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

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Annotation: Moraxella catarrhalis is an opportunistic human pathogen responsible for respiratory tract infections, particularly in individuals with chronic obstructive pulmonary disease (COPD). Despite its clinical significance, knowledge gaps persist regarding its virulence mechanisms and resistance factors. This study reviews key virulence factors, including adhesion proteins and biofilm formation mechanisms, as well as antibiotic resistance genes, such as bro-1, bro-2, and mcr genes, which contribute to multidrug resistance. The research utilized a literature review approach to analyze the bacterium's pathogenicity and antimicrobial resistance. Findings indicate that M. catarrhalis employs various strategies to evade the immune system and resist antibiotic treatment, posing challenges to clinical management. The results highlight the necessity of targeted therapeutic approaches and vaccine development to mitigate the impact of M. catarrhalis-related infections.

These insights contribute to a better understanding of bacterial resistance trends, ultimately aiding in the development of more effective treatment strategies.

Keywords: Moraxella catarrhalis, virulence factors, antibiotic resistance, respiratory infections, chronic obstructive pulmonary disease (COPD), vaccine development.

Introduction

Moraxella catarrhalis Is a human-restricted opportunistic bacterial pathogen of the respiratory tract. Colonization of The nasopharynx peaks in young children and steadily declines towards adulthood before rising again in the elderly (Blakeway, L.V *et al* 2017).

M. catarrhalis is exclusively a human pathogen and commensal of the upper respiratory tract. All attempts to establish long-term respiratory tract colonization in non-human primates or other vertebrates have failed.

M. catarrhalisis a gram-negative, aerobic, variably piliated, nonmotile, strongly autoagglutinating and non-encapsulated diplococcus, which microscopically resembles *Neisseria meningitidis* and *Neisseria gonorrhoeae* but is more closely related genetically to Acinetobacter spp. and the Pseudomonadales (Aebi, C., 2010).

All other members of the genus Moraxella are gram-negative rods. The molecular basis of the exquisite tropism of *M. catarrhalis* for humans has not entirely been elucidated. Some data indicate that the organisms' iron- uptake apparatus requires a specific ligand–receptor interaction between human iron transport proteins (e.g., lactoferrin and transferrin) and specific binding proteins on the bacterial surface (e.g., lactoferrin-binding protein B) (Aebi, C., 2010).

Currently, *M. catarrhalis* is a recognized pathogen of upper and lower respiratory tract infections (Aebi C.2011). It has been found as the causative agent in infections, such as empyema, endocarditis, otitis media, and pneumonia, both in children and adults.(Brooks GF *et al* ., 2013; Sy MG *et al*., 2010).

The beta-lactamase producing *M. catarrhalis* not reported before 1976 is the significant cause of varying patterns of (Khan MA *et al*., 2010). The increase in occurrence of beta-lactamase strains can be regarded as the fastest dissemination of beta-lactamases within a bacterial species. *M. catarrhalis* has particularly become an important pathogen in patients with immunocompromised status and inpatients with chronic pulmonary diseases (Khan MA *et al* 2010).

Several virulence factors of *M.catarrhal* is have been identified and characterized, and many of these are trans-ported through the plasma membrane and are either localized to the outer membrane (i.e., outer membrane proteins [OMPs]) or secreted outside the cell. These molecules then mediate processes such as adherence to epithelial cells, complement resistance, biofilm formation, and nutrient acquisition in order to colonize and cause disease in the human host. Many of these traits are multi- factorial. For example, *M. catarrhalis* expresses several adhesins that mediate adherence to human epithelial cells, including UspA1 , OMP CD and the FHA-like proteins MhaB1 and MhaB 2 (Buskirk S.W. and Lafontaine E.R., 2014)

M. catarrhalis Is commonly seen in polymicrobial infections with other respiratory pathogens

such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (Weimer KE *et al* ., 2011) In such infections, this bacterium is thought to enhance the survival of both itself and other co- inhibiting pathogens against the effect of complement mediated attacks and β-lactam antibiotics (Perez AC *et al* .,2014) This can be devastating to the patient's clinical outcome when the strains are also resistant to other classes of antibiotics. Although *M. catarrhalis* is one of the most commonly isolated bacteria in children with respiratory infections ,(Simusika P *et al*.,2015) little is known about its pathogenic potential or its antimicrobial susceptibility patterns. The **aim** of the study is to review the virulence and antibiotic resistance genes that *M.catarrhalis is* possesses , which help it invade and Pathogenesis .

