Moraxella catarrhalis: Pathogenic Significance in Respiratory Tract Infections Treated by Community Practitioners

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We prospectively studied the pathogenic significance of Moraxella (Branhamella) catarrhalis isolated from 212 patients of community practitioners in Australia. This organism was most commonly isolated during winter and early spring, and 92% of isolates were β-lactamase producers. On the basis of predetermined clinical and microbiological criteria, 42% of the isolates were definitely pathogenic, 7% were probably pathogenic, 21% were of indeterminate pathogenicity, and 30% were nonpathogenic. Factors associated with pathogenic significance included pneumonia or bronchitis (87% of patients), predisposing respiratory or systemic conditions (62%), isolation from sputum, and pure isolation. Thirty-six percent of patients were <5 years old, but only 9% of isolates from these patients were pathogenic or probably pathogenic, a finding that reflects the fact that nasopharyngeal-aspirate sampling is a common practice. Isolates from older patients were more likely to be pathogenically significant. An assessment of the pathogenic significance of M. catarrhalis isolated from a patient in a community practice should take into consideration factors such as the patient’s age, clinical illness, and underlying conditions; the presence of other organisms; and the source of the isolate.

Moraxella (Branhamella) catarrhalis was once considered a nonpathogenic commensal of the upper respiratory tract (RT). However, over the past 10 years it has gained respect as a potential pathogen [1]. The three clinical conditions most commonly associated with this organism are otitis media (in children), acute bronchitis or pneumonia (in adults with chronic obstructive pulmonary disease), and sinusitis [2]. It can also cause a wide range of RT and systemic infections. The apparent increase in pathogenicity has coincided with an increase in the number of β-lactamase-producing strains. Prior to 1980, <10% of isolates were β-lactamase-positive, while more recent reports suggest a 90% positivity rate [2–4].

M. catarrhalis is also a common colonizing agent of the upper RT. Colonizing rates of 54%–78% have been reported with regard to children [5, 6], whereas significantly lower rates (2%–3%) have been reported for adults [7, 8]. Colonization of the upper RT occurs most commonly in winter [9] and in otitis media–prone children [5]. Investigators using an in vitro oropharyngeal cell assay have shown that adherence of M. catarrhalis to epithelial cells is increased in the winter [10] and in the elderly, especially those with underlying disease [11]. It is likely that colonization and adherence precede and facilitate infection in the upper and lower RT.

We have previously examined the pathogenic significance of isolates of M. catarrhalis recovered from hospitalized patients [3]. We now report on a prospective study of the clinical and epidemiologic characteristics and the pathogenic role of this organism in community practice. Our aim was to identify factors that would assist a clinician in determining the likelihood that isolation of M. catarrhalis from any given patient is clinically significant.

Methods

Our study cohort consisted of consecutive patients from whom M. catarrhalis was isolated, as reported by a single laboratory to community practitioners. Specimens were processed according to the standard laboratory practice appropriate for the specimen type. For this study, only sputum samples of high bacteriologic quality were analyzed. A specimen was considered adequate if it contained <10 epithelial cells and >25 neutrophils per low-power field and if moderate to numerous gram-negative diplococci were seen on the gram stain; a sample was considered appropriate only if it consisted of material from the infected site [12]. All isolates were cultured on either 5% horse blood agar or chocolate agar. They were identified on the basis of typical colonial morphology, gram-stain appearance, oxidase and butyrate esterase positivity, and failure to produce acid from glucose, maltose, sucrose, and lactose [2, 13]. β-lactamase testing
was carried out by means of the standard chromogenic cephalosporin test (Nitrocefin; Oxoid, Melbourne, Victoria, Australia). Antibiotic susceptibilities were determined with use of the disk diffusion method of the National Committee for Clinical Laboratory Standards. M. catarrhalis isolates recovered by a large private pathology service between May 1992 and October 1994 were included in the study. The pathology service’s catchment area includes the Brisbane metropolitan area and most of Southern Queensland and northern New South Wales.

