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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

Table 1
Detectable drug resistant genes carried by *M. morganii*

Resistance phenotype	Gene	Gene name	Location	Author(citation)
β-lactams	*dha-1*	β-lactamase DHA-1	Int; P	Verdet et al.,[40]; Mahrouki et al.,[41];
	dha-5	β-lactamase DHA-5	C	Olaitan et al.,[2]
	ampC	Penicillin-binding protein AmpC	C	Sheng et al.,[42]
	ampD	Penicillin-binding protein AmpD		Sinha et al.,[43]
	ampH	Penicillin-binding protein AmpH	C	Olaitan et al.,[2]
	ampR	Penicillin-binding protein AmpR	C	Chen et al.,[17]
	pse-1	β-lactamase	P	Olaitan et al.,[2]
	blaNDM-1	New Delhi metallob-lactamase-1	P	Olaitan et al.,[2]
	blaOXA-2	OXA-2 β-lactamase	Int	Power et al.,[44]
	blaOXA-181	Class D β-lactamase OXA-181	P	McGann et al.,[45]
	blaOXA-48	Class D β-lactamase OXA-48		Jamal et al.,[46]
	bla(CTX-M)	CTX-M β-lactamases	C	Mahrouki et al.,[47]
	blaKPC-2	*Klebsiella pneumonia* carbapenemases	P	Shi et al.,[8]
	blaTEM-1	Class A Extended-Spectrum β-lactamase TEM1		Mahrouki et al.,[38]
	blaTEM-2	Class A extended-spectrumβ-lactamase TEM2		Mahrouki et al.,[38]
	blaTEM-24	Class A extended-spectrumβ-lactamase TEM24		Mahrouki et al.,[38]
	blaVIM-1	Metallo- β-lactamase VIM-1	Int	Tsakris et al.,[39]
	blaP1b	Carbenicillinase	Int	Rojas et al.,[9]
Aminoglycosides	*aphA6*	Aminoglycoside 3′-phosphotransferase	P	Olaitan et al.,[2]
	aadA1	Aminoglycoside adenylyltransferase	Int	Tsakris et al.,[39]
	aadA2	Aminoglycoside adenylyltransferase	P; Int	Olaitan et al.,[2]; Rojas et al.,[9]
	aadA13	Aminoglycoside adenylyltransferase		Machado et al.,[48]
	aadB	Aminoglycoside adenyltransferase	Int	Rojas et al.,[9]
	aacA4	Aminoglycoside acetyltransferase	Int	Power et al.,[44]
	aacA7	Aminoglycoside-acetyltransferase-6-type Ib	Int	Tsakris et al.,[39]
	rmtB	16S rRNA methylases	P	Yao et al.,[49]
Phenicols	*catA1*	Chloramphenicol acetyltransferase	C	Olaitan et al.,[2]
	catA2	Chloramphenicol aminotransferase	C	Chen et al.,[17]
	catB3	Chloramphenicol acetyltransferase	Int	Rojas et al.,[9]
	catB3-like	CatB3-like putative acetyltransferase	C	Chen et al.,[17]
Macrolides ERY	*ereA2*	Erythromycin esterase	P	Olaitan et al.,[2]
	mph (A)	Macrolide 2′-ohosphotransferase	P	Olaitan et al.,[2]
Tetracycline	*tet(A)*	Tetracycline efflux protein	C	Olaitan et al.,[2]
	tet(D)	Tetracycline efflux protein	C	Henriques et al.,[50]
Trimethoprim	*dfrA1*	Dihydrofolate reductase	Int	Tsakris et al.,[39]
	dfrA19	Dihydrofolate reductase	P	Olaitan et al.,[2]
Fluoroquinolones	*gyrA*(S83R) [§]	DNA gyrase	C	Olaitan et al.,[2]
	gyrB(S464Y)[§]	DNA gyrase	C	Nasri et al.,[37]
	parC(S80I) [§]	Topoisomerase IV	C; Int	Nasri et al.,[37]; Mahrouki et al.,[38]
	parE(S458Y)[§]	Topoisomerase IV	C	Olaitan et al.,[2]
	qnrA6	Quinolone resistance determinatant A6	P	Mahrouki et al.,[38]
	qnrS1	Quinolone resistance determinatant S1	P	Mahrouki et al.,[41]
	qnrD	Quinolone resistance determinatant D	P	Seija et al.,[12]
The others	*bcr*	Bicyclomycin resistance gene	C	Chen et al.,[17]
	ksgA	Kasugamycin resistance gene	C	Chen et al.,[17]
	acrA	AcrAB efflux pump		Ruzin et al.,[51]

