Moraxella catarrhalis: The virulence factor and pathogenesis strategy

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Abstract
Moraxella catarrhalis is a Gram-negative diplococcus bacterium, formerly known as Neisseria catarrhalis or Branhamella catarrhalis. The bacterium colonizes the nasopharynx as innocent commensal, the recent recognition of M. catarrhalis as an important pathogen in both the upper and lower respiratory tract. It is important human-restricted pathogen responsible for sinusitis and otitis media in children as well as infections of the lower respiratory tract, causing exacerbation of chronic obstructive pulmonary disease in adults. The mechanisms of colonization and pathogenesis of M. catarrhalis have been extensively studied and many virulence factors have been identified to date. The objective of this study summarized important virulence factor and pathogenesis strategy of M. catarrhalis.

Keywords: Moraxella, virulence factors, pathogenesis

Introduction
Moraxella catarrhalis

The genus Moraxella belongs to the family Moraxellaceae, the most significant species is Moraxella catarrhalis (M. catarrhalis), also known as Branhamella catarrhalis, Micrococcus catarrhalis, and Neisseria catarrhalis. Moraxella catarrhalis is a gram-negative, aerobic, unencapsulated, oxidase-positive diplococcus (de Vries, et al., 2010; Shi et al., 2018)[29, 89]. Bacterium was first isolated in 1896, it was considered to be a harmless commensal of the upper respiratory tract for a long period of time. The bacterium rapidly colonizes the nasopharynx soon after birth asymptomatically (Blakeway et al., 2017)[16]. The bacterium has now firmly established its position as an etiological cause of human respiratory tract (de Vries, et al., 2010)[29]. This institution is polymicrobial community with other pathogens such as Streptococcus pneumoniae and Haemophilus influenza (Sethi and Murphy, 2008)[87]. However, it is now associated with a number of respiratory infections affecting both children and adults, including laryngitis, bronchitis and pneumonia (Suzanne et al., 2011; Bernhard et al., 2014)[14]. It is a causative agent of otitis media in children and lower respiratory tract infections in adults suffering from chronic obstructive pulmonary disease (COPD) (Schwingel et al., 2019; Tan et al., 2020)[87, 99]. Rarely, M. catarrhalis can also cause endocarditis, sepsis and meningitis (Aebi, 2011)[2]. Thus, idea has arisen that organism is not simply a commensal colonizer and important bacterial pathogen.

The strategies of pathogenesis and virulence factors of M. catarrhalis have been briefly studied. Usually, the virulence factors associated with whole bacteria or can be driven in part by the release of outer membrane vesicles (OMVs) (Augustyniak et al., 2018)[19]. It is not identified if virulence is linked with certain strains or subpopulations of M. catarrhalis, or if variances in clinical appearance can be attributed to the heterogeneous expression of specific M. catarrhalis virulence factors in the socializing population (Blakeway et al., 2017)[16]. Generally, some of these mechanisms which contain several virulence factors facilitating the transfer of periplasmic and outer membrane components to the host (Kaparakis-Liaskos, 2015)[44]. Moreover, OMVs can confer pathogen existence and colonization after their interaction with the other bacterial species (Tan et al., 2007; Schaar et al., 2011)[100, 85]. Recently, Moraxella catarrhalis is commonly found in several community of clinical isolates. This pathogen uses several virulence mechanisms to colonize and survive in its host (Masaki et al., 2011; Perez and Murphy, 2017)[58, 76].
In this review, we will summarize important virulence factor and pathogenesis strategy of this organism.

**Virulence factors of *Moraxella catarrhalis***

Several virulence factors of *M. catarrhalis* have been identified and characterized, and many of these are raised through the plasma membrane and are either generalized to the outer membrane protein (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 abilities are multifactorial as showed in below.

### A- External Structures

#### 1. Lipooligosaccharides

Lipopolysaccharides (LPS) a major constituent of surface structures it has been shown that act as adhesions modules in several bacteria, which facilitate the attachment of a bacterium to host cells (Jacques, 1996) [42]. *Moraxella catarrhalis* has been shown to express a lipooligosaccharide (LOS) as important virulence factor and plays a crucial role in the initial stage of attachment and colonization of bacteria to human pharyngeal epithelial cells (Akgul et al., 2005) [43].

#### 2. Outer Membrane Proteins

Gram-negative bacteria produce small round structures 20–250 nm in diameter are called outer membrane vesicles (OMVs). OMVs are made when small portions of OM swell disseminate far from the cell and release (Grenier et al., 1987) [32]. OMVs contain soluble proteins and as outside adherent material that perform various biological functions on the environment and on other cells, including playing a role in pathogenesis, bacterial stress response, nutrient acquirement, biofilm development, and horizontal gene transfer (Mashburn et al., 2005) [59]. For example, *M. catarrhalis* expresses several adhesins that mediate adherence to human epithelial cells, including UspA1 (LaFontaine et al., 2000) [36], Hag/MID (Holm et al., 2003.) [40], McaP (Timpe et al., 2003) [103], OMP CD (Holm et al., 2004) [41], and the FHA-like proteins MhaB1 and MhaB2 (Balder et al., 2007) [12].

OMVs act as delivery vehicles, and as contributors to bacterial survival and virulence (Furuta et al., 2009) [31]. OMVs enable bacteria to secrete insoluble molecules in addition to soluble material used in bacterial envelope components. OMVs permit enzymes to reach reserved targets in a concerted, protected, and targeted formula (Kulp and Kuehn, 2010) [48]. Eight major proteins (A through H) designated OMPs ranging from 21 to 98 kDa were identified (Murphy, 1990) [66].

#### 3. Pericellular Structures

Pili or fimbriae structures are used by bacteria to attached to mucusal epithelial cells of the host and initiated of disease by a wide range of pathogenic bacteria. Pili are composed of polymerized protein subunits called pilins, the pilin subunit of *M. catarrhalis* appears to be more highly conserved as there are no major pilin variants produced by a single strain and only two major PilA antigenic variants, termed clade 1 and clade 2, have been observed between strains (Luke-Marshall et al., 2011) [57].

Genes encoding Pil A (the major pilin subunit) and Pil Q (the outer membrane secretin through which the pilus filament is extruded) identified and cloned whereas Pil T (the NT Pase that mediates pilin) disassembly and retraction (Luke et al., 2004) [56]. Accordingly, some strains may be pilus positive whereas others have been proven to lack pili (Ahmed et al., 1991) [3]. Some studies have previously showed that bacteria with fimbriae bind more competently to lower bronchial epithelial cells than bacteria without fimbriae (Rikitomi et al., 1997) [83], that may explain a role of these pili in the pathogenesis of pathogen bacteria.

