Yersinia Species

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Yersinia spp. are non-spore-forming Gram-negative bacilli. They comprise only three species known to cause disease in humans, namely *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*. Since infective endocarditis (IE) is rarely caused by *Yersinia*, the management of these infections can be problematic due to the lack of experience.

Keywords: Yersinia ; endocarditis

1. Introduction

Yersinia spp. are non-spore-forming Gram-negative bacilli of 1–3 μm in length and 0.5–0.8 μm in width. Apart from *Y. pestis*, all species are motile between temperatures of 22 and 30 °C and they are non-motile at 37 °C. *Yersinia spp.* are grown in aerobic and anaerobic cultures on non-selective and selective media, between 0 and 45 °C [1][2]. Initially, the *Yersinia* genus was discovered in 1894 by Alexander Yersin and Shibasaburo Kitasato and it currently consists of 18 species, while only three are known to cause disease in humans, namely *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*. Even though *Y. pestis* is known to cause plague and has caused the deaths of millions of people, *Y. enterocolitica* and *Y. pseudotuberculosis* are known to give rise to self-limited gastrointestinal diseases [1]. In particular, *Y. enterocolitica* consists of a heterogenous group of strains which are traditionally classified by biotyping into six biogroups, according to their phenotype, and into more than 57 O serogroups, based on their O surface antigen [2]. However, few of those serogroups, mainly serogroups O:3, O:5,27, O:8 and O:9, cause disease in humans [3]. Although gastroenteritis is the most frequent clinical manifestation of yersiniosis, other clinical manifestations may occur, including terminal ileitis, mesenteric adenitis, septicemia and reactive arthritis.

On the other hand, infective endocarditis (IE) is a rare disease that is associated with notable morbidity and mortality [4][5]. Even though it is very uncommon, IE by Gram-negative bacteria can be quite problematic due to inadequate experience and the paucity of data and guidelines regarding its treatment [5]. More specifically, IE by non-HACEK [Haemophilus, Aggregatibacter (previously Actinobacillus), Cardiobacterium, Eikenella, Kingella] Gram-negative bacteria is an entity that used to be associated with intravenous drug users for decades, even though in recent years, there are increasing reports of IE by these microorganisms associated with the healthcare system [6][7]. IE by non-HACEK Gram-negative bacteria is associated with a notable risk of mortality and morbidity, such as development of intracardiac abscess and vascular complications such as peripheral embolism or stroke [6][7]. The most commonly identified Gram-negative microorganisms associated with IE by Gram-negative bacteria in the literature are Escherichia coli, Pseudomonas aeruginosa and Klebsiella species; however, IE caused by other non-HACEK Gram-negative bacteria has been described in the literature [6][8][9]. This disease often requires a combination of antimicrobials along with surgery in order to achieve a cure [6]. However, depending on the species, there may be specific problems associated with its treatment, such as antimicrobial resistance [8].

Interestingly, even though there are some case reports with a literature review on IE by *Yersinia* species, a review adequately summarizing all available evidence on the topic is lacking [10].

2. Infective Endocarditis by *Yersinia* Species

We identified *Y. enterocolitica* as the only species causing IE among the *Yersinia* genus. The mitral valve was the most commonly infected site, while diagnosis was facilitated by transthoracic echocardiography in more than half of the cases. The most frequent clinical presentations were fever and sepsis. Aminoglycosides, cephalosporins and quinolones were the most commonly used antimicrobials, while less than 15% of patients died.

Yersinia spp., with the exception of *Y. pestis*, which is the cause of plague, are known to cause a variety of infections such as enterocolitis, mesenteric adenitis and urinary, respiratory and musculoskeletal infections, and on rare occasions, they may cause bacteremia or IE [1]. Septicemia by *Y. enterocolitica* mostly affects people with predisposing conditions such as

chronic liver disease, alcoholism, malnutrition, immunosuppression or iron overload [1][11][12]. IE is a quite rare complication of *Yersinia spp.* Local abnormalities in the valves may play an important role in the pathophysiology by facilitating the targeting of the valvular tissue by *Yersinia* and subsequent bacterial growth. To that end, three types of adhesins that are produced by enteropathogenic strains of Yersinia may be of clinical importance, namely invasin, YadA and Ail [13][14]. Among these adhesins, YadA may be the most important virulent factor and also the most important for the pathophysiology of IE since it allows *Yersinia* to adhere to cells and extracellular matrix, resist phagocytosis and auto-agglutinate [13]. On the other hand, the ability of *Yersinia spp.* to form biofilms implies that attachment to a cardiac valve may allow them to multiply and then generate biofilms, thus leading to IE [15][16].

