Macrolide and Tetracycline Resistance in *Moraxella catarrhalis* Isolates from 2009-2011 is Higher in the Asia-Pacific Region than in Other Regions of the World

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Amended Abstract

Objective: To evaluate the activity of macrolides and other agents against *Moraxella catarrhalis* by geographic region for isolates from 2009-2011. *M. catarrhalis* are generally susceptible to most agents except penicillins due to the production of β-lactamases. Resistance (R) to tetracycline (TET), cephalosporins, and macrolides is generally <1% in most regions of the world.

Methods: Susceptibility (S) testing for *M. catarrhalis* was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology on isolates from 2009-2011 from medical centers in the SENTRY Antimicrobial Surveillance Program platform in the European Union (EU), United States (USA), Latin America (LA), and Asia-Pacific region (APAC). S interpretations were performed using CLSI guidelines (Clarithromycin [CLR], S ≤2 mg/L; TET, S ≤2 mg/L; trimethoprim/sulfamethoxazole [TMP/SXT], S ≤0.5 mg/L).

Results: In the EU, there were more than 400 isolates and none were R to CLR or TET. In the USA there was 1 (0.1%) isolate R to CLR and 1 (0.1%) R to TET. In LA, no isolate was CLR- or TET- (0/70) R. However in the APAC region 13 of 172 (7.6%) isolates were CLR-R and 8 of 251 (3.2%) were TET-R. 12 of 13 of the CLR-R and 7 of 8 of the TET-R isolates were from China. 5.8% of the isolates in APAC had telithromycin MIC values ≥2 mg/L (isolates were from China and Korea). TMP/SXT-R ranged from 5.1% in the US and EU to 6.0 and 7.1% in APAC and LA, respectively. β-lactamase production ranged from 97.1% (EU) to 98.6% (LA). 10.4% (APAC) to 15.7 % (LA) of the isolates had cefepime MIC values ≥2 mg/L. In APAC 2.8% of MIC values for ciprofloxacin were ≥0.5 mg/L.

Conclusions: Macrolide and tetracycline R in *M. catarrhalis* for isolates from the period 2009-2011 was ≤0.2% in NA and EU. In the APAC region, CLR-R and TET-R were significantly elevated (3.2-7.6% R). The higher rate in the APAC region was primarily due to isolates from multiple sites in China. TMP/SXT-R occurred in all regions ranging from 5.1 to 7.1%.

Introduction

Moraxella catarrhalis is exclusively a human pathogen that resides in the respiratory tract. *M. catarrhalis* is a common cause of otitis media in children where it may be responsible for 15-20% of episodes, exacerbations of chronic obstructive pulmonary disease where it may be responsible for about 10% of cases, sinusitis where it may be responsible for about 20% of cases in children, and pneumonia where it occurs infrequently in the elderly and in children.

M. catarrhalis is typically very susceptible to most antimicrobial agents, however, it is frequently resistant (>90%) to ampicillin due to the production of β-lactamase (typically BRO-1 or BRO-2). Most *M. catarrhalis* infections can be treated by oral agents such as amoxicillin/clavulanate, extended spectrum cephalosporins, macrolides, trimethoprim/sulfamethoxazole, tetracyclines, and fluoroquinolones. Resistance to tetracycline, cephalosporins, and macrolides is generally <1% in most regions of the world. In this study, we evaluated the activity of macrolides and other agents against *M. catarrhalis* in North America, Europe, Latin America, and the Asia-Pacific region for isolates collected in 2009-2011.

Materials and Methods

Bacterial isolates: A total of 1,656 clinical isolates of *M. catarrhalis* were collected during 2009-2011 from >100 medical centers located in the United States (USA) and three other geographic regions. The collection of clinical isolates consisted of 470 isolates from the European Union (EU), 865 from the USA, 251 from Asia-Pacific (APAC) and 70 from Latin America (LA).

Susceptibility testing: Susceptibility testing was performed by reference broth microdilution method per Clinical and Laboratory Standards Institute (CLSI; M45-A2; 2010) using validated dry-form panels produced by ThermoFisher Scientific Inc, formerly TREK Diagnostics (Cleveland, Ohio, USA). The medium used was cation-adjusted Mueller-Hinton broth. Interpretive breakpoint criteria were those published in CLSI (M45-A2; 2010) and EUCAST (2012). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M45-A2; 2010) quality control (QC) strains: *S. aureus* ATCC 29213 and *E. coli* ATCC 35218. Susceptibility testing as described above was performed by JMI Laboratories (North Liberty, Iowa, USA) using current CLSI (M07-A9; 2012) and Good Laboratory Practice (GLP) quality assurance practices.