### 4. Biofilm formation

Biofilm formation is a significant virulence factor for persistence of bacteria during the period in the host and severity of disease by many pathogenic species for example *M. catarrhalis* (Perez et al., 2014) [77]. Inside the biofilm, the bacteria are covered in a protective polymeric matrix, which expresses resistance to host immune defenses. And the bacteria in biofilms are in an abbreviated metabolic state and capability alternative gene expression shapes, contributing to enhanced resistance to antimicrobial action (Bakale et al., 2012) [13]. The respiratory tract problems such as OM and COPD caused by three ecological bacteria *M. catarrhalis*, *Haemophilus influenza* and pneumococcus. From several studies, samples of respiratory tract patient and experimental models of disease show that *M. catarrhalis* forms polymicrobial biofilms with both *Streptococcus pneumoniae* and *Haemophilus influenzae* within the host (Perez et al., 2014) [7]. Actually, polymicrobial biofilm formation with *M. catarrhalis* enhances survival *in vivo* of both species in contrast to single species biofilms. A formation of multispecies biofilms can consider a contributing factor to antimicrobial action failure, especially in combining with ß-lactamase producing bacteria like *M. catarrhalis*.

### 5. Capsule

In both G-positive and G-negative bacteria, the presence of capsules are considered an important virulence factor. Ahmed et al., (1991) [3] has been previously suggested a polysaccharide capsule. A capsule is not detectable when colonies of *M. catarrhalis* are examined on agar plates resemble the site in many other bacterial pathogens. More research is necessary to definitely determine the presence of a capsule and to explain its role in virulence.

### B. Producing of ß-Lactamase

Previously, *M. catarrhalis* that producing beta-lactamase was not described. But, with cumulative of investigations about antibiotic resistance in this organism all over the world was recorded (Beekmann et al., 2005) [13]. The increase in occurrence of beta-lactamase strains especially in *M. catarrhalis* can be regarded as the fastest spreading of beta-lactamases (Khan et al., 2010) [45], approximately 95–99% of clinical isolates now appear to resist to penicillin and other classes of antibiotics (Khan et al., 2010; Prashanth et al., 2011) [45, 79]. Abuse of antibiotics, including physicians over-suggesting and unfinished depletion of antimicrobial courses by patients, contribute to the fast and spread of antibiotic resistance genes in many pathogens, including *M. catarrhalis* (Pereza and Murphy, 2017) [76]. As well, traditional treatment of mixed infections caused by other airway pathogens associated with resistant problem (Prashanth et al., 2011) [79]. Detection of antibiotic resistance genes in *M. catarrhalis* strains were recorded that more than
Pathogenesis strategies

The dynamics inducing the pathogenesis of *M. catarrhalis* infection are not exactly understood. Generally, the pathogenicity of this bacterium, like other microorganisms, depends on the ability for binding to epithelial and mucus layer and escape from the host defense mechanisms (Liu et al., 2016). *M. catarrhalis* can attach to numerous types of cells, involving epithelial cells of bronchial, small airway, and type 2 alveolar cells (De Vries et al., 2013) [28]. This review is planned to provide a detailed overview of understanding of the virulence features of *M. catarrhalis* pathogenesis and particularly underlines recent studies linking with adhesion, invasion, biofilm formation, evasion of the host immune system.

Adhesion to Host Epithelium

An essential step in the process of bacterial colonization and infection of respiratory tract epithelium is adherence to the respiratory mucosa (Siegel and Weiser, 2015) [90]. An important virulence trait of *M. catarrhalis* is an effective adhesion to epithelial cells (de Vries et al., 2013) [28]. The general mechanism of cellular adherence of *M. catarrhalis* to mucosal surfaces is mediated by binding of multifactorial incident macromolecules to surface receptors on eukaryotic target cells by numerous studies. These studies showed the presence or absence of fimbrae did not influence the capacity of the bacterium to adhere.

Molecules including fimbrial adhesins such as type IV pili (TFP) and LOS structures (Spanioli et al., 2008) [97] and non-fimbrial adhesins like, the outer membrane proteins (OMPs) including the ubiquitous surface proteins A (UspAs) (Lafontaine et al., 2000) [50], *M. catarrhalis* immunoglobulin D (IgD) binding protein/hemagglutinin (MID/Hag) (Forsgren, 2001) [30], *M. catarrhalis* adherence protein (McaP) (Timpe et al., 2003) [103], OMP CD (Holm et al., 2004) [41], *M. catarrhalis* filamentous Hag (FHA)-like proteins (Mha proteins) (Plamondon and Campagnari, 2007) [78], have been identified.

Pili are important element for adhesion and colonization for *Moraxella catarrhalis* (Luke et al., 2007) [55], pili may initiate adhesion at long range, while outer membrane proteins (OMPs) may be involved during more close contact (Hill et al., 2005) [39]. The different adhesion molecules bind to an array of receptors or fundamental molecules expressed on epithelial cells of respiratory tract: for instance the OMP CD of *M. catarrhalis* was shown to specifically attach to the mucin molecules from the nasopharynx and middle ear but not to mucin from the saliva and tracheobronchial mucin. Interactions such as these represent the first steps in the process of bacterial colonization and infection (Bernstein and Reddy, 2000) [15]. In addition to, the influence of charge on adherence and interaction between the negatively charged surface of *M. catarrhalis* cells and positively charged domains called micropleca on pharyngeal epithelial cells was found (Ahmed et al., 2000) [4].

There is relationship between *M. catarrhalis* colonization of the human respiratory tract epithelium and increased risk of disease, specifically in children (Verhaegh, 2011) [110]. Therefore, it is reasonable to expect that an effective immune response raised proteins associated with OMVs of *M. catarrhalis* are involved in diverse biological functions. Many of them are important virulence factors permitting infection and colonization of host (Blakeway et al., 2017) [16]. The ubiquitous surface proteins (UspAs) are among the major virulence factors. UspAs are multifunctional proteins with important adhesion properties. They can be divided into three main groups: UspA1 (88-kDa), UspA2 (62-kDa), and UspA2H (92-kDa) proteins (Lafontaine, 2000) [50]. UspA1 mediating binding to epithelial cells and extracellular matrix (ECM) components (Brooks et al., 2008) [22], and binding to carино-embryonic antigen-related cellular adhesion molecule 1 (CEACAM1) (Hill and Virji, 2003) [38]. As well as, UspA2/UspA2H proteins predominantly playing a role in immune evasion (Attia et al., 2005) [7]. Purpose of the modular structure of the predicted UspA1 and UspA2H proteins shown the presence of the VEEG-NINNY-VEEG amino acid sequence motif involved in binding to Chang conjunctival cells or fibronecin (Brooks et al., 2008) [25]. Given the fact that these variable domains appear to contribute to different functional characteristics of the UspA proteins, idea exchange could lead to getting of specific functional characteristics. HEP-2 laryngeal epithelial cells (McMichael, 1998) [69], and A549 type II alveolar epithelial cells (Brooks et al., 2008) [22]. In addition to it binds to the ECM proteins fibronecin (Tan et al., 2005) and laminin (Tan et al., 2006) [101]. Host receptors for other adhesin molecules of *M. catarrhalis* such as MID/Hag or McaP remain to be identified and is needed more research.