Most of the microbiological investigations carried out were bacterial cultures. This is consistent with the usual practice of community-based doctors, who do not routinely look for evidence of “atypical” organisms such as Chlamydia species.

Information on the age of the patient, date of the specimen, specimen type, microscopic findings, presence of other organisms in culture, β-lactamase production, and susceptibility patterns was collected. The local doctor who initiated the testing was contacted by phone to obtain information about the patient. Symptoms, signs, presumptive diagnosis, results of other tests performed, antibiotic(s) used, and whether the patient was hospitalized were all documented. The local doctor was also questioned about whether the patient’s condition improved with initial treatment or whether administration of a different antibiotic was required.

The following factors were considered the criteria for determining the pathogenic significance of an isolate: (1) positive clinical evidence of infection, consistent with the disease spectrum associated with M. catarrhalis (e.g., a history of recent cough with sputum production, sinusitis, or otitis media); (2) M. catarrhalis as the predominant potential pathogen isolated from an appropriate and adequate specimen; and (3) subsequent clinical response to treatment with an antibiotic to which the isolate was susceptible.

The pathogenicity of M. catarrhalis isolates was considered to be significant if criteria 1, 2, and 3 were present; probably significant if criteria 1 and 2 were present but criterion 3 was unknown (usually because the patient was not seen again by the local doctor and was therefore presumed to be cured or to be feeling better); indeterminate if criterion 1 was present but 2 was not, irrespective of whether 3 was present; and not significant if criterion 1 was not present. In order to minimize subjectivity the data were collated independently by one author (B. J.), and the decision to allocate an isolate to a specific pathogenic category was made independently by another author (G. W.) but was discussed with the third (J. McC.) when any doubt arose. Statistical analysis was carried out by regression analysis and calculation of the standard error of differences of proportions.

Results

Over the 30-month study period, 212 M. catarrhalis isolates were recovered from 212 patients. One hundred and eleven (52%) were from males and 101 (48%) were from females. β-lactamase production was noted in 194 of the 212 isolates (92%). Susceptibility of the isolates to the following commonly tested antibiotics was determined: erythromycin (97%), trimethoprim-sulfamethoxazole (93%), tetracycline (98%), and ceftriaxone (100%).

The 30-month study period included three winters. As expected, submission rates for RT specimens were higher during the winter months than at other times. However, the isolation rates for M. catarrhalis as a percentage of the total number of specimens received by the laboratory were also higher during winter and early spring (figure 1).

With use of the criteria defined above, 90 (42%) of the 212 isolates were judged to be significant; 14 (7%), probably significant; 45 (21%), of indeterminate significance; and 63 (30%), not significant (table 1). A total of 63 patients (61%) among those whose isolates were of significant or probably significant pathogenicity (14 with pneumonia, 45 with bronchitis, and 4 with bronchiectasis) had an underlying predisposing condition, as listed in table 1. Of the 104 patients with significant or probably significant isolates, 91 (87%) had either bronchitis or pneumonia. Hospitalization was a more likely outcome for patients whose isolates were significant or probably significant than for other patients (29/104 [28%] vs. 11/108 [10%; P < .01]). No patient required prolonged hospitalization. Other than patients who had a chronic lung condition such as chronic bronchitis or bronchiectasis, nobody had a chronic or prolonged cough.

Mixed organisms (≥2 isolates) were recovered from 58 of the 212 patients (27%). However, of the 104 patients infected with significant or probably significant organisms, isolates were recovered from a mixed growth for only 19 (18%); in all except two of these, M. catarrhalis was the predominant pathogen. In these two cases M. catarrhalis was grown in equal proportion
Discussion

When a physician receives a report from a microbiology laboratory indicating growth of *M. catarrhalis* from a clinical specimen, it is often unclear what this means and how it should be dealt with. Is the isolated organism colonizing or pathogenic? Is it clinically significant? Should changes in antibiotic therapy be based on this isolation? We attempted to answer these questions with regard to hospitalized patients in an earlier study [3] and now provide some data to assist such decision-making in community practice.

