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Review RTID

Review: Virulence Factors, Resistance Genes and Pathogenicity of *Moraxella Catarrhalis*

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Abstract

An estimated 2–4 million cases of chronic obstructive pulmonary disease (COPD) in adults are exacerbated by Moraxella catarrhalis annually in the US, making it a pathogen of increasing significance for respiratory tract infections. It often colonizes the nasopharynx without causing any symptoms and an opportunistic bacterial infection of the respiratory mucosa that is exclusive to humans. In our study, we reviewed references about the important virulence factors that M. catarrhalis possess that help them penetrate and attack the host, which are: adhesion factors that are involved in production of biofilms include Hemagglutinin-M. catarrhalis Immunoglobulin D-Binding Protein (MID-Hag), M. catarrhalis Adherence Protein (McaP), Outer Membrane Proteins (OMPs), Universal Surface Protein A. (UspA), and Cartilage Oligomeric Matrix Protein (COMP), which prevents M. catarrhalis from being phagocytically killed by human neutrophils. Its resistance to antibiotics was reviewed because it possesses resistance genes that help it survive and cause diseases such as, its capacity to produce beta-lactamases highlights its diverse resistance patterns even further. This resistance is largely due to the expression of the genes that encode to beta-lactamase enzymes BRO-2 as well as BRO-1, respectively. Colistin is no longer an effective antibiotic against bacteria, thanks to lipid A phosphorethanolamine (PEtN) transferases. Plasmid-borne PEtN transferase (mcr) genes have shown strong potential for these resistance elements to be distributed widely. The Moraxella species is the source of mcr-1. In many Gram-negative organisms, multidrug efflux pumps are a crucial factor in both pathogenicity and antibiotic resistance. In M. catarrhalis, mutants missing the acrB, acrA and oprM genes were generated to gain a better understanding of the role of the AcrA, B-OprM- efflux pump in antibiotic resistance.

Keywords: *Moraxella catarrhalis*, virulence factors, antibiotic resistance, beta-lactamase, efflux pump

INTRODUCTION

Moraxella catarrhalis, is an opportunistic infection of the respiratory system that is exclusive to humans. Establishment of Colonization The nasopharynx peaks in early childhood, gradually decreases until maturity, and then rises once more in old age [1].

The only human pathogen that is commensal with the upper respiratory system is *M. catarrhalis*. In non-human primates or other animals, long-term respiratory tract colonization has never been established. Microscopically resembling *Neisseria meningitidis* and *Neisseria gonorrhoeae*, Gram-negative, non-encapsulated diplococcus, aerobic, variable piliated, nonmotile, powerfully autoagglutination is known as *M. catarrhalis*. However, genetically, it is more closely linked to Acinetobacter species and Pseudomonadales [2].

Gram-negative rods make up the remaining members of the Moraxella genus. It is still unclear what are the molecular underpinnings of *M.*

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catarrhalis exceptional tropism for humans, according to some research, The organism's mechanisms for absorbing iron depends on a specific ligand–receptor interaction between human iron transport proteins (such as lactoferrin and, transferrin) and binding proteins on the bacterial surface (such lactoferrin-binding protein B) [2].

According to research by Aebi [3], *M. catarrhalis* leads to infections of the upper and lower respiratory system. This has been discovered to be the underlying cause of illnesses in both adults and children, including pneumonia, endocarditis, otitis media, and empyema [4, 5].

The major reason for the different patterns of is the *M. catarrhalis* that produces beta-lactamases, which, before 1976, was unknown. The quickest spread of beta-lactamases within a bacterial species might be the rise in the prevalence of beta-lactamase strains. Especially in patients who are immunocompromised and inpatients who suffer from long-term respiratory conditions, *M. catarrhalis* has emerged as a significant pathogen [6].

Numerous *M. catarrhal* virulence factors have been identified and detailed; many of them – also known as outer membrane proteins, or OMPs – are moved across the plasma membrane and either released outside the cell or localized there. Then, to infiltrate and infect the human host, these molecules mediate processes like adhesion of epith. cells, complement-resistance, the formation of biofilms, and acquiring nutrition. Numerous characteristics are multifactorial. One example of an adhesin that mediates adhesion to epith. cells that are expressed with *M. catarrhalis* is UspA1, together with (OMP CD, and the FHA-like proteins) MhaB1, and MhaB2 [7].