Risk factors associated with *M. catarrhalis* colonization have been previously studied in several countries and age groups, and the findings have indicated that crowding and contact with children are risk factors for colonization, not only for *M. catarrhalis*, but also for *S. pneumoniae* and *H. influenzae* (Labout et al., 2008) [49]. Other reported risk factors are genetics (Yamanaka et al., 2008) [116], smoking (Brook et al., 2008) [23], socio-economic status (Smith-Vaughan et al., 2006) [90], synergy and interference with other micro-organisms (Brook and Gober, 2006) [23], frequency and location of sampling (Hendley et al., 2005) [37], season (Hendley et al., 2005) [37], gender (Kilpi et al., 2001) [46] and vaccination (Dagan, 2004) [27].

Invasion of the host epithelium

After *M. catarrhalis* has established itself at its colonization sites, a critical step of *M. catarrhalis* appears to be invasion of host cells, which would allow the bacterium to survive both the host immunological response (cellular and humoral) and environmentally challenging conditions, such as iron limitation and effects of antibiotic treatment (de Vries et al., 2009) [29]. Adhesion between host epithelial cells and surface-exposed macromolecules, such as OMPs is an essential step for assisting pathogenesis of *M. catarrhalis* (de Vries et al., 2009) [29]. The aggressive capacity of *M. catarrhalis* to invade different epithelial cell types was demonstrated by several studies (Slevogt et al., 2007) [94]. The actual mechanism of *M. catarrhalis* invasion into epithelial cells noticed by Spanioli et al., (2008) [97], who found that the level of invasion of Chang cells by *M. catarrhalis* O35E was actually fivefold higher than the level of invasion of A549 cells by the same strain. These authors
also proven that the addition of a purified OMP preparation resulted in reductions of both adhesion and invasion, and a lack of UspA1 reduced both adhesion and invasion. Also, the invasion process was dependent on clathrin polymerization, which looked to oppose the earlier findings of Slevogt et al. (2007) [84]. Additionally, actin polymerization was also found to contribute to the invasion process, and antibodies directed to fibronectin and integrin 51 were able to inhibit invasion (Spaniol et al., 2008) [97]. In another publication, Hill et al. (2005) [39] indicated the importance of CEACAM1 binding for both adhesion and invasion by blocking a recombinant peptide (rD3-7) that representing the CEACAM1-binding domain of UspA1 resulted in inhibition of cell invasion by M. catarrhalis, *H. influenzae*, and *N. meningitides*. Further, *M. catarrhalis* would be adept to interact with B lymphocytes through MID/Hag when existing within the sub epithelial barrier of lymphoid tissues (Heiniger et al., 2007) [66].

At the present, the exact mechanism of epithelial cell invasion by *M. catarrhalis* is not completely understood, but it appears to be an active process involving several host cell and bacterial contrivances.

### Biofilm Formation

Microbial biofilms have been include cells adhered to surfaces that are enclosed by a self-produced exopolymeric matrix that protects biofilm cells against different external worries (Melo and Azevedo, 2021) [63]. A colonization of host mucosal surfaces is a first and necessary step in the infectious process, biofilm formation has already been demonstrated to be an important manner involved in colonization and persistence of mixed bacterial etiology in the nasopharynx (Bair and Campagnari, 2019) [10].

These biofilm description of bacterial invasion of human cells leads to failure in antibiotic therapy, various studies have shown that pathogenic bacteria such as *Moraxella catarrhalis*, produce biofilm-like structures within the host cells and anti-bacterial agents cannot reach intracellular biofilm in normal concentrations (Mizraei et al., 2020) [63]. A study by Bair and Campagnari, (2019) [10] characterized both monomicrobial and polymicrobial biofilms using an *in vitro* nasopharyngeal colonization model. Biofilm assays were designed to simulator the nasopharynx and bacterial persistence was measured over time. The information propose that colonization with *M. catarrhalis* stimulates stable polymicrobial biofilms with other pathogens. Indeed, the capacity of *M. catarrhalis* to form biofilms has been confirmed using *in vivo* assay, and role of biofilms formed by otopathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*) that contribute to otitis media repeated and established as chronic. The characters of biofilms formed by these bacteria and that factors influence them, and how these affect the host inflammatory response is important for the development of new strategies for the treatment of otitis media (Silva and Sillankorva, 2019) [91].

Previously, there were try to identify genes essential for biofilm formation by use of a transposon mutagenesis (Pearson et al., 2006) [74]. This study confirmed that the existence of UspA1 positively marks biofilm formation, while the presence of Hag has a negative influence. In addition to, UspA1 and UspA2H genes have played a role in biofilm formation (Pearson et al., 2007) [74]. The study performed by Verhaegh et al., (2008) [105] suggested the isolates carrying UspA2 mutant gene have more efficient biofilm formation than isolates carrying UspA2H mutant gene, signifying that uspA2 could also play a role in biofilm formation.

The ability for formation of biofilms was related with frequency of UspA2 in the strains, a rate children isolates (5 years of age), and adults isolates (20 years of age) indicated reduced frequency of UspA2 (Verhaegh et al., 2008) [105]. Additionally, the formation of micro colonies and biofilms formation was studied *In vitro* by using a pil A mutant and illuminated role of TFP micro colony and biofilm formation (Luke et al., 2007) [55].

*M. catarrhalis* O35E was exposed for mutation of Host factor 1 (Hfq), the result showed reducing in growth when it osmotic and oxidative stresses also an changed OMP composition, considered by slightly increased expressions of OMP J, OMP G1b, and Cop B (Attia et al., 2008) [8]. Additionally, the hfq mutant strain showed a growth improvement in a biofilm system, which could be the (indirect) result of a changed outer membrane composition (Attia et al., 2008) [8].

### Evasion of the host immune system

The first line of defense against bacterial pathogens (*M. catarrhalis*) was faces the tactics host’s innate immune system in resisting a forging microbe. After colonization of mucosal surfaces and evasion the tissue by *M. catarrhalis*, the bacteria was exposed these tactics of immune system.

Usually, the innate immune system contains several main components, such as the complement system and pattern recognition receptors (PRRs), which include the Toll-like receptors (TLRs), NOD-like receptors, and mannose receptors of macrophages (Akira et al., 2006) [6]. The important strategies of microbe to avoid the innate immune system involve:

1. Avoidance of complement-mediated killing mainly via intervention with regulatory proteins (Liu et al., 2016) [53].
2. Polyclonal, non-specific B cell activation and relaying of adaptive immunity (Vidakovics et al., 2010) [108].
3. Hiding inside lymphoid tissue, which is the main pool simplifying the host invasion (Heiniger et al., 2007) [66].
4. Formation of biofilm (Perez et al., 2014) [73].
5. Participation in protease- anti protease imbalance (Parameswaran et al., 2009) [72].

