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Comparison of *S. pneumoniae* and *H. influenzae* Susceptibilities from Community-Acquired Respiratory Tract Infections and Hospitalized Patients with Pneumonia: 5-Year Results of the SENTRY Antimicrobial Surveillance Program

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ABSTRACT

Background: Pathogens which cause a significant number of community-acquired respiratory tract infections (CARTI) and pneumonias in hospitalized patients (HP) include *S. pneumoniae* (SPN) and *H. influenzae* (HI). The SENTRY Program (North America) has monitored SPN and HI from 1997 - 2001, and the susceptible (S) patterns of these species from both patient populations were compared using several drug classes.

Methods: A total of 6,726 HI and 6,515 SPN isolates were tested at a central laboratory against > 30 antimicrobials using reference NCCLS methods. HI were tested in HTM broth and SPN using Mueller-Hinton broth supplemented with 3 - 5% lysed horse blood. Tested agents included ß-lactams, erythromycin (ER), fluoroquinolones (FQ), vancomycin (VAN), trimethoprim/sulfamethoxazole (T/S) and tetracycline (TET). 11,012 isolates were from CARTI and 2,229 were from HP. Among the HI and SPN, 82.4 and 83.9% were from CARTI and 17.6 and 16.1% were from HP, respectively.

Results: Resistance (R) to ampicillin (AMP) among HI was nearly identical for CARTI (24.5%) and HP (25.5%). ß-lactamase-neg. Amp-R (BLNAR) strains were only detected in HP (0.3%). FQs had good activity (≤ 0.03 µg/ml) against HI isolates , however, elevated MICs (ciprofloxacin [CIPRO], ≥ 0.12 µg/ml) were detected in both patient populations (≤ 0.2%). Penicillin- and ER-R was higher for CARTI (17.7 and 22.1%) compared to HP (12.2 and 20.2%). FQ (levofloxacin)-S was > 99.2% in both CARTI and HP. However, strains with potential R target mutations (CIPRO, > 2 µg/ml) were higher in HP (4.0%) versus CARTI (2.7%), and were more prevalent in 2001 (5.0%) compared to 1997 (0.7%). T/S-R was particularly higher among CARTI (25.0%) compared to HP (6.7%).

Conclusions: There were distinct differences in R among isolates from CARTI > HP for SPN tested against PEN, ER and T/S. Potential FQ-R mutations were observed more often among HP isolates. These differences show the continued need for surveillance programs to monitor R rates from different patient populations.

INTRODUCTION

Community-acquired respiratory tract infections (CARTI), such as bronchitis and pneumonia are most frequently caused by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Among hospitalized patients with pneumonia, *H. influenzae* and *S. pneumoniae* are also the causative pathogens usually acquired outside of the hospital. However, pathogen occurrence and resistance rates among certain key pathogens and antimicrobial agents can differ greatly between hospitalized patients, and those diagnosed and treated for CARTI.

It has been estimated that *S. pneumoniae* causes at least 500,000 cases of pneumonia every year in the United States. Penicillin resistance in pneumococci was first described in the 1960's and due to the resistance mechanism (altered penicillin-binding proteins [PBPs]), the activity of other ß-lactams such as amoxicillin/clavulanate and cephalosporins are diminished. Among *H. influenzae*, there are two mechanisms of clinical importance effecting amino-penicillins 1) production of ß-lactamases; and 2) ß-lactamase-negative, ampicillin-resistant strains (BLNAR) with altered PBPs. It has been documented that more than 30% of *H. influenzae* strains produce ß-lactamase in North America.

Due to the decreasing activity of traditional antimicrobials used to treat pneumonia, new options such as the fluoroquinolones are being utilized more frequently in both the outpatient and inpatient populations. The SENTRY Antimicrobial Surveillance Program has monitored susceptibility rates of *S. pneumoniae* and *H. influenzae* from both patient types from 1997 to the present. The purpose of this study was to compare and report the susceptibility rates of these pathogens from CARTI and patients hospitalized with pneumonia during a five year period (1997 - 2001) against several drug classes.

MATERIALS AND METHODS

During the years 1997 to 2001, the SENTRY Program collected a total of 6,726 *H. influenzae* and 6,515 *S. pneumoniae* isolates from CARTI (11,012 isolates) or patients hospitalized with pneumonia (2,229 isolates). Among these strains, 82.4% of *H. influenzae* and 83.9% of *S. pneumoniae* were from patients diagnosed with CARTI.

Participating medical centers each collected 100 clinically significant isolates (per the study protocol) from both patients diagnosed with CARTI as well as inpatients. Pure cultures were forwarded to the SENTRY Program monitors. Species identification was provided by the referring laboratories. Upon arrival, all isolates received confirmatory biochemical tests for identification. Susceptibility testing for all isolates was performed utilizing NCCLS reference broth microdilution methods. The isolates were tested against a variety of Gram-positive and -negative focused and broad-spectrum agents including ß-lactams, erythromycin, fluoroquinolones, vancomycin, trimethoprim/sulfamethoxazole and tetracycline. MIC values were interpreted using NCCLS M100-S12 guidelines.

