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REVIEW

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Are there Patients with Peritonitis Who Require Empiric Therapy for Enterococcus?

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Abstract Enterococci are an increasingly important cause of nosocomial infections. While the clinical impact of enterococci in cases of bacteremia and super-infections in selected patient populations has been well-established, their role as primary pathogens in polymicrobial intra-abdominal infections remains controversial. While it has been suggested that the presence of enterococci increases the rate of infectious post-operative complication, it has also been demonstrated that polymicrobial intra-abdominal infections involving enterococci can be treated successfully with appropriate surgical drainage and antibiotics, such as cephalosporins, that are not active against enterococci. Therefore, the question arises of whether or not antibiotic coverage against enterococci should be included in the empirical treatment of peritonitis in certain high-risk patient populations. An extensive literature review revealed some evidence arguing in favour of using empirical therapy with enterococcal coverage for intra-abdominal infections in the following cases: (i) immunocompromised patients with nosocomial, post-operative peritonitis; (ii) patients with severe sepsis of abdominal origin who have previously received cephalosporins and other broad-spectrum antibiotics selecting for *Enterococcus* spp.; (iii) patients with peritonitis and valvular heart disease or prosthetic intravascular material, which place them at high risk of endocarditis. The ideal therapeutic regimen for these high-risk patients remains to be determined, but empirical therapy directed against enterococci should be considered.

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Introduction

Peritonitis is a frequent and life-threatening disease [1]. During the last century, however, great progress has been made in the management of this condition [2]. Although antimicrobial treatment has certainly helped to improve patient outcome [3, 4], adequate source control by early surgical intervention remains the cornerstone of treatment [5, 6].

While enterococci are an increasingly important cause of nosocomial infections, their clinical significance in peritonitis has been the subject of a long-lasting and ongoing debate [7, 8, 9, 10, 11]. Several recent articles have attempted to better delineate the profile of patient populations at high risk of invasive enterococcal peritonitis and have suggested that empiric anti-enterococcal coverage in these patients may be beneficial [12, 13]. Based on a selection of relevant articles, the present review attempts to summarise published evidence arguing in favour of empiric anti-enterococcal coverage in selected patient groups. More specifically, the following questions are addressed: (i) What basic coverage is absolutely needed in the empiric therapy of peritonitis? (ii) Are enterococci able to cause treatment failures and adverse outcomes in patients with intra-abdominal infection? (iii) Which surgical patients are at risk of enterococcal bacteremia? (iv) What is the potential impact of inadequate enterococcal coverage in septic high-risk patients? (v) What is the profile of patients for whom empiric enterococcal coverage should be advocated?

What Basic Coverage is Required for Empiric Therapy of Peritonitis?

The goals of antimicrobial therapy in the treatment of peritonitis are as follows: (i) to prevent the local spread of existing infection in the early phase; (ii) to control bacteremia and avoid distant hematogenous spread (e.g. hepatic abscess); and (iii) to reduce late complications after bacterial intra-abdominal contamination (e.g. post-

Table 1 Overview of studies investigating whether enterococci are able to cause treatment failures and adverse outcomes

Type of study	Reference, year	Design and population	Data
Experimental animal study	[28], 1997	mice and rats with polymicrobial peritonitis	evidence for a pro-inflammatory role of *Enterococcus faecalis*
Case series	[7], 1983	19 surgical patients	breakthrough enterococcal sepsis associated with a high case-fatality ratio
Cohort study	[30], 1995	secondary analysis of a randomised clinical trial (n=330)	presence of *Enterococcus* spp. associated with treatment failure
Cohort study	[12], 2002	120 critically ill patients with secondary peritonitis	presence of *Enterococcus* spp. predictive of death; no impact of antibiotic therapy
Cohort study	[13], 2002	longitudinal observational study of 200 patients	enterococci often involved in postoperative infectious complications

operative abscess). In cases of secondary peritonitis, empiric antibiotic regimens should at least include coverage of aerobic gram-negative bacteria in order to decrease early mortality induced by bacterial endotoxins causing septic shock; they should also include coverage of anaerobic microorganisms to prevent the development of late post-operative abscesses [10, 14]. Several clinical studies performed in the 1970s showed that in the absence of adequate anti-anaerobic coverage, the late complication rate after intra-abdominal infection was high, with an incidence of post-operative abscesses of up to 30% [15, 16].

Ample evidence suggests that complicated, community-acquired intra-abdominal infections involving mixed flora can be treated with surgery and different classes of antibiotics without consistent anti-enterococcal activity (e.g. cephalosporins, fluoroquinolones) [11, 17, 18, 19, 20, 21, 22, 23]. For example, a review of six clinical trials examining the use of antibiotics without in-vitro activity against enterococci in the treatment of intra-abdominal infections noted no cases of treatment failure due to *Enterococcus* spp., despite the fact that 20–30% of cultures grew enterococci [10]. Thus, the frequent practice of adding ampicillin or penicillin to cover enterococcal infection is not justified in most cases. Conventional wisdom even argues against the necessity of adding anti-enterococcal coverage if initial intraperitoneal cultures showed enterococcal growth [9].