### Complement Resistance

The complement system is a fundamental component of the immune response that results in direct killed of pathogens or opsonization for increased phagocytosis. Therefore, complement resistance is an important virulence feature of various pathogens that subsequently increases the survival rate among bacteria within the human host (Blom et al., 2009) [17]. All virulent bacterial species need to defeat the innate immune system in order to colonize and survive in their hosts. The human respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis* are have developed novel mechanisms to avoid complement-mediated killing (Riesbeck, 2020) [81].

Plamondon et al., (2007) [78] showed 89% strains of *M. catarrhalis* isolated from lower respiratory tract infections are resistant to complement-mediated killing, whereas strains from the upper respiratory tract of children are mostly sensitive (58%). *M. catarrhalis* does possess
mechanisms that have evolved to inhibit activation of complement pathways. The activation of the complement system via 3 different routes, the classical pathway, alternative, and/or mannose-binding lectin pathway, all of which leads to the terminal pathway resulting in formation of the membrane attack complex (MAC) and opsonization of bacteria for phagocytic killing. All pathways are tightly controlled by human fluid-phase or membrane-bound regulators (Bernhard et al., 2014) [44].

Previous reviews documented that *M. catarrhalis* may stimulate both the classical and alternative pathways (Riesbeck et al., 2006) [82] and is a weak activator of the mannose-binding lectin pathway (Singh et al., 2010; Hallstrom et al., 2011)[100, 103]. *Moraxella catarrhalis* is mainly dependent on outer membrane proteins, a family ubiquitous surface proteins (Usp) has been studied most thoroughly for its role in pathogenesis (Singh et al., 2010) [90], Usp A1 and Usp A2 that interact with complement factor 3 (C3) and complement inhibitor C4b binding protein (C4BP) preventing the alternative and classical pathways of the complement system respectively (Singh et al., 2010) [92].

Several of complement binding proteins are important adhesins and interactions with the host. Thus, some of the OMP are viable targets for new therapeutics, including vaccines aimed at preventing respiratory tract diseases such as otitis media in children and chronic obstructive pulmonary disease in elderly (Riesbeck, 2020) [63]. Although, the structural details facilitating these interactions are still unknown. Riesbeck, (2020) [63] showed lipooligosaccharides avoiding complement actions and consume host complement regulators C4b binding protein and factor H to impede the classical and alternative pathways of complement activation, respectively. In addition, the binding of human vitronectin, an inhibitor of the terminal pathway of complement, a bacterium motivated vitronectin to disrupt complement-mediated killing. Hybrid UspA2 (UspA2H) bind vitronectin at the highly diverse N-terminal head domain (Su et al., 2013) [98]. UspA2 also has the capacity to attract vitronectin that in turn binds C9 and thereby inhibits membrane attack complex (MAC) formation. UspA2 as a major vitronectin binding protein and hence the UspA2/vitronectin interaction was studied in detail (Singh et al., 2010; Hallstrom et al., 2011; Bernhard et al., 2014) [92, 93, 14]. Indeed, most clinical isolates of *M. catarrhalis* are able to survive complement-mediated killing by normal human serum (Verhaegh et al., 2008) [105].

Recently, it was proven that *Moraxella catarrhalis* bacteria also bind plasminogen, which is converted to plasmin that degrades C3b and C5. (UspA2) and (UspA2H) were recognized as the plasminogen-binding factors in the outer membrane proteome of *Moraxella*. Moreover, expression of a series of truncated recombinant UspA2 and UspA2H proteins followed by a detailed analysis of protein-protein interactions suggested that the N-terminal head domains bound to the kinglet domains of plasminogen (Singh et al., 2015) [93].

C. Virulence-associated genes of *M. catarrhalis*

There are other a number of virulence factors and virulence-associated genes, have been identified in a number of respiratory pathogens, as *M. catarrhalis* isolates. Pathogenicity of some virulent strains contributes to possess a highly mutable genes (Blakeway et al., 2017) [10]. Although, the development of a vaccine against *M. catarrhalis* has been delayed by the absence of a suitable animal model. Increased knowledge of the organism’s pathogenic properties and the host response to it may service to detect suitable vaccine targets or lead to other strategies to prevent infection. The characteristics of an active vaccine can be detected: surface epitopes, stimulate the immunity response, appearance in vivo at sites of pathogenesis, prevention, and stable state (Perez and Murphy, 2017) [70].

Moreover, many related genes have been identified in the genomes of a wide variety of bacterial species, suggesting the presence of the outer membrane protein genes and the potential for pathogenesis specially UspA1 and UspA2 antigens (Attia et al., 2006; Spaniol et al., 2008) [97]. Meier et al., (2002) [61] evaluated the frequency of uspA1 and uspA2 genes as 99% and 77%, respectively. Also, study by Verhaegh et al., (2011) [106] were identified frequency of uspA1 gene (99%) compared to uspA2 (76%). Addition to UspA1 and UspA2, a number of different gene products of *M. catarrhalis* have been associated with colonization and complement evasion, including CopB (Sethi et al.,1997), lipooligosaccharide (LOS) (Akgul et al., 2005) [3], Hag (Pearson et al., 2006) [73], and OMPCD (Akimana et al., 2007) [52].

However, much of the evidence for the maintenance and manifestation of these factors e.g. G1a and G1b (Adlowitz et al., 2004) [1], *M. catarrhalis* adherence protein (Lipski et al., 2007) [93], Moraxella surface proteins 22, 75 and 78 (Ruckdeschel et al., 2008) [84], substrate-binding protein 2 (Otsuka et al., 2014) [71], lactoferrin-binding protein A (Bonnah et al., 1999) [19] and transferrin binding protein A (Myers et al., 1998) [70] is derived from studies that only examined a small number of isolates, or in the case of CysP (Murphy et al., 2016) [16] and AfeA (Murphy et al., 2017) [66], what can be gleamed from genomes available online. All of these vaccine candidates have been associated with the production of antibody (Murphy et al. 2005) [69]. An antibody response in humans to various *M. catarrhalis* antigens, including highly conserved outer membrane proteins, has been demonstrated. As well as, their vaccine potential still is matter of current investigations. In several studies performed by Verhaegh et al. (2008) [105] to define the frequency of virulence genes in *M. catarrhalis*. He was observed the prevalence of ompJ and ompCD genes in 100% and mcpA gene in 99% of the strains. Whereas in other study, he was confirmed the presence of MID/Hag gene in 85 strains, giving a frequency of 83% (Verhaegh et al., 2011) [107]. But study by Mollenkvist et al. (2003) [65] showed the frequency of MID/Hag gene in all clinical isolated strains (100%). The molecular techniques reported about copB gene frequency in *M. catarrhalis* genes was 100% (Bootsma et al., 2000; Verhaegh et al., 2008) [20, 5]. However, other studies was 50% to 55% (Mitov et al., 2010; Liu et al., 2017) [64, 54]. As well as, Zaleski et al., (2000) [111] showed role of Gal gene in serum-mediated killing and susceptible to complement attack. Also, several virulence genes have been stimulated immune response of host, making them potential vaccine candidate genes. A genotyping variation of these genes are designed and studied of role with colonization (Perez et al., 2009).
Conclusion

*M. catarrhalis* was formerly believed a nonpathogenic member of the resident flora of the upper respiratory tract. But, with augmented investigations, the bacterium has delivered as a real pathogen, especially in patients with airway problems for both children and elderly persons. The first step of bacterium to be successful infected was adhere and colonize with their hosts. Bacterial infection induced by a wide virulence factors that can often be serious.