M. catarrhalis is frequently observed in polymicrobial infections caused by other respiratory pathogens including *Haemophilus influenzae* and *Streptococcus pneumoniae* [8]. According to Perez [9], bacteria is believed to improve its own and other co-inhibiting pathogens' survival in such infections by mitigating the consequences of β-lactam medications and complement-mediated attacks. When the bacteria exhibit resistance to other antibiotic classes, this can have a catastrophic effect on the clinical result for the patient. Despite being one of the bacteria that are most frequently isolated from children who have respiratory illnesses [10], information regarding M. catarrhalis's pathogenic potential and antibiotic susceptibility patterns is scarce. The study aims to review the genes that *M. catarrhalis* contains for virulence and antibiotic resistance, which aid in its invasion and pathogenesis [11, 12].

LITERATURE REVIEW

Moraxella Catarrhalis

Moraxella catarrhalis is a gram-negative, aerobic, oxidase positive. More knowledge of the pathogen's DNA and how isolates differ from one another is required because *M. catarrhalis* clinical isolates include the opportunistic human pathogen Gamma-Proteobacterium, and almost universal resistance to beta lactam antibiotics [13]. Even though *M. catarrhalis*-induced otitis media is typically thought to be less severe than pneumococcal disease, recently, several putative virulence factors have been identified, and it has been demonstrated that multiple *M. catarrhalis* surface elements produce mucosal inflammation. It is now estimated that *M. catarrhalis* causes about 10% of acute inflammatory exacerbations in people with chronic obstructive pulmonary disease (COPD).

With reports of 97.7% in the 1990s, more ampicillin-resistant *M. catarrhalis* cases are seen in Taiwan than other nations. Examining changes in *M. catarrhalis* resistance to several oral antibiotic classes and contrasting antimicrobial medication, minimum inhibitory concentrations (MIC) against *M. catarrhalis* isolates have been noticed from 1993–1994 and 2001–2004 [14].

VIRULENCE FACTORS

During infection, gram-negative bacteria interact with host cells by a specific secretion mechanism known as outer membrane vesicles (OMVs), which include recognized surface proteins, such as those found on a broad scale [15–17].

Phosphatidyl ethanolamine, cardiolipin (CL), and phosphatidyl glycerol are the principal phospholipid elements of *M. catarrhalis* linings. Conversely, though, the synthesis of these phospholipids by *M. catarrhalis* and their mechanism of action are poorly understood. The researchers found in a study that a cardiolipin synthase (CLS) known as MclS is present in *M. catarrhalis*, which oversees the bacterium's production of CL [18]. One notable heat-modifiable OMP that has showed promise as a possible vaccine is *M. catarrhalis'* outer membrane protein CD (OMPCD). The OMPCD gene of *M. catarrhalis* strains was rendered inactive through the application of nucleotide sequence analysis and insertional mutagenesis. Comparing the ompCD mutant strains in comparison to the wild-type strains, they displayed a minor impairment in growth [19].

Effective adhesion to epithelial cells is considered a vital component of *M. catarrhalis'* pathogenicity because the bacterium must adhere to cells in a variety of host environments, encompassing the nasopharynx and the lungs. The bacterium's adhesion factors, which are involved in the production of biofilms, MID/Hag (hemagogluctinin/*M. catarrhalis* immunoglobulin D-binding protein), McaP (*M. catarrhalis* adhesion protein), OMPs (outer membrane proteins), and UspA (ubiquitous surface protein A) [20]. There has been recent incidence data of macrolide-resistant *M. catarrhalis* instances, especially among Chinese youngsters. It is reported that resistance reduces the virulence of the resistant bacteria by increasing their fitness cost. To investigate the association between the pathogenicity and macrolide susceptibility of the organism, the entire genomes of seventy isolates of *M. catarrhalis* from four clonal complexes with different levels of susceptibility were sequenced [20, 21].

To aid in colonization, the bacterial species possesses a variety of adhesins. Moraxella illness requires the immune system to successfully evade the body. To thwart the bacteriolytic attack on the host, this tactic involves causing an overabundance of proinflammatory responses, intervening in the recruitment of granulocytes to the area of infection, finalizing the reprogramming of antigen-presenting cells by stimulating certain pattern recognition receptors and cellular adhesion molecules. Moraxella.sp also makes advantage of host immunomodulator chemicals to aid in the development of resistance to complement and bactericidal agents in the host. Therefore, understanding the fundamentals of Moraxella defense strategies is essential for developing ahead treatments that effectively manage Moraxella illness [22].