Literature review

Moraxella Catarrhalis

Moraxella catarrhalisis a gram-negative, aerobic, oxidase positive gamma-proteobacterium and an opportunistic human pathogen and nearly ubiquitous resistance to beta lactam antibiotics among *M. catarrhalis* clinical isolates, a greater understanding of this pathogen's genome and its variability among isolates is needed (Davie *et al*., 2011)**.**

Although otitis media caused by M. catarrhalis is generally believed to be mild in comparison with pneumococcal disease, numerous putative virulence factors have now been identified and it has been shown that several surface components of M. catarrhalis induce mucosal inflammation. In adults with chronic obstructive pulmonary disease (COPD), M. catarrhalis is now a well established trigger of approximately 10% of acute inflammatory exacerbations (Aebi *et al*., 2010).

The prevalence of ampicillin- resistant *M. catarrhalis* has been higher in Taiwan than in other countries, with reports of 97.7% in the 1990s. The study wereto assess resistance trends for *M. catarrhalis*, which causes respiratory tract infections, against several classes of oral antibiotics and to compare the minimum inhibitory concentration (MIC) of antimicrobial agents against *M. catarrhalis* isolates between 1993–1994 and 2001– 2004 (Hsu , 2012).

Virulence Factors

The specific secretion machinery known as outer membrane vesicles (OMVs, contained known surface proteins such as ubiquitous surface proteins) is a mechanism by which Gram-negative pathogens interact with host cells during infection and *Moraxella* IgD - binding protein (MID) (Schaar *et al*.,2011).

The major phospholipid constituents of *M. catarrhalis* membranes are phosphatidyl glycerol , phosphatidyl ethanolamine, and cardiolipin (CL). However, very little is known regarding the synthesis and function of these phospholipids in *M. catarrhalis*. In a study he discovered that *M. catarrhalis* expresses a cardiolipin synthase (CLS), termed MclS , that is responsible for the synthesis of CL within the bacterium (Buskirk, 2014)

M. catarrhalis outer membrane protein CD (OMPCD) is a major heat- modifiable OMP with demonstrable potential as a vaccine candidate. The gene encoding OMPCD of *M. catarrhalis* strains was subjected to nucleotide sequence analysis and then inactivated by insertional mutagenesis. The *ompCD* mutant strains exhibited a modest growth defect in comparison with the wild-type strains (Saito ,2013).

M. catarrhalis needs to adhere to epithelial cells of different host niches such as the nasopharynx and lungs, and consequently, efficient adhesion to epithelial cells is considered an important virulence trait of *M. catarrhalis* (de Vries *et al.*,2013).The adhesion factors of this bacterium that play a role in biofilm formation include Outer Membrane Proteins (OMPs), ubiquitous surface protein A (UspA), Hemagglutinin / *M. catarrhalis* Immunoglobulin D-Binding Protein (MID/Hag), and *M. catarrhalis* Adherence Protein (McaP) (Eghbali.,2019). Recently, the prevalence of macrolide - resistant *M. catarrhalis* has been reported, especially among Chinese children. The fitness cost of resistance is reported to render the resistant bacteria less virulent.

To investigate the correlation between macrolide susceptibility of *M. catarrhalis* and pathogenicity, the whole genome of 70 *M. catarrhalis* isolates belonging to four clonal complexes with different macrolide susceptibilities was sequenced (Liu.,2022).

The bacterial species is equipped with various adhesins to facilitate its colonization. Successful evasion of the human immune system is a prerequisite for Moraxella infection. This strategy involves induction of an excessive proinflammatory response, intervention of granulocyte recruitment to the infection site, activation of selected pattern recognition receptors and cellular adhesion molecules to counteract the host bacteriolytic attack, as well as, finally, reprogramming of antigen presenting cells. Host immunomodulator molecules are also exploited by Moraxella to aid in resistance against complement killing and host bactericidal molecules. Thus, breaking the basis of Moraxella immune evasion mechanisms is fundamental for future invention of effective therapy in controlling Moraxella infection(Su.,2012).