So, future studies were needed to compare *Moraxella* isolated as normal flora or pathogen and investigation some virulence factors other than those studied in this review.

References

1. Adlowitz DG, Hiltke T, Lesse AJ, Murphy TF. Identification and characterization of outer membrane proteins G1a and G1b of *Moraxella catarrhalis*. Vaccine. 2004;22:2533-2540.
2. Aebi C. *Moraxella catarrhalis*-pathogen or commensal? Adv Exp Med Biol. 2011;697:107-16.
3. Ahmed K, Rikitomi N, Ichinose A, Matsumoto K. Possible presence of a capsule in *Branhamella catarrhalis*. Microbiol. Immunol. 1991;35:361-366.
4. Ahmed K, Nakagawa T, Nakano Y, Martinez G, Ichinose A, Zheng CH, *et al.* Attachment of *Moraxella catarrhalis* occurs to the positively charged domains of pharyngeal epithelial cells. Microb. Pathog. 2000;28:203-209.
5. Akgul G, Erturk A, Turkoz M, Turan T, Ichinose A, Nagatake T, *et al.* Role of Lipooligosaccharide in the Attachment of *Moraxella catarrhalis* to Human Pharyngeal Epithelial Cells. Microbiol. Immunol. 2005;49(10):931-935.
6. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006;124:783-801.
7. Attia AS, Lafontaine ER, Latimer JL, Aebi C, Syrigianopoulos GA, Hansen EJ. The UspA2 protein of *Moraxella catarrhalis* is directly involved in the expression of serum resistance. Infect. Immun. 2005;73:2400-2410.
8. Attia AS, Sedillo JL, Wang W, Liu W, Brautigam CA, Winkler W, *et al.* *Moraxella catarrhalis* expresses an unusual Hfq protein. Infect. Immun. 2008;76:2520-2530.
9. Augustyniak D, Seredyński R, McClean S, Roszkowiak J, Roszniocki B, Smith DL, *et al.* Virulence factors of *Moraxella catarrhalis* outer membrane vesicles are major targets for cross-reactive antibodies and have adapted during evolution. Scientific reports. 2018;8:4955.
10. Bair KL, Campagnari A. *Moraxella catarrhalis* Promotes Stable Polymicrobial Biofilms With the Major Otopathogens. Front Microbiol. 2019;10:3006.
11. Bakaletz LO. Bacterial biofilms in the upper airway - evidence for role in pathology and implications for treatment of otitis media. Paediatr Respir Rev. 2012;13:154-9.
12. Balder R, Hassel J, Lipski S, Lafontaine ER. *Moraxella catarrhalis* strain O35E expresses two filamentous hemagglutinin-like proteins that mediate adherence to human epithelial cells. Infect. Immun. 2007;75:2765-2775.
13. Beeckmann SE, Heilmann KP, Richter SS, Garcia-de-Lomas J, Doern GV. Antimicrobial resistance in *Streptococcus pneumoniae*, Haemophilus influenzae, *Moraxella catarrhalis* and group a beta-haemolytic Streptococci in. Results of the multinational GRASP surveillance program. Int J Antimicrob Agents. 2005;25:148-56.
14. Bernhard S, Fleury C, Su Y-C, Zipfel PF, Koske I, Nordström T, *et al.* Outer Membrane Protein Opa Contributes to *Moraxella catarrhalis* Serum Resistance via Interaction with Factor H and the Alternative Pathway. The Journal of Infectious Diseases. 2014 Oct 155;210(8):1306-1310.
15. Bernstein JM, Reddy M. Bacteria-mucin interaction in the upper aerodigestive tract shows striking heterogeneity: implications in otitis media, rhinosinusitis, and pneumonia. Otolaryngol. Head Neck Surg. 2000;122:514-520.
16. Blakewy LV, Tan A, Peak IRA, Seib KL. Virulence determinants of *Moraxella catarrhalis*: distribution and considerations for vaccine development. Microbiology (Reading). 2017;163(10):1371-1384.
17. Blom AM, Hallstrom T, Riesbeck K. Complement evasion strategies of pathogens-acquisition of inhibitors and beyond, Mol Immunol. 2009;46:2808-17.
18. Bonnah RA, Wong H, Loosmore SM, Schryvers AB. Characterization of Moraxella (Branhamella) catarrhalis lbpB, lbpA, and lactoferrin receptor orf3 isogenic mutants. Infect Immun. 1999;67:1517-1520.
19. Bonnah RA, Yu R, Schryvers AB. Biochemical analysis of lactoferrin receptors in the Neisseriaceae: identification of a second bacterial lactoferrin receptor protein. Microb. Pathog. 1995;19:285-297.
20. Bootsma HJ, Van Dijk H, Vauterin P, Verhoeef J, Mooi FR. Genesis of BRO beta-lactamase-producing *Moraxella catarrhalis*: Evidence for transformation-mediated horizontal transfer. Mol Microbiol. 2000;36(1):93-104.
21. Brodies A, Dagan R, Greenberg D, Givon-Lavi N, Leibovitz E. Acute otitis media caused by *Moraxella catarrhalis*: Epidemiologic and clinical characteristics. Clin Infect Dis. 2009;49(11):1641-7.
22. Brook I, Gober AE. Recovery of potential pathogens in the nasopharynx of healthy and otitis media-prone children and their smoking and nonsmoking parents. Ann Otol Rinhol Laryngol. 2008;117(10):727-30.
23. Brook I, Gober AE. Increased recovery of *Moraxella catarrhalis* and Haemophilus influenzae in association with group A β-haemolytic streptococci in healthy children and those with pharyngo-tonsillitis. J Med Microbiol. 2006;55(8):989-92.
24. Brooks MJ, Sedillo JL, Wagner N, Wang W, Attia AS, Wong H, *et al.* *Moraxella catarrhalis* binding to host cellular receptors is mediated by sequence-specific determinants not conserved among all UspA1 protein variants. Infect. Immun. 2008;76:5322-5329.
25. Brooks MJ, Sedillo JL, Wagner N, Laurence CA, Wang W, Attia AS, *et al.* Modular arrangement of allelic variants explains the divergence in *Moraxella catarrhalis* USPA protein function. Infect. Immun. 2008;76:5330-5340.
26. Dabin R, Pichichero ME. Vaccine targets against *Moraxella catarrhalis*. Expert Opin Ther Targets. 2016;20(1):19-33.
27. Dagan R. The potential effect of widespread use of pneumococcal conjugate vaccines on the practice of
pediatric otolaryngology: the case of acute otitis media. Curr Opin Otolaryngol Head Neck Surg. 2004;12(6):488-94.

