Gram-negative Diplococcal Respiratory Infections

*Nargis Naheed, MD, Maqsood Alam, MD, and Larry I. Lutwick, MD**

Address
*Infectious Diseases, VA New York Harbor Health Care System, 800 Poly Place (IIIE), Brooklyn, NY 11209, USA.
E-mail: larry.lutwick@med.va.gov

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Human respiratory tract infections caused by gram-negative diplococci continue to remain significant issues in health care. Although not addressed as frequently as the classical diplococcal pneumonia, the gram-positive *Streptococcus pneumoniae* (the pneumococcus), infections due to *Neisseria meningitidis* (the meningococcus), and *Moraxella catarrhalis* (formerly called both *Neisseria catarrhalis* and *Branhamella catarrhalis*) are addressed here including their microbiology, respiratory tract manifestations, antimicrobial treatment, and potential prevention with immunization.

Introduction

Respiratory tract infections due to gram-negative diplococci have been well recognized, particularly since the 1918–1919 influenza pandemic. This review discusses the manifestations of the two major players in this arena, *Neisseria meningitidis* and *Moraxella catarrhalis*, the respiratory tract manifestations that they may produce, as well as therapeutic and preventative strategies.

Pneumonia Due to *Neisseria meningitidis* (the Meningococcus)

Neisseria meningitidis is considered to be an uncommon cause of pneumonia but has been recognized as a clinical syndrome for more that 80 years. Meningococcal lobar and bronchopneumonia were well recognized during the 1918–1919 influenza pandemic [1]. In more recent years, case reports of the infection have continued to appear (predominantly in adults and adolescents), confirming that the meningococcus can be a primary lower respiratory pathogen [2–5]. Primary meningococcal pneumonia is defined as pneumonia caused by *N. meningitidis* without the evidence of a pre-existing meningeal focus or previous meningococcemia [6].

Microbiology

Neisseria meningitidis is a gram-negative diplococcus with the adjacent sides flattened to produce the typical biscuit shape. The organism produces a polysaccharide capsule, the basis of the serogroup typing system. On solid media, the meningococcus grows as transparent, nonpigmented, nonhemolytic colonies approximately 1 to 5 mm in diameter. The colonies are convex and, if large amounts of polysaccharide are present, will appear mucoid rather than smooth.

Because it is considered fastidious in its growth conditions, appropriate media and growth conditions are necessary. Optimal meningococcal growth conditions are achieved in a moist environment at 35° C to 37° C under an atmosphere of 5% to 10% carbon dioxide. The organism will grow well on a number of medium bases, including blood agar base, trypticase soy agar, supplemented chocolate agar, and Mueller-Hinton agar.

Confirmation of the presence of this organism in clinical specimens is dependent on a series of carbohydrate fermentations. The meningococcus produces acid from both maltose and glucose without gas formation but not from sucrose or lactose. The shift in pH caused by this reaction has been traditionally used to differentiate meningococci from gonococci that fail to oxidize maltose. In addition, the organism contains cytochrome oxidase in its cell wall. This enzyme will oxidize the dye tetramethylphenylenediamine from colorless to deep pink. This latter test was initially thought to be specific for *Neisseria* species, but subsequent studies have shown that other genera also exhibit high oxidase activities, including *Moraxella*, *Pseudomonas*, and *Aeromonas*. Some of the biochemical characteristics of this group of organisms are shown in Table 1.

Iron appears to be an important factor in meningococcal pathogenicity as iron-loaded animals seem more susceptible to mortality from meningococcal infection [7]. The meningococcus does not produce a soluble siderophore but rather a number of membrane proteins that scavenge for iron from hemoglobin, transferrin, and lactoferrin [8,9].

