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ANTIBIOTIC SUSCEPTIBILITY OF PATHOGENS ISOLATED FROM PATIENTS WITH COMMUNITY-ACQUIRED RESPIRATORY TRACT INFECTIONS IN PAKISTAN—THE ACTIVE STUDY

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Background: Respiratory tract infections (RTIs) are amongst the most wide spread and serious infections, accounting for over 50 million deaths globally each year. In developing countries, infants under 4 years of age are at greatest risk of lower RTIs, whereas in developed countries the severity of infection and rate of mortality are greater in elderly. The objective of the survey was to determine the *in vitro* susceptibility of antibiotics commonly prescribed RTIs against *Streptococcus pneumoniae* (SP), *Haemophilus influenzae* (HI) and *Streptococcus pyogenes*, isolated from patients with community-acquired RTIs globally. This survey involved 9 countries. In this study we present the results from Pakistan where SP and HI only were tested. **Methods:** A total of 200 isolates were included in the study. Both SP and HI were in equal number. Antibiotic susceptibility testing was performed by using Clinical and Laboratory Standards Institute guidelines and E test for determination of the minimal inhibitory concentration. For non-US products the Committee of the Antibiogram of the French Society of Microbiology Breakpoints was used. **Results:** All SP were found susceptible to amoxicillin, co-amoxiclavate and cefixime, 72% isolates were found sensitive to macrolide and 97% to levofloxacin. All HI were found sensitive to co-amoxiclavate and to cefixime, 97% to ampicillin, 98% to clarithromycin and 99% to levofloxacin. **Conclusion:** In isolates collected from Pakistan, SP resistance rate was elevated for macrolide. SP and HI remain susceptible to β -lactams as well as to levofloxacin.

Keywords: Community acquired pneumonia, antibiotic susceptibility, respiratory pathogens

INTRODUCTION

Respiratory tract infections (RTIs) are amongst the most wide spread and serious infections, accounting for over 50 million deaths globally each year. RTIs also are the most common reason for physician visits and prescription of antibiotics.^{1,2} Infections of lower respiratory tract include community-acquired pneumoniae (CAP) and acute exacerbations of chronic bronchitis (AECB), which are associated with significant rates of mortality and are among the top 10 causes of death in developed world. In developing countries, infants under 4 years of age are at greatest risk of lower RTIs, whereas in developed countries the severity of infection and rate of mortality are greater in elderly.³ Antibacterial resistance among the pathogens commonly involved in community-acquired RTI such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, has increased over the last decades and may jeopardize the effectiveness of the treatment of RTI.

In Pakistan, most RTIs are treated empirically, perhaps due to higher cost of laboratory services or non availability of standardized laboratories. Surveillance studies are important tool for defining regional patterns of antimicrobial resistance, guiding empirical therapy and establishment of guidelines. Therefore, this study was conducted to determine susceptibility patterns of common respiratory tract pathogens seen in community.

MATERIALS AND METHODS

This study was conducted in the Clinical Microbiology Laboratory of Aga Khan University

Hospital in 2006. A total of 200 isolates were included in the study. Both *S. pneumoniae* and *H. influenzae* were in equal number. Single isolate from each patient with the diagnosis of community-acquired LRTIs, i.e., pneumonia, AECB, acute exacerbation of chronic obstructive airways disease, presumed secondary bacterial infection of acute bronchitis was included in the study. Clinical isolates of upper respiratory infections such as sinusitis and acute otitis media were also included.

Both pathogens were identified as per standard methodology.⁴ *S. pneumoniae* was identified on the basis of gram stain characteristics, colony morphology, catalase test and susceptibility to optochin. For *H. influenzae* gram stain characteristics, colony morphology and requirement of XV factors was used.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed by using Kirby Bauer disk diffusion method as per Clinical Laboratory Standards Institute (CLSI) Guidelines.⁵ Following antibiotics were included: ampicillin (10 μ g) amoxicillin (10 μ g), co-amoxiclavate (30 μ g) cefixime (5 μ g) erythromycin (15 μ g) levofloxacin (5 μ g), clarithromycin (15 μ g). E test (Bio Meurex) was used for determination of the Minimal Inhibitory Concentration (MIC). The results were interpreted according to CLSI guidelines.

Statistics

All statistical analyses were conducted on SAS[®], Release 9.1 (SAS Institute, SAS Campus Drive, Cary

NC 27513), and run under Microsoft Windows XP® for a personal computer. Electronic data capturing and data validation was conducted by sanofi-aventis, Midrand, South Africa. Categorization of test outcomes (as susceptible, intermediate or resistant) was done centrally by sanofi-aventis, Midrand, South Africa.

RESULTS

DEMOGRAPHIC DATA

The age distribution of patