Cefazolin; ceftazidime; empirical therapy; methicillin-resistant; peritoneal dialysis; peritonitis.

INTRODUCTION

Despite the technical advances in peritoneal dialysis (PD) therapy, peritonitis is still a significant cause of morbidity and mortality in PD patients^{1,2}. Peritonitis mortality rates have not changed markedly over the past two decades. Peritonitis has been associated with 15% of the deaths occurring over the course of PD treatment. Higher incidences of more aggressive forms of peritonitis in more debilitated patients may explain the lack of improvement in mortality rates^{3,4}.

During PD the peritoneal membrane is continuously exposed to bioincompatible dialysis solutions

that contain potential activators of a proinflammatory response. This chronic inflammatory state is exacerbated by peritonitis, resulting in thickening of the submesothelial space and alteration of the microvessel structure, compromising technique survival^{5,6}. The most suitable peritonitis treatment is currently under debate.

The International Society for Peritoneal Dialysis (ISPD) revised its peritoneal dialysis-related infections guidelines⁷ in 2005. Empiric antibiotic therapy must cover both Gram-positive and Gram-negative organisms. While vancomycin was used as initial treatment in the past because of its exceptional coverage of Gram-positive agents^{7,8}, the high incidence of vancomycin-resistant *Enterococcus* species and the emergence of *Staphylococcus aureus* with intermediate susceptibility to vancomycin led the ISPD committee to recommend the use of first-generation cephalosporins (cefazolin)^{7,9,10}. This recommendation was difficult to approve due to the increasing frequency of methicillin-resistant coagulase-negative *Staphylococci* (CoNS)^{11,12}. Gram-negative infections should be covered with ceftazidime⁷. The risk of resistance in *Enterobacteriaceae* must be a matter of concern¹³.

This study describes our eight-year experience in PD-related peritonitis treatment with intraperitoneal (IP) cefazolin and ceftazidime as empirical initial therapy.

■ PATIENTS AND METHODS

We retrospectively analysed the PD-related peritonitis episodes between January 1998 and December 2005 in our unit. Table I shows the population characteristics. Patients with peritonitis episodes treated with the instituted antibiotic protocol were included in this study. Fifteen peritonitis episodes not initially treated with the antibiotic protocol were excluded. Peritonitis episodes were diagnosed by the presence of at least two of the following criteria: abdominal pain, cloudy dialysate and more than 100 white cells/ μ L dialysate with more than 50% polymorphonuclear cells. Dialysate differential cell count, Gram stain and cultures with antibiotics susceptibility testing were performed.

Table I

Clinical characteristics of patients

Patients (n)	96
Sex (male/female)	60/36
Age (years)	49 \pm 17
Mean follow up (months)	26 \pm 21.3
Mean peritonitis rate (peritonitis/patient.year)	0.37
Underlying disease (%)	
Diabetes mellitus	34
Chronic glomerulonephritis	32
Hypertension	16
Polycystic kidney disease	3
Other or unknown	15

■ Antibiotic protocol

After clinical diagnosis, antibiotic therapy was initiated with IP cefazolin and ceftazidime 15mg/kg daily in a 6-hour dwell. Patients on automated peritoneal dialysis (APD) were temporarily transferred to continuous ambulatory peritoneal dialysis (CAPD) and patients with residual renal function (>100 ml/day urine output) underwent continuous dosing (all exchanges). Duration of therapy was usually 14 days, except in cases of *Staphylococcus aureus* infections, when it lasted 21 days. Antibiotic therapy was adjusted in cases of antibiotic resistance or unsuccessful clinical outcome. Our centre does not use any topical antibiotic prophylaxis at the exit site.

■ Outcome

The protocol was successful at first intention if there was a sterilisation of the dialysate or no relapse within 4 weeks after removal of the antibiotics. If the antibiotic therapy had to be adapted to dialysate culture with subsequent sterilisation of the dialysate and absence of relapse, the success was at second intention. The protocol failed in cases of catheter removal due to persisting peritonitis despite antibiotic adaptation, or peritonitis relapse at the end of antibiotic therapy, or if the patient died.

RESULTS

During this period we analysed 41 peritonitis episodes in 32 patients (19 males, 13 females; mean age at first peritonitis episode 47 years; 7 diabetic patients; 24 episodes in APD, 17 episodes in CAPD).

In 32 episodes (78%) the dialysate cultures were positive (Table II), with 28 Gram-positive (68%), 3 Gram-negative (7.5%) and 1 multiorganisms isolated. No organism was identified in 9 (22%) peritonitis episodes. There were no peritonitis episodes caused by fungus. No significant microbiology data differences were found between APD and CAPD patients.

Half of the Gram-positive agents (n=14) were CoNS, 7 *Streptococcus viridans* and 7 *Staphylococcus aureus*. *Serratia marcescens*, *Enterobacter cloacae* and *Acinetobacter baumannii* were the Gram-negative organisms identified. The polymicrobial peritonitis was caused by CoNS, *Streptococcus viridans* and *Neisseria sp.*

Twenty-one percent (n=3) of the CoNS were resistant to methicillin but all of them were susceptible to vancomycin. No methicillin-resistant *Staphylococcus aureus* (MRSA) were identified. All the Gram-negative bacilli were susceptible to ceftazidime.