Virulence factors

A number of constituents of *N. meningitidis* have been identified as important virulence determinants [10••]. The meningococcus exclusively infects humans, and the pathogen has become very adapted to the human host using a variety of virulence factors to adhere to and invade human

Table 1. Some biochemical characteristics of *Neisseria* and some related gram-negative diplococci

Organism	Acid from					Nitrate reduction	Tributyrin hydrolysis
	Glucose	Maltose	Lactose	Sucrose	Fructose		
Neisseria meningitidis	+	+	-	-	-	-	-
Neisseria gonorrhoeae	+	-	-	-	-	-	-
Neisseria lactamica	+	+	+	-	-	-	-
Neisseria cinerae	-	-	-	-	-	-	-
Neisseria subflava	+	+	-	V	V	-	-
Neisseria sicca	+	+	-	+	+	-	-
Moraxella catarrhalis	-	-	-	-	-	+	+

V—variable.

epithelial and endothelial cells as well as sophisticated mechanisms to evade the human immune response. The principal virulence factors that have been identified to date include the following discussed below.

Capsular polysaccharides

Meningococcal capsular polysaccharides are polyanionic, well-hydrated structures that produce a physical barrier around the diplococcus and may also assist in determining access of molecules and ions to the cell outer membrane. As highly charged, hydrophilic structures, the capsules also act as barriers to phagocytosis and complement-mediated lysis. Serogrouping of meningococcal strains into at least 13 serogroups is based on the capsular polysaccharide type. The overwhelming majority of disease worldwide is caused by five serogroups: A, B, C, Y, and W-135. The immunogenicity of the capsule in part appears to be related to the molecular size of the polymers. The capsule of type B meningococcus, made up of a polymer of N-acetylneuraminic acid, however, is poorly immunogenic in humans.

Lipooligosaccharide

The lipooligosaccharide (LOS) of *N. meningitidis* is the analog of the lipopolysaccharide (LPS) of enteric gram-negative bacilli, although there are a number of differences between LOS and LPS structurally [11]. Distinct serotypes of LOS are recognized with differences in invasive potential associated with them. LOS is generally present on gram-negative pathogens (pathogenic *Neisseria*, *Haemophilus*, *Moraxella*, and *Bordetella*) that infect nonenteric surfaces (some *Campylobacter* species are the exception). LOS lacks the repeating O-antigen of the LPS. The lipid A portion of meningococcal LOS is structurally similar to the lipid A of the enterobacterial LPS that is the endotoxin moiety of these organisms.

Pili (fimbriae)

The pili of *N. meningitidis* are attachment organelles that undergo both phase and antigenic variation. The pili of pathogenic *Neisseria* are composed of a pilin subunit that is encoded in the expression locus. Other, incomplete copies of pilin genes are found in silent loci. The genes in the expression and silent loci undergo frequent recombinational events causing an extraordinarily high rate of antigenic variation.

In addition to the principal pilus subunit (pilin or PilE), *N. meningitidis* produces low quantities of a phase-variable PilC that is implicated in pilus biogenesis and pilus-mediated epithelial cell adherence [12,13].

Outer membrane and adhesion proteins

Invasive and colonizing isolates of *N. meningitidis* express one or more of a family of closely related opacity proteins on their outer membranes [14]. Studies have been performed with several variants expressing different Opa proteins (A, B, D) and Opc with the following findings. 1) Opc was the most efficient protein in increasing bacterial interaction with endothelial cells in experiments with mutant nonpiliated strains also deficient in polysaccharide capsule [15]. 2) By contrast, OpaB enhanced attachment to human epithelial cells to the same degree as Opc and also increased bacterial invasion of Chang conjunctival cells compared with Hep2 larynx carcinoma or A549 lung carcinoma cells. Interactions with epithelial cells were inhibited by monoclonal antibody directed at OpaB [15]. 3) Surface sialic acids on capsule and LPS influence attachment and entry. Opc interaction with the proteoglycan receptor was decreased in the presence of sialic acid on the surface of the organism [16]. Opa-mediated interactions were also largely eliminated in mutants expressing capsule or sialylated LPS [15].