Pathogenicity

is an acknowledged respiratory tract pathogen and The bacterium has the capacity to colonize the nasopharynx, and may be isolated in pure culture or together with other bacterial pathogens, e.g. *Staphylococcus aureus*, *Streptococcus pneumoniae* and/or *Haemophilus influenzae* (Verhaegh *et al.,2010).* it is a human-restricted opportunistic bacterial pathogen of the respiratory mucosa and It frequently colonizes the nasopharynx asymptomatically, but is also an important causative agent of otitis media (OM) in children, and plays a significant role in acute exacerbations of chronic obstructive pulmonary disease (COPD) in adults (Blakeway *et al*., 2017).

M. catarrhalis isolates were the predominant or only bacterial isolates from the sputum samples analyzed and The findings provide supportive evidence for the pathogenic potential role of this bacterium in pediatric pneumonia. High multidrug resistance was also observed amongst the isolates, which can result in affected patients not responding to standard treatment, leading to prolonged illness, increased healthcare costs, and risk of death (Nawa.,2022).*M. catarrhalis* possesses distinct structural components, secretes a number of proteins, and undergoes various biological changes, which work together toward its attachment to and invasion of host cells, and evasion of host innate and adaptive immune responses. Many of *M. catarrhal* is outer membrane proteins and other surface proteins have shown potential as vaccine candidates. Given the ability of *M. catarrhalis* to acquire resistance to β-lactam and other antibiotic classes, it is critically important to speed up vaccine development before *M. catarrhalis* goes beyond our total control.

Resistance-Associated Factors

M. catarrhalis conferred beta-lactamase-dependent passive protection from beta-lactam killing to pneumococci within polymicrobial biofilms. Moreover, pneumococci increased resistance of *M.catarrhalis* to macrolide killing in polymicrobial biofilms. However, pneumococci increased colonization in vivo by *M. catarrhalis* in a quorum signal- dependent manner (Perez *et al*.,2014) environment, *M. catarrhalis* may be resistant to macrolides and quinolones; hence, these should not be recommended as an alternative treatment in community-acquired lower respiratory tract infections caused by *M. catarrhalis*. However, a study of larger sample size should be conducted to determine if the recommendations are required to be changed (Shaikh *et al*.,2015).

Cartilage oligomeric matrix protein (COMP) functions as a structural component in cartilage, as well as a regulator of complement activity. Importantly, COMP is detected in resident macrophages and monocytes, alveolar fluid, and the endothelium of blood vessels in lung tissue. We show that the majority of clinical isolates of *M. catarrhalis* (n = 49), but not other tested bacterial pathogens, bind large amounts of COMP. COMP interacts directly with the ubiquitous surface protein A2 of *M. catarrhalis*. Binding of COMP correlates with survival of *M. catarrhalis* in human serum by inhibiting bactericidal activity of the complement membrane attack complex. Moreover, COMP inhibits phagocytic killing of *M. catarrhalis* by human neutrophils (Liu *et*

al.,2016).

The first step in *M. catarrhalis* colonization is adherence to the mucosa, epithelial cells, and extracellular matrix (ECM). The objective of this study was to evaluate the role of *M. catarrhalis* interactions with collagens from various angles. Clinical isolates (n = 43) were tested for collagen binding, followed by a detailed analysis of protein-protein interactions using recombinantly expressed proteins. *M. catarrhalis*- dependent interactions with collagen produced by human lung fibroblasts and tracheal tissues were studied by utilizing confocal immunohistochemistry and high-resolution scanning electron microscopy (Singh *et al*.,2016).

carry lipo oligosaccharides preventing complement attacks and attract and utilize host complement regulators C4b binding protein and factor H to inhibit the classical and alternative pathways of complement activation, respectively. In addition, the regulator of the terminal pathway of complement activation, vitronectin , is hijacked by both bacteria. An array of different outer membrane proteins (OMP) in *H. influenzae* and *M. catarrhalis* simultaneously binds complement regulators, but also plasminogen . Several of the bacterial complement- binding proteins are important adhesins and contain highly conserved regions for interactions with the host (Riesbeck *etal*.,2020).