28. De Vries SPW, Eleveld MJ, Hermans PWM, Bootsma HJ. Characterization of the Molecular Interplay between Moraxella catarrhalis and Human Respiratory Tract Epithelial Cells. PLoS ONE 2013;8(8):e72193.

29. De Vries SPW, Van Huijum S.A.F.T. Schuler W, Riesbec K, Hays JP, Hermans PWM, et al. Genome analysis of Moraxella catarrhalis strain RH4: a human respiratory tract pathogen. Journal of Bacteriology. 2010;192:3574-3583.

30. Forsgren A, Brant M, Mollenkvist A, Muyombwe A, Janson H, Woin N, et al. Isolation and characterization of a novel IgD-binding protein from Moraxella catarrhalis. J. Immunol. 2001;167:2112-2120.

31. Furuta N, Takeuchi H, Amano A. Entry of Porphyromonas gingivalis outer membrane vesicles into epithelial cells causes cellular functional impairment. Infect. Immun. 2009;77:4761-4770.

32. Grenier D, Mayrand D. Functional characterization of extracellular vesicles produced by Bacteroides gingivalis. Infect. Immun. 1987;55:111-117.

33. Hallstrom T, Nordstrom T, Tong Tan T, Manolov T, Lambris JD, Isenman DE, et al. Immune Evasion of Moraxella catarrhalis Involves Ubiquitous Surface Protein A-Dependent C3d Binding. J Immunol. 2011;186(5):3120-3129.

34. Hamze M, Osman M, Mallat H, El Achmar M. First data on antimicrobial susceptibility patterns of Moraxella catarrhalis isolates in Lebanon. International Arabic Journal of Antimicrobial Agents. 2019, 9(2).

35. Hays JP. Moraxella catarrhalis: a mini review. Pediatr. Infect. Dis. J. 2009;4:211-220.

36. Heiniger N, Spaniol V, Troller R, Vischer M, Aebi C. A reservoir of Moraxella catarrhalis in human pharyngeal lymphoid tissue. J Infect. Dis. 2007;196:1080-1087.

37. Hendley JO, Hayden FG, Winther B. Weekly point prevalence of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis in the upper airways of normal young children: effect of respiratory illness and season. APMIS. 2005;113(3):213-20.

38. Hill DJ, Virji M. A novel cell-binding mechanism of Moraxella catarrhalis ubiquitous surface protein UspA: specific targeting of the Ndomain of carcinoembryonic antigen-related cell adhesion molecules by UspA1. Mol Microbiol. 2003;48:117-129.

39. Hill DJ, Edwards AM, Rowe HA, Virji M. Carcinoembryonic antigen-related antigen-related cell adhesion molecule (CEACAM)-binding recombinant polypeptide confers protection against infection by respiratory and urogenital pathogens. Mol. Microbiol. 2005;55:1515-1527.

40. Holm MM, Vanlerner SL, Sledjeski DD, Lafontaine ER. The Hag protein of Moraxella catarrhalis strain O35E is associated with adherence to human lung and middle ear cells. Infect. Immun. 2003;71:4977-4984.

41. Holm MM, Vanlerner SL, Foley IM, Sledjeski DD, Lafontaine ER. The Moraxella catarrhalis porin-like outer membrane protein CD is an adshein for human lung cells. Infect. Immun. 2004;72:1906-1913.

42. Jacques M. Role of lipo-oligosaccharides and lipopolysaccharides in bacterial adherence. Trends Microbiol 934 G. AKGUL ET AL. ol. 1996;4:408-410.

43. Jordan KL, Berk SH, Berk SL. A comparison of serum bactericidal activity and phenotype characteristics of bacteremic, pneumonia-causing strains, and colonizing strains of Branhamella catarrhalis. Am J Med. 1990;88(5A):285-328.

44. Kaparakis-Liaskos M, Ferrero RL. Immune modulation by bacterial outer membrane vesicles. Nat. Rev. Immunol. 2015;15:1-13.

45. Khan MA, Northwood JB, Levy F, et al. BRO beta lactamases and antibiotic resistances in a global cross sectional study of Moraxella catarrhalis from children and adults. J Antimicrob Chemother. 2010;65:91-97.

46. Kilpi T, Herva E, Kaalainen T, et al. Bacteriology of acute otitis media in a cohort of Finnish children followed for the first two years of life. Pediatr Infect Dis J. 2001;20(7):654-62.

47. Klingman KL, Murphy TF. Purification and characterization of a high-molecular-weight outer membrane protein of Moraxella (Branhamella) catarrhalis. Infect. Immun. 1994;62:1150-1155.

48. Kulp A, Kuehn MJ. Biological Functions and Biogenesis of Secreted Bacterial Outer Membrane Vesicles. Annu Rev Microbiol. 2010;64:163-184.

49. Labout JA, Duijts L, Arends LR, et al. Factors associated with pneumococcal carriage in healthy Dutch infants: the Generation R Study. J Pediatr. 2008;153(6):771-6.

50. Lafontaine ER, Cope LD, Aebi C, Latimer JL, McCracken GH Jr, Hansen EJ. The UspA1 protein and a second type of UspA2 protein mediate adherence of Moraxella catarrhalis to human epithelial cells in vitro. J Bacteriol. 2000;182(5):1364-73.

51. Leitao JH. Microbial Virulence Factors. Int. J. Mol. Sci. 2020;21:5320.

52. Lipski SL, Akimana C, Timpe JM, Wooten RM, Lafontaine ER. The Moraxella catarrhalis autotransporter McaP is a conserved surface protein that mediates adherence to human epithelial cells through its N-terminal passenger domain. Infect Immun. 2007;75:314-324.

53. Liu G, Gradstedt H, Ermert D, Marshall ET AL. A bacterial outer membrane protein (BOMP) from Moraxella catarrhalis enhances resident innate immunity via targeting cartilage oligomeric matrix protein. J Immunol. 2016;196(3):1249-58.

54. Liu YL, Xiao M, Cheng JW, Xu HP, Xu ZP, Ye S, et al. Moraxella catarrhalis evades host innate immunity via targeting cartilage oligomeric matrix protein. J Immunol. 2007;120:1249-58.

55. Luke NR, Junciscek JA, Bakalez LO, Campagnari AA. Contribution of Moraxella catarrhalis type IV pili to nasopharyngeal colonization and biofilm formation. Infect. Immun. 2007;75:5559-5564.