C, chromosome; P, plasmid; Int, integron.
[§] Position of the mutations in the protein level.

metallo-β-lactamase 1 (NDM-1).[56] NDM-1 was first described in 2008 in Sweden from a patient who had previously been hospitalized in New Delhi, India;[57] thereafter, a rapid worldwide dissemination of the said carbapenemase followed.[58,59] Multiple resistant genes (e.g., NDM-1 and *qnrD1*) carried in a single strain may cause *M. morganii* to be an XDR, which has been found in patient with sepsis.[12] Experiences of therapeutic options for the treatment of invasive infections caused by MDR or XDR of *M. morganii* should be accumulated. The first $bla_{\text{CTX-M-2}}$-containing class 1 integron, termed In116, was detected in a plasmid from a cephalosporin-resistant *M. morganii* strain, producing CTX-M-2 β-lactamase.[44] Other integrons were also identified in clinical *M. morganii* strains, e.g. In3Mor[39], *sul1-type* integron[38,40], which were found to carry various resistant genes (Table 1).

Adaptive resistance has been well established in various bacterial species, including *Escherichia coli*, *Salmonella enterica*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[31,32] When these bacteria are exposed to successive steps of increasing antibiotic concentration, they will rapidly yield populations with high levels of resistance, and this resistance is highly reversible. However, no report has focused on adaptive resistance in *M. morganii*, and further investigation is suggested.

4. Virulence factors and virulence evolution of *M. morganii*

Virulence is a primitive character for a pathogen. Genome sequence revealed that the virulence factors of *M. morganii* include fimbrial adhesins, LPS, IgA protease, hemolysins, ureases, and insecticidal and apoptotic toxins, as well as proteins found in flagella, iron acquisition system, type-III secretion system (T3SS), and two-component systems (TCSs) (Table 2). Among them, fimbrial adhesins, ureases, and TCSs play an important role in

Table 2
Virulence factors of *M. morganii*

Category	Genes
Fimbrial adhesins	Three MR/P(mannose-resistant/Proteus-like fimbria) operons, 13 *mrpJ* paralogous, one fimbrial chaperone, two UCA(uroepithelial cell adhesin) operons, one PMF(*P. mirabilis* fimbria) operon, and two other operons; six putative type IV pili genes *hofCB* and *ppdABCD*; two putative trimeric auto transporter secretion genes MM2011 and MM2042
Motility/flagellum-related	*cheA*, *cheW*, *cheD*, *tap*, *cheR*, *cheB*, *cheY*, *cheZ*, *umoABCD*, *rssBA*, *rcsBCD*
T3SS	Type III secretion system needle complex (20 genes), and effectors, *ipaCBD* operon
Iron acquisition system	*hmuSTUV*, *afuABC*, *feoAB*, *ireA*, *btuCD*, *btuB*, and *yfeDCBA*, 18 other related genes (*fecR*, ABC transporters, TonB-dep. receptors)
IgA protease	*zapABCD*
Toxin	*hmpBA*, *tccB*, *tccA*, *tcdB2*, *xptA1*, *xptC1*, *tcdA4*, *tcaC*, *tccB3*, and *tcaC* *rtxA*, *xaxAB*, intimin/invasion, HlyD toxin secretion, toxin transporter
Two-component systems	19 potential TCSs were identified. *qseBC*, *yedWV*, BarA/UhpA, *phoP/phoQ*.
LPS and the cell capsule	*wzzE*, *rffC*, *rffA*, *wzxE*, *pagP*, *arnT*, *msbA*, *lpxK*, *kdsB*, *kdsC*, *fepE/wzz*, *htrB/waaM*, *rfaD/waaD*, *rfaF/waaF*, *rfaC/waaC*, *wabH*, *wabG*, *waaQ/rfaQ*, *waaA*, *waaE*, *coaD*, *rfaL*, *hldE/rfaE*, *lpxD*, *lpxA*, *lpxB*, *msbB*, *kdsA*, *rfaB*, *lpxH*, *pgi*, *galU*, *lpxC*, *gale*, *wecA*, *rffE*, *wecC*, *rffG*, *rffH*, *rffT*, *wzyE*, *rffMrcsB*, *rcsC*, *rcsD* and *rcsF*.
Ureases	*ureABCEFGD*