Yamada *et al*, (2014) documented that antimicrobial susceptibility and the molecular mechanism underlying low level resistance to fluoroquinolones in 70 non-duplicate clinical isolated *M. catarrhalis*. The isolated were collected in a general hospital in Tokyo, Japan, between January and October 2013 from 38 men and 32 women; most of the isolates (48 out of 70, 68.5 %) were obtained from post-nasal drips of children and they determined of The antimicrobial susceptibility of *M. catarrhalis* with an Etest, and low-level fluoroquinolone-resistant isolates were subtyped by PFGE and they investigated that Mutations in the *gyrA* and *parC* genes were determined by PCR and sequencing that was PCR products of the *gyrA* and *parC* genes from the low-level fluoroquinolone-resistant isolates were transformed into a fluoroquinolone-susceptible strain. aPDT with PF significantly reduced *M. catarrhalis* viability. Although PF-aPDT caused higher killing in planktonic grown organisms (5–6 log kill), biofilm grown bacteria also demonstrated a statistically significant reduction in viable organisms (3–4 log decrease in recoverable bacteria) following treatment as compared to saline only controls (Luke *et al.,*2014).

Chronic lung diseases in which bacterial infection plays an important role in the course and pathogenesis of the disease include chronic obstructive pulmonary disease (COPD) , bronchiectasis and cystic fibrosis. In addressing the question of the possible benefit of a vaccine to prevent *M. catarrhalis* infection in these settings , the role that *M. catarrhalis* plays in these settings should be considered. Based on studies of the bacteriology of bronchiectasis and cystic fibrosis, *M. catarrhalis* does not appear to play a significant role in these clinical settings. On the other hand , *M. catarrhalis* is one of the key bacterial pathogens in the setting of COPD. Preventing *M. catarrhalis* infection in adults with COPD would bring an enormous benefit to these patients. Thus, we will first review COPD and the role that *M. catarrhalis* plays in the course and pathogenesis of the disease to outline the rationale for developing an *M. catarrhalis* vaccine in this clinical setting (Perez *et al*.,2019)**.**

Prashanth *et al*, (2011) 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 underline *M. catarrhalis* as a notable pathogen in respiratory infections, emphasizing the importance of microbiological and clinical criteria in its diagnosis.

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Resistance genes

researchers isolated two strains of *M. catarrhalis* from in-patients, labeled R17123922_R and R18013231_R. These strains were confirmed to be resistant to macrolide antibiotics using disk diffusion and broth microdilution methods in accordance with CLSI guidelines and the found an indel in the MCR_0492 gene, which encodes the TonB-dependent receptor protein. Researchers suggest that this receptor may play a significant role in the resistance of *M. catarrhalis* to macrolide antibiotics (Zhang *et al.,*2022).

Raveendran *et al* (2020) The first resistant strain was identified in 1977 in Sweden, and since then, resistance to penicillin has become widespread, with over 95% of strains now resistant. This resistance is largely due to the production of beta-lactamase enzymes BRO-1 and BRO-2, encoded by the bro-1 and bro-2 genes, respectively. The results indicated a high level of resistance across the strains studied. The conclusion highlights the growing concern of antibiotic resistance in *M. catarrhalis*, with a particular focus on beta-lactamase production.

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. All isolates were found to be susceptible to the tested substances 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 (Morris *et al*., 2022).

Lipid A phosphorethanolamine (PEtN) transferases render bacteria resistant to the last resort antibiotic colistin. The recent discoveries of pathogenic bacteria harboring plasmid-borne PEtN transferase (mcr) genes have illustrated the serious potential for wide dissemination of these resistance elements. The origin of mcr-1 is traced to Moraxella species co-occupying environmental niches with Enterobacteriaceae (Stogios *et al*.,2018).