*M. catarrhalis* isolation rates were higher in winter and spring in community practice (figure 1), just as they are in hospital practice [3]. The winter of 1993 was particularly mild in Queensland and northern New South Wales, and the rates of isolation of *M. catarrhalis* were correspondingly lower during this season than during the other two winters. A similar pattern has been observed for almost all RT pathogens in epidemiologic studies. While some of the *M. catarrhalis* isolates may have been associated with RT infections of undetermined cause, there was no particular identifiable outbreak in this part of Australia during the three winter periods studied.

Our study shows that in 49% of patients *M. catarrhalis* can be considered a significant or probably significant pathogen (table 1). Thirty percent of our isolates were not clinically significant, while in 21% of cases it was impossible to decide. In broad terms, therefore, of every 10 isolates, 5 will be pathogens, 3 will be colonizers, and 2 will be of undeterminable pathogenic significance. In our study of hospitalized patients [3], we considered 50% of our isolates to be pathogens and 50% to be commensals; we did not include an indeterminate category. In that study, one-third of the isolates were associated with nosocomial infection and 18% were associated with intubation [3]. Obviously, there were no such conditions in this study of community infections. By far the commonest diagno-

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Table 1. Clinical diagnosis at the time of isolation and clinical (pathogenic) significance of *M. catarrhalis*.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total no. of isolates</th>
<th>Significant</th>
<th>Probably significant</th>
<th>Indeterminate*</th>
<th>Not significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>23*</td>
<td>19</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>82*</td>
<td>60</td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otitis media</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Upper RT infection</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>Viral lower RT infection</td>
<td>5§</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total (%)</td>
<td>212</td>
<td>90 (42)</td>
<td>14 (7)</td>
<td>45 (21)</td>
<td>63 (30)</td>
</tr>
</tbody>
</table>

* Eleven specimens were inadequate; the remainder were inappropriate.

† In 14 (70%) of the 20 cases involving significant or probably significant isolates, infection complicated chronic obstructive pulmonary disease (COPD; 3), asthma (2), cardiac failure (2), prednisone therapy (1), recent surgery (1), lymphoma (1), lung carcinoma (1), or disseminated carcinoma (3).

§ In 45 (63%) of the 71 cases involving significant or probably significant isolates, infection complicated COPD (25), asthma (8), lung carcinoma (2), disseminated carcinoma (2), IgA deficiency (1), aplastic anemia (1), myasthenia gravis (1), systemic lupus (1), lymphoma (1), or chronic lymphocytic leukemia (1).

* All had a positive ELISA for respiratory syncytial virus.

** This patient had mastoiditis.

† These patients had otitis externa (2), impetigo (2), blocked tear duct (1), pertussis (1), heart block (1), esophageal reflux (1), postoperative atelectasis (1), or laryngeal spasm (1).
isolates of Moraxella catarrhalis recovered ($y = 29.2 + 0.79x; r = 0.77$). Only 9% of isolates from children under the age of 5 years were significant or probably significant. For older children and adults the percentages varied between 33% (6–10 years old) and 100% (81–90 years old). The majority of isolates from children were obtained from nasal swab specimens or nasopharyngeal aspirates (81% of those aged <5 years and 50% of those aged 6–10 years).

Figure 2. Regression analysis showed a correlation between patients’ ages and the percentage of significant or probably significant isolates in this study were pneumonia and bronchitis (87% of patients). The hospitalization rate of 27% in this group indicates the potential severity of these infections.