Are Enterococci Able to Cause Treatment Failures and Adverse Outcomes in Patients with Intra-Abdominal Infection?

While the clinical impact of antibiotic-resistant enterococci in bacteremia and super-infections in selected patient populations (e.g., burn patients with infections due to vancomycin-resistant enterococci) has been well established [24, 25], the role of antibiotic-susceptible enterococci as primary pathogens in polymicrobial intra-abdominal infections is still controversial. Animal models have shown that monomicrobial, intra-abdominal enterococcal infections have limited pathogenicity, since the organism lacks virulence and the capacity to induce late abscess formation [26, 27]. It has been postulated that enterococci may express bacterial synergy and pro-inflammatory activity only in the presence of more virulent bacteria by inhibiting phagocytosis and intracellular killing of those primary pathogens [28].

Clinical data about the harmful effect of enterococcal peritonitis is also limited, since many types of organisms are usually cultured from intra-abdominal infections. A case series published 2 decades ago analysed enterococcal breakthrough sepsis in 19 surgical patients and found a crude case-fatality rate of 68% [29]. In 1995, the secondary analysis of a randomised clinical trial involving 330 patients postulated that the presence of *Enterococcus* spp. may be a marker for a complicated course in hospitalised patients with peritonitis and that the presence of this microorganism was associated with a higher likelihood of treatment failure [30].

More recent studies have suggested that the presence of enterococci increases the infectious post-operative complication rate and even the risk of death [12, 13]. For instance, Sitges-Serra et al. [13] have looked at post-operative enterococcal infections after treatment of complicated intra-abdominal sepsis. They found a high proportion (50%; n=34) of enterococci in post-operative peritonitis. Independent risk factors for enterococcal infection were tertiary peritonitis, high severity of illness and inappropriate empirical antibiotic coverage against enterococci. Post-operative enterococcal infections were associated with higher mortality (21% vs. 4%; P<0.001). The authors of this study concluded that empirical antibiotic therapy covering enterococci "should be contemplated in some circumstances" [13]. Table 1 summarises the different types of studies that have investigated potential adverse outcomes associated with enterococcal intra-abdominal infection.

Which Surgical Patients Are at Risk of Enterococcal Bacteremia?

Most authorities agree that enterococcal bacteremia is a clinical condition requiring adequate antibiotic treatment, since serious adverse outcomes can arise [24]. In one case series, 15% of all episodes of nosocomial enterococcal

bacteremia were complicated by endocarditis [31]. Therefore, the following question arises: Have previous investigations already pre-defined the risk profile of surgical patients at high risk of enterococcal bacteremia? Surprisingly, although many studies have analysed the risk factors for vancomycin-resistant enterococcal infections [32, 33, 34] or the risk factors for enterococcal bacteremia in hospital-wide studies [35, 36, 37], few studies have analysed in detail the risk factors for enterococcal bacteremia in surgical patients [38]. For instance, Barrall et al. [39] performed a descriptive cohort study without multivariable analysis and found that enterococcal bacteremia was preceded by antibiotic use, exposure to central-venous catheters, other-organism bacteremia and intra-abdominal operations. Clearly, more precise and well-conducted studies are needed to better delineate the risk profile of patients undergoing general surgery who are at high risk of enterococcal bacteremia.

Immunocompromised patients permanently exposed to the health-care setting are at high risk of enterococcal bacteremia. It is a frequent infectious complication in liver transplant patients having previously received selective bowel decontamination, as previously shown by Patel et al. [40]. In their large cohort study, among 405 liver transplant patients, 114 had bacteremia with any type of microorganism and 52 had enterococcal bacteremia (incidence, 13%).

What Is the Potential Impact of Inadequate Enterococcal Coverage in High-Risk Patients with Enterococcal Sepsis?

Antibiotic selection pressure increases the risk of enterococcal super-infection and bacteremia either with drug-susceptible or -resistant strains [34]. Enterococcal super-infection may be prevented by avoiding prolonged prophylactic or broad-spectrum therapeutic regimens (such as those with cephalosporins) that lack anti-enterococcal activity [41]. In cases of enterococcal sepsis in critically ill patients, inadequate empiric antibiotic therapy may increase the risk of death. As shown in a prospective multicentre study among patients with monomicrobial enterococcal bacteremia, the receipt of effective anti-enterococcal therapy within 48 hours independently predicted survival (odds ratio [OR] for death, 0.21; 95% confidence interval [CI], 0.06–0.80) [24].

We performed a secondary analysis of a randomised clinical trial of 904 patients with microbiologically documented severe sepsis and found that inadequate antimicrobial treatment of severe sepsis of abdominal origin (n=123) was associated with a significantly increased risk of death after adjusting for confounding factors (OR, 2.8; 95%CI, 1.3–5.9); inadequately treated enterococcal infection contributed to this increased risk [42]. Certainly, new diagnostic approaches and interventions aimed at improving the detection and treatment of early gram-positive sepsis are urgently needed.

