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Branhamella catarrhalis: epidemiological and clinical aspects of a human respiratory tract pathogen

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Branhamella catarrhalis is now recognised as an important lower respiratory tract pathogen in humans. The recognition of the bacterium as a human pathogen has been delayed for several reasons: (1) *B catarrhalis* sometimes colonises the upper respiratory tract of children and adults in the absence of infection, so the presence of the bacterium in sputum does not necessarily establish aetiology in an individual; (2) the colony morphology of *B catarrhalis* is indistinguishable from that of commensal *Neisseria* which frequently colonise the human respiratory tract and, as a result, *B catarrhalis* has frequently been overlooked in the clinical microbiology laboratory; (3) *B catarrhalis* causes relatively non-invasive infections and therefore the organism is seldom recovered from normally sterile body fluids such as blood and pleural fluid.

The recognition of *B catarrhalis* as a significant human respiratory tract pathogen has stimulated much interest in clinical and basic research. Knowledge of the epidemiology of infection, the antigenic structure of the bacterial surface, and the immune response to colonisation and infection are expanding rapidly. This review will focus on clinical aspects of *B catarrhalis* lower respiratory tract infection in adults, including epidemiology, clinical manifestations, diagnosis, and treatment.

History and nomenclature

*B catarrhalis* was first described almost a century ago by Ghon and Pfeiffer and was suspected by Sir William Osler to be the cause of his own terminal pneumonic illness in 1919. The organism was subsequently regarded as an upper respiratory tract commensal until the late 1970s. Since then, several lines of evidence have established its importance as a pathogen. The bacterium has undergone several name changes as a result of an uncertain taxonomic relationship between *B catarrhalis* and *Moraxella* and other related genera. The changing and unstable nomenclature of the bacterium has been a frustration for practising physicians and investigators working on the organism. It was first called *Micrococcus catarrhalis* by Ghon and Pfeiffer. The bacterium was subsequently called *Neisseria catarrhalis* because of its similarities in phenotype and ecological niche with *Neisseria* species.

*B catarrhalis* was transferred from *Neisseria* to the new genus, *Branhamella*, in 1970 on the basis of differences in fatty acids content and DNA hybridisation studies compared with other Neisseriaceae. An alternative scheme has *Branhamella* as a subgenus of *Moraxella*. Experimental data to support both schemes exist. The name *Branhamella catarrhalis* is most rational at this time for two reasons: (1) this nomenclature places rod-shaped bacteria (*Moraxella*) and cocci (*Branhamella*) in separate species, and (2) *B catarrhalis* is an important and common human respiratory tract pathogen, whereas *Moraxella* species are unusual human pathogens. Classifying them in separate species emphasises this distinction. The nomenclature of these bacteria continues to be controversial and further changes may occur.

Epidemiology and respiratory tract colonisation

*B catarrhalis* has been recovered exclusively from humans. The bacterium colonises primarily the human respiratory tract although it has occasionally been recovered from the genital tract. Studies from several centres have assessed the prevalence of colonisation of the upper respiratory tract by *B catarrhalis* in various populations. A strong relationship between age and colonisation rates exists.

PREVALENCE OF COLONISATION IN ADULTS

About 1–5% of healthy adults are colonised by *B catarrhalis*. Infants and children are colonised at a higher rate. Adults with chronic lung diseases appear to have a higher rate of respiratory tract colonisation than healthy adults. Several studies have surveyed culture results of sputum samples and examined the clinical status of patients from whom *B catarrhalis* has been isolated and have shown that sputum samples which contain *B catarrhalis* are more likely to be recovered from patients with chronic lung disease than from healthy adults. *B catarrhalis* was recovered...
Branhamella catarrhalis from 28% of patients with bronchiectasis followed prospectively in Birmingham, UK. In a prospective study of patients with chronic bronchitis in Buffalo, New York, B catarrhalis has been recovered from approximately 10% of sputum samples (author’s unpublished observation). These observations suggest that adults with chronic lung disease are colonised with B catarrhalis at a higher rate than healthy adults. However, this comparison has not yet been studied rigorously.

SEASONAL VARIATION
Several studies have revealed an increased incidence of colonisation and infection caused by B catarrhalis during winter months. Restriction endonuclease analysis of genomic DNA from the longitudinally collected strains revealed that children eliminated and acquired new strains of B catarrhalis frequently. Similarly, Klingman et al studied strains of B catarrhalis recovered prospectively from adults with bronchiectasis. Analysis of strains by pulse field gel electrophoresis of large fragments of genomic DNA demonstrated that the mean duration of colonisation by individual strains was only 2.3 months.

These studies in two distinct patient populations indicate that colonisation of the upper respiratory tract by B catarrhalis is a dynamic process with frequent elimination and acquisition of new strains.

DYNAMICS OF COLONISATION
Two prospective studies have examined the dynamics of respiratory tract colonisation by B catarrhalis. Faden et al followed 120 children from birth to two years of age. Restriction endonuclease analysis of genomic DNA from the longitudinally collected strains revealed that children eliminated and acquired new strains of B catarrhalis frequently. Similarly, Klingman et al studied strains of B catarrhalis recovered prospectively from adults with bronchiectasis. Analysis of strains by pulse field gel electrophoresis of large fragments of genomic DNA demonstrated that the mean duration of colonisation by individual strains was only 2.3 months.

Branhamella catarrhalis as a human pathogen
B catarrhalis causes lower respiratory tract infections in adults in three separate but related clinical settings: (1) exacerbations in patients with chronic obstructive pulmonary disease (COPD); (2) pneumonia in the elderly; and (3) more recently it has been recognised as a nosocomial respiratory tract pathogen.

