ORIGINAL ARTICLE

Susceptibility of clinical *Moraxella catarrhalis* isolates in British Columbia to six empirically prescribed antibiotic agents

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BACKGROUND: *Moraxella catarrhalis* is a commensal organism of the respiratory tract that has emerged as an important pathogen for a variety of upper and lower respiratory tract infections including otitis media and acute exacerbations of chronic bronchitis. Susceptibility testing of *M catarrhalis* is not routinely performed in most diagnostic laboratories; rather, a comment predicting susceptibility based on the literature is attached to the report. The most recent Canadian report on *M catarrhalis* antimicrobial susceptibility was published in 2003; therefore, a new study at this time was of interest and importance.

OBJECTIVE: To determine the susceptibility of *M catarrhalis* isolates from British Columbia to amoxicillin-clavulanate, doxycycline, clarithromycin, cefuroxime, levofloxacin and trimethoprim-sulfamethoxazole.

METHODS: A total of 117 clinical *M catarrhalis* isolates were isolated and tested from five Interior hospitals and two private laboratory centres in British Columbia between January and December 2012. Antibiotic susceptibility of *M catarrhalis* isolates was characterized using the Etest (E-strip; bioMérieux, USA) according to Clinical Laboratory Standards Institute guidelines.

RESULTS: All isolates were sensitive to amoxicillin-clavulanate, doxycycline, clarithromycin, levofloxacin and trimethoprim-sulfamethoxazole. One isolate was intermediately resistant to cefuroxime, representing a 99.15% sensitivity rate to the cephem agent. Cefuroxime minimum inhibitory concentrations (MICs) inhibiting 50% and 90% of organisms (MIC50 and MIC90) were highest among the antibiotics tested, and the MIC90 (3 µg/mL) of cefuroxime reached the Clinical Laboratory Standards Institute breakpoint of susceptibility.

DISCUSSION: The antibiotic susceptibility of *M catarrhalis* isolates evaluated in the present study largely confirms the findings of previous surveillance studies performed in Canada. Cefuroxime MICs are in the high end of the sensitive range and the MIC50 and MIC90 observed in the present study are the highest ever reported in Canada.

CONCLUSION: Although cefuroxime MICs in *M catarrhalis* are high, all agents tested showed antimicrobial activity, supporting their continued therapeutic and empirical use.

Key Words: *Amoxicillin-clavulanate; Antibiotic resistance; British Columbia; Cefuroxime; Clarithromycin; Doxycycline; Levofloxacin;* Moraxella catarrhalis; *Regional Hospital; TMP/SMX*

La susceptibilité des isolats cliniques de *Moraxella catarrhalis* à six antibiotiques prescrits de manière empirique en Colombie-Britannique

HISTORIQUE : Le *Moraxella catarrhalis* est un organisme commensal des voies respiratoires, qui se révèle un pathogène important dans diverses infections des voies respiratoires supérieures et inférieures, y compris l'otite moyenne et les exacerbations aiguës de la bronchite chronique. Dans la plupart des laboratoires diagnostiques, les tests de susceptibilité au M *catarrhalis* ne sont pas effectués systématiquement. Un commentaire en prédisant la susceptibilité d'après les publications est joint au rapport. Le dernier rapport canadien sur la susceptibilité du M *catarrhalis* aux antimicrobiens a été publié en 2003. Il est donc judicieux et important de publier une nouvelle étude à ce sujet.

OBJECTIF : Déterminer la susceptibilité des isolats de M *catarrhalis* provenant de la Colombie-Britannique à l'amoxicilline-clavulanate, à la doxycycline, à la clarithromycine, à la céfuroxime, à la lévofloxacine et au triméthoprime-sulfaméthoxazole.

MÉTHODOLOGIE : Au total, 117 isolats cliniques de M *catarrhalis* provenant de cinq hôpitaux de l'intérieur et de deux laboratoires privés de la Colombie-Britannique ont été prélevés et examinés entre janvier et décembre 2012. Les chercheurs ont caractérisé la susceptibilité aux antibiotiques des isolats de M *catarrhalis* au moyen de l'Etest (E-strip; bioMérieux, États-Unis), conformément aux lignes directrices du *Clinical Laboratory Standards Institute*.