What Is the Profile of Patients for Whom Empiric Enterococcal Coverage Should Be Advocated?

Figure 1 summarises a tentative proposal of those highly selected patients who may benefit from empiric anti-enterococcal coverage in case of secondary or tertiary peritonitis. Although empiric therapy directed at enterococci may not always be necessary, reasonable indications for specific therapy include the presence of septic shock in patients pre-treated with cephalosporins, immunosuppressed patients at high risk of bacteremia, presence of prosthetic heart valves, or persistent or recurrent intra-abdominal infection with signs of severe sepsis.

Presentation of an Exemplary Case History in which Empiric Anti-Enterococcal Therapy for Peritonitis was Considered Adequate and Beneficial

In June 2003, an 86-year-old female patient with a history of type II diabetes, severe post-rheumatic valvulopathy and secondary pulmonary arterial hypertension experienced a first episode of moderate diverticulitis. She was treated as an outpatient with 2 g of ceftriaxone i.v./day for 10 days without anaerobic coverage. After initial improvement, the patient was hospitalised 2 months later with symptoms of lower abdominal pain, fever (38°C) and leukocytosis (18.5 G/l). On admission, there was no peritonitis, but clinical exam revealed a recto-vaginal fistula. An abdominal computed tomography scan showed multiple small abscesses.

The patient refused surgical treatment and was treated empirically with a combination of ceftriaxone and metronidazole. Blood cultures grew *Escherichia coli* sensitive to ceftriaxone. Despite antibiotic treatment, on day 9 of hospitalisation she developed signs of peritonitis and severe sepsis. Antibiotic treatment was immediately changed to a broad-spectrum regimen covering *Enterococcus faecalis*, the presence of which was confirmed 4

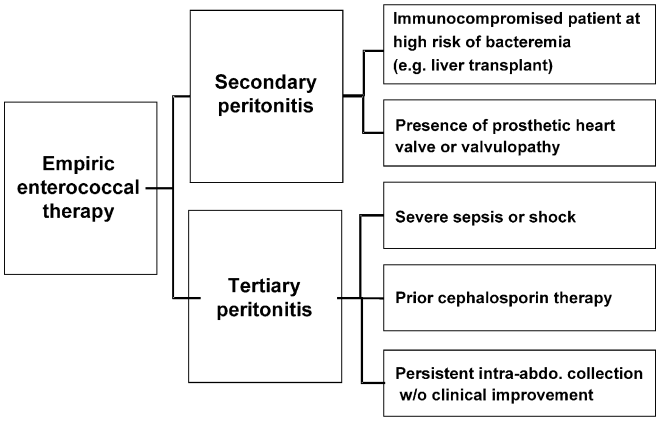

Fig. 1 Tentative treatment recommendation for selected cases of intra-abdominal infection where empiric coverage of enterococci may be considered

days later in two sets of blood cultures. The patient improved and was discharged 18 days later without surgical intervention. This case shows that empiric anti-enterococcal coverage may be warranted and beneficial in the presence of risk factors for enterococcal super-infection and endocarditis.

Conclusions

Enterococcal infections are becoming increasingly prevalent, because of the widespread use of cephalosporins, often neglected environmental reservoirs in the hospital setting, and a greater number of immunosuppressed patients [43]. Although many invasive enterococcal infections are of intra-abdominal origin, the pathogenic role of *Enterococcus* spp. in peritonitis remains controversial. Many studies have demonstrated that polymicrobial intra-abdominal infections that contain enterococci can be treated successfully with appropriate surgical drainage and antibiotics such as cephalosporins that are not active against enterococci. Therefore, in the recently published IDSA-guidelines for the selection of antibiotic therapy for complicated intra-abdominal infections, strong evidence was cited against routine coverage of *Enterococcus* spp. in community-acquired intra-abdominal infections [14].

In contrast, there is some evidence (although of rather weak quality) to justify the use of empiric antibiotic therapy covering enterococci in post-operative, nosocomial peritonitis in certain high-risk patient populations. Based on the literature review presented here, we found evidence arguing in favour of using empirical enterococcal coverage in the treatment of intra-abdominal infections in the following cases: (i) immunocompromised patients with nosocomial, post-operative peritonitis; (ii) patients with severe sepsis of abdominal origin who have previously received cephalosporins or other broad-spectrum antibiotics selecting for *Enterococcus* spp.; (iii) patients with peritonitis and valvular heart disease or prosthetic intravascular material, which may increase the risk of enterococcal endocarditis.

The ideal therapeutic regimen for these high-risk patients remains to be determined, but empirical therapy directed against enterococci should be considered. Extended-spectrum penicillins with anaerobic coverage may be effective empiric regimens for those selected cases, since they offer adequate therapy for mixed intra-abdominal infections. In cases of confirmed enterococcal bacteremia (without vancomycin resistance), patients should be treated with bactericidal, combination antibiotic therapy including a penicillin and an aminoglycoside.

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