56. Luke NR, Howlett AJ, Shao J, Campagnari AA. Expression of Type IV Pili by Moraxella catarrhalis Is Essential for Natural Competence and Is Affected by Iron Limitation. Infect Immun. 2004 Nov;72(11):6262-6270.

57. Luke-Marshall NR, Sauberan SL, Campagnari AA. Comparative analyses of the Moraxella catarrhalis
type-IV pilus structural subunit PilA. Gene. 2011;477(1-2):19-23.

58. Masaki H, Qin L, Zhou Z, Onizuka T, Watanabe K, Hu B, et al. A prospective study of intrafamilial transmission and antimicrobial susceptibility of Moraxella catarrhalis. 2011.

59. Mashburn LM, Whiteley M. Membrane vesicles traffic signals and facilitate group activities in a prokaryote. Nature. 2005;437:422-425.

60. McMichael JC, Fiske MJ, Fredenburg RA, Chakravarti DN, VanDerMeid KR, Barniak V, et al. Isolation and characterization of two proteins from Moraxella catarrhalis that bear a common epitope. Infect. Immun. 1998;66:4374-4381.

61. Meier PS, Trollier R, Grivea IN, Syriogiannopoulos GA, Aebi C. The outer membrane proteins UspA1 and UspA2 of Moraxella catarrhalis are highly conserved in nasopharyngeal isolates from young children. Vaccine. 2002;20(13-14):1754-60.

62. Melo LDR, Azevedo NF. New Insights on Biofilm Antimicrobial Strategies. Antibiotics. 2021;10:407.

63. Mirzaei R, Mohammadzadeh R, Sholeh M, Karampoor S, Abdi M, Dogan E, et al. The importance of intracellular bacterial biofilm in infectious diseases; MicroPath. 2020;147:104393.

64. Mitov IG, Gergova RT, Ouzounova-Raykova VV. Distribution of genes encoding virulence factors ompB2, ompCD, ompE, betalactamase and serotype in pathogenic and colonizing strains of Moraxella catarrhalis. Arch Med Res. 2010;41(7):530-5.

65. Mollenkvist A, Nordstrom T, Hallen C, Christensen JJ, Forsgren A, Riesbeck K. The Moraxella catarrhalis immunoglobulin D-binding protein MID has conserved sequences and is regulated by a mechanism corresponding to phase variation. J Bacteriol. 2003;185(7):2285-95.

66. Murphy TF, Brauer AL, Johnson A, Wilding GE, Koszelak Rosenbium M et al. A cation-binding surface protein as a vaccine antigen to prevent Moraxella catarrhalis otitis media and infections in chronic obstructive pulmonary disease. Clin Vaccine Immunol: Epub ahead of print. 2017.

67. Murphy TF, Kirkham C, Johnson A, Brauer AL, Koszelak Rosenbium M et al. Sulfate-binding protein, CysP, is a candidate vaccine antigen of Moraxella catarrhalis. Vaccine. 2016;34:3855-3861.

68. Murphy TF. Studies of the outer membrane proteins of Branhamella catarrhalis. Am. J Med. 1990;88:41S-45S.

69. Murphy TF. Vaccine development for non-typeable Haemophilus influenzae and Moraxella catarrhalis: progress and challenges. Expert Rev Vaccines. 2005;4:843-53.

70. Myers LE, Yang YP, Du RP, Wang Q, Harkness RE, et al. The transferrin binding protein B of Moraxella catarrhalis elicits bactericidal antibodies and is a potential vaccine antigen. Infect Immun. 1998;66:4183-4192.

71. Otsuka T, Kirkham C, Johnson A, Jones MM, Murphy TF. Substrate binding protein SBP2 of a putative ABC transporter as a novel vaccine antigen of Moraxella catarrhalis. Infect Immun. 2014;82:3503-3512.

72. Parameswaran GI, Wrona CT, Murphy TF, Sethi S. Moraxella catarrhalis acquisition, airway inflammation and proteaseantiprotease balance in chronic obstructive pulmonary disease. BMC Infect. Dis. 2009;9:1-10.

73. Pearson MM, Laurence CA, Guinn SE, Hansen EJ. Biofilm formation by Moraxella catarrhalis in vitro: Roles of the UspA1 adhesin and the Hag hemagglutinin. Infect Immun. 2006;74(3):1588-96.

74. Pearson MM, Hansen EJ. Identification of gene products involved in biofilm production by Moraxella catarrhalis ETSU-9 in vitro. Infect. Immun. 2007;75:4316-4325.

75. Pearson MM, Lafontaine ER, Wagner NJ, Joseph W St, Gane III, Hansen EJ. A hag mutant of Moraxella catarrhalis strain O35E is deficient in Hemagglutination, Autoagglutination, and Immunoglobulin D-Binding Activities; Infect Immun. 2002;70(8):4523-4533.

76. Perez AC, Murphy TF. A Moraxella catarrhalis vaccine to protect against otitis media and exacerbations of COPD: An update on current progress and challenges. Hum Vaccin Immunother. 2017;13(10):2322-31.

77. Perez AC, Pang B, King LB, Tan L, Murrah KA, Reimche JL, et al. Residence of Streptococcus pneumoniae and Moraxella catarrhalis within polymicrobial biofilm promotes antibiotic resistance and bacterial persistence in vivo. Pathogens Dis. 2014;70:280-8.

78. Plamondon P, Luke NR, Campagnari AA. Identification of a novel two-partner secretion locus in Moraxella catarrhalis. Infect. Immun. 2007;75:2929-2936.

79. Prashanth H, Saldanha R, Shenoy S. Moraxella catarrhalis—a rediscovered pathogen, International Journal of Biological and Medical Research. 2011;2(4):979-981.

80. Raveendran S, Kumar G, Namachivayam S, Dias M. Moraxella catarrhalis: A Cause of Concern with Emerging Resistance and Presence of BRO Beta-Lactamase Gene—Report from a Tertiary Care Hospital in South IndiaInternational Journal of Microbiology. 2020;2020(4):1-5.

81. Riesbeck K. Complement evasion by the human respiratory tract pathogens Haemophilus influenzae and Moraxella catarrhalis. FEBS Letters. 2020;594:2586-2597.

82. Riesbeck K, Tan TT, Forsgren A. MID and UspA1/A2 of the human respiratory pathogen Moraxella catarrhalis, and interactions with the human host as basis for vaccine development. Acta Biochim. Pol. 2006;53:445-456.

83. Rikitiomi N, Ahmed K, Nagatake T. Moraxella (Branhamella) catarrhalis adherence to human bronchial and oropharyngeal cells: the role of adherence in lower respiratory tract infections. Microbiol. Immunol. 1997;41:487-494.