RÉSULTATS : Tous les isolats étaient sensibles à l'amoxicilline-clavulanate, à la doxycycline, à la clarithromycine, à la lévofloxacine et au triméthoprime-sulfaméthoxazole. Un isolat était moyennement résistant à la céfuroxime, représentant un taux de sensibilité de 99,15 % à l'agent céphème. Les concentrations minimales inhibitrices (CMI) de la céfuroxime inhibant 50 % et 90 % des organismes (CMI50 et CMI90) étaient les plus élevées des antibiotiques à l'étude, et la CMI90 (3 µg/mL) de la céfuroxime atteignait le seuil de susceptibilité du *Clinical Laboratory Standards Institute*.

EXPOSÉ : La susceptibilité des isolats de M *catarrhalis* aux antibiotiques évalués dans la présente étude confirme largement les observations tirées d'études de surveillance antérieures effectuées au Canada. Les CMI de la céfuroxime se situent dans la plage supérieure de sensibilité. De plus, la CMI50 et la CMI90 observées dans la présente étude sont les plus élevées jamais déclarées au Canada.

CONCLUSION : Même si les CMI de la céfuroxime dans les isolats de M *catarrhalis* sont élevées, tous les agents étudiés présentaient une activité antimicrobienne, ce qui appuie la poursuite de leur utilisation dans un cadre thérapeutique et empirique.

Moraxella catarrhalis is a Gram-negative aerobic proteobacteria and a commensal of the respiratory tract that has emerged as an important pathogen for a variety of community-acquired respiratory tract infections (1,2). Such infections frequently affect children, commonly manifest as otitis media and are frequently the cause of acute exacerbations of chronic bronchitis in the elderly population

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TABLE 1
Minimum inhibitory concentration (MIC) distributions and antibiotic susceptibility of *Moraxella catarrhalis* (n=117) according to Clinical Laboratory Standards Institute breakpoints*

	MIC, µg/mL			Susceptibility category, %		
Antibiotic	Range	MIC50	MIC90	Susceptible	Intermediate	Resistant
Amoxicillin-clavulanate	0.016–0.38	0.125	0.25	100	0	0
Doxycycline	0.094–0.38	0.19	0.38	100	0	0
Clarithromycin	0.047–0.75	0.25	0.38	100	0	0
Cefuroxime	0.125–8	1.5	3	99.15	0.85	0
Levofloxacin	0.023–0.75	0.032	0.047	100	0	0
TMP/SMX	0.064–4	0.25	0.5	100	0	0

**The actual MIC values obtained are reported here. These values were converted using the doubling-dilution interpretation to use Clinical Laboratory Standards Institute breakpoints for susceptible, intermediate and resistant categorizations. MIC50 MIC inhibiting 50% of organisms; MIC90 MIC inhibiting 90% of organisms; TMP/SMX Trimethoprim-sulfamethoxazole*

(especially in men) (3). M *catarrhalis* has also been shown to be an important etiological agent of sinusitis and conjunctivitis and, more rarely, has been implicated in pneumonia, bacteremia/septicemia and meningitis (1).

Unfortunately, most strains of M *catarrhalis* are now capable of producing the enzyme β-lactamase, rendering antibiotics such as penicillin and its available analogues ineffective (1,3). This concern necessitates the use of other agents such as those currently in use and those evaluated in the present study: amoxicillin-clavulanate, doxycycline, clarithromycin, cefuroxime, levofloxacin and trimethoprim-sulfamethoxazole (TMP/SMX). Recently, however, this pathogen has shown resistance to some of these agents. In Taiwan, resistance rates of 18.5% and 19.8% were found for TMP/SMX and tetracycline, respectively (4). Similarly, 18.4% of M *catarrhalis* were found to be resistant to TMP/SMX in Turkey (5). In mainland China, a 5.8% resistance rate was found for clarithromycin (6), and an 11.3% resistance rate was observed for the standard dose of amoxicillin-clavulanate in the United States (7). The most recent surveillance study in Canada, however, was nearly 10 years ago, when Zhanel et al (2) evaluated each of the six antibiotics (and more) included in the present study. They observed some development of M *catarrhalis* resistance (ie, a 1.5% resistance rate to TMP/SMX).