PATHOGENICITY

Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, and *Moraxella catarrhalis* are the recognized pathogens of the respiratory system that can populate the nasal cavity. It can be alone in a civilization that is pure or in combination alongside other pathogenic germs, like *Staph. Aureus*, *Haemo. influenzae*, and/or *Strep. Pneumoniae* [12]. The nasopharynx is frequently colonized by this human-limited, opportunistic infection of the respiratory mucosa without any symptoms. It further performs a major role in the adults experiencing sudden worsening of their obstructive pulmonary disease and is a primary factor in children's otitis media [1].

Based on the sputum samples analyzed, isolates of *M. catarrhalis* constituted the majority, perhaps the only isolates of bacteria. Results offer evidence in favor of the probable detrimental outcome of this bacterium in pediatric pneumonia. Among the isolates, there was also evidence of high multidrug resistance, which can cause patients to become unresponsive to routine treatments, prolonging their illness and raising their risk of death [17].

The unique structural elements, diverse protein secretions, and biological modifications that *M. catarrhalis* experiences, all contribute to its capacity to follow and infiltrate host cells additionally elude immune systems of the host, both innate and adaptive. Several of the proteins on the external membrane of *M. catarrhal* are candidates for vaccines, as they have other surface proteins. It is vital to expedite development of vaccines prior to *M. catarrhalis* escapes our total authority, given its capacity to evolve vulnerability to other antibiotic families and β-lactams.

RESISTANCE-ASSOCIATED FACTORS

Pneumococci in polymicrobial biofilms received beta-lactamase-dependent passive protection against beta-lactam death from *M. catarrhalis.* Furthermore, in polymicrobial biofilms, pneumococci strengthened *M. catarrhalis'* resistance to macrolide killing. On the other hand, pneumococci enhanced *M. catarrhalis* colonization in vivo in a manner that was dependent on quorum signals [9].

Since *M. catarrhalis* can grow resistant to macrolides and quinolones in its natural habitat, these should not be suggested as other treatments for M. catarrhalis-caused diseases of the lower respiratory tract contracted in the community. To ascertain whether the suggestions need to be modified, a bigger sample size study ought to be carried out [23–25].

In addition to serving as a structural element of cartilage, cartilage oligomeric matrix protein (COMP) controls complement activity. Notably, COMP is found in lung tissue's endothelium of blood vessels, alveolar fluid, and resident macrophages and monocytes. We demonstrate that a significant quantity of COMP is bound by the majority of *M. catarrhalis* clinical isolates (n = 49), but not by other bacterial pathogens under investigation. COMP directly interacts with *M. catarrhalis's* widespread surface protein A2. Because binding of COMP inhibits the complement membrane attack complex's bactericidal effect, it is connected to *M. catarrhalis'* ability to survive in human serum. Additionally, COMP prevents human neutrophils from phagocytically eliminating *M. catarrhalis* [26, 27].

Colonization begins when *M. catarrhalis* attaches itself to the mucosa, epithelial cells, and extracellular matrix. The interactions between *M. catarrhalis* and collagens are examined from several angles. After testing for collagen binding on 43 clinical isolates, a thorough investigation of protein-protein interactions was conducted utilizing proteins that had been recombinantly produced. Applying high-resolution scanning electron microscopy (SEM) and confocal immune-histochemistry, the interactions between *M. catarrhalis* and investigations were conducted on the collagen produced by human lung fibroblasts and tracheal tissues [28] transport lipo oligosaccharides that thwart complement attacks. They also draw in and make use of factor H and C4b binding protein, two host complement regulators, to prevent complement activation via the traditional and unconventional routes, respectively. Furthermore, both bacteria take control of vitronectin, a regulator of the complement activation terminal pathway. Different outer membrane proteins are present in both *H. influenzae* and *M. catarrhalis* that bind plasminogen and complement regulators concurrently. Many of the bacterial complement-binding proteins have highly conserved domains for host-bacterial interactions, making them significant adhesins [29].