M. morganii colonization and pathogenicity. In pathogenicity and colonization, adhesion is the first step in which a pathogen interacts with the host. Fimbrial adhesins help in biofilm formation and *M. morganii* colonization. With the exception of the genes that encode two LysR family transcriptional regulators, the organization of flagellar genes in *M. morganii* is similar to that of *P. mirabilis*.[2] Rapid urea hydrolysis is a prominent phenotype of *Proteeae* organisms.[6] The non-inducible urease gene cluster consisting of *ureABCEFGD* was detected in *M. morganii*. However, this gene cluster lacks the *ureR* regulatory gene that was detected in *P. mirabilis* HI4320 and *Providen ciarettgeri* DSM1131.[2] Urease production serves as a fitness factor that facilitates bacterial growth and biofilm formation during urinary tract infections, which may explain why *M. morganii* mainly causes the urinary tract infection. Importantly, ureases from *M. morganii* urease gene cluster are required for bacterial virulence.[60]

A most important achievement of bacteria is its ability to adapt to the changing environmental conditions. Competition with other microorganisms has led a plethora of bacterial mechanisms to adapt to a wide variety of stress conditions rapidly. Standard virulence evolution theory assumes that virulence factors are maintained because they aid bacterial colonization, thereby increasing bacterial growth within and/or transmission between hosts.[49] *M. morganii* has developed several systems to cope with the varied environment, such as TCSs, which constitute a most sensible and efficient regulatory mechanism in bacteria. TCSs generally contain paired sensor kinase and response regulator proteins and form the primary apparatus for sensing and responding to environmental cues in bacteria. Nineteen potential TCSs were identified in *M. morganii*.[17] These TCSs play important roles in the virulence and fitness of *M. morganii*. Nevertheless, *pmrA/pmrB* was not detected in the genome of *M. morganii* and other *Proteeae* members.[2] The pathogenic genes allow the usage of computation approaches to identify potential drug targets, such as the conserved proteins found in common pathogens. The presence of *eut* (which includes *pduST*) and *cob-cbi* operons in *M. morganii* but not in other *Proteeae* genomes studied may explain why *M. morganii* is more frequently associated with nosocomial bacterial infections.[17] ArnT mediates lipid A modification. Two copies of the *arnT* gene were detected in the genome of *M. morganii* and other *Proteeae* members, whereas non-*Proteeae* bacteria have only one copy.[2]

ICE*Pm1*, a highly modular and highly conserved pathogenicity island (PAI), is commonly found in *M. morganii* strains. This 94-kb PAI (ICE*Pm1*) encodes 91 open reading frames (ORFs) with a G+C content of 44.84%, which differs substantially from that of the *M. morganii* genome (51%).[61] ICE*Pm1* carries several genes involved in DNA mobility, characteristic for PAIs, including an integrase, six transposases, and five plasmid-transfer related proteins. An important core segment found in ICE*Pm1*(PMI2569 to PMI2592) shows homology to a type-IV secretion system that is important for DNA transfer of ICE*Hin1056*.[62] A T3SS, which comprises gene products MM0224 through MM0247 and has a low G+C content (43.7%), resides in a 20.8-kb PAI.[17] This PAI encodes 24 ORFs and shares homologous syntenic blocks with *P. mirabilis*,[63] which contains all the components needed to assemble a T3SS needle complex. Sequence comparison between *M. morganii* KT and the 14 members of the *Enterobacteriaceae* family, revealed that 459 CDSs found in *M. morganii* are not found in the other *Proteeae* species studied, and 295 CDSs found in *M. morganii* are not found in any of the 14 *Enterobacteriaceae* genomes studied. The genes specific to *M. morganii* include the genes in the *eut* operon, *cob-cbi* operon, eight insecticidal toxin genes, nine T3SS genes, and 17 copies of the IS4 family transposase gene.[17] However, the evidence that *M. morganii* shares features with other non-*Proteeae* enterobacteria suggests that horizontal gene transfer has occurred between *M. morganii* and other intestinal bacteria.

