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Review

Morganella morganii, a non-negligent opportunistic pathogen

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ABSTRACT

Morganella morganii belongs to the tribe *Proteeae* of the *Enterobacteriaceae* family. This species is considered as an unusual opportunistic pathogen that mainly causes post-operative wound and urinary tract infections. However, certain clinical *M. morganii* isolates present resistance to multiple antibiotics by carrying various resistant genes (such as *blaNDM-1*, and *qnrD1*), thereby posing a serious challenge for clinical infection control. Moreover, virulence evolution makes *M. morganii* an important pathogen. Accumulated data have demonstrated that *M. morganii* can cause various infections, such as sepsis, abscess, purple urine bag syndrome, chorioamnionitis, and cellulitis. This bacterium often results in a high mortality rate in patients with some infections. *M. morganii* is considered as a non-negligent opportunistic pathogen because of the increased levels of resistance and virulence. In this review, we summarized the epidemiology of *M. morganii*, particularly on its resistance profile and resistant genes, as well as the disease spectrum and risk factors for its infection.

1. Introduction

Morganella morganii is a facultative anaerobic rod Gram-negative enteric bacterium, which was first isolated in 1906 by Morgan *et al.* from a pediatric fecal culture.[1] The genome size of *M. morganii* is about 4,000,000 bp, and the number of its protein-coding sequences (CDSs) is about 4,000.[2] *M. morganii* was formerly classified as *Proteus morganii* [3] and later assigned to the genus *Morganella*, which belongs to the tribe *Proteeae* of the *Enterobacteriaceae* family on the basis of DNA–DNA hybridization determinations.[4] Although members of the tribe *Proteeae*, including *Proteus*, *Providencia* and *Morganella*, share homologous genes acquired from horizontal gene transfer via mobile transposition or conjugative integration, the overall G+C contents in the genomes of other *Proteeae* members range from 39% to 43%, which are lower than that of the *M. morganii* (51%); therefore, the G+C contents provides genetic evidence for distinguishing *M. morganii* from other species.[5]

The genus *Morganella* currently consists of a single species (*M. morganii*) with two subspecies, namely, *morganii* and *sibonii*.[6] Biologically, *M. morganii* is a motile, non-lactose fermenting bacterium, which shares with the *Proteus* members on the capacity for urease production and presence of phenylalanine deaminase. *M. morganii* is widely distributed in nature. This bacterium is commonly found in the environment and intestinal tracts of humans, mammals, and reptiles as part of the normal flora.[7] The drug resistance of *M. morganii* is increasing in recent years, and this resistance is mainly introduced via extra genetic[8,9] and mobile elements.[10,11] The infections caused by multidrug-resistant (MDR) or even the extensively drug-resistant (XDR) *M. morganii* often result in clinical treatment failure.[12,13] Generally, *M. morganii* can produce virulence factors, such as urease, hemolysins, and lipopolysaccharide (LPS); these virulence factors pose *M. morganii* an opportunistic pathogen that mainly causes wound and urinary tract infections.[14–16] Comparative genome analysis revealed several pathogenicity-related genes, and novel genes carried by *M. morganii* genome are not found in the genomes of other *Proteeae* members, which may provide important information concerning the virulence and fitness determinants in *M. morganii*.[17] The disease spectrum of *M. morganii* infection varies and is changeable according to its virulence evolution. This review aims to summarize the epidemiology of *M. morganii*, focus on its resistance profile and resistant genes, and discuss its disease spectrum and risk factors for infection.

2. Epidemiology of *M. morganii*

As a member of the family *Enterobacteriaceae*, *M. morganii* is considered as a rare cause of nosocomial infection. Farmer *et al.*[18] classified the bacteria of *Enterobacteriaceae* among 11 levels

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according to the relative frequency of a certain bacterium isolated from the clinical specimen. The relative frequency increases from 0 (not known to occur) to 10 (most common), in which that of *M. morganii* is 4, i.e., an opportunistic pathogen that causes rare infection.

Originally, *M. morganii* was thought to be a cause of summer diarrhea and considered to be a very unimportant pathogen.[1] This bacterium was first found to be a cause of urinary tract infection in 1939. In the 1970s, *M. morganii* was shown to be a primary cause of nosocomial infection in adults and a rare cause of bacteremia. Adler *et al.*[19] isolated six *M. morganii* strains from 71 cases of *Proteusbacillus vulgaris* bacteremia through investigating the characteristics of *P. vulgaris* infections and epidemiology in a general hospital. In the early 1980s, Tucci and Isenberg reported 13 *M. morganii* infections scattered over four services and five floors of a hospital; this outbreak was eventually resolved when strict aseptic techniques, i.e., hand washing, were reinforced.[14] Following that incident, *M. morganii* has been identified as a significant cause of nosocomial infection, but recognized as an increasingly important pathogen in recent years. Over a six-year period (2006–2011), samples from all patients who presented symptoms of Gram-negative bacterial infections at Changhua Christian Hospital, Taiwan, were collected. Of the 82,861 samples, 1,219 (1.47%) are positive for *M. morganii*, which is the ninth prevalent cause of clinical infections in patients at the said hospital.[17] In addition to Taiwan, other regions including Japan, USA, and Spain are also the most frequent areas with reported *M. morganii*-associated infections. However, the *M. morganii*-associated case reports are scattered and often present in immunocompromised patients.[12,20–26] No link exists between case reported areas and economic status, sanitary condition, natural environment, and population mobility.