We considered all 48 isolates from patients with upper RT infections to be nonpathogenic. These were patients with “colds,” who had no symptoms or signs suggestive of extension of infection beyond the nose or nasopharynx; the majority of specimens were obtained with nasal swabs. These infections are usually caused by viruses, and the pathogenic role of Moraxella catarrhalis in this setting is doubtful. While viral upper RT infection may facilitate spread of Moraxella catarrhalis further afield in the RT or into the bloodstream, this is probably a rare event and certainly not common enough to warrant antibiotic therapy. Sinus aspiration and tympanocentesis are not commonly carried out in community practice in Australia. The high rate of indeterminate isolates associated with cases of sinusitis (14 of 16) and otitis media (15 of 17) reflects this, and while Moraxella catarrhalis may have been pathogenic in some of these cases, we felt unwilling to designate them as such (table 1).

The majority of our patients (70% with pneumonia and 63% with bronchitis) from whom significant or probably significant isolates were recovered suffered from an underlying pulmonary or systemic condition that predisposed them (to varying degrees) to Moraxella catarrhalis infection (table 1). The presence of these conditions may enhance colonization with and decrease clearance of Moraxella catarrhalis. The factors that facilitate spread of Moraxella catarrhalis rather than other colonizing organisms remain unknown.

In 27% of our patients, Moraxella catarrhalis infection was mixed (i.e., at least one other organism was isolated). It is difficult to decide in these cases if both organisms are pathogenic or if one is a colonizing agent. One organism may promote pathogenicity in the other (e.g., by coadherence) and may inhibit therapeutic responses [14]. It is generally considered likely that if one organism predominates in terms of growth characteristics in the laboratory, then it is more pathogenic, but such a correlation has not been validated. Often the only means of determining relative pathogenicity is the selective use of antimicrobial agents and the monitoring of response, but the information thus provided will always be retrospective. In our study, mixed infections occurred less commonly in patients whose isolates were significant or probably significant (18%) than in those whose isolates were of indeterminate (36%) or nonsignificant (38%) pathogenicity ($P < .01$).

Age was a critical determinant of the pathogenic significance of an isolate of Moraxella catarrhalis (figure 2). Although there was a strong representation of children under the age of 5 years in our study, the isolate was considered to be significant or probably significant in only 9% of these cases. With advancing age the pathogenic significance of the isolates became greater, culminating in 100% significance in the age group of 81–90 years. These data are affected by the greater difficulty in collecting clinically relevant samples from children, the higher colonization rates in children than in adults [5, 6, 7, 8], and the higher incidence of predisposing conditions in adults (table 1). A similar trend (greater pathogenicity with advancing age) was observed in hospitalized patients [3].

It is important when assessing the pathogenic significance of an Moraxella catarrhalis isolate to take account of its origin. Our study shows that sputum was a valuable specimen type, since 77% of isolates from such specimens were significant or probably significant (table 2). Obviously, sinus aspirate, eye-swab,
and blood culture specimens will also usually yield useful information on pathogenic significance, but few such specimens were available in our study. By contrast, nasal swab specimens and nasopharyngeal aspirates, the majority taken from children, were useless in determining the pathogenic implications of \textit{M. catarrhalis} isolates. These samples are generally used for other diagnoses (e.g., respiratory syncytial virus and pertussis infections) but are of no clinical value for diagnosis of \textit{M. catarrhalis} infections.

Our study demonstrates that \textit{M. catarrhalis} is a significant cause of lower RT infections encountered in community practice, especially bronchitis and pneumonia. Isolated organisms are likely to be of pathogenic significance in adults and older children, especially those with underlying RT or systemic conditions. Isolates from sputum are likely to be pathogenic, while those from nasal swab specimens or nasopharyngeal aspirates are not. In children under the age of 5 years and in patients with viral upper RT infections, \textit{M. catarrhalis} is unlikely to be pathogenic. The significance of an isolate of \textit{M. catarrhalis} from patients with sinusitis or otitis media is difficult to determine, unless it is recovered from a specimen obtained directly from a sinus or middle-ear cavity. These guidelines should prove useful to physicians in assessing the significance of \textit{M. catarrhalis} isolated from a patient. In view of the high \(\beta\)-lactamase-positivity rate observed in our study, antibiotics such as penicillin or amoxicillin are not appropriate for treatment if this organism is considered to be the cause of infection.

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