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REVIEW

Aerococci and aerococcal infections

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Summary *Aerococcus* is a genus that comprises seven species, of which *Aerococcus urinae*, and *Aerococcus sanguinicola* are emerging human pathogens. Aerococci are gram positive cocci that are easily misidentified as streptococci or staphylococci, and thus the incidence of aerococcal infections has been underestimated. With the introduction of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) clinical microbiologists now have access to a rapid and accurate method to identify aerococci. *A. urinae* and *A. sanguinicola* are isolated in a small proportion of urinary specimens in many laboratories and many patients with bacteriuria with aerococci have symptoms of urinary tract infection (UTI). *A. urinae*, and also *A. sanguinicola*, cause invasive infections including infective endocarditis (IE) with many reported fatalities. Especially older men with urinary tract abnormalities are at risk for bacteraemia with *A. urinae* but the prognosis of bacteraemia without IE is favourable. Penicillin is appropriate for treatment of invasive infections and in IE, addition of an aminoglycoside should be considered. Treatment of UTI with aerococci is complicated by uncertainty about the effect of trimethoprim–sulphametoxazole and fluoroquinolones on aerococci. This review will discuss identification of *Aerococcus spp.*, antibiotic resistance, the clinical presentation and management of aerococcal infections as well as the virulence mechanisms of these bacteria.

Introduction

Aerococci have long been regarded to be uncommon in human infections. Recent findings, however, suggest that both *Aerococcus urinae* and *Aerococcus sanguinicola* may be more common causes of both urinary tract infections (UTI) and invasive infections, such as infective endocarditis (IE), than previously thought.[1–4] Medical microbiologists have often failed to identify aerococci, as the bacteria can easily be misidentified as alpha haemolytic streptococci with which they share colony morphology, with staphylococci with which they share their microscopic appearance, or with enterococci with which they partly share antibiotic resistance patterns. Some commonly used

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diagnostic systems based on biochemical reactions do not readily identify aerococci, adding to the misidentification of these bacteria.[2] Thus as new diagnostic tools are introduced, aerococci will be increasingly identified and most likely recognized as significant human pathogens.

Aerococcus was first described in 1953 as a catalase-negative environmental Gram positive coccus growing in small clusters, and a type isolate of *Aerococcus viridans* was defined.[5] During the 35 years that followed, only scarce reports about human aerococcal infections were published,[6–8] however it was noted that aerococci other than *A. viridans*, denoted *Aerococcus*-like organisms (ALO), were encountered in cases of IE and of UTI.[9–12] These ALO have later been assigned to the distinct aerococcal species *A. urinae*.[13] *A. urinae* and *A. sanguinicola*[14] are commonly isolated from human infections. *Aerococcus christensenii*[15] and *Aerococcus urinaehominis*[16] have also been isolated from humans but these species seem to be uncommon causes of human infections.

This review will focus on aerococci as human pathogens. The characteristics of the bacteria, including biochemical properties, virulence mechanisms and antibiotic resistance, will be accounted for. The clinical manifestations of aerococcal infections will be described and their management will be discussed. Much work remains to be carried out in this field and the aim of this review is to stimulate further research on this emerging pathogen.

Difficulties in identification

If an *Aerococcus* comes to the diagnostic laboratory in a urinary specimen, it is likely to be classified as an alpha-haemolytic *Streptococcus* due to its appearance on blood agar plates unless the laboratory performs microscopic examination of the bacteria. If an *Aerococcus* grows in a blood culture flask, the preliminary identification, based on microscopy, will be a *Staphylococcus* (see Fig. 1A). Depending on the subsequent routines at the laboratory, a correct diagnosis can be reached but there are many pitfalls and numerous aerococci have likely been classified as other bacteria.[3] A correct identification of aerococci in urinary cultures is important since streptococci are often regarded as contaminants whereas aerococci probably cause UTI (see below). In cases of bacteraemia with aerococci, as well as with streptococci and enterococci, IE should always be considered, but the focus of an aerococcal bacteraemia should be sought in the urinary tract.

Aerococci appear as pairs, tetrads or clusters in the Gram stain (Fig. 1A), but unlike staphylococci they do not produce catalase.[5] On blood agar plates, they are alpha-haemolytic and resemble streptococci, displaying small semi-transparent colonies (Fig. 1B). Growth occurs both under aerobic and anaerobic conditions.[5] *A. viridans* was the first species to be defined and it later became evident that the genus harboured additional species with different biochemical characteristics.[10,12,16] Several biochemical tests, including the ability to hydrolyse different sugars as well as pyrrolidonyl amino-peptidase and arginine dihydrolase activity, have been found to be valuable to differentiate between aerococcal species.[10,14,16] A proposed scheme for biochemical identification of *Aerococcus spp* based on publications by Lawson and co-workers[14,16] is given in Table 1. Secure biochemical identification is however complicated, requires substantial work, and the results do not always concur perfectly with genetic methods.[17] Of the commercially available systems, the API system and BBL-Crystal-GP readily identifies *A. urinae,* whereas the Vitek 2 system often fails to identify this species.[2,17] Both the API and Vitek misidentify *A. sanguinicola* as *A. viridans*. This makes reports of infections caused by *A. viridans* problematic when identification is based on these methods.[18–20] The antibiograms of different *Aerococcus spp* and related bacteria have also been used for taxonomic purposes.[21] *A. urinae* is resistant to sulphametoxazole and gentamicin and sensitive to penicillin, whereas *A. viridans* is not.[21]

The gold standard for species determination of *Aerococcus* relies on sequencing of the gene encoding16S rRNA. These sequences safely identify aerococci and separate them from other genus and from each other.[14,16] This method is however time-consuming and impractical for routine use. It is therefore promising that matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has shown good results for species determination of *Aerococcus*. When used for species determination of a panel of 35 *Aerococcus spp*, MALDI-TOF MS correctly identified all of these isolates to the species level.[22] We have demonstrated that MALDI-TOF MS not only has a good sensitivity but also has a high specificity when used in a clinical diagnostic setting (Senneby et al., *submitted*). Thus, with the introduction of MALDI-TOF MS in diagnostic microbiological laboratories, a rapid and accurate method for identification of aerococci to species level will be available.

Antibiotics and resistance

Most aerococci are sensitive to beta-lactam antibiotics as well as to several other groups of antibiotics. The pattern of susceptibility, however, shows some important differences among the different species. *A. urinae* and *A. sanguinicola* have very low MICs for penicillin and also relatively low MICs for cephalosporins and carbapenems.[23,24] The MIC_{50} and the percentage of sensitive isolates of *A. urinae* and *A. sanguinicola* for some relevant antibiotics are given in Table 2. The data are mainly from two studies where exact MICs are given[23,24] but data from other studies have also been included.[1-3] *A. viridans* displays higher MICs for penicillin and acquired resistance to penicillin is well documented.[2,21,25] *Aerococcus spp*. have either low or high level of resistance to aminoglycosides with *A. urinae* generally displaying the highest MICs.[2,21,23,24] Importantly, the combination of penicillin and netilmicin or gentamicin has been demonstrated to have a synergistic killing effect on two *A. urinae* endocarditis isolates *in vitro*.[26] *Aerococcus* spp are sensitive to vancomycin, although elevated MICs have been reported.[1,2,21,23,24,27] Antibiotics such as tetracycline, erythromycin, clindamycin, and rifampicin are probably rarely used against infections with aerococci but they are generally effective *in vitro*.[2,21,23,24]

The pattern of antibiotic resistance is more complex for antibiotics relevant for treating UTI. *A. urinae* is, like enterococci, intrinsically resistant to sulphonamides and most