Quality control was performed by the routine testing of American Type Culture and Collection (ATCC) strains: *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and 49766, *Staphylococcus aureus* ATCC 29213, and *Esherichia coli* ATCC 25922 and 35218.

RESULTS

- Among the *H. influenzae* and *S. pneumoniae* isolates, 82.4 and 83.9% were from CARTI and 17.6 and 16.1% were from hospitalized patients, respectively.
- Among the *H. influenzae*, resistance to ampicillin was nearly identical for CARTI (24.5%) and hospitalized patients (25.5%) (Table 1). However, ß-lactamase-negative ampicillin-resistant (BLNAR) strains were only detected in hospitalized patients at a rate of 0.3%.
- The vast majority of *H. influenzae* isolates (99.6 - 100.0%) have remained susceptible to amoxicillin/clavulanate, newer parenteral cephalosporins, and fluoroquinolones.
- Against *H. influenzae*, the fluoroquinolones demonstrated excellent activity. Garenoxacin and levofloxacin both had MIC_{50} values of ≤ 0.03 µg/ml and 100.0% of isolates were susceptible. Nearly all (99.9%) of the *H. influenzae* isolates were susceptible to ciprofloxacin, however, with a range of ≤ 0.015 - > 2 µg/ml, there were elevated ciprofloxacin MICs (≥ 0.12 µg/ml) in both patient populations at rates of approximately ≤ 0.2%.
- Among the *S. pneumoniae*, high-level penicillin resistance was greater for CARTI (16.7%) compared to hospitalized patients (12.1%) for all five years monitored (Table 2). Similarly, erythromycin resistance was slightly higher for CARTI (22.1%) isolates than for hospitalized patients (20.2%).
- Susceptibility of *S. pneumoniae* isolates to levofloxacin was > 99.2% in both CARTI and hospitalized patients. All isolates were susceptible to garenoxacin and the $MIC_{50/90}$ values of 0.06 µg/ml were found for both patient populations. However, strains with potential target mutations (ciprofloxacin, > 2 µg/ml) occurred more frequently in hospitalized patients at a rate of 4.0% versus 2.7% for CARTI and were more prevalent in 2001 (6.0% and 5.0%) compared to 1997 (2.9% and 0.7%) for both patient populations (data not shown).
- Resistance of *S. pneumoniae* to trimethoprim/sulfamethoxazole was significantly (p=<0.05) higher among CARTI (25.0%) compared to hospitalized patients (6.7%).

Table 1. Comparison of antimicrobial agents between community-acquired respiratory tract infections (CARTI) and hospitalized patients with pneumonia caused by *H. influenzae* (1997 - 2001).

	CARTI patients (n=5,545)				Hospitalized patients (n=1,181)			
	MIC (µg/ml)		% by category[a]		MIC (µg/ml)		% by category[a]	
Antimicrobial agent	50%	90%	Susceptible	Resistant	50%	90%	Susceptible	Resistant
Penicillin	0.5	>4	-[b]	-[b]	0.5	>16	-[b]	-[b]
Ampicillin	≤0.5	>4	72.1	24.5	1	>16	73.6	25.5
Amoxicillin/clavulanate	0.5	2	99.9	0.1	≤2	≤2	99.6	0.4
Ceftriaxone	≤0.008	≤0.008	100.0	0.0	≤0.25	≤0.25	100.0	0.0
Cefepime	≤0.06	0.25	100.0	0.0	≤0.12	0.25	100.0	0.0
Azithromycin	1	2	99.5	-[b]	1	2	99.3	-[b]
Clarithromycin	8	16	81.1	1.9	8	16	75.6	2.2
Quinupristin/dalfopristin	>2	8	-b	-[b]	4	8	-[b]	-[b]
Tetracycline	≤2	≤2	99.2	0.6	≤4	≤4	99.3	0.7
Trimethoprim/sulfamethoxazole	≤0.5	>4	78.6	16.1	≤0.5	>2	81.7	15.5
Vancomycin	>16	>16	-[b]	-[b]	>16	>16	-[b]	-[b]
Ciprofloxacin	≤0.015	≤0.03	99.9	-[b]	≤0.015	≤0.25	99.9	-[b]
Levofloxacin	≤0.03	≤0.5	100.0	-[b]	≤0.03	≤0.5	100.0	-[b]
Garenoxacin	≤0.03	≤0.03	100.0c	-[b]	≤0.03	≤0.03	100.0c	-[b]

a. Categories assigned per NCCLS criteria.
b. No interpreted breakpoint value has been established.
c. Proposed breakpoint of ≤ 4 µg/ml [Fung-Tomc, 2000].