84. Ruckdeschel EA, Kirkham C, Lesse AJ, Hu Z, Murphy TF. Mining the Moraxella catarrhalis genome: identification of potential vaccine antigens expressed during human infection. Infect Immun. 2008;76:1599-1607.

85. Schaar V, Nordström T, Mörgelin M, Riesbeck K. Moraxella catarrhalis outer membrane vesicles carry β-lactamase and promote survival of Streptococcus pneumoniae and Haemophilus influenzae by
inactivating amoxicillin. Antimicrob. Agents Chemother. 2011;55:3845-3853.
86. Schwingel JM, Edwards K, Cox A, Masoud H. Use of Moraxella catarrhalis Lipooligosaccharide Mutants to Identify Specific Oligosaccharide Epitopes Recognized by Human Serum Antibodies. Infection and Immunity. 2019;77(10):4548-58.
87. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N. Engl. J Med. 2008;359:2355-2365.
88. Shaikh SBU, Ahmed Zafar S, Arsalan A, Shafiq S. Prevalence and resistance pattern of Moraxella catarrhalis in community-acquired lower respiratory tract infections. Infection and Drug Resistance. 2015;8:263-267.
89. Shi W, Wen D, Chen C, Yuan L, Gao W, Tang P, et al. β-Lactamase production and antibiotic susceptibility pattern of Moraxella catarrhalis isolates collected from two county hospitals in China. BMC Microbiology. 2018;18:77.
90. Siegel SJ, Weiser JN. Mechanisms of Bacterial Colonization of the Respiratory Tract. Annual Review of Microbiology. 2015;69:425-444.
91. Silva MD, Sillankorva S. Otitis media pathogens – A life entrapped in biofilm communities. Critical Reviews in Microbiology. 2019;45:5-6.
92. Singh B, Blom AM, Unal C, Nilson B, Mörgelin M, Riesbeck K. Vitronectin binds to the head region of Moraxella catarrhalisubiquitous surface protein A2 and confer complement-inhibitory activity. Molecular Microbiology. 2010;75(6):1426-1444.
93. Singh B, Al-Jubair T, Voraganti C, Andersson T, Mukherjee O, Su YC, et al. Moraxella catarrhalis binds plasminogen to evade host innate immunity. Infect Immun. 2015;83:3458-3469.
94. Slevogt H, Seybold J, Tiwari KN, Hocke AC, Jonatat C, Dietel S, et al. Moraxella catarrhalis is internalized in respiratory epithelial cells by a trigger-like mechanism and initiates a TLR2- and partly NOD1-dependent inflammatory immune response. Cell. Microbiol. 2007;9:694-707.
95. Smith H. The state and future of studies on bacterial pathogenicity. In J. A. Roth, C. A. Bolin, K. A. Brogden, C. Minion, and M. J. Wannemueller (ed.), Virulence of bacterial pathogens, 2nd ed. American Society for Microbiology, Washington, D.C. 1995, 335-357.
96. Smith-Vaughan H, Byun R, Nadkarni M, et al. Measuring nasal bacterial load and its association with otitis media. BMC Ear Nose Throat Disord. 2006;6:10-44. Chapter 3.
97. Spaniol V, Heiniger N, Trollor R, Aebi C. Outer membrane protein UspA1 and lipooligosaccharide are involved in invasion of human epithelial cells by Moraxella catarrhalis. Microbes Infect. 2008;10:3-11.
98. Su Y, Hallström B, Bernhard S, Singh B, Riesbeck K. Impact of sequence diversity in the Moraxella catarrhalis UspA2/UspA2H head domain on vitronectin binding and antigenic variation. Microbes Infect. 2013;15(5):375-87.
99. Tan A, Blakeway LV, Taha YY, Zhou Y, Atack JM, et al. Moraxella catarrhalis phase-variable loci show differences in expression during conditions relevant to disease. PLoS ONE. 2020;15(6):e0234306.
100. Tan TT, Mörgelin M, Forsgren A, Riesbeck K. Haemophilus influenzae survival during complement-mediated attacks is promoted by Moraxella catarrhalis outer membrane vesicles. J Infect. Dis. 2007;195:1661-1670.
101. Tan TT, Forsgren A, Riesbeck K. The respiratory pathogen Moraxella catarrhalis binds to laminin via ubiquitous surface proteins A1 and A2. J Infect Dis. 2006;194:493-497.
102. Tanaka H, Oishi K, Sonoda F, Iwagaki A, Nagatake T, Matsumoto K. Chemical analysis of lipopolysaccharides from respiratory pathogenic Branhamella catarrhalis strains and the role of anti-LPS antibodies in Branhamella respiratory infections. Kansenshogakuzasshi. 1992;66:709-715. (in Japanese)
103. Timpe JM, Holm MM, Vanlerberg SL, Basrur V, Lafontaine ER. Identification of a Moraxella catarrhalis outer membrane protein exhibiting both adhesion and lipolytic activities. Infect. Immun. 2003;71:4341-4350.
104. Verhaegh SJ, Snippe ML, Levy F, Verbrugh HA, Jaddoe VW, Hofman A. Colonization of healthy children by Moraxella catarrhalis is characterized by genotype heterogeneity, virulence gene diversity and cocolonization with Haemophilus influenzae. Microbiology. 2011;157(1):169-78.
105. Verhaegh SJ, Streefland A, Dewnarain JK, Farrell DJ, Van Belkum A, Hays JP. Age-related genotypic and phenotypic differences in Moraxella catarrhalis isolates from children and adults presenting with respiratory disease in 2001–2002. Microbiology. 2008;154:1178-1184.
106. Verhaegh SJC. Epidemiology and Pathogenesis of Moraxella catarrhalis Colonization and Infection. ISBN: 978-94-6169-043-2 © S.J.C. Verhaegh. 2011.
107. Verhaegh SJC, Hays JP. Chapter 80 Moraxella. In: Liu, D. (ed), Molecular Detection of Human Bacterial Pathogens. Taylor & Francis CRC Press, Boca Raton, FL, USA, 2011, 1-9.
108. Vidakovics MLAP, et al. B cell activation by outer membrane vesicles - a novel virulence mechanism. PLoS Pathog. 2010;6:1-19.
109. Walker ES, Neal CL, LaFfan E, Kalbfleisch JH, Berk SL, Levy F. Long-term trends in susceptibility of Moraxella catarrhalis: a population analysis. J Antimicrob. Chemother. 2000;45:175-182.
110. Yamanaka N, Hotomi M, Billal DS. Clinical bacteriology and immunology in acute otitis media in children. J Infect Chemother. 2008;14(3):180-7.
111. Zaleski A, Scheffler NK, Densen P, Lee FK, Campagnari AA, Gibson BW et al. Lipooligosaccharide P(k) (Gal1-4Gal1-4Glc) epitope of Moraxella catarrhalis is a factor in resistance to bactericidal activity mediated by normal human serum. Infect. Immun. 2000;68:5261-5268.