The global cure rate with this antibiotic regimen was 78%, including 68% (n=28) at first intention and 10% (n=4) at second intention. Vancomycin 1g IP in a 6-hour dwell was added in the

polymicrobial peritonitis and ampicillin 250mg IP in all exchanges in one case of *Streptococcus viridans* infection. Ciprofloxacin 500mg BID orally was used with success in the *Enterobacter sp* infection and gentamicin 80mg IP in a 6-hour dwell in the *Serratia sp* peritonitis.

The protocol was unsuccessful in 9 (22%) peritonitis episodes due to persisting (n=2) or relapsing infections (n=6) leading to catheter removal, and one patient death. Gram-positive agents caused all the cases. Persistent infections were caused by CoNS (n=2); relapsing infections by *Streptococcus viridans* (n=2), CoNS (n=3) and *Staphylococcus aureus* (n=1) and one patient died due to *Staphylococcus aureus* peritonitis. All of these infections led to catheter removal except those caused by *Streptococcus viridans*. Four weeks after finishing the antibiotic treatment a new catheter was reimplanted.

DISCUSSION

We instituted the protocol for PD-related peritonitis with IP cefazolin and ceftazidime as empirical initial treatment. The bacteriological profile of our population was a standard one, with most infections caused by Gram-positive organisms. Although we had a high rate of culture-negative peritonitis (22%), this incidence decreased after the introduction of enriched culture media. Later years have seen fewer cases than earlier years.

Table II

	N (%)	Antibiotic sensitivity		
		Cefazolin	Ceftazidime	Vancomycin
Gram positives	28 (68)			
CoNS	14	S11 R3		S14
<i>Streptococcus viridans</i>	7	S7		S7
<i>Staphylococcus aureus</i>	7	S7		S7
Gram negatives	3 (7.5)			
<i>Acinetobacter baumannii</i>	1	R1	S1	
<i>Enterobacter cloacae</i>	1	S1	S1	
<i>Serratia marcescens</i>	1	S1	S1	
Multiorganisms	1 (2.5)	S1	S1	
Negative cultures	9 (22)			

CoNS = coagulase negative *Staphylococcus epidermidis*; S = sensitive; R = resistant.

Our overall peritonitis success rate was 78%, including 68% at first intention, which is comparable with other protocols, including vancomycin, and using other routes of administration (oral and intravenous)^{8,14-16}.

Several studies have shown a better cure rate with vancomycin than with cefazolin^{17,18}. Flanigan *et al.*¹⁹ reported a cure rate of 87% with vancomycin vs. 67% with cefazolin ($p=0.01$), and also lower rates of hospital stay, superinfection and relapse.

The use of first-generation cephalosporins raises the problem of inefficacy against methicillin-resistant organisms, most commonly CoNS¹¹. Vas *et al.*²⁰ found a 55% failure rate^{8,14} when treating methicillin-resistant CoNS PD-related peritonitis with cefazolin. In the past years methicillin resistance is no longer restricted to CoNS and there has been an increasing proportion of MRSA^{8,11}. Some programmes have a very high methicillin resistance rate (>50%), justifying the results previously described and the use of vancomycin as first-line therapy¹¹.

In our study CoNS and *Staphylococcus aureus* were responsible for 34 and 17 percent of the peritonitis episodes in turn. Only 22% of the CoNS were resistant to cefazolin and all of them were sensitive to vancomycin. No methicillin-resistant staphylococci were identified. The low prevalence of methicillin resistance in our centre explains the reasonably successful outcome with cefazolin. Vancomycin as first option is probably excessive in our centre.

Other authors had similar results with IP cefazolin and gentamicin. They achieved a clinical cure rate of 78% and 95%, as effective as the vancomycin-based regimen^{15,21}. This study also reported a low incidence of MRSA¹⁵. Two authors found that cefazolin is as effective as vancomycin for *St. epidermidis* peritonitis, despite high resistance to methicillin^{22,23}. More recently Lévesque *et al.*²⁴ also concluded that cefazolin is as effective as vancomycin for the treatment of peritonitis in PD patients despite the fact that more than 25% of the Gram-positive cocci were *in vitro* oxacillin resistant. This might be explained by the fact that *in vitro* resistant does not always means *in vivo* resistance, especially when using high doses of IP cefazolin (15mg/Kg).

We also had a significant number of *Streptococcus viridans* peritonitis ($n=7$). Two of them relapsed

despite being sensitive to cefazolin, and they were cured without removing the catheter; only with antibiotic therapy. A retrospective analysis demonstrated a slower response, reasonable outcome and high rates of recurrence in streptococcal peritonitis²⁵. This led us to follow the ISPD recommendations using IP ampicillin in all streptococcus peritonitis independent of the cefazolin resistance⁷.

Gram-negative organisms were responsible for 3 peritonitis episodes. Ceftazidime was the antibiotic used in all of them with success (3/3 agents were sensitive *in vitro*). However ceftazidime is prone to induce resistances in *Enterobacteriaceae*⁸. Although we had a low percentage of Gram-negative peritonitis, it is important to monitor the resistance profile.

It can be concluded that the combination of IP cefazolin and ceftazidime as empirical initial therapy for PD-related peritonitis is efficient. The absence of methicillin-resistant microorganisms and the low resistance to first generation cephalosporins in our unit justifies not using vancomycin as empirical treatment. Ceftazidime also provided good results in Gram-negative peritonitis. However, close monitoring of the local epidemiology is essential in order to apply the most rational therapy to each unit.

Conflict of interest statement. None declared.

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