Seventy non-duplicate clinically isolated cases of *M. catarrhalis*, revealed vulnerability to antimicrobials and the molecular basis underlying low fluoroquinolone resistance. January through October of last year, the isolates were collected from a general hospital in Tokyo, Japan, by 38 men and 32 women; 48 out of 70 isolates, or 68.5 percent, were found from post-nasal drips in children, and it was determined when the Etest was employed to determine the *M. catarrhalis's* vulnerability to antimicrobials, and PFGE was used to subtype isolates with low levels of fluoroquinolone resistance. They also investigated changes in the genes parC and gyrA that were discovered using sequencing and PCR. It caused the gyrA and parC gene PCR products from the low-level fluoroquinolone-resistant isolates to change, creating a strain that was drug-susceptible. Significantly less *M. catarrhalis* viability was achieved with aPDT and PF. In contrast to saline-only controls, A 3–6 log decrease in recoverable bacteria was seen in biofilm-grown bacteria, indicating a statistically significant decline in viable organisms after intervention with PF-aPDT, even though the latter induced higher mortality in organisms growing in plankton (5–6 log kill). Examples of chronic lung illnesses where bacterial infection is a contributing factor including cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease, is a significant factor in the pathophysiology and progression of the disease. *M. catarrhalis* plays a role in various environments, which should be taken into consideration when discussing the potential benefits in these circumstances of a vaccination to avoid contracting bacteria.

M. catarrhalis does not seem to be important in the bacteriology of cystic fibrosis and bronchiectasis, according to research on these conditions. However, in the setting of COPD, *M. catarrhalis* is one of the most significant bacterial infections. For people with COPD, preventing *M. catarrhalis* infection would be quite beneficial. To explain the logic behind creating an *M. catarrhalis* vaccination in this specific clinical situation, let us first go over COPD and *M. catarrhalis's* involvement in the progression and pathogenesis of the illness [26, 30, 31] focused on assessing *M. catarrhalis's* role in lower respiratory tract infections by examining sputum samples of high bacteriological quality from suspected patients. They noted the bacterium showed high sensitivity to Tetracycline and Amoxyclav and they found one important pathogen for respiratory diseases is *M. catarrhalis*, emphasizing the importance of microbiological and clinical criteria in its diagnosis [32].

RESISTANCE GENES

Researchers isolated two strains of *M. catarrhalis* from in-patients, labeled R17123922_R and R18013231_R. Using disk diffusion and broth microdilution techniques in compliance with CLSI recommendations, these bacteria's resistance to macrolide antibiotics was validated. Furthermore, The MCR_0492 gene was found to have an indel, which codes for the TonB-dependent receptor protein, considering research, the reason behind M. catarrhalis' resistance to macrolide antibiotics may be mostly dependent on this receptor [33, 34].

The initial resistant variation was Discoveries in Sweden in 1977, subsequently, over 95% of strains are now resistant to penicillin, indicating a widespread spread of resistance to the antibiotic. This resistance is largely causing the production of beta-lactamase enzymes. The genes (bro-1/2) encode (BRO-1 and BRO-2) in that order. The findings showed that all the strains under study had a high level of resistance. The conclusion emphasizes the increasing worry about *M. catarrhalis* antibiotic resistance, with an emphasis on beta-lactamase development in particular [35].

Some researchers have tested bacterial isolates for drug susceptibility against various groups of antimicrobials, including trimethoprim/sulfamethoxazole, macrolides, fluoroquinolones, cephalosporins, and penicillins, using disk diffusion method and Etest for tetracycline MIC values. It was discovered that every isolate was vulnerable to the chemicals under evaluation and possessed the tet B gene, indicating tetracycline resistance. They also produced β-lactamases, were serotype A LOS, and had genes for virulence factors (copB, hag/mid, uspA1, uspA2), but not for UspA2H protein [36]. Colistin, the last-resort antibiotic, is no longer effective against bacteria due to lipid A phosphorethanolamine (PEtN) transferases. Recent findings of dangerous bacteria carrying PEtN transferase (mcr) genes on plasmids have highlighted the grave risk of these resistance elements spreading widely. The Moraxella species that co-occur in environmental niches with Enterobacteriaceae are the source of mcr-1 [37].

To check for mutations, PCR and/or sequencing were performed on the four 23S rRNA alleles, the ribosomal proteins L4 and L22, and the methylase genes erm (B) and erm (F). This strain exhibited a significant degree of resistance to clindamycin, josamycin, clarithromycin, azithromycin, and erythromycin. This strain contains four 23S rRNA, alleles. carried the *Escherichia coli* numbering mutation A2058T [38].

