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Susceptibility Trends of *H. influenzae* and *M. catarrhalis* Against Orally Administered Antimicrobial Agents: Five Year Report from the SENTRY Antimicrobial Surveillance Program

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ABSTRACT

Background: Community-acquired respiratory tract infections (CARTI) are the leading cause of physician office visits, and HI and MCAT are significant pathogens for these maladies. In this report, the activity of several orally administered antimicrobials were analyzed against *H. influenzae* (HI) and *M. catarrhalis* (MCAT) isolates during a five-year period.

Methods: A total of 9,320 HI and 4,050 MCAT CARTI strains were collected by SENTRY Program (1997 - 2001) participants in North (NA), Latin America (LA) and Europe (EU) and tested at a central laboratory using NCCLS methods. Identification was confirmed and ß-lactamase (BL) production was assessed by the nitrocefin test. Forty compounds were tested (20 reported here) including fluoroquinolones (FQ), penicillins alone, amoxicillin/clavulanate (A/C), cefprozil (CZIL), clarithromycin (CLAR), tetracycline and trim/sulfa (T/S).

Results: For HI Amp-R was higher in NA (27.9%) compared to EU and LA (≤ 16.3%). CLAR (81.1%), CZIL (84.3), and loracarbef (93.3) were markedly less active against NA isolates compared to LA or EU. T/S-R in LA (40.7%) was higher than EU (24.7%) and NA (21.4%). Rifampin-R was rarely observed in all regions (0.5 - 1.2%). FQ-R HI (ciprofloxacin [CIPRO] MIC, ≥ 0.12 µg/ml) isolates were noted in LA (1), EU (4), and NA (8, including 1 isolate with CIPRO MIC > 2 µg/ml in 2000). For MCAT, BL production was detected in > 95% of MCAT isolates. MCAT T/S-R in LA (10.5%) was much higher than in EU (4.1%) or NA (3.5%). FQ-R MCAT isolates were observed in EU (2), LA (5) and NA (7, including 1 isolate with MICs of ≥ 2 µg/ml for CIPRO and newer FQs in 1998).

Conclusions: Results of this five year SENTRY Program sample shows that commonly prescribed oral agents for HI and MCAT from CARTI continue to be effective in these reported regions, except for reduced activity of T/S in LA, and CLAR and CZIL in NA. Interestingly, isolates with potentially refractory FQ MICs for HI and MCAT were most often seen in NA and should be monitored closely.

INTRODUCTION

The SENTRY Antimicrobial Surveillance Program was established in 1997 as a global longitudinal investigation designed to monitor antimicrobial resistance among a variety of infections. In addition, the in vitro activity of newly developed agents against a wide assortment of clinically important pathogens can be assessed. One of the objectives of this surveillance program was to monitor community-acquired respiratory tract infections (CARTI) and the three most common causative bacterial pathogens (*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*) for this indication. CARTI are the primary cause of physician office visits and the majority of antimicrobial prescriptions are used for the treatment of these maladies. Standard clinical treatment is empiric therapy with broad-spectrum oral antimicrobial agents.

Among *H. influenzae* and *M. catarrhalis*, ß-lactamases are a common mechanism of resistance. The percentage of ampicillin-resistant *H. influenzae* varies around the world with rates of > 25% in North America compared to ≤ 15% in Latin America and Europe. Strains of *H. influenzae* resistant to macrolides, oral cephalosporins and other commonly used antimicrobial agents have been described. The vast majority of *M. catarrhalis* produce ß-lactamase (> 95%) and increased rates of resistance to trimethoprim/sulfamethoxazole have been recently reported. Perhaps most alarming, albeit rare, are the isolated cases of fluoroquinolone-non-susceptible (MICs, ≥ 0.12 µg/ml) strains of *H. influenzae* and *M. catarrhalis*. Due to the prevalence of resistant species, the results of surveillance programs can be very useful as a guide to empiric therapy for local clinicians treating CARTI.

In this study, we compare the in vitro activity of 20 orally administered antimicrobial agents against 13,370 clinical isolates of *H. influenzae* and *M. catarrhalis*. The organisms were obtained from patients diagnosed with CARTI in the SENTRY Antimicrobial Surveillance Program during 1997 to 2001 by medical centers in North America, Latin America, and Europe.