Table 2. Comparison of antimicrobial agents between community-acquired respiratory tract infections (CARTI) and hospitalized patients with pneumonia caused by *S. pneumoniae* (1997 - 2001).

	CARTI patients (n=5,467)				Hospitalized patients (n=1,048)			
	MIC (µg/ml)		% by category[a]		MIC (µg/ml)		% by category[a]	
Antimicrobial agent	50%	90%	Susceptible	Resistant	50%	90%	Susceptible	Resistant
Penicillin	≤0.03	2	65.0	16.7	≤0.03	2	69.8	12.1
Ampicillin	≤0.5	4	-[b]	-[b]	≤2	4	-[b]	-[b]
Amoxicillin/clavulanate	≤0.25	2	93.2	3.0	≤2	≤2	95.6	1.7
Ceftriaxone	0.03	1	94.7	1.6	≤0.25	1	96.3	1.5
Cefepime	≤0.06	1	96.2	0.5	≤0.12	1	97.4	0.4
Erythromycin	≤0.25	4	77.0	22.1	≤0.25	4	78.8	20.2
Clindamycin	0.12	≤0.25	93.0	6.6	≤0.06	0.12	92.2	7.5
Quinupristin/dalfopristin	0.5	0.5	99.9	0.0	0.5	0.5	99.9	0.0
Tetracycline	≤2	>16	84.2	15.2	≤4	>8	85.5	14.2
Trimethoprim/sulfamethoxazole	≤0.5	>4	68.5	25.0	≤0.5	>2	74.4	6.7
Vancomycin	0.25	0.5	100.0	0.0	0.25	0.5	100.0	0.0
Ciprofloxacin	1	2	-	2.7[c]	1	2	-	4.0[c]
Levofloxacin	1	1	99.2	0.7	1	2	99.4	0.5
Garenoxacin	0.06	0.06	100.0[d]	0.0	0.06	0.06	100.0[d]	0.0

a. Categories assigned per NCCLS criteria.
b. No interpreted breakpoint value has been established.
c. Proposed breakpoint of ≥ 4 µg/ml [Chen et al., 1999].
d. Proposed breakpoint of ≤ 4 µg/ml [Fung-Tomc, 2000].

CONCLUSIONS

- Distinct differences in resistance rates among *S. pneumoniae* were demonstrated between CARTI and hospitalized patients in North America. Both penicillin and erythromycin were less effective in CARTI isolates (16.7 and 22.1% resistant) compared to hospitalized patient isolates (12.1 and 20.2% resistant). Resistance of *S. pneumoniae* to trimethoprim/sulfamethoxazole was much higher in CARTI (25.0%) than in hospitalized patients (6.7%).
- Potential fluoroquinolone-resistant target mutations in pneumococci were observed more often in patients needing hospitalization (4.0%) compared to CARTI (2.7%) and they have increased significantly over the five-year interval.
- All fluoroquinolones demonstrated good activity against *H. influenzae* isolates.
- Among the *H. influenzae*, ampicillin resistance was approximately 25.0% for both patient populations. However, BLNAR strains were only detected in hospitalized patients at a rate of 0.3%.
- These differences show the continued need for surveillance programs to monitor evolving resistance rates from different patient populations having respiratory tract infections.

SELECTED REFERENCES

Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *New England Journal of Medicine* 1999; 341:233-239.

Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY Antimicrobial Surveillance Program. *Clinical Infectious Disease* 1998; 27:764-770.

Fung-Tomc JC, Minassian B, Kolek B, et al. Antibacterial spectrum of a novel des-fluoro(6)quinolone, BMS284756. *Antimicrobial Agents and Chemotherapy* 2000; 44:3351-3356.

Jenigan DB, Cetran MS, Breiman RF. Minimizing the impact of drug resistant *Streptococcus pneumoniae* (DRSP). *Journal of the American Medical Association* 1996; 275:206-209.

Jones RN, Pfaller MA. In vitro activity of newer fluoroquinolones for respiratory tract infections and emerging patterns of antimicrobial resistance: Data from the SENTRY Antimicrobial Surveillance Program. *Clinical Infectious Diseases* 2000; 31(Suppl 2):S16-S23.

Mendelman PM, Chaffin DO, Stull TL, Rubens CE, Mack KD, Smith AL. Characterization of non-ß-lactamase-mediated ampicillin resistance in *Haemophilus influenzae*. *Antimicrobial Agents and Chemotherapy* 1984; 26:235-244.

National Committee for Clinical Laboratory Standards. (2000). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: Approved standard M7-A5.* Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2002). *Performance standard for antimicrobial susceptibility testing. Document M100-S12.* Wayne, PA:NCCLS.