Environmental factors controlling capsule and LPS phenotype have been observed to affect the invasiveness of *N. meningitidis* strains. This effect may be based on the ability to downregulate outer membrane protein–mediated binding to cells. Of the five classes of outer membrane proteins, the three porin proteins have been used to developed a typing system in which all meningococci have a class 1 and either class 2 or class 3. The capsular serogroup along with the class 2/3 OMP serotype and class 1 serosubtype together make up the phenotypic designation of a meningococcal strain.

Pathogenesis

The pathogenesis of *N. meningitidis* begins at the human nasopharynx, a mixed epithelial surface containing both

ciliated secretory and nonciliated nonsecretory cells. The airway epithelial surface is covered with a mucus layer through which the meningococcus must penetrate. The penetration mechanism is not clearly understood. After traversing the mucus layer, the meningococcus uses adherence factors to bind to the nonciliated cells. Pili enhance this attachment but are not necessary for it [17], acting as long range attachment organelles that bind to CD46 antigen on the mucosal cell surface.

As the organisms draw closer to the airway epithelial cell, outer membrane surface proteins play a role in attachment and may be important in defining the tissue specificity of the organism. LOS phase variation appears to play a role in the adherence process. Only unencapsulated meningococci enter epithelial cells, and capsular biosynthesis has been shown to stop as the meningococcus enters the epithelial cell [18].

The factors leading to pneumonia after nasopharyngeal colonization are not clearly understood. Possibility of microaspiration of upper respiratory tract secretions containing *N. meningitidis* in particular hosts at risk could lead to the establishment of pathogens in the lower respiratory tract leading to pneumonia.

Epidemiology

The human nasopharynx is the only natural reservoir for the meningococcus. Asymptomatic nasopharyngeal carriage of meningococci is crucial for transmission of the organism as most patients developing meningococcal disease do not have a history of contact with other symptomatic persons. Rates of carriage of this obligate human parasite vary according to the season and are increased under conditions of crowding. Transmission is largely through droplet aerosols [19]. Significantly, nosocomial acquisition of the organism, producing either clinical disease or asymptomatic carriage, has been reported [19–21].

Close physical contact or crowding in closed populations, such as groups of military recruits, is associated with more efficient spread of the organism [4]. Meningococci can be cultured from the nasopharynx of 2% to 15% of healthy individuals during nonepidemic periods, but carriage rates may rise to 20% to 40% among close contacts of persons with meningococcal disease. In closed populations, carriage rates may rise to 75% or more. The incidence of meningococcal disease is highest in late winter and spring, corresponding to the seasonal peak of influenza and other upper respiratory tract infections.

The development of invasive meningococcal disease seems closely related to the recent acquisition of a pathogenic strain by an immunologically susceptible individual. The development of systemic immunity to a particular meningococcal strain appears to develop within 2 weeks of mucosal acquisition [22], but invasive disease such as bacteremia, meningitis, or pneumonia can occur if disease progression occurs prior to the development of bactericidal antibody. It has been observed that, in a stable prevalence setting, the mean duration of carriage appears to be about 21 months [23••]. Invasive disease rarely occurs in individuals with established carrier states.

Neisseria meningitidis is recognized as a cause of sporadic pneumonia but is more frequently linked to epidemic pneumonia in enclosed populations, such as military recruits [4,24]. Five percent to 15% of asymptomatic individuals transiently harbor meningococci in the nasopharynx [25]. Serogroups B, Y, and W-135 are most commonly associated with respiratory disease [24]—serogroup Y [26,27] in particular—but any of the serogroups may cause pneumonia. The estimated annual incidence of sporadic meningococcal pneumonia is 0.4 cases per 100,000 adults [24].

An underlying illness or risk factors were identified in 46% of patients [24]. In adults 50 years of age or older, 81% had at least one chronic underlying illness [24]. There appears to be a bimodal distribution of meningococcal pneumonia showing an average age of patients less than 1 year of age [28•] on one extreme and more than 40 years of age [6,29] on the other extreme.