The present surveillance study was intended to evaluate the current state of M *catarrhalis* resistance in British Columbia, as well as to help contribute to a body of knowledge clinicians in our province may use to make better decisions when formulating antibiotic therapies for *Moraxella* infections. It is of critical importance that the resistance patterns of this pathogen be monitored because many laboratories do not perform susceptibility testing, but instead include a comment indicating drugs of choice for treatment.

METHODS

A total of 117 M *catarrhalis* isolates were collected at five Interior hospitals and two private laboratory centres in British Columbia. Of the 117 isolates, 59 were collected between January and December 2012 from five regional Interior hospitals including Royal Inland Hospital (Kamloops), Kelowna General Hospital (Kelowna), Vernon Jubilee Hospital (Vernon), Penticton Regional Hospital (Penticton) and East Kootenay Regional Hospital (Cranbrook). A private laboratory in the Lower Mainland also collected 77 isolates between October and December 2012, of which 58 were tested. The private laboratory collected isolates from Vancouver, Surrey, Richmond, North Vancouver, White Rock, Delta, Port Coquitlam, Langley, Tsawwassen, Cloverdale and New Westminster. The Lower Mainland laboratory also collected three isolates from Prince George in Northern British Columbia, bringing the total number of isolates tested to 117. M *catarrhalis* isolates were obtained predominantly from sputum specimens, and from eye and ear swabs. More than 90% of the private laboratory specimens were from these three sites, and hospital laboratory site sources were similar, with lower respiratory tract specimens predominating. One hospital isolate was isolated from the blood culture; to the authors' knowledge, this was the only invasive isolate. Identification of the organism was performed by the commonly used Gram stain, oxidase reaction and butyrate esterase detection test.

Antibiotic susceptibility of M *catarrhalis* isolates was characterized using the Etest (E-strip, BioMérieux Inc, USA) according to Clinical Laboratory Standards Institute (CLSI) guidelines. Each isolate was subcultured twice on 5% sheep blood Tryptone Soya Agar (Oxoid, Canada). The second subculture (16 h to 18 h) was then used to inoculate 5 mL of normal saline in a test tube using a sterile swab. Turbidity comparisons were performed visually with a 0.5 McFarland standard. The absorbance at 625 nm was then obtained using a spectrophotometer and inoculations were adjusted until an absorbance of between 0.08 and 0.1 was reached. A new sterile swab was then used to streak a 150 mm 5% sheep blood Mueller Hinton plate for confluent growth using the standardized inoculum. This test plate was allowed to dry before six antibiotic E-strips were placed radially on the plate using sterile forceps: amoxicillin-clavulanate, doxycycline, clarithromycin, cefuroxime, levofloxacin and TMP/SMX. All subculturing and testing of M *catarrhalis* isolates was performed at 35°C in 5% CO_2. Testing plates were incubated for 20 h to 24 h before minimum inhibitory concentrations (MICs) were read. Any isolates showing resistance were tested again and reidentified using Gram stain, oxidase reaction, butyrate esterase detection test and matrix-assisted laser desorption/ionization/time-of-flight analysis.

Positive controls were also implemented in accordance with CLSI guidelines: *Staphylococcus aureus* ATCC 29213 was used as a control for doxycycline, clarithromycin, cefuroxime, levofloxacin and TMP/SMX, and *Escherichia coli* ATCC 35218 was used as an amoxicillin-clavulanate control. Subculturing and inoculum standardization was identical to that of the M *catarrhalis* isolates; however, testing of control organisms was performed on unsupplemented 100 mm Mueller Hinton plates at 35°C under an ambient atmosphere. MIC readings were similarly performed within 20 h to 24 h of incubation. No control MIC values were outside of the CLSI acceptable range.

Interpretations of 'susceptible' (S), 'intermediately susceptible' (I) and 'resistant' (R) were performed using the M45 2008 CLSI standards document (8).

