Enterococcal peritonitis in peritoneal dialysis patients: last name matters

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Prevention and management of peritonitis remains a for nephrologists and for patients undergoing peritoneal dialysis (PD). As the incidence of peritonitis becomes a lesser —although still unresolved— problem, more attention is being focused on the prevention and management of clinically aggressive infections, which represent a fearsome source of suffering, technique failure, and mortality.

Clinical presentation is closely linked to the microbes causing the infection—yeasts and enteric bacteria being the main agents producing complicated infections. The capacity of these micro-organisms to inflict severe and persistent harm is related both to the particular conditions in which they commonly appear (debilitated patients, un- derlying abdominal disease) and to their intrinsic aggressiveness and ability to persist under adverse conditions (taking advantage of resistance to common antibiotic regimens and of a capacity to produce biofilms and to take shelter in plastic materials, among other factors). This issue of *Peritoneal Dialysis International* provides relevant information on peritoneal infections caused by bacteria of the genus *Enterococcus,* unquestionably candidates for membership in this unpleasant club.

Enterococci are gram-positive, catalase-negative, non-spore-forming facultative anaerobic bacteria belonging to the group of so-called lactic acid bacteria (1). They can be seen as isolated cocci, pairs, short chains, and even long chains. Nearly 30 different

species have been identified, but 2   —namely, *E. faecalis* and *E. faecium*— cause most of the human infections in which this genus is involved (2). Species identification is laborious, and with the exception of *E. faecalis,* quite inaccurate using standard automated or rapid biochemical methods (1). In fact, the routine of many laboratories does not include differentiation, at least beyond the 2 main species. As will be evident later, the latter may be relevant in the clinical setting, because of their distinct virulence and antibiotic susceptibility patterns.

Enterococci are well adapted to survival in the gastrointestinal tract of humans, where they live in symbiosis with the immune system and other bacteria. Broad-spectrum antibacterials, particularly those with anti-anaerobic activity or biliary excretion, or both, favor proliferation of these organisms in the gut and emergence of vancomycin-resistant strains (VREs). These phenomena are a consequence of the eradication of gram-negative bacteria (mainly anaerobes), which results in downregulation of the intestinal expression of the antimicrobial peptide Reg IIIγ, the latter being essential to control the proliferation of gram-positive intestinal micro-organisms (3). Increased stomach pH also appears to favor enterococcal outgrowth (1). The foregoing factors explain why the gut is more heavily colonized by these bacteria in hospitalized patients than in the general population (4). On the other hand, the hospital environment appears to be frequently colonized by antibiotic-resistant enterococci (5), and the hands of health personnel may be a prime source of transmission of those bacteria.

Risk factors for persistent colonization by VRE include debilitating conditions (immunosuppression, comorbidity), prolonged stay in a hospital or long-term care facility, proximity to other colonized patients or to their environment, invasive procedures, and as indicated earlier, previous treatment with vancomycin or wide-spectrum antibiotics (1).

Enterococci were individualized as a genus as late as 1984. For some years, they were considered harm- less to humans. They were actually used in the food industry as probiotics or starter cultures because of their capacity to produce bacteriocins (6). However, consecutive reports starting in the 1990s and multiplying since the year 2000 have clearly demonstrated that they can cause severe infections. Bacteremia, endocarditis, and urinary tract infections have received the most at- tention, but enterococci can also

produce meningitis, hepatobiliary sepsis, neonatal sepsis, and skin and soft-tissue infections (1).

As expected in a gastrointestinal tract host, enterococci are frequently isolated in intrabdominal infections, usually together with other gram-negative and anaerobic bacteria. Interestingly, the pathogenic role of enterococci in these infections has been a matter of controversy. Some studies have shown that polymicrobial intra-abdominal infections can be successfully treated with antibacterials that lack enterococcal activity (7), and others have indicated that the presence of enterococci increases the risk of treatment failure in such infections (8). The explanation for this apparent inconsistency is not clear, but the presence of these bacteria has been suggested possibly to represent a specific concern only in infections caused by antibiotic-resistant strains or only in debilitated patients.

The virulence of enterococci is linked to their abilities to thrive in the gastrointestinal tract and to adhere to extracellular matrix proteins and epithelia (2). Their capacity to produce biofilms is crucial to their pathogenicity. In addition, they can secrete virulence factors, in- cluding cytolysin, hyaluronidases, gelatinase, and serine protease, which promote tissue damage and spread of the infection; provide nutrients to the bacteria by degrading host tissue; facilitate biofilm formation; and eliminate bacterial competence (2).

Antibiotic susceptibility is a prime issue in the clinical setting of enterococcal infections. These bacteria are naturally tolerant to the activity of penicillin and other beta-lactams. True resistance is less frequent and is usually mediated either by production of beta-lactamases or by mutations in the *pbp4* (*E. faecalis*) (9) or *pbp5* (*E. faecium*) gene (10). Resistance to penicillins and carbapenems is far more frequently observed in *E. faecium* than in *E. faecalis* (1). On the other hand, a growing fraction of these bacteria show resistance to glycopeptides and aminoglycosides, and multidrug resistance is becoming progressively more common (2). Again, resistance to glycopeptides is often species-specific, being much more frequent for *E. faecium* than for *E. faecalis.* It involves a 2-component system, with mutations in the genes *vans* and *vanr,* which modulate changes in the composition of the cell wall that decrease its affinity for vancomycin by a factor of as much as 1000. At least 6 gene clusters associated with glycopeptide resistance have been indentified in *Enterococcus* species, the main types being *vanA, vanb,* and *vanC* (2).