Clinical presentation

Early cases of meningococcal pneumonia were associated with outbreaks of influenza such as in the epidemic of 1918–1919 [1,30] and have also been observed in more modern outbreaks of influenza as well [31]. Overall, meningococcal pneumonia is not distinguishable from other common types of bacterial pneumonia on the basis of clinical and roentgenographic findings [5,32]. In a review by Winstead *et al.* [28•], documented fever was present in 84% with or without chills, productive cough in 31%, and 23% of patients reported shortness of breath. It should be noted, however, that bronchial infection with the meningococcus without a clear pneumonia can also occur.

Koppes *et al.* [4] reviewed 68 Air Force recruits with group Y meningococcal pneumonia. In this series, a history of cough, chest pain, chills, and previous upper respiratory infection occurred in over half of the patients. Rales and fever occurred in almost all patients, and evidence of pharyngitis was present in more than 80%. The disease involved more than one lobe in 40%, with the right lower and middle lobes involved most frequently. The prognosis was good, with no deaths occurring in the 68 patients with pneumonia. The mortality rate in the Winstead *et al.* review [28•] was 8.6%. Those who died had an average age of 65.6 years in comparison with 47.8 in the survivors.

Laboratory diagnosis

Rates of isolation of the organism from blood, cerebrospinal fluid, and pleural fluid from patients with meningococcal pneumonia are highly variable [4,24]. Diagnosis usually rests on recovering the agent from specimens of sputum or other respiratory tract specimen. The appearance of *Neisseria* in sputum (polymorphonuclear leukocytes with intracellular gram-negative diplococci) is similar

Table 2. Chemoprophylaxis for close contacts of meningococcal disease

Antimicrobial	Age group	Dosing	Duration and route
Rifampin*	Children < 1 month of age	5 mg/kg	q 12 h PO for 2 days
	Children > 1 month of age	10 mg/kg	q 12 h PO for 2 days
	Adults	600 mg	q 12 h PO for 2 days
Ciprofloxacin†	Adults	500 mg	One dose PO
Ceftriaxone	Children < 15 years of age	125 mg	One dose IM
	Adults	250 mg	One dose IM

*Rifampin is not recommended in pregnancy. Additionally, the drug stimulates hepatic metabolism of many drugs such as oral contraceptives and warfarin.
†Ciprofloxacin is not generally used in children less than 18 years of age or during pregnancy or lactation.
IM—intramuscular; PO—oral; q—every.

to that of *Moraxella* pneumonia and, south of the diaphragm, gonococcal urethritis. *Acinetobacter* (and perhaps *Haemophilus*) may be mistaken for meningococcus in purulent sputum but are really more slender coccobacilli rather than biscuit-shaped diplococci.

Because of the infrequent occurrence of meningococcal pneumonia and the significant rate of asymptomatic carriage of the organism, only an adequately screened expectorated sputum sample or respiratory specimen obtained by an invasive procedure provides useful diagnostic information. A specimen that is purulent, contains many intracellular gram-negative diplococci, and yields substantial growth of *N. meningitidis* on culture is highly suggestive of lower respiratory tract infection with the organism.

In the Winstead *et al*. [28•] review, sputum cultures were positive in 83.3% and blood cultures were positive in 79.3% of meningococcal pneumonia cases.

Treatment and prevention

Aqueous penicillin G for 10 days, in daily doses of 4 to 6 million units intravenously, is adequate therapy for adults with meningococcal pneumonia. Coexistence of septicemia or meningitis, however, warrants increasing the dose to 18 to 24 million units per day. In penicillin-allergic patients, an expanded-spectrum cephalosporin such as ceftriaxone is a suitable alternative if used cautiously since most penicillin-allergic patients will tolerate cephalosporins. Otherwise, chloramphenicol may be used and ciprofloxacin (and the other fluorinated quinolones) have good activity. In the Winstead *et al*. [28•] review, 80% of the patients from 1974 through 1990 were treated with penicillin and 80% from 1991 through 1998 with cephalosporins. Isolates with decreased susceptibility to penicillin have been well described [33,34] but are not yet a significant problem in the United States. Resistance to sulfonamide drugs is well known.

