in renal function or is the result of chronic primary renal disease or is seen in patients with well functioning renal transplants which obviously have low filtration rates. We postulate that it makes a lot of sense to maintain the 25(OH)D concentration in the upper normal range, i.e. above the threshold of 30 ng/ml (75 nmol/l) in all individuals. It is hoped that this simple strategy will help to reduce the prevalence of secondary hyperparathyroidism in individuals with or without primary renal disease.

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References

10. Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. Osteoporos Int 1998; 8: S24–S29
11. Scharla SH. Prevalence of subclinical vitamin D deficiency in different European countries. Osteoporos Int 1998; 8: S7–S12

Peritoneal-dialysis-related peritonitis: the art of rope-dancing

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Introduction

Although incidence rates of peritonitis have decreased substantially with the introduction of the flush-before-fill double-bag principle, and the emergence of improved connection systems [1], peritonitis remains an Achilles tendon for peritoneal dialysis (PD) [2]. Mortality directly related to peritonitis is low, but peritonitis episodes cause psychosocial problems and are in the long run related to both technique failure and mortality [3]. Repetitive or protracted peritonitis episodes can also damage the peritoneal membrane [4]. Despite the overall decreasing incidence of peritonitis, mortality and technique failure attributable to it did not improve. This is due to the greater severity of infections caused by Gram-negative and Staphylococcus aureus infections, two types of infections that are less related to connection systems, and the incidence of which has remained stable [5]. Although infection rates in haemodialysis are at least as high as those in PD [6], most nephrologists and many patients will point to the risk of peritonitis as one of the reasons not to perform PD. Because of all these arguments, prevention and treatment of peritonitis are still a matter of great concern.
The ‘ideal’ empirical treatment protocol for PD-related peritonitis has been the subject of many debates, as well as of emotional editorial comments and letters to the editor. The main topic of this debate is the use of vancomycin [7,8]. The ad hoc advisory committee of the International Society for Peritoneal Dialysis (ISPD) issued new guidelines in 2001 [9]. Unfortunately, these contradict, at least partially, the guidelines of the same committee in 1996 [10] and 1993 [11]. Besides the general guidelines of this expert panel, different alternative regimens are being proposed on a regular basis, further adding to the general confusion. The plethora of opinions and different treatment approaches indicates that ‘the’ optimal antibiotic therapy does not exist. Rather, the selection of an empirical treatment protocol is an exercise in rope-dancing, balancing between different, often contradictory, requirements. The nephrologist has to consider not only the individual patient, but also the repercussions of his treatment on the macro-environment. The treatment should (i) provide broad coverage of all organisms, (ii) without disturbing the patient’s normal flora, and without side-effects or risk for the patient, (iii) should not provoke the emergence of resistant germs, (iv) should be convenient to administer, and cheap. It is clear that such a perfect treatment does not exist. This editorial will try to discuss some important issues in an attempt to help the reader to select a treatment regimen that meets most of his/her needs. The points that we will deal with are: (i) the local epidemiology and sensitivity pattern of causative organisms, (ii) the pharmacokinetic and pharmacodynamic profile of different antibiotics, and the related clinical efficiency of the applied regimen, (iii) the potential side-effects of different antibiotics, and (iv) prevention of peritonitis.

**Local epidemiology**

The ISPD expert committee revised its opinion from advocating to discouraging the use of vancomycin. This decision was largely based on the emergence of vancomycin-resistant enterococci, and the ensuing threat of the appearance of vancomycin-resistant staphylococci. Although there are probably more papers on this topic than there are actual cases [12], the concern about the emergence of resistant micro-organisms is appropriate both from an epidemiological and ecological point of view. Therefore it is recommended that vancomycin be avoided as much as possible. Unfortunately, some centres do have an important problem of methicillin-resistant staphylococci (MRSA or MRSE), making the use of vancomycin mandatory [13]. Therefore, an analysis of the local epidemiology of peritonitis is a conditio sine qua non in the treatment of peritonitis. All centres should keep a registry of their peritonitis cases, the causative germs and their sensitivity patterns. Only in this way can a sensible empirical treatment protocol that covers most of the organisms be developed. Such a database may also be of value for the individual patient. In our centre the on-call physician can immediately access the information of the latest peritonitis episode of every patient with regard to the causative organism, the antibiotics administered, the result of the treatment, and eventual observed side-effects. In this way the treatment is not only tailored to the centre, but also to the patient.