Antibiotic resistance can be rapidly disseminated to antibiotic-susceptible enterococci by pheromone-mediated conjugative plasmids or transposons (2).

Enterococci do not possess cytochrome enzymes and thus cannot produce the energy required to take up antibiotics into the cell. As a consequence, they are intrinsically resistant to all aminoglycosides at low concentrations (11), although the addition of agents that block peptidoglycan synthesis markedly increases the uptake of those antibacterials. Moreover, only gentamycin and streptomycin are suitable for the treatment of enterococcal infections, because the presence of the aminoglycoside $N(6')$-acetyltransferase (intrinsic to *E. faecium*) and the *aph(3')-IIIa* gene confer a natural resistance to all other common aminoglycosides (12). Remarkably, the acquisition of ribosomal mutations or aminoglycoside-modifying enzymes that confer high-level resistance to those drugs is extending worldwide, abrogating the advantages of synergistic combinations of aminoglycosides with cell-wall agents (12).

Should susceptibility patterns permit it, the first- line treatment of invasive enterococcal infections is the combination of a beta-lactam, preferably ampicillin or an ureidopenicillin, and an aminoglycoside (gentamy- cin or streptomycin). Monotherapy with a beta-lactam may be associated with a poor outcome, particularly in endovascular infections (1). The main reason is a narrow bactericidal margin, because enterococci are tolerant to low concentrations of these antibacterials, and concentrations that are too high may also result in suboptimal bactericidal activity through the so-called Eagle effect (12). The latter may be of particular concern in patients with kidney failure, in whom very high levels of beta- lactams can easily be reached.

Vancomycin and teicoplanin still enjoy significant acceptance for the treatment of infections by betalactam–resistant enterococci, but the expansion of vancomycin-resistant *E. faecium* has reduced somewhat the role of glycopeptides for the treatment of these infections (1). Oritavancin shows enhanced activity against VRE, but the available evidence of its efficacy in the treatment of such infections is limited.

Alternative options for the treatment of infections by multidrug-resistant enterococci have been reviewed in detail recently (12). Linezolid has been approved for this indication, but there are some doubts about its ef- fectiveness because of its lack of bactericidal effect and a paucity of clinical evidence. Quinupristin–dalfopristin is very active against *E. faecium,* but *E. faecalis* exhib- its natural resistance to this drug. Current guidelines

underline the convenience of using it in combination with other drugs. Daptomycin is another alternative, but resistance is relatively frequent after standard-dose monotherapy. Consequently, combinations of high-dose daptomycin with other antibiotics are recommended, particularly in severe infections. Tigecycline may also play a role (in association with bactericidal agents), but again, controlled clinical data are necessary to define its use in clinical practice.

What about enterococci as agents of peritoneal infection in patients undergoing PD?

These bacteria may cause between 2% and 6% of PD-related peritonitis episodes (13–16). As a rule, their identification is a hallmark of a gastrointestinal origin of the infection. In fact, almost one half of enterococcal isolations during PD-related peritonitis appear to occur in an enteric polymicrobial setting (16). By contrast, enterococci have been reported to be present in 17% of all polymicrobial peritonitis (17); however, the expected percentage is likely higher, if the focus is on infections by enteric bacteria. For instance, these micro-organisms were present in 24 of 59 episodes (41%) of overt enteric peritonitis diagnosed at our center between 1990 and 2010 (unpublished data).

Most enterococcal monobacterial infections may have a gastrointestinal origin too, but in this case, other possibilities must be considered. First, pathogenic enterococci can cause a variety of invasive extra-abdominal infections, including some affecting the oral cavity (1). Consequently, bacteremia and saliva-borne contamination are potential sources of enterococcal PD-related peritonitis, although it is unclear how often such a scenario may occur. Second, persistent colonization of the skin and nares by *Enterococcus* species appears to be rare in the regular PD patient (18), but the ability of these micro-organisms to colonize hospital-like environments entails a risk of acquiring peritonitis by touch contamination (1). On the other hand, the incidence of enterococcal catheter-related peritonitis is probably low. Reported rates of catheter exit-site infection by these bacteria are lower than 4 episodes per 1000 patient–years (14). At our center, we have observed only 3 such instances in an observation period involving more than 1700 patient–years, and none was associated with peritonitis.

Overall, and unless otherwise demonstrated, an endogenous enteric origin should be suspected for enterococcal peritonitis. That situation has management implications, including attention to the late growth of other enteric microbes (particularly anaerobes)

and the convenience of an abdominal diagnostic work-up in case of aggressive or relapsing infections.