MATERIALS AND METHODS

Organisms Tested. The Gram-negative fastidious species tested in this study were collected by more than 60 geographically diverse medical centers in North America, Latin America, and Europe from 1997 to 2001 as part of the SENTRY Antimicrobial Surveillance Program. The 13,370 isolates tested included *H. influenzae* (9,320 strains) and *M. catarrhalis* (4,050 strains) from patients diagnosed with CARTI. Organism identification was confirmed at the monitoring site (Iowa City, IA) using colony morphology, oxidase and butyrate disks for *M. catarrhalis*. Production of ß-lactamases was assessed for all strains tested using the nitrocefin disk test.

Antimicrobial Agents. Forty antimicrobial compounds were tested and 20 orally administered agents are reported here. These include fluoroquinolones, ß-lactams, macrolides-lincosamides, chloramphenicol, rifampin, tetracycline, and trimethoprim/sulfamethoxazole.

Susceptibility Testing. All strains were tested using reference broth microdilution methods (NCCLS) in validated dry form panels (TREK Diagnostics, Westlake, OH, USA). Overnight cultures were suspended in cation-adjusted Mueller-Hinton broth to a standard inoculum density (0.5 McFarland). Fifty microliters were inoculated in 10 ml of cation-adjusted Mueller-Hinton broth (*M. catarrhalis*) or Haemophilus Test Medium (*H. influenzae*). The final concentration target was 5 x 10^4 CFU per well. Trays were incubated in ambient air at 35ºC for 16 - 24 hours. Minimum inhibitory concentration endpoints were determined visually and susceptibility breakpoints were those defined by the NCCLS [2002] tables. Quality control was monitored using the following organisms: *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *H. influenzae* ATCC 49247, and *Escherichia coli* ATCC 25922. All results were within published control limits [NCCLS, 2002].

RESULTS

- The ampicillin resistance rates (Table 1) for *H. influenzae* were higher in NA (27.9%) compared to EU (16.2%) and LA (16.3%). ß-lactamase producing *M. catarrhalis* although high (> 95%) in all regions, was highest in LA.
- NA isolates of *H. influenzae* were less susceptible to clarithromycin (81.1%) and cefprozil (84.3%) compared to those from the other regions (89.9 and 94.0%, respectively).
- Rifampin-resistant *H. influenzae* strains were rarely observed in any of the study regions (0.5 - 1.2%), thus remaining an efficient agent for prophylaxis.
- Trimethoprim/sulfamethoxazole resistance (≥ 2-fold higher rates) in LA was much greater for *H. influenzae* (40.7%) and *M. catarrhalis* (10.5%) than in the other regions.
- With the exception of penicillin, all oral agents had significant (≥ 95% susceptible) activity against the *M. catarrhalis* isolates.
- A total of 13 *H. influenzae* isolates and 14 *M. catarrhalis* isolates with elevated fluoroquinolone MICs (ciprofloxacin MIC, ≥ 0.12 µg/ml) were observed indicating possible QRDR mutations. Fifteen (55.6%) of these strains were isolated in NA.

CONCLUSIONS

- The comprehensive results of this five year SENTRY Program study on the activity of commonly prescribed oral antimicrobial compounds against *H. influenzae* and *M. catarrhalis* show continued effective activity with the notable exceptions of amino-penicillins (ß-lactamase-mediated), clarithromycin, cefprozil and trimethoprim/sulfamethoxazole in NA.
- Trimethoprim/sulfamethoxazole activity was particularly compromised in LA (59.3% susceptible for *H. influenzae*).
- Isolates of *H. influenzae* and *M. catarrhalis* with elevated fluoroquinolone MICs were observed in all regions with the greatest occurrence in NA. This emerging resistance problem should be actively monitored by surveillance systems to confirm possible trends.

Table 1. Antimicrobial activity of 18 orally administered compounds tested against 9,320 H. influenzae strains isolated in SENTRY Antimicrobial Surveillance Program (1997-2001) medical centers in North America, Latin America, and Europe.