Because meningococci can be transmitted from patients with pneumonia to susceptible contacts, respiratory droplet isolation should be implemented during the initial days of treatment [19,20,35]. Antimicrobial chemoprophylaxis of close contacts of persons who have sporadic meningococcal disease is the primary means for prevention of meningococcal disease in the United States [36••]. Chemoprophylaxis with rifampin, 600 mg twice daily for 2 days, is advised for household and other intimate contacts of the patient [36••]. Alternative regimens (Table 2) for prophylaxis include ceftriaxone, 250 mg intramuscularly, or a single oral dose of ciprofloxacin, 500 mg (not recommended in children and pregnant women) [36••]. Recommendations for prophylaxis are based on studies concerning meningitis; however, the epidemiology of meningococcal infections suggests that a similar benefit can be derived by prophylaxis of pneumonia contacts.

The quadrivalent polysaccharide meningococcal vaccine (which protects against serogroups A, C, Y, and W-135) is recommended for control of non-B serogroup meningococcal disease outbreaks and for use among persons in certain high-risk groups. Travelers to countries in which disease is hyperendemic or epidemic may benefit from vaccination. In addition, college freshmen, especially those who live in dormitories, should be educated about meningococcal disease and the vaccine so that they can make an educated decision about vaccination [36••]. Conjugate serogroup C meningococcal vaccines were recently introduced into routine childhood immunization schedules in the United Kingdom. These vaccines should be available in the United States within 2 to 4 years, offering a better tool for control and prevention of meningococcal disease [36••].

Respiratory Tract Infections Due to *Moraxella catarrhalis*

Moraxella catarrhalis is a gram-negative human mucosal pathogen. The bacterium was first described by Ghon and Pfeiffer [37] a century ago. Originally, the organism was thought to be a commensal, classified as *Neisseria catarrhalis* based on phenotypic characteristics and colony morphology [38]. In 1970, DNA hybridization studies failed to show homology between *N. catarrhalis* and the other *Neisseria* species [39] and it was transferred to the new genus *Branhamella*. The name *M. catarrhalis* was subsequently proposed and this is the most widely accepted name at present, although controversy remains unresolved.

Microbiology

Now recognized as a significant upper and lower respiratory tract pathogen, *M. catarrhalis* is a gram-negative diplo-

coccus that can not be distinguished from *Neisseria* species by Gram staining. Colonies display the "hockey puck sign" by sliding along the surface of the agar when pushed. Because samples from the respiratory tract frequently contain nonpathogenic *Neisseria*, suspicious colonies should be tested for the possibility that they are *M. catarrhalis* that produce oxidase, catalase, and DNase [40].

The antigens of *M. catarrhalis* are not as well characterized as the meningococcus. The bacterium is not known to secrete an exotoxin, and while both capsule and fimbriae have been reported [41], there is little information on their characterization. The antigens can be classified by the function served. One set appears to promote adhesion to host tissues and includes the hemagglutinins and ubiquitous surface protein A1 (UspA1). A second set is involved in nutrient acquisition. These include the lactoferrin binding proteins A and B (LbpA and LbpB), the transferrin binding proteins A and B (TbpA and TbpB), the Cd and E porins, and the *catarrhalis* outer membrane protein B (CopB). A third group is composed of antigens involved in virulence and it includes LOS and the ubiquitous surface protein A2 (UspA2) [42].