**Pharmacokinetics, pharmacodynamics and clinical effectiveness**

The pharmacokinetic behaviour of the selected antibiotic can impact substantially on the outcome of the peritonitis episode. First, the administered antibiotic can only be active if sufficiently high concentrations are maintained at the site of the infection. In PD patients, besides the option of oral and intravenous administration, there is also the possibility of the intraperitoneal (IP) route for administration of antibiotics. IP administration has the advantage of a high concentration of the antibiotic at the site of infection. The major drawback is that injection of the antibiotic into the bag induces a potential extra risk of contamination. In this regard, once-daily IP administration has great advantages. Intravenous administration should be avoided as this can destroy vascular access possibilities that are precious for the future [14]. Vancomycin has an extremely advantageous pharmacokinetic profile, as one single intraperitoneal dose of 15–30 mg/kg results in adequate serum and dialysate concentrations for several days, at least in CAPD patients [15,16]. In patients with substantial residual renal clearance, the dose should be increased and serum levels should be monitored on day 3 and day 5, to avoid sub-therapeutic dosing. Vancomycin precipitates in alkaline milieu, and for this reason it cannot be injected into bags containing bicarbonate. The best way to administer it is to prescribe a long dwell with icodextrin, unless a sterile peritonitis caused by icodextrin is suspected. In contrast to its favourable pharmacokinetic profile, the pharmacodynamic profile of vancomycin is less favourable, as it is only a bacteriostatic and not a bactericidal antibiotic [15]. Sub-therapeutic serum levels have been related to relapse of infection [17], and they are probably also related to the emergence of vancomycin resistance. Therefore, if the causative organism is methicillin sensitive, or if methicillin is not a problem in an individual centre, the bactericidal methicillin-derivatives should be preferred. If vancomycin is used, the dose and duration of treatment and the achieved dialysate and serum levels should be adequate.

Administration of cephalosporin, selecting a loading dose of 500 mg/l dialysate and a maintenance dose of 125 mg/l dialysate results in consistently adequate levels. There is also evidence that once-daily (OD) administration results in acceptable serum and dialysate levels: 1.5 g cephalosporin IP has a serum half-life...
of 31.5 h, yielding an average serum concentration of 52.4 mg/dL after 24 h [18]. Ceftazidime 1 g IP OD has been shown to achieve adequate serum and dialysate levels for more than 24 h [19]. Both cefazolin and ceftazidime are bactericidal drugs. It should also be kept in mind that some streptococci and most corynebacteria are resistant to cephalosporins. Proponents of the cefazolin regimen claim that the IP concentrations of the drug are far above the MIC values, and are therefore effective, even if the antibiogram shows resistance, as the latter takes the ‘normal’ serum levels of the antibiotic as the reference. Studies evaluating the clinical efficacy of cefazolin in monotherapy have, however, yielded conflicting results. Vas et al. [20] reported a reasonably successful outcome with an OD cefazolin plus tobramycin regimen. Clinical treatment failure was, however, seen in five of nine patients with MRSA. In the study of Lai et al. [21], 18 of 19 patients were clinically cured with a combination of OD cefazolin 1.5 g and OD gentamicin. In the report of Goldberg et al. [22], the same regimen resulted in a clinical cure rate of only 78%. In addition, in this study only 55% of cases had Gram-positive micro-organisms, and only two of 23 Gram-positive infections were MRSA. Nevertheless, vancomycine had to be used as rescue therapy in nine cases (13%) with streptococcal infections. In a randomized prospective trial, de Fijter et al. [23] found that cefadrine in monotherapy yielded clinical success in only 50% of the cases. It is thus important to monitor not only the laboratory sensitivity of the causative organisms, but also the clinical results.

With ofloxacin, sufficient peritoneal concentrations, both after oral administration and after OD IP administration of 200 mg [24] can be achieved. The penetration of ciprofloxacin into the dialysate after oral administration is, however, problematical, and 2 x 750 mg/day has to be administered to obtain adequate dialysate levels above the MIC of Staph aureus and pseudomonas [25]. Such high doses are, however, often poorly tolerated. Because of the slow equilibration, the dwell time should at least be 6 h. It should also be stressed that all quinolones are adsorbed by phosphate binders. Therefore they should be taken without meals. Shalit et al. [26] reported that IP concentrations of ciprofloxacin reached adequate dialysate levels only 24 h after oral administration. Therefore the treatment should always start with an IP loading dose. If gentamicin is administered IP according to the ISPD guidelines (0.6 mg/kg), the resultant peak serum levels are below 4 µg/mL, whereas the dialysate concentrations remain above this level for more than 4 h. In view of the strong post-antibiotic effect of aminoglycosides and their high bactericidal capacity, a single, higher dose of 0.8 or even 1 mg/kg is probably preferable compared to the repetitive dosing of 0.6 mg/kg. Repetitive dosing of aminoglycosides enhances the risk of deterioration of residual renal function and should therefore be avoided if possible [27].

**Prevention of peritonitis**

Of course, the most important aspect in the management of peritonitis is prevention. There is plenty of evidence that the introduction of the flush-before-fill double-chamber bag has reduced the incidence of Gram-positive infections [28]. Good connection technique and a clean exchange procedure remain essential to avoid peritonitis.