5. Disease spectrum and risk factors for *M. morganii* infection

M. morganii is an unusual opportunistic pathogen that is clinically and often isolated as a cause of nosocomial infection in adults, specifically in urinary tract or wound infections. Urinary tract is the major portal for *M. morganii* entry, followed by the hepatobiliary tract, skin and soft tissue, and blood. However, *M. morganii* has been recognized an increasingly important pathogen because of its virulence and increasing drug resistance, which has resulted in a high mortality rate in some infections. To date, a total of 136 cases with *M. morganii* infection have been reported. The disease spectrum associated with *M. morganii* infections is summarized in Table 3. The diseases caused by *M. morganii* are diversified; these diseases include pyelonephritis, septic shock, urinary tract infection, osteomyelitis, peritonitis, abscess, purple urine bag syndrome, joint effusions, meningitis, sepsis, necrotizing fasciitis, pericarditis, pneumonia, aortic aneurysm, hemorrhagic bullae, bacteremia, septic arthritis, endophthalmitis, Waterhouse–Friderichsen syndrome, Ludwig's angina, pancreatitis, gangrenosum, chorioamnionitis, pyomyositis, ulcer, cellulitis, and wound infection. The mortality of *M. morganii* infections remains high in reported cases.[22,23,70,76,77,92–94,97,109,124] *M. morganii* mainly causes sepsis (11.0%, 15/136), abscess (9.6%, 13/136), urinary tract infection (8.1%, 11/136), bacteremia (7.4%, 10/136), purple urine bag syndrome (5.9%, 8/136), chorioamnionitis (5.9%, 8/136), cellulitis (5.9%, 8/136), and wound infection (5.9%, 8/136). Remarkably, among the *M. morganii*-associated sepsis cases, 11 cases are neonates. Maternal chorioamnionitis,

Table 3
Major diseases caused by *M. morganii*

Diagnosis	No. of isolates	Author(citation)
Pyelonephritis	6	Nasri et al.,[37]; Falagas et al.,[64].
Septic shock	2	Tan et al.,[65]; Cornely and Schirmacher,[66].
Urinary tract infection	11	Tucci and Isenberg,[14]; Sakaguchi et al.,[15]; Sakai et al.,[16]; Jamal et al.,[46]; Volpato et al.,[67]; Ibara et al.,[68].
Osteomyelitis	2	Smithson et al.,[69]; Koyuncu and Ozan,[70].
Peritonitis	3	Tsai et al.,[26]; Atalay et al.,[71]; Isobe et al.,[72].
Abscess	13	Zaid et al.,[25]; McGann et al.,[45]; Carruth and Wladis,[73]; Chen and Lin,[74]; Chou et al.,[75]; Osanai et al.,[76]; Abdalla et al.,[77]; Lim et al.,[78]; Pomeranz et al.,[79]; Sumioka et al.,[80]; Huang et al.,[81];Vijaya et al.,[82];Patil et al.,[83].
Purple urine bag syndrome	8	Iglesias et al.,[84]; Muneoka et al.,[85]; Matsuo et al.,[86].
Joint effusions	1	Sanz et al.,[87]
Meningitis	5	Mastroianni et al.,[20]; Milligan and Barenkamp,[88]; Ndiaye et al.,[89]; Samonis et al.,[90]; Isaacs and Ellis-Pegler,[91].
Sepsis	15	Seija et al.,[12]; Chang et al.,[92]; Ovalle et al.,[93]; Kim et al.,[94]; Golubic-Cepulic et al.,[95].
Necrotizing fasciitis	3	Soleimanian et al.,[96]; Krebs et al.,[97]; Kohagura et al.,[98].
Pericarditis	3	Cho et al.,[99]; Yang et al.,[100]; Sica et al.,[101].
Pneumonia	5	Falagas et al.,[64]; Mounir et al.,[102]; Choi et al.,[103]; Garcia-Garai et al.,[104]; Martin et al.,[105].
Aortic aneurysm	1	Kwon et al.,[106]
Haemorrhagic bullae	2	Lee et al.,[7]; Bagel and Grossman,[107].
Bacteraemia	10	Sakai et al.,[16]; Adler et al.,[19]; Mahrouki et al.,[41]; Pappas et al.,[108]; Ghosh et al.,[109].
Septic arthritis	6	Gautam et al.,[21]; Isaacs and Ellis-Pegler,[91].
Endophthalmitis	5	Kuang et al.,[110]; Christensen et al.,[111]; Tsanaktsidis et al.,[112]; Zaninetti et al.,[113]; Cunningham et al.,[114].
Waterhouse-Friderichsen syndrome	1	Tourrel et al.,[115]
Pancreatitis	1	Yeh et al.,[116]
Gangrenosum	2	Falagas et al.,[64]; Del et al.,[117].
Chorioamnionitis	8	Rowen and Lopez,[24]; Sinha et al.,[43]; Chang et al.,[92]; Ovalle et al.,[93]; Johnson and Feingold,[118]; Carmona et al.,[119]; Boussemart et al.,[120]; Ranu and Valencia,[121].
Pyomyositis	1	Arranz-Caso et al.,[22]
Ulcer	5	Falagas et al.,[64]; McDermott and Mylotte,[122]; Lachish et al.,[123].
Cellulitis	8	Falagas et al.,[64]
Wound infection	9	Tucci and Isenberg,[14]; Falagas et al.,[64].