RESULTS

E-strip susceptibility testing of M *catarrhalis* to amoxicillin-clavulanate, doxycycline, clarithromycin, cefuroxime, levofloxacin and TMP/SMX yielded important results for clinicians (Table 1). All 117 M *catarrhalis* isolates tested were sensitive to amoxicillin-clavulanate, doxycycline, clarithromycin, levofloxacin and TMP/SMX; however, one isolate from Royal Inland Hospital was intermediately resistant to cefuroxime. This isolate demonstrated a cefuroxime MIC of 8 µg/mL, contributing to a 99.15% susceptibility rate to this cephem agent. Additionally, the MICs inhibiting 50% and 90% of organisms (MIC50 and MIC90) for cefuroxime were the highest of all antibiotics within the M *catarrhalis* samples tested. The cefuroxime MIC90 was at the sensitive breakpoint of ≤4 µg/mL for the antibiotic (3 µg/mL is treated as 4 µg/mL using doubling-dilution interpretation). Unlike previous Canadian studies (2,12,13) all TMP/SMX MICs were in the susceptible range and the MIC

TABLE 2
Comparing minimum inhibitory concentration inhibiting 50% and 90% of organisms (MIC 50 and MIC90) values between isolates collected from the Interior and Lower Mainland regions of British Columbia*

	Interior (n=63)		Lower Mainland (n=51)	
Antibiotic	**MIC50, µg/mL**	**MIC90, µg/mL**	**MIC50, µg/mL**	**MIC90, µg/mL**
Amoxicillin-clavulanate	0.125	0.25	0.125	0.25
Doxycycline	0.25	0.38	0.19	0.25
Clarithromycin	0.25	0.38	0.25	0.38
Cefuroxime	1.5	3	1.5	2
Levofloxacin	0.032	0.047	0.032	0.047
TMP/SMX	0.25	0.5	0.25	0.5

**This comparison does not include the three isolates from Northern British Columbia that are included in Table 1 results. The actual MIC values obtained are reported here. TMP/SMX Trimethoprim-sulfamethoxazole*

TABLE 3
Comparison of Canadian *Moraxella catarrhalis* susceptibility studies to date, including the present study

				Antibiotic					
Author (reference), year	**Method**	**Isolates, n**	**MIC, µg/mL**	**Amoxicillin-clavulanate**	**Doxycycline**	**Clarithromycin**	**Cefuroxime**	**Levofloxacin**	**TMP/SMX**
Blondeau et al (14), 1999*	Etest	64	MIC50	–	–	0.125	1.5	–	–
			MIC90	–	–	0.25	2.0	–	–
			Range	–	–	≤0.016–0.5	0.5–4.0	–	–
			Susceptibility, %	–	–	100	100	–	–
Zhanel et al (13), 2000†	Broth microdilution	428	MIC50	≤0.25/0.12	0.5	≤0.12	1	0.06	0.25/4.8
			MIC90	≤0.25/0.12	1	≤0.12	2	0.06	1/19
			Range	≤0.25/0.12–1/0.5	≤0.25–16	≤0.12–0.5	≤0.5–16	≤0.03–0.5	≤0.12/2.4–>16/304
			Susceptibility, %	100	99.3	100	99.3	100	84.3
Blondeau et al (12), 2001*†	Etest	178	MIC50	0.094	0.38	0.094	1	–	0.19
			MIC90	0.19	0.75	0.19	2	–	0.5
			Range	≤0.016–0.38	0.032–1.5	≤0.016–0.38	0.19–8	–	0.032–8
			Susceptibility, %	100	100	100	99.4	–	99.5
Zhanel et al (2), 2003	Broth microdilution	2314	MIC50	0.25/0.12	≤0.25	0.06	1	≤0.03	0.25/4.5
			MIC90	0.5/0.25	0.5	0.12	2	0.06	0.5/9.0
			Range	≤0.03–2	≤0.25–16	≤0.06–2	≤0.25–≥8	≤0.03–1	≤0.12/2.4–≥16/304
			Susceptibility, %	100	99.7	100	99.2	100	97.5
Present study	Etest	117	MIC50	0.125	0.19	0.25	1.5	0.032	0.25
			MIC90	0.25	0.38	0.38	3	0.047	0.5
			Range	0.016–0.38	0.094–0.38	0.047–0.75	0.125–8	0.023–0.75	0.064–4
			Susceptibility, %	100	100	100	99.15	100	100