Mutations in the four 23S rRNA alleles, the ribosomal proteins L4 and L22, and methylase genes erm(B) and erm(F) were tested by PCR and/or sequencing. This strain showed high-level resistance to erythromycin, clarithromycin, azithromycin, clindamycin and josamycin, and contained the A2058T mutation (Escherichia coli numbering) in four of the 23S rRNA alleles (Saito *et al*.,2012).

Mutations involving the insertion of an antibiotic resistance cartridge into the *M. catarrhalis* uspA2 gene resulted in the conversion of a serum- resistant strain to a serum-sensitive phenotype and the deletion of the entire uspA2 gene from the serum-resistant *M. catarrhalis* strain O35E resulted in a serum-sensitive phenotype and did not affect either the rate of growth or the lipo oligosaccharide expression profile of this mutant. Inactivation of the classical complement pathway in normal human serum with Mg2+ and EGTA resulted in the survival of this uspA2 mutant. In contrast, blocking of the alternative complement pathway did not protect this uspA2 mutant from complement-mediated killing (Attia *et al*.,2005).

the AcrAB-OprM efflux pump in antibiotic resistance was investigated by constructing mutants that lack the acrA, acrB, and oprM genes in *M. catarrhalis* strain O35E and decrease in the MICs of amoxicillin and cefotaxime. the MICs of clarithromycin for acrA, acrB, and oprM mutants in comparison with the wild-type O35E strain. Exposure of the *M. catarrhalis* strains O35E and 300 to amoxicillin triggered an increased transcription of all AcrAB-OprM pump genes, and exposure of strains O35E, 300, and 415 to clarithromycin enhanced the expression of acrA and oprM mRNA. Inactivation of the AcrAB-OprM efflux pump genes demonstrated a decreased

ability to invade epithelial cells compared to the parental strain, suggesting that acrA, acrB, and oprM are required for efficient invasion of human pharyngeal epithelial cells (Spaniol *et al*.,2015).

Yamada *et al*(2014) investigated antimicrobial susceptibility and the molecular mechanism underlying low-level resistance to fluoroquinolones in 70 non-duplicate clinical isolates of *M. catarrhalis*. Mutations in the gyrA and parC genes were determined by PCR and sequencing. PCR products of the gyrA and parC genes from the low-level fluoroquinolone-resistant isolates were transformed into a fluoroquinolone-susceptible strain and they found that the low-level resistance to fluoroquinolones in *M. catarrhalis* is due to an amino acid substitution of Thr80 to Ile in GyrA. This is the first evidence of low- level fluoroquinolone resistance in *M. catarrhalis*.

Wang *et al*,(2007), discovered that the genome of *M. catarrhalis* ATCC 43617 was annotated to understand its metabolic capabilities and limitations. Notably, it lacked gene products for utilizing external carbohydrates, consistent with previous observations. However, it possessed enzymes for aerobic energy generation and some associated with anaerobic systems. Enzymes for synthesizing most amino acids were present except for proline and arginine. DNA microarrays containing oligonucleotide probes were designed from the genome data and used to analyze gene expression in different growth conditions.

When *M. catarrhalis* was grown in biofilms, genes encoding nitrate, nitrite, and nitric oxide reductases 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 expression of genes involved in energy generation and defense against the host immune system.

Table 1 . Some resistance genes to *Moraxella Catarrhalis*

NO.	Gene	Function
1	MCR_0492 gene	play a significant role in the resistance of *M. catarrhalis* to macrolide antibiotics
2	bro-1 and bro-2 genes	production of beta-lactamase enzymes BRO-1 and BRO-2 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	PEtN transferase (mcr) genes	illustrated the serious potential for wide dissemination of these resistance elements
5	L4 and L22, and methylase genes erm(B) and erm(F)	Resistanceto erythromycin, clarithromycin, azithromycin, clindamycin and josamycin,
6	uspA2 gene	antibiotic resistance
7	acrA, acrB, and oprM genes	decrease in the MICs of amoxicillin and cefotaxime
8	gyrA and parC genes	low-level resistance to fluoroquinolones

Conclusion

1.*Morexella catarrhalis* human-restricted opportunistic bacterial pathogen of the respiratory mucosa and It frequently colonizes the nasopharynx.

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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