	Region (no. tested)					
	North America (5,545)		Latin America (1,073)		Europe (2,702)	
Antimicrobial agent	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]
Ampicillin	≤0.5/>4	72.1	≤0.5/>4	83.7	≤0.5/>4	83.8
Amoxicillin/Clavulanate	0.5/2	99.9	0.5/1	100.0	0.5/1	99.7
BMS-284756	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Ciprofloxacin	≤0.015/≤0.03	99.9	≤0.015/≤0.03	100.0	≤0.015/≤0.03	100.0
Gatifloxacin	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Levofloxacin	≤0.03/≤0.5	100.0	≤0.03/≤0.5	100.0	≤0.03/≤0.5	100.0
Moxifloxacin	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Azithromycin	1/2	99.5	1/2	99.7	1/2	99.8
Clarithromycin	8/16	81.1	8/8	91.0	8/16	89.6
Cefdinir	0.25/1	98.1	0.25/0.5	98.1	0.25/1	97.8
Cefpodoxime	0.06/0.12	100.0	0.06/0.12	100.0	0.06/0.12	100.0
Cefprozil	4/16	84.3	2/8	94.4	2/8	94.2
Cefuroxime	1/2	97.9	1/2	98.6	1/2	98.3
Loracarbef	2/8	93.3	1/4	97.3	1/4	97.5
Chloramphenicol	≤2/≤2	99.5	≤2/≤2	97.6	≤2/≤2	98.1
Rifampin	≤1/≤1	98.8	≤1/≤1	99.0	≤1/≤1	99.5
Tetracycline	≤2/≤2	99.2	≤2/≤2	97.2	≤2/≤2	97.0
Trimethoprim/ Sulfamethoxazole	≤0.5/>4	78.6	≤0.5/>4	59.3	≤0.5/>4	75.8

a. Susceptibility as defined by the NCCLS [2002].

Table 2. Antimicrobial activity of 17 orally administered compounds tested against 4,050 *M. catarrhalis* strains isolated in SENTRY Antimicrobial Surveillance Program (1997-2001) medical centers in North America, Latin America, and Europe.

	Region (no. tested)					
	North America (2,640)		Latin America (342)		Europe (1068)	
Antimicrobial agent	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]
BMS-284756	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Ciprofloxacin	≤0.03/0.06	99.9	≤0.03/0.06	100.0	≤0.03/≤0.03	100.0
Gatifloxacin	≤0.03/≤0.03	99.9	≤0.03/0.06	100.0	≤0.03/≤0.03	100.0
Levofloxacin	≤0.5/≤0.5	99.9	≤0.5/≤0.05	100.0	≤0.05/≤0.05	100.0
Moxifloxacin	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0
Penicillin[b]	>4/8	4.9	4/>4	2.3	4/>4	4.8
Amoxicillin/Clavulanate	≤0.25/≤0.25	99.9	≤0.25/≤0.25	100.0	≤0.25/≤0.25	100.0
Erythromycin[a]	≤0.25/0.5	99.4	≤0.25/0.5	98.8	≤0.25/≤0.25	99.2
Cefdinir	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0
Cefpodoxime	0.5/1	99.7	0.5/1	100.0	0.5/1	100.0
Cefprozil	2/8	97.2	2/4	98.8	2/4	99.8
Cefuroxime	1/2	99.4	1/2	99.7	1/2	99.9
Loracarbef	1/2	99.6	0.5/1	100.0	0.5/1	99.8
Chloramphenicol	≤2/≤2	99.9	≤2/≤2	99.7	≤2/≤2	99.5
Rifampin	≤1/≤1	100.0	≤1/≤1	99.6	≤1/≤1	100.0
Tetracycline	≤2/≤2	99.7	≤2/≤2	99.7	≤2/≤2	97.8
Trimethoprim/ Sulfamethoxazole	≤0.5/≤0.5	96.5	≤0.5/≤0.5	89.5	≤0.5/≤0.5	95.9

a. Susceptibility as defined by the NCCLS [2002] for *H. influenzae* was used for all drugs except erythromycin where guidelines for staphylococci were applied (≤ 0.5 µg/ml).
b. Penicillin MIC of ≤ 0.06 µg/ml correlates with a ß-lactamase-negative result.

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