IE is a rare but potentially lethal disease that is usually derived from Gram-positive microorganisms. However, Gram-negative microorganisms can account for some cases of IE, especially in patients who have been previously exposed to the healthcare system [6][17]. In particular, IE caused by *Yersinia* species comprises a very rare disease that has been mainly analyzed through case reports.

The mean age at diagnosis of patients with *Yersinia* IE was 67 years, which is slightly higher than the age at diagnosis of IE by non-HACEK Gram-negative bacilli in the literature, which is in the range of 40 to 63 years [6][7][8][9][18]. A male predominance among patients with IE by *Yersinia* species was noted, as in other cases of IE caused by non-HACEK Gram-negative bacilli [6][7][8][9][18]. A prosthetic valve was present in 17% of patients with IE by *Yersinia*, which is lower than the rate mentioned in other studies of IE by non-HACEK Gram-negative bacilli, which is between 25% and 59% [6][7][8][9][18].

The most commonly infected intracardiac sites were the mitral valve in 58% of patients and the aortic valve in 33%. The aforementioned data are in complete agreement with a study with IE by non-HACEK Gram-negative bacilli, where the mitral valve was the most commonly infected valve in 31% of patients, followed by the aortic valve in 24% [12]. However, other studies have mentioned that the aortic valve was the most commonly infected valve in 33% to 45% of cases, followed by either the mitral valve in 27% to 40% of patients [9][19] or the tricuspid valve in 33% of patients [13].

Regarding patients' clinical signs, fever was the most common symptom, occurring in 92% of patients, while 70% of patients were septic. In studies with IE caused by non-HACEK Gram-negative bacilli, presence of fever was noted in 91% to 100% [6][7][8][9] and sepsis in 79% to 85% of patients [8][9]. Notably, 15% of patients with IE caused by *Yersinia* developed heart failure, a proportion similar to that in cases of non-HACEK Gram-negative IE which ranged from 8% to 37% [6][7][8][9]. Embolic phenomena in *Yersinia* IE were present in 42% of patients, which is in line with other cases of IE by non-HACEK Gram-negative bacilli, where the rate is from 17% to 65%, while immunologic phenomena were present in 8% of patients, which is lower than the corresponding rate in non-HACEK Gram-negative bacilli IE, where that rate is between 14% and 27% [6][7][8][9][18]. Among patients with IE caused by *Yersinia*, 8% presented a paravalvular abscess, which is lower than the corresponding rate in IE by non-HACEK Gram-negative bacilli, which was in the range of 13% to 42% [6][7][8][9]. Interestingly, presence of a paravalvular abscess was associated with increased mortality.

Regarding antimicrobial resistance, *Y. enterocolitica* has varying antimicrobial susceptibility patterns among serogroups but is generally considered susceptible in vitro to aminoglycosides, third-generation cephalosporins, quinolones, co-trimoxazole, tetracycline and chloramphenicol, but resistant to penicillin, aminopenicillins and first-generation cephalosporins, due to the chromosomally encoded beta-lactamase-producing genes blaA and blaB [2][19]. Herein, we confirmed that *Y. enterocolitica* presents high resistance to aminopenicillins, but we also noted alarming rates of resistance to quinolones, which are considered the first-line treatment in infections by this pathogen [2]. This is in contrast to another study that shows minimal resistance rates to quinolones [20]. Importantly, resistance to cephalosporins, another class of antimicrobials commonly used in the treatment of these infections, was 18%, while resistance to aminoglycosides, an antimicrobial commonly used for synergy in serious infections and IE, was less than 10%.

As expected, aminoglycosides, cephalosporins and quinolones were used in 83%, 42% and 42% of cases, respectively. These rates may have been the highest among the antimicrobials used, but they should be read with caution, since in some older studies in this systematic review, quinolones were not available. With the above-mentioned data, it is reasonable to suggest that treatment of IE by *Yersinia spp.* should include a combination of a third-generation cephalosporin or a quinolone with an aminoglycoside. However, a preference towards cephalosporins over quinolones in the case of IE by non-HACEK Gram-negative bacteria is noted in the guidelines [21]. In all instances, treatment should be guided based on the results of antimicrobial susceptibility testing. Duration of treatment should be at least 6 weeks, as suggested by the guidelines [21].

Mortality was relatively low, with about 17% of patients dying, all due to IE. This rate was relatively lower than the one in studies of IE by non-HACEK Gram-negative bacilli, where mortality was as high as 44% [6][7][8][9][18].

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