The two UspA proteins, UspA1 and UspA2, share sequence homology and, at one time, they were thought to be the same protein. The UspA1 protein appears to be an adhesin since strains with mutations in the UspA1 gene lack the capacity to adhere to human epithelial cells [43], and UspA1-specific antibodies block adherence [44]. UspA2 appears to have a role in protecting the bacterium from the host's innate immune response. In comparative studies, the *M. catarrhalis* mutants defective in UspA2 expression are extremely sensitive to killing by normal human serum, whereas the UspA1 mutant was completely resistant [43]. Both proteins elicit bactericidal antibodies in mice and guinea pigs [44].

Lipooligosaccharide represents another prominent bacterial surface component of *M. catarrhalis* similar to other gram-negative human mucosal pathogens. *M. catarrhalis* LOS contains lipid A that is serologically identical and structurally similar to the lipid A expressed by members of the Enterobacteriaceae family [45]. *M. catarrhalis* LOS contains oligosaccharide epitopes that share homology with the LOS of other gram-negative bacteria, including *N. meningitidis*, *Neisseria gonorrhoea*, and *Haemophilus influenzae* [46]. A LOS serologic typing system has been developed for *M. catarrhalis*. Three major LOS serotypes, designated A, B and C, have been identified using hyperimmune rabbit sera [46]. These serotypes encompass 95% of all strains studied to date.

Epidemiology

As with the meningococcus, the natural habitat of *M. catarrhalis* is believed to be exclusively humans [47]. The organism has been isolated from the nasopharynx and pharynx, and occasionally from the conjunctiva and the genital tract. The prevalence of colonization is highly dependent on age. In infancy, colonization of the upper respiratory tract with *M. catarrhalis* is common [48,49]. Faden *et al*. [50] showed that 66% of infants in Buffalo, NY became colonized during the first year of life, with colonization reaching 78% by the age of 2 years. The proportion of older children colonized by *M. catarrhalis* tends to decrease with age [49]. The carriage rate of *M. catarrhalis* was found to be 7% in children 4 to 15 years of age compared with 54% in children 1 to 48 months of age [49].

Nasopharyngeal colonization with *M. catarrhalis* can also be associated with acute or recurrent otitis media [50]. Recurrent otitis media is more common in children colonized with *M. catarrhalis* than with healthy children [50]. Some studies have shown a higher rate of colonization during winter. This high rate may be due to the appearance of respiratory viral illnesses predisposing to secondary bacterial infection during winter months.

In adults, colonization is much less common as only 1% to 5% of healthy adults are colonized with *M. catarrhalis* [48,49]. The data available on colonization rates in the elderly is limited. One study [48] reported a 26.5% rate of colonization in persons older than 60 years. This finding suggests an increase in the carriage rate in the elderly compared with younger adults. The rates of colonization appear to vary with a number of contributing factors including age, health, socioeconomic condition, and geographic location.

Colonization with *M. catarrhalis* appears to be a dynamic process as acquisition of a new strain of *M. catarrhalis* occurs frequently [51] with an average duration of 2.3 months. Similarly, Faden *et al*. [50] showed that in the period from birth to 2 years of age, children frequently lost and acquired new strains of the organism.

Clinical manifestations

Moraxella catarrhalis is one of the more common causes of lower respiratory tract infection in adults, particularly in the setting of chronic obstructive pulmonary disease (COPD). However, the frequent isolation of the organism from healthy individuals and its previous role of a commensal served to delay the acceptance of this organism as a pathogen in this population. Several lines of evidence have established that *M. catarrhalis* may be associated with exacerbations of COPD [52].

Moraxella catarrhalis was found as the predominant organism in Gram stains of sputum in a subset of patients with exacerbation of COPD [53,54]. Treatment with appropriate antimicrobials in patients with suspected *M. catarrhalis* infection resulted in clinical improvement, and the organism can be isolated by transtracheal needle aspiration in chronic bronchitis and patients with clinical evidence of lower respiratory tract infections [53]. The organism has also been isolated from blood and pleural effusion of patients with COPD and pneumonia [53].

The clinical features of COPD exacerbations caused by *M. catarrhalis* are similar to the clinical features of exacer-

bations caused by other bacteria. Patients complain of increased cough and sputum production, increased sputum purulence, and increased dyspnea.