which were found in five cases among *M. morganii*-associated neonatal sepsis, is the most common antenatal risk.[24,43,92,120,121] All reported cases are premature, with antenatal exposure to ampicillin/amoxicillin being reported in several cases.[23,24,92,120,121] The above situation could be explained by the common practice of administering ampicillin and antenatal steroids to mothers with threatened premature delivery. Routine intrapartum antibiotic prophylaxis with ampicillin may lead to the emergence of infections because of resistant Gram-negative organisms. Antenatal steroids are beneficial in accelerating maturity of fetal lung and other organ systems; they also have an established role in the management of women with preterm rupture of membranes.[125] However, the use of these steroids may increase the risk of infection.[126] The use of dexamethasone and ampicillin in mothers leads to ampicillin resistance of *M. morganii*. This pathogen can be spread to babies by vertical transmission from the mother's genitourinary tract during delivery.

As an opportunistic pathogen, several risk factors may be involved in *M. morganii* infection. In 1994, McDermott *et al.* reported that these risk factors include old age, presence of concomitant bacteremia, hospitalization, recent surgery, and concurrent antibiotic use.[122] *M. morganii* can be derived from the bacterial flora of the oral cavity of animals and cause infections in humans through bites[127,128] or scratch.[7] Therefore, some animals should be considered a potential risk for transmitting *M. morganii* to persons, specifically in immunocompromised hosts. Administration of patients infected with *M. morganii* could be potentially dangerous and should not be overlooked. Treatment for *M. morganii* infections mainly includes antibiotic therapy, debridement, and drainage. Proper use of antibiotics and supportive care are important in improving cure rate. Antibiotic use is mainly suggested to be based on the antibiotic sensitivity results from bacterial cultures and clinical improvement. *M. morganii* is characteristically resistant to many β-lactam antibiotics, thus a third-generation cephalosporin alone or with gentamicin for 10–14 days is effective in treating *M. morganii* infections.[92] Addition of an aminoglycoside to a cephalosporin may decrease the potential resistance to broad-spectrum cephalosporins. *M. morganii* causing intracranial infections are noteworthy and warrant continued monitoring because antibiotic selection for treatment is affected not only by the organism's intrinsic susceptibilities but also by the antibiotic's ability to penetrate and maintain therapeutic levels. Treating *M. morganii* infection in the central nervous system is usually difficult. For the treatment of a patient infected with XDR *M. morganii* harboring *NDM-1* and *qnrD1*, Seija *et al.* proposed the use of fosfomycin and double doses of meropenem.[12]

6. Conclusion and perspective

M. morganii has been recognized as an increasingly important pathogen. The disease spectrum associated with *M. morganii* infections is broad, and the mortality of such infections remains high in reported cases. Previously, not much attention was given to this pathogen because of its rarity and low potential for nosocomial epidemics. Infections with *M. morganii* are particularly worrisome epidemiologically because of the organism's inducible resistance to β-lactam antibiotics. Although *M. morganii* is an unusual clinical opportunistic pathogen, this important pathogen cannot be neglected. Considering the increased frequency of *M. morganii* infection, to develop a rapid detection method and enhance research on this pathogen are important. The genome sequence of *M. morganii* provides important information concerning virulence and determinants of fitness. Further investigation is needed to ascertain the pathogenic mechanism of *M. morganii* and block the development of *Morganella* infections. The above suggestions would help in re-classification of *M. morganii* as a rare pathogen.

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