The risk profiles, clinical presentations, outcomes, and management guidelines for enterococcal peritoneal infections have been a subject of limited attention in the past, but at least three relevant studies have addressed those questions in recent months. A report from ANZDATA (the Australia and New Zealand Dialysis and Transplant Registry) reviewed 116 episodes of enterococcal peritonitis in 103 patients (16). Older age, renovascular disease, and coronary artery disease were associated with a higher risk of these infections. As expected, polymicrobial infections were more severe, but monobacterial episodes were also relatively serious, with clinical outcomes comparable to those seen in infections by *staphylococcus aureus.* The overall mortality rate was 4%, catheter removal was necessary in 37% of the cases, and relapse occurred in 15% of patients. Vancomycin, usually as monotherapy, was the most frequent antibiotic approach. Microbiologic characterization beyond genus and antibiotic susceptibility patterns were not specified.

The International Pediatric Peritonitis Registry recently reported 20 episodes of monobacterial enterococcal peritonitis, representing 5.9% of the registered infections (15). As in the ANZDATA survey, the enterococcal species were not reported. All the tested strains were susceptible to carbapenems, but 31% were resistant to amdinocillins, and 21% to glycopeptides. The clinical outcomes were rather benign, with null mortality and only 1 case of catheter removal. As in the ANZDATA study, 15% of episodes relapsed at least once. This latter finding contrasts with results from other studies (19), which did not report such high relapse rates for enterococcal peritonitis.

In this issue of *Peritoneal Dialysis International,* Yip *et al.* (20) report on 29 cases of monobacterial enterococcal peritonitis, after excluding 20 other cases observed in a polymicrobial setting. Enterococci were present in 2% (monobacterial) to 3% (overall) of the episodes of peritonitis observed during the study period. Beyond the usual limitations of single-center retrospective surveys, including statistical power insufficient for subgroup analyses and multivariate approaches, the study provides interesting clues. For instance, *E. faecium* caused 31% of the episodes, a relevant finding considering the issues of virulence and antibiotic resistance raised by this species. Interestingly, no instance of resistance to vancomycin was recorded, but 41.4% of the isolations were resistant to

ampicillin, and 20.7% showed resistance to high-dose gentamycin. Resistance to ampicillin resulted in the frequent use of vancomycin, but did not seem to influence the outcome of the infections, which fell approximately between those for peritonitis caused by coagulase-negative *staphylococcus* species and by *Escherichia coli.*

In agreement with reports from the general popula- tion (12), previous antibiotic therapy was a predictor of resistance to ampicillin. Unfortunately, the size of the sample precluded an analysis of species-related severity beyond the antibiotic susceptibility patterns. Overall, the findings of this study by Yip and colleagues support the notion that management of enterococcal peritonitis is a complex issue, demanding agile and efficient microbiology methods and well-designed antibiotic treatment approaches.

The current recommendations from the International Society for Peritoneal Dialysis for the antibiotic treatment of enterococcal peritonitis adhere to the general guidelines for invasive infections by these bacteria (21). Ampicillin plus gentamycin is endorsed as the optimal approach, should drug susceptibility permit it. Glyco- peptides —often as monotherapy— represent a common approach (16), but expansion of *E. faecium* and patterns of antibiotic resistance are becoming an important issue, undermining the traditional reliability of those agents. Peritonitis by VRE may not have the dismal prognosis observed in older reports (22), but resistant infection unquestionably complicates management and out- come. Linezolid and quinupristin–dalfopristin are the current recommendations to treat peritonitis involving ampicillin-resistant organisms and VRE (21). Both drugs have been successful in controlling *E. faecium* peritonitis in small reports (23–26). Daptomycin could also be an option, but it must be administered intraperitoneally because of its poor penetration to the peritoneal cavity when given intravenously. Its potential instability in glucose-based solutions is another issue (27,28). Other newer alternatives, including tigecycline or oritavancin, have not been tested in enterococcal PD-related peritonitis. Therapy should be maintained for at least 2 weeks, although the significant relapse rates reported by recent studies suggest that longer schedules should be considered in selected cases (clinically aggressive infections, antibiotic-resistant strains, *E. faecium*).

Prevention of enterococcal peritonitis demands adherence to general recommendations in this field. Judicious use of antibacterials will likely help to reduce colonization by antibiotic-resistant strains. Traditional measures destined to minimize the risk of enteric

peritonitis (ad- equate patient selection, eradication of abdominal foci, and avoidance of constipation, among others) may be limited in effect, but are also commendable. Of course, steps destined to prevent touch contamination and catheter-related infections also apply here. So far, no evidence supports the convenience of systematic screening of patients or their environment for colonization by antibiotic-resistant enterococci.

In summary, enterococcal PD-related peritonitis represents a significant problem, not so much for clinical aggressiveness as for the diagnostic and therapeutic challenges such episodes may pose. The possibility of a complicated enteric origin, with late growth of other microbes, should always be kept in mind, particularly in aggressive infections. Species identification is recommended, and antibiotic susceptibility testing is essential for an optimal management. Efficient alternatives for the treatment of infections by ampicillin- and glyco-peptide-resistant strains are currently available, but as with other infections, prevention remains the most rewarding strategy.

DISCLOSURES

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