**Used β-lactamase-positive isolates and Etest (BioMérieux Inc, USA) results; †Tetracycline was tested and reported in the study. MIC50 Minimum inhibitory concentration (MIC) inhibiting 50% of organisms; MIC90 MIC inhibiting 90% of organisms; TMP/SMX Trimethoprim-sulfamethoxazole*

range was lower for TMP/SMX (Table 2). The MICs of the invasive isolate were amoxicillin-clavulanate 0.25 µg/mL, doxycycline 0.125 µg/mL, clarithromycin 0.25 µg/mL, cefuroxime 2 µg/mL, levofoxacline 0.047 µg/mL and TMP/SMX 0.38 µg/mL. These values were near the MIC50 values for all of the antibiotics.

DISCUSSION

M catarrhalis has emerged as an important respiratory pathogen in recent years. The organism is almost universally capable of producing β-lactamase, with previous studies reporting production in >90% of isolates (1,3). Penicillin/β-lactamase inhibitor combinations, such as amoxicillin-clavulanate, have, therefore, been used as an alternative treatment for *M catarrhalis* infections. Other antibiotic agents, such as clarithromycin, levofloxacin, doxycycline, cefuroxime and TMP/SMX, have also been used empirically to treat *M catarrhalis* infections in Canada and throughout the world with apparent success; however, the threat of antibiotic resistance must keep the clinical community vigilant. The present surveillance study of clinical isolates in British Columbia aimed to evaluate the susceptibility of *M catarrhalis* to these commonly used agents in the hopes of aiding clinicians in developing effective antibiotic therapies for *M catarrhalis* infections while monitoring the integrity of their use for future applications.

As expected, all isolates showed susceptibility to amoxicillin/clavulanate, clarithromycin and levofloxacin, which is consistent with the most current Canadian research (Table 3) and most international research (4,6,7,9-11). Complete sensitivity of all isolates to doxycycline and TMP/SMX was also observed, despite Canada-wide (2,12,13) (Table 3) and international studies (4,5,9,11) showing some resistance. The cefuroxime susceptibility (99.15%) determined in the present study was similar to that observed in previous Canadian studies (2,12,13) and in studies performed abroad such as in Taiwan (98.7%) (4) and the USA (98.4%) (7).

The results of the present study also revealed that the cefuroxime MIC90 (n=117) was at the sensitive breakpoint of ≤4 µg/mL. No significant difference was observed when MIC values from Lower Mainland isolates were compared with those from the Interior (Table 2). When compared with the cefuroxime MIC distribution results in the Canadian literature, the MIC90 reported here (3 µg/mL) is slightly higher than any reported cefuroxime MIC90 (Table 3). The cefuroxime MIC50 of 1.5 µg/mL is also higher than the three most recent Canadian studies (Table 3). The MIC range (0.125 µg/mL to

8 µg/mL), however, is similar to that of the other Canadian studies (Table 3). The MIC range for TMP/SMX in our study was lower than in previous Canadian studies (Table 3) and no resistant isolates were found.

Although the sensitivity of tested M *catarrhalis* isolates to clarithromycin in Canada was confirmed, the MIC50 and MIC90 observed in the present study were the highest reported in the country (Table 3). Conversely, the doxycycline MIC50 and MIC90 found here were the lowest among reported values in Canada, and the distribution range was also comparably lower and narrower than previously reported (Table 2). Amoxicillin-clavulanate MIC50 and MIC90 were higher than those found in the most recent Canadian study using the Etest method (12) (although not higher than the most recent available study that used broth microdilution); however, the MIC range matched that found by Blondeau et al (12) in 2001 (Table 3).

Before the present study, previous susceptibility testing of M *catarrhalis* to levofloxacin in Canada had only been performed via broth microdilution (2,13). In addition to confirming susceptibility to this antibiotic, the present study also found that the MIC50, MIC90 and MIC range obtained here largely matches previous findings (using the doubling-dilution interpretation).

Overall, the results from the present surveillance study yield encouraging results for clinicians and diagnostic laboratories. The antimicrobial activities of the six agents tested in the present study support their continued therapeutic and empirical use to treat M *catarrhalis* infections. The high MIC values of M *catarrhalis* versus cefuroxime observed in the present study and other studies warrants continue further monitoring.

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