

## *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 infection are expanding rapidly.<sup>1</sup> 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<sup>2</sup> and was suspected by Sir William Osler to be the cause of his own terminal pneumonic illness in 1919.<sup>3</sup> 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.<sup>2</sup> 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.<sup>4</sup> An alternative scheme has *Branhamella* as a subgenus of *Moraxella*.<sup>5</sup> Experimental data to support both schemes exist.<sup>6</sup> 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,<sup>7</sup> 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.<sup>8,9</sup> 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*.<sup>10–13</sup> Infants and children are colonised at a higher rate.<sup>10,14–17</sup> 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<sup>11,18,19</sup> 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

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from 28% of patients with bronchiectasis followed prospectively in Birmingham, UK.<sup>20</sup> 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.<sup>11 14 19 21-23</sup> Predisposing viral infection has been proposed as a mechanism for the seasonal variation of *B. catarrhalis* infections but this is unproved.

#### DYNAMICS OF COLONISATION

Two prospective studies have examined the dynamics of respiratory tract colonisation by *B. catarrhalis*.<sup>15 20</sup> Faden *et al*<sup>15</sup> 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*<sup>20</sup> 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.

#### ***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.<sup>1</sup> 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*.<sup>1</sup>

#### 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.<sup>24</sup>

(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 stain and nearly pure cultures of *B. catarrhalis*.<sup>25-29</sup>

(2) Pure cultures of *B. catarrhalis* have been obtained in transtracheal aspirates from patients experiencing exacerbations and pneumonia.<sup>30-34</sup>

(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  $\beta$ -lactamase. Patients with  $\beta$ -lactamase positive strains who do not respond to  $\beta$ -lactam antibiotics show clinical improvement following administration of an antibiotic active against *B. catarrhalis*.<sup>26 29</sup>

(4) The organism is occasionally recovered from blood or pleural fluid of patients with evidence of lower respiratory tract infection.<sup>27 30 35-38</sup> The recovery of the organism from blood or pleural fluid represents definitive evidence for an aetiological role of the organism. Such patients are unusual and represent the most invasive end of the spectrum of disease caused by *B. catarrhalis*.

(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.<sup>25</sup> 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*.<sup>39</sup>

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*.<sup>10</sup> Based on a review of the literature, the mean age of patients with lower respiratory tract infection due to *B.*

*catarrhalis* is 64.8 years.<sup>30</sup> 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.<sup>10</sup> 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.<sup>22 30</sup> 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.<sup>22 23 30 41</sup>

#### NOSOCOMIAL RESPIRATORY TRACT INFECTIONS

Nosocomial outbreaks of *B catarrhalis* infections have been recognised since the mid 1980s.<sup>42-56</sup> Most nosocomial clusters involve respiratory tract infections and several of the reported outbreaks have occurred in respiratory units.<sup>45 49 51 52 54</sup> The presence of a population of patients with underlying cardiopulmonary disease predisposing to *B catarrhalis* undoubtedly contributes to the nosocomial outbreaks. Analysis of strains by various typing methods have indicated that some of the clusters involved infections with several different strains of *B catarrhalis*,<sup>52 53</sup> whereas in other clusters person to person transmission of *B catarrhalis* was implicated.<sup>45 54</sup> It will be important to elucidate the factors responsible for nosocomial clusters so that rational strategies for prevention can be implemented.

#### Diagnosis

When *B catarrhalis* is present in the sputum of a patient with lower respiratory tract infection the organism is generally present in large numbers.<sup>10</sup> A Gram stained sputum sample which shows a predominance of Gram negative diplococci is highly predictive for the presence of *B catarrhalis*.<sup>10 26 30 39 57</sup> Indeed, this is the single most useful diagnostic test in establishing *B catarrhalis* lower respiratory tract infection. The organism tends to resist decolorisation.<sup>58</sup> Characteristic features of the sputum Gram stain are the abundance of leucocytes, the presence of large numbers of Gram negative diplococci as the exclusive bacterial form, and the presence of intracellular bacteria in leucocytes.

Culture of sputum will confirm the presence of *B catarrhalis* in sputum and will allow for antimicrobial susceptibility testing of isolates. A variety of commercially available kits is available to establish the identity of *B catarrhalis* in the laboratory.<sup>59-64</sup>

The detection of bacterial pathogens in sputum by using the polymerase chain reaction (PCR) is increasing in popularity. PCR with primers corresponding to the autolysin gene in *S pneumoniae* is a sensitive and specific method for detecting the bacterium in sputum.<sup>65</sup> A study utilising a PCR-based method for detecting *B catarrhalis* in middle ear fluids indicates that this approach is likely to be feasible in detecting *B catarrhalis* in sputum.<sup>66</sup> The potential advantages of PCR-based methods are increased sensitivity and more rapid identification of the organism. As with all studies involving sputum, the method will be limited by the quality of the sputum sample. Further study in the next several years will elucidate the usefulness of PCR-based methods for the rapid detection of *B catarrhalis* and other bacterial pathogens in sputum.

#### Treatment

About 90% of strains of *B catarrhalis* produce  $\beta$ -lactamase.<sup>67 68</sup> The  $\beta$ -lactamase of *B catarrhalis* is inducible, remains cell associated, is more active against penicillins than cephalosporins, and its activity is inhibited by  $\beta$ -lactamase inhibitors such as clavulanic acid and sulbactam.  $\beta$ -lactamase-producing strains show an inoculum-dependent susceptibility to ampicillin so ampicillin should not be used for  $\beta$ -lactamase-producing strains regardless of the results of susceptibility testing. One study showed persistently positive middle ear cultures during ampicillin therapy for *B catarrhalis* otitis media caused by a  $\beta$ -lactamase producing strain.<sup>14</sup> Most *B catarrhalis* infections can be treated with orally administered antimicrobial agents. Oral agents active against *B catarrhalis* include trimethoprim-sulfamethoxazole, tetracycline, ciprofloxacin, azithromycin, clarithromycin, extended spectrum cephalosporins, and the combination of amoxicillin and clavulanic acid.<sup>67-69</sup> *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.<sup>70 71</sup>

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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