From a theoretical point of view, the newer more biocompatible dialysis solutions should be less toxic to the resident cells in the peritoneal cavity. It has been shown that oxidative burst and production of cyto- kines are less suppressed when neutral pH, low GDP-containing solutions [29] are used. Such improved biocompatibility can result in a decreased incidence of peritonitis [30].

Several studies found a lower peritonitis incidence in patients on automated peritoneal dialysis (APD) compared to patients on CAPD. This effect is probably related to a reduced number of exchanges in APD [31]. On the other hand, there is substantial concern that the delayed discovery of peritonitis in APD patients might be harmful for the peritoneal membrane. Yishak et al. [32] found an adverse outcome of peritonitis in 6/100 (6%) of CAPD vs 6/49 (12%) of APD patients, although this difference was not statistically significant because of the low number of patients. Rodriguez-Carmona et al. [31] found no difference in the outcome of peritonitis between APD and CAPD patients.

Studies reveal that 40–60% of PD patients are carriers of Staph aureus. A chronic Staph aureus carrier state is a risk factor for the development of exit-site infection and of peritonitis [33]. An exit-site and/or tunnel infection with Staph aureus is extremely difficult to eradicate and often results in the removal of the catheter [34]. Earlier treatment protocols tried to eradicate colonization by Staph aureus by application of intranasal antimicrobial ointment, mostly mupirocin. This practice resulted in a reduction of the nasal carrier state, and a significant reduction of Staph aureus-related exit-site infection. However, the overall incidence of exit-site and tunnel infections did not decrease significantly, and the incidence of Staph aureus-related peritonitis did not decline [35]. Some centres have advocated the use of systematic screening and local prophylaxis based on these results. There are, however, some concerns regarding this policy. Firstly, there is the risk of resistance to the antimicrobial agent used. Several reports have pointed to the emergence of resistance to mupirocin after long-term use [36,37]. Secondly, although the treatment might be clinically effective, the debate continues as to whether it is cost-effective [38]. Amato et al. [39] showed that 70% of patients with Staph aureus peritonitis had the same strain of micro-organism at the exit site, whereas only 40% had the same organism in the nose, an incidence which was not different from that of carrier status in the partner. For this reason it seems more logical to apply the antimicrobial agents not to the nose, but to...
the catheter exit site. In addition, pharmaco-economic evaluation showed that in most countries the cost of screening for, and treatment of, nasal carrier state was higher than the savings obtained by the avoidance of exit-site infection and peritonitis. Two studies have shown a decreased incidence of *Staph aureus*-related exit-site infection and peritonitis using a preventive eradication strategy [40,41] with application of mupirocin at the exit site in all patients without screening. However, cost calculations were not performed, and the risk of the emergence of resistant micro-organisms remains, of course. Davey et al. [38] pointed out that the cost-effectiveness ratio would be different if the treatment cost of mupirocin or the cost of screening is less, or if the incidence of *Staph aureus*-related infections is higher. It appears once again that in the decision whether or not to eradicate, local circumstances such as the incidence of staphylococcal exit-site infection, treatment costs for mupirocin and peritonitis, and ease of catheter replacement are more important than dogmatic belief or disbelief in this strategy in general.

**Conclusions**

Although infections in HD patients are more serious, the fear of peritonitis remains a major concern of many patients and physicians, influencing the selection of a renal replacement modality. Peritonitis has a substantial impact on technique success, outcome and cost. Effective prevention and treatment is thus warranted. The empirical treatment of PD-related peritonitis should be a balance between the right of the individual patient to receive rapid-acting and highly effective treatment without side-effects on the one hand, and the rights of the society to prevent emergence of multi-resistant organisms, and to avoid unnecessary expensive treatments. The present guidelines of the *ad hoc* advisory committee are of great value in this regard. Nevertheless, they should not be interpreted as dogmatic rules that necessarily provide optimal treatment in all circumstances and all centres. Nephrologists should be stimulated to adapt and optimize the general guidelines to their local conditions. To this end, a thorough understanding of the local epidemiology, as well as of pharmaco-kinetic and pharmaco-dynamic principles is invaluable. Consideration of all these points will hopefully bring this rope-dancing exercise to a satisfactory conclusion.

**References**

7. Teitelbaum I. Vancomycin for the initial therapy of peritonitis: don’t throw out the baby with the bathwater. *Perit Dial Int* 2001; 21: 235–238
23. de Fijter CW, ter Wee PM, Oe LP, Verbrugh HA. Intrapерitoneal cefpiroxalone and rifampicin versus cephradine as initial treatment of (C)APD-related peritonitis: a prospective randomized multicenter comparison (CIPPER trial). *Perit Dial Int* 2001; 21: 480–486