In addition to lower respiratory tract infections in adults, B catarrhalis is the third most common cause of otitis media in infants and children, based on cultures of middle ear fluid obtained by tympanocentesis. It is also a cause of sinusitis in children and adults. Finally, invasive infections are a less common manifestation of infection caused by B catarrhalis.

EXACERBATIONS OF COPD
Non-typeable Haemophilus influenzae and Streptococcus pneumoniae have long been recognised as causes of purulent exacerbations of COPD. More recently, B catarrhalis has been implicated as an aetiological agent in such exacerbations. Five principal lines of evidence implicate B catarrhalis in this setting.

1. Using strict criteria to evaluate the quality of sputum samples, a subset of patients with exacerbations of COPD have sputum smears which show a predominance of Gram negative diplococci on Gram strain and nearly pure cultures of B catarrhalis.

2. Pure cultures of B catarrhalis have been obtained in transtracheal aspirates from patients experiencing exacerbations and pneumonia.

3. Clinical improvement is seen in patients with B catarrhalis infections following the administration of specific antibiotic therapy. Many penicillins are not active against B catarrhalis because most strains produce β-lactamase. Patients with β-lactam positive strains who do not respond to β-lactam antibiotics show clinical improvement following administration of an antibiotic active against B catarrhalis.

4. The organism is occasionally recovered from blood or pleural fluid of patients with evidence of lower respiratory tract infection.

5. Patients with chronic bronchitis who experience exacerbations associated with clinical and laboratory evidence of B catarrhalis infection develop a bactericidal antibody response to the homologous strain. The observation of a specific immune response to the organism following clinical infection provides evidence that the bacterium is the cause of the infection.

Taken together, these five lines of evidence indicate that B catarrhalis causes lower respiratory tract infection in adults, particularly in those with COPD. It is difficult to estimate the proportion of exacerbations that are due to B catarrhalis. However, one study performed in a Veterans Administration facility found that 30% of exacerbations were caused by B catarrhalis.

The clinical manifestations of exacerbations caused by B catarrhalis are similar to those of other bacteria such as non-typeable H influenzae. Exacerbations of COPD are characterised by cough, purulent sputum which is sometimes copious, and shortness of breath. When fever is present, it is usually low grade.

PNEUMONIA IN THE ELDERLY
While it is difficult to state the precise proportion of pneumonia in the elderly caused by B catarrhalis, studies from centres in Europe and the United States indicate that the bacterium causes a significant number of these infections. A prospective study estimated that 10% of community acquired pneumonia in the elderly is caused by B catarrhalis. Based on a review of the literature, the mean age of patients with lower respiratory tract infection due to B
B catarrhalis is 64.8 years. A careful study of carrier rates of B catarrhalis showed that 5.4% of adults under the age of 60 years are colonised with B catarrhalis while 26.5% of adults over the age of 60 years are colonised. These observations all indicate that the elderly are at increased risk of respiratory tract infection due to B catarrhalis compared with younger adults.

Most elderly patients who experience pneumonia due to B catarrhalis have underlying cardiopulmonary disease including COPD, bronchiectasis, congestive heart failure, predisposition to aspiration, and others. Other predisposing conditions associated with infection include corticosteroid therapy, diabetes mellitus, and malignancies. While B catarrhalis pneumonia causes a significant illness in elderly patients, fulminant pneumonia is uncommon. The typical clinical picture is characterised by fever as high as 103°F, cough, purulent sputum, and shortness of breath. Auscultation sometimes reveals signs of consolidation. Chest radiography shows either patchy or lobar alveolar infiltrates. Pleural effusion and empyema are uncommon.

Treatment
About 90% of strains of B catarrhalis produce β-lactamase. The β-lactamase of B catarrhalis is inducible, remains cell associated, is more active against penicillins than cephalosporins, and its activity is inhibited by β-lactamase inhibitors such as clavulanic acid and sulbactam. β-lactamase-producing strains show an inoculum-dependent susceptibility to ampicillin so ampicillin should not be used for β-lactamase-producing strains regardless of the results of susceptibility testing. One study showed persistence of positive middle ear cultures during ampicillin therapy for B catarrhalis otitis media caused by a β-lactamase producing strain. Most B catarrhalis infections can be treated with orally administered antimicrobial agents. Oral agents active against B catarrhalis include trimethoprim-sulfamethoxazole, tetracycline, ciprofloxacin, azithromycin, clari-thromycin, extended spectrum cephalosporins, and the combination of amoxicillin and clavulanic acid. B catarrhalis is also uniformly susceptible to ticarcillin, piperacillin, mezlocillin, azlocillin, most cephalosporins, chloramphenicol, and aminoglycosides. B catarrhalis is resistant to penicillin, ampicillin, vancomycin, clindamycin, and methicillin.

Consideration of the antimicrobial susceptibility pattern of B catarrhalis highlights the central role of the sputum Gram stain in guiding the choice of antibiotic, particularly in the treatment of exacerbations of COPD. Ampicillin and amoxicillin are widely used to treat such exacerbations. However, these agents are inadequate treatment for B catarrhalis infection. It is therefore important to determine whether B catarrhalis is causing the lower respiratory tract infection. Examination of sputum by Gram stain should be performed in patients experiencing exacerbations of COPD, elderly patients with pneumonia, and hospitalised patients with pneumonia. A Gram stained smear of sputum which reveals a predominance of Gram negative diplococci is highly predictive of B catarrhalis as the aetiological agent of the lower respiratory tract infection. In this circumstance an antimicrobial agent which is
effective against *B. catarrhalis* should be administered.


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