Results

- β-lactamase production ranged from 97.1 (USA) to 98.6% (LA and APAC). 10.4 (APAC) to 15.7% (LA) of the isolates had cefepime MIC values at ≥2 mg/L.
- The MIC distributions and cumulative frequencies for clarithromycin, tetracycline, trimethoprim/sulfamethoxazole, and ciprofloxacin for β-lactamase-positive and -negative *M. catarrhalis* are found in Table 1. For clarithromycin, there were 14 isolates with MIC values at ≥2 mg/L. For ciprofloxacin and trimethoprim/sulfamethoxazole, there were one and 51 isolates, respectively, with MIC values ≥2 mg/L. For tetracycline, there were nine isolates with MIC values at ≥8 mg/L.
- In the EU, all 470 isolates were susceptible to clarithromycin, erythromycin, or tetracycline when applying CLSI interpretive criteria (Table 2); however, when applying EUCAST interpretive criteria, three (0.6%), 19 (4.0%), and three (0.2%) isolates were non-susceptible, respectively (Table 2). There was only one isolate (MIC, >4 mg/L) that was non-susceptible to ciprofloxacin when applying either CLSI or EUCAST interpretive criteria (Table 2).
- There were 865 isolates obtained from the USA (Table 2). Applying CLSI interpretive criteria, only one (0.1%) isolate was non-susceptible to clarithromycin, two (0.2%) isolates were non-susceptible to erythromycin, and one (0.1%) isolate was non-susceptible to tetracycline (Table 2). When applying EUCAST criteria, 0.8% of isolates were non-susceptible to clarithromycin, 7.0% were non-susceptible to erythromycin, and one (0.1%) isolate was non-susceptible to tetracycline (Table 2).
- In LA, no isolate was resistant to clarithromycin, erythromycin, tetracycline, or ciprofloxacin when applying CLSI interpretive criteria (Table 2). But when applying EUCAST criteria, one (1.4%) organism was non-susceptible to clarithromycin, and 4.8% were non-susceptible to erythromycin (Table 2).
- In the APAC region, 7.6/3.5% of isolates were non-susceptible to clarithromycin/erythromycin by CLSI interpretive criteria (Table 2). Also 9.9 and 21.3%, respectively, were non-susceptible when applying EUCAST criteria (Table 2). For tetracycline, 3.2 and 3.6% of isolates were non-susceptible to tetracycline when applying CLSI and EUCAST interpretive criteria, respectively (Table 2).
  1. All but one of the clarithromycin non-susceptible (12/13) and tetracycline non-susceptible (7/8) isolates from APAC were from China.
  2. 10.5% of the isolates in APAC were non-susceptible to telithromycin (EUCAST interpretive criteria; see Table 2).
- 5.1% of the isolates in the USA and EU and 6.0 and 7.1% in APAC and LA, respectively, were non-susceptible to trimethoprim/sulfamethoxazole (Table 2).

Conclusions

- Macrolide and tetracycline resistance in *M. catarrhalis* for isolates from the period 2009-2011 were low in the USA and EU (≤0.2%, CLSI interpretive criteria).
- Macrolide and tetracycline non-susceptibility was higher in the APAC region. Macrolide susceptibility ranged from a low of 78.7% (erythromycin, EUCAST criteria) to 96.5% (erythromycin; CLSI and EUCAST criteria). From 3.2 to 3.6% of isolates (CLSI and EUCAST criteria, respectively) were non-susceptible to tetracycline.
- The higher rate in the APAC region was primarily due to isolates from multiple medical centers in China.

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Table 1. MIC distribution and cumulative frequency for select agents for *M. catarrhalis* (2009-2011).