The serum-resistant *M. catarrhalis* strain O35E became serum-sensitive after both the full deletion of the uspA2 gene and the insertion of an antibiotic resistance cartridge into the uspA2 gene of the strain. The expression profile of lipo-oligosaccharides and the growth rate of the mutant were unaffected by these modifications. When $Mg2^{+}$ and EGTA were used to deactivate the classical complement system in normal human serum, this uspA2 mutant persisted. However, even with the other complement route inhibited, this uspA2 mutant remained vulnerable to complement-mediated death [39].

By creating mutants in *M. catarrhalis* strain O35E that absence of oprM, acrA, and acrB genes, as well as a decrease in the minimum inhibitory concentrations (MICs) of cefotaxime and amoxicillin, it

was investigated how the AcrAB-OprM- efflux pump contributes to antibiotic resistance. The clarithromycin half-lives (MICs) for the (oprM, acrA, and acrB), mutants relative to the O35E wild-type strain. All AcrAB-OprM pump genes were shown to be more transcriptionally active when Amoxicillin was given to *M. catarrhalis* strains (O35E and 300), and Clarithromycin was introduced to strains (O35E, 300, and 415), which enhanced the mRNA expression of oprM and acrA. Compared to the ancestral strain, the AcrAB-OprM, efflux pump genes being rendered inactive resulted in a reduced ability to encroach upon epithelial cells, suggesting that ito effectively invade human pharyngeal epithelial cells, oprM, acrA, and acrB are required [40].

Investigated the molecular mechanisms underlying the low-level fluoroquinolone resistance and antimicrobial susceptibility in Seventy clinical isolates of *M. catarrhalis* that were absence of duplicates. By using PCR and sequencing, genes (parC and gyrA) were found to have mutations. They discovered that GyrA's amino acid change of Thr80 for Ile is the reason behind *M. catarrhalis's* low-level fluoroquinolone resistance. A strain that was resistant to low-level fluoroquinolones was made susceptible to them by using PCR products of the (gyrA and parC) genes. This is the first indication that *M. catarrhalis* exhibits low levels of fluoroquinolone resistance [40].

Discovered that to comprehend *M. catarrhalis* ATCC 43617's metabolic potential and constraints, its genome was annotated. Notably, it lacked gene products for utilizing external carbohydrates, consistent with previous observations. However, it possessed enzymes for aerobic energy generation, and some connected to anaerobic environments. All the amino acid synthesizing enzymes were present, except for proline and arginine. Using genomic data, DNA microarrays with oligonucleotide probes were created and used to analyze gene expression in different growth conditions.

During the growth of *M. catarrhalis* in biofilms, (Table 1) genes for the reductases of nitrate, nitrite, and nitric oxide showed significant upregulation, indicating a shift in energy metabolism and potential resistance to the immune response. Real-time reverse transcriptase PCR validated these findings. Overall, growth in a biofilm environment triggered the way that genes involved in energy production are expressed and defense against the host immune system [41].

Table 1. Some resistance genes to *Moraxella catarrhalis.*

S.N.	Gene	Function
1	MCR_0492 gene	Contribute significantly to *M. catarrhalis's* resistance to macrolide medicines.
2	genes bros (1, 2)	Production among the enzyme beta-lactamases (BRO-2 and BRO-1), give resistance to penicillin.
3	tetB gene.	They also produced β-lactamases, were serotype A LOS, and had genes for virulence factors (copB, hag/mid, uspA1, uspA2), but not for UspA2H protein.
4	mcr genes for PEtN transferase	Demonstrated the grave risk of these opposition components spreading widely.
5	Genes erm (B) and erm (F) that encode methylases, as well as L4 and L22	Resistance to erythromycin, clarithromycin, azithromycin, clindamycin and josamycin.
6	uspA2 gene	Antibiotic resistance.
7	acrA, acrB, and oprM genes	Reduction in cefotaxime and amoxicillin MICs.
8	genes parC and gyrA	Minimal fluoroquinolone resistance.

CONCLUSION

1. An opportunistic bacterial illness limited to humans of the mucosal respiratory tract, *Morexella catarrhalis* commonly invades the nasal cavity.
2. Important virulence factors that *M. catarrhalis* possess that help them penetrate and attack the host, which are adhesion factors.

3. *M. catarrhalis* possesses resistance genes that help it survive and cause diseases such as, genes resistant to macrolides and quinolones and beta-lactamase-produce.

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