The majority of respiratory isolates come from the elderly population. In one report from Texas [54], 81% of patients with *M. catarrhalis* infections were over 55 years of age. High short-term mortality rate was also found in infections in the older population, with 45% of patients dying within 3 months of developing *M. catarrhalis* pneumonia [54].

About 80% of children experience at least one episode of otitis media by the age of 3 years. *M. catarrhalis* is responsible for approximately 15% of all otitis media cases [55]. Recurrent acute otitis media is also prevalent in young children. Repeated episodes of otitis media may result in hearing loss and are associated with developmental and learning problems in children [56]. The true impact of *M. catarrhalis* respiratory infections becomes apparent when one considers the substantial health costs associated with middle ear disease in the United States. It is estimated that *M. catarrhalis* is responsible for 3 to 4 million cases of otitis media annually [52].

Nosocomial outbreaks of *M. catarrhalis* infections may occur [57]. Most of these nosocomial clusters involved the respiratory tract and have occurred in pulmonary intensive care units [57]. The presence of a susceptible population of adults with underlying cardiopulmonary disease may be important in these outbreaks. Increased acquisition rates of *M. catarrhalis* have been associated with length of hospital stay. The exact mode of transmission is unclear, but contamination of the environment can occur and the organism has been found to survive in sputa for up to 3 weeks, potentially allowing infection of patients from environment [58].

Treatment and prevention

The first β-lactamase-positive clinical isolate was identified in 1977 [59]. The organism produces three novel β-lactamases, BRO-1, BRO-2, and BRO-3. Results from TRUST surveillance program 1999–2000 reported that 93.4% of strains were β-lactamase positive, a prevalence similar to that found in 1998–1999 [60]. Strains possessing BRO-1 manifest greater antibiotic resistance than those expressing BRO-2 [61]. The difference in resistance is thought to be mediated by an increase of BRO-1 rather than a difference in enzyme activity, since BRO-1 expression is two to three times greater than BRO-2 [62].

Despite resistance to the β-lactams, *M. catarrhalis* remains sensitive to the extended-spectrum cephalosporins such as ceftriaxone, fluoroquinolones, macrolides, tetracyclines, amoxicillin-clavulanate, and the fixed combination of trimethoprim and sulfamethoxazole [63]. *M. catarrhalis* is resistant to penicillin, ampicillin, vancomycin, clindamycin, and methicillin.

Vaccine development for *M. catarrhalis* is now moving toward clinical testing. The most likely indication for the first vaccines will be otitis media in young children and respiratory infections of the elderly. The lack of a completely satisfactory animal model or a proven correlate of protection does not allow precise prediction of which *M. catarrhalis* antigen might be superior to another or if a mixture of antigens will be needed to achieve good efficacy in high-risk human populations [42].

Table 3. Other gram-negative diplococci causing lower respiratory infections

Neisseria cinerea
Neisseria gonorrhoeae
Neisseria sicca
Neisseria perflava
Moraxella nonliquefaciens
Veillonella parvula

Other Gram-negative Diplococcal Causes of Pneumonia

In addition to *N. meningitidis* and *M. catarrhalis*, several other gram-negative diplococci have been rarely be associated with human lower respiratory infections. Among the case reports are primarily other members of the same genera above (Table 3).

Conclusions

One current member of the *Neisseria* genus (*N. meningitidis*) and one former member (*M. catarrhalis*) are the organisms that primarily cause gram-negative diplococcal respiratory tract infections. *N. meningitidis*, although best known as the cause of person-to-person transmitted bacterial meningitis, can cause pneumonia and the same criteria for close contact prophylaxis must be kept in mind. *M. catarrhalis* is a reasonably common cause of pneumonia and a frequent cause of childhood otitis. Its production of β-lactamase must be kept in mind in choosing appropriate antimicrobial therapy.

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