	MIC in mg/L (cum. % inhibited)					
Antimicrobial (no. tested)	≤0.25	0.5	1	2	4	≥8
Clarithromycin[a] (1,531)	1,503 (98.2)	13 (99.0)	1 (99.1)	2 (99.2)	2 (99.4)	10 (100.0)
Clarithromycin[b] (41)	41 (100.0)	-	-	-	-	-
Tetracycline[a] (1,612)	999 (62.0)	151 (71.3)	4 (71.6)	449[c] (99.4)	0 (99.4)	9 (100.0)
Tetracycline[b] (43)	25 (58.1)	4 (67.4)	0 (67.4)	14[c] (100.0)	-	-
Trimethoprim/sulfamethoxazole[a] (1,613)	-	1,525[d] (94.5)	37 (96.8)	25 (98.4)	22[e] (99.8)	4 (100.0)
Trimethoprim/sulfamethoxazole[b] (43)	-	43[d] (100.0)	-	-	-	-
Ciprofloxacin[a] (1,613)	-	1,605[d] (99.5)	7 (99.9)	-	-	1 (100.0)
Ciprofloxacin[b] (43)	-	42[d] (97.7)	1 (100.0)	-	-	-

a. β-lactamase positive isolates. c. ≤2 mg/L. e. Includes 10 isolates with MIC values at >2mg/L.
b. β-lactamase negative isolates. d. ≤0.5 mg/L.

Table 2. Activity of antimicrobial agents against 1,656 isolates of *M. catarrhalis* by region.

Region/Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Europe (470)					
Clarithromycin	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	99.4 / 0.2
Erythromycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	96.0 / 0.0
Telithromycin	0.12	0.12	≤0.06 – 2	- / -	99.8 / 0.2
Doxycycline	≤0.12	0.25	≤0.12 – 0.25	- / -	100.0 / 0.0
Tetracycline	≤2	2	≤2 – 2	100.0 / 0.0	99.8 / 0.0
Ciprofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.8 / -	99.6 / 0.4
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.8 / -	99.8 / 0.2
Moxifloxacin	≤0.5	≤0.5	≤0.5 – >4	- / -	99.8 / 0.2
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	94.9 / 0.6	94.9 / 2.3
USA (865)					
Clarithromycin	≤0.25	≤0.25	≤0.25 – 4	99.9 / -	99.2 / 0.1
Erythromycin	0.12	0.25	≤0.06 – 4	99.8 / -	93.0 / 0.2
Telithromycin	0.12	0.25	≤0.06 – 1	- / -	99.3 / 0.1
Doxycycline	≤0.12	0.25	≤0.12 – 0.5	- / -	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 8	99.9 / 0.1	99.9 / 0.1
Ciprofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	94.9 / 1.8	94.9 / 3.0
Latin America (70)					
Clarithromycin	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	98.6 / 0.0
Erythromycin	0.12	0.25	0.12 – 0.5	100.0 / -	95.2 / 0.0
Telithromycin	0.12	0.12	≤0.06 – 0.25	- / -	100.0 / 0.0
Doxycycline	≤0.12	≤0.12	≤0.12 – 0.25	- / -	100.0 / 0.0
Tetracycline	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >4	92.9 / 1.4	92.9 / 2.9

Region/Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Asia-Pacific (251)					
Clarithromycin	≤0.25	≤0.25	≤0.25 – >16	92.4 / -	90.1 / 7.6
Erythromycin	0.25	0.5	≤0.06 – >8	96.5 / -	78.7 / 4.3
Telithromycin	0.12	0.5	≤0.06 – >8	- / -	89.5 / 6.4
Doxycycline	0.12	0.25	≤0.06 – 4	- / -	99.5 / 0.5
Tetracycline	≤2	≤2	≤2 – >8	96.8 / 3.2	96.4 / 3.2
Ciprofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	97.2 / 2.8
Levofloxacin	≤0.5	≤0.5	≤0.5 – 2	100.0 / -	99.2 / 0.8
Moxifloxacin	≤0.5	≤0.5	≤0.5 – 1	- / -	99.6 / 0.4
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	94.0 / 2.4	94.0 / 4.8
All regions (1,656)					
Clarithromycin	≤0.25	≤0.25	≤0.25 – >32	99.6 / -	98.8 / 0.5
Erythromycin	0.12	0.25	≤0.06 – >8	99.5 / -	92.5 / 0.6
Telithromycin	0.12	0.25	≤0.06 – >8	- / -	99.2 / 0.3
Doxycycline	≤0.12	0.25	≤0.12 – 4	- / -	99.9 / 0.1
Tetracycline	≤2	≤2	≤2 – >8	99.4 / 0.6	99.3 / 0.6
Ciprofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.9 / -	99.6 / 0.4
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.9 / -	99.9 / 0.1
Moxifloxacin	≤0.5	≤0.5	≤0.5 – >4	- / -	99.9 / 0.1
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	94.6 / 1.6	94.6 / 3.1

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. Trimethoprim/sulfamethoxazole.