Given the wide distribution of *M. morganii* in nature, *M. morganii* can commendably adapt to the environment for survival.[27] Therefore, *M. morganii* dissemination may be advanced, including the mechanisms for *M. morganii* to cause diseases in both humans and animals. To assess the carriage of *Enterobacteriaceae* in the anterior nares in pig-exposed persons, Fischer *et al.*[28] demonstrated that 66.7% (76/114) of the participants are positive for *Enterobacteriaceae* bacteria, with the predominant species of *Proteus mirabilis* (14.9%,17/114), followed by *Pantoea agglomerans* (11.4%, 13/114), *M. morganii* (7.9%, 9/114), *Citrobacter koseri* (7.9%, 9/114), *Klebsiella pneumoniae*, *Escherichia coli*, and *P. vulgaris* (each 7.0%, 8/114). Their studies suggest a possible transmission pathway between human, and the closely contiguous animal may exist; further investigation is also needed.

3. Drug resistance and carriage of resistant genes in *M. morganii*

The intensive selection pressure of the widely used antibiotics results in a considerable acceleration of the evolution and spread of resistant genes in bacteria; moreover, drug resistance has posed a significant challenge for bacterial infection control.[29] The bacterial isolates with MDR, XDR, and pandrug-resistant phenotypes are increasingly observed.[13] Various mechanisms can theoretically lead to antibiotic resistance; these mechanisms include intrinsic, acquired, and adaptive resistances.[30,31] Intrinsic resistance is the innate ability of a certain bacterial species to resist the activity of a particular antimicrobial agent through its inherent structural or functional characteristics. Such intrinsic insensitivity can be due to the lacking affinity of the drug for the bacterial target, inaccessibility of the drug into the bacterial cell, or extrusion of the drug by chromosomally encoded molecules with active exportation activities. Acquired resistance occurs when a particular bacterial cell obtains the ability to resist the activity of a particular antimicrobial agent to which it was susceptible previously. This phenomenon can result from the acquisition of foreign resistance genes that are horizontally transferred between different strains or even species via conjugation, or/and from the mutation in certain genes involved in normal physiological processes and cellular structures. However, adaptive resistance happens when the bacterial population is subjected to gradual antibiotic increases; this resistance is characterized by a rapid emergence of resistance and reversibility to the normal phenotype when the antibiotic is removed.[32] Adaptive resistance may require epigenetic inheritance and modification of gene expression patterns in the particular bacterial population.

All three kinds of resistances may occur in a particular bacterial species. *M. morganii* has intrinsic resistance to oxacillin, ampicillin, amoxicillin, most of the first- and second-generation cephalosporins, macrolides, lincosamides, glycopeptides, fosfomycin, fusidic acid, and colistin; this pathogen is also normally sensitive to aztreonam, aminoglycosides, antipseudomonal penicillins, third- and fourth-generation cephalosporins, carbapenems, quinolones, trimethoprim/ sulfamethoxazole, and chloramphenicol.[33] A unique biochemical character of *M. morganii* is that this organism has the capability for extracellular biosynthesis of crystalline silver nanoparticles, which was found independent of environmental changes.[34] Three chromosomal gene homologues (*silE*, *silP* and *silS*) identified in *M. morganii* were characterized to be responsible for the biosynthesis of silver nanoparticles in the presence of Ag^+ ions, as well as the silver-resistant phenotype of the strain.[35] Nevertheless, the acquired resistance is increasingly observed in *M. morganii*. According to the recent data from the SENTRY antimicrobial resistance surveillance program, *M. morganii* ranks 12th among the Gram-negative organisms that cause bloodstream infections.[36] The acquired resistance of *M. morganii* is commonly introduced via genetic elements,[8–11] however, mutations in certain genes are also observed. Bacterial genetic elements consist of prophage, plasmid, transposon, inserted sequence, integron, and so on. Among them, plasmid, transposon, and integrin, are often related to antibiotic resistance, and can be transferred between homogeneous and even heterogeneous bacteria. Antibiotic resistance of *M. morganii* is mainly mediated by conjugative plasmids [2,8], mutation in certain genes [2,37] and integrons[9,38–40]. Current genome sequence and determination with polymerase chain reaction revealed that the antibiotic-resistant genes carried by *M. morganii* are increasing (Table 1). Similar to *Enterobacter* spp. and *Citrobacter freundii*, *M. morganii* normally has an inducible AmpC (encodes–lactamase), which confers resistance to those β-lactam antibiotics (e.g., ampicillin) that induce its strong synthesis and are labile to its action. Derepression of AmpC, which is typically caused by mutation at *ampD*, causes constitutive β-lactamase hyperproduction and confers resistance to third-generation cephalosporins. *M. morganii* shows resistance to gentamycin.[37] Aminoglycoside resistance among *Morganella* species is mediated by various enzyme combinations; the most frequent of these combinations is the modifying enzyme ANT(2)-I, which confers resistance to gentamicin, tobramycin, and kanamycin.[52] A prevalence of quinolone resistance determinant exists among *M. morganii*. The plasmid-mediated quinolone resistant gene *qnrD* was first reported in 2009 in a human clinical isolate of *Salmonella enteric* serovar Kentucky and three *Salmonella enteric* serovar Bovismorbificans isolates from China.[53] Mazzariol *et al.* (2011) demonstrated the presence of *qnrD* in isolates of *P. mirabilis* and *M. morganii*; they proposed that *qnrD* gene is closely linked to the bacteria of the tribe *Proteeae*.[54] Carbapenems have been used in clinics as the antibiotics of last resort for the treatment of nosocomial infections caused by *Enterobacteriaceae*.[55] Resistance to carbapenems is mostly driven by the production of carbapenemases, such as carbapenemase 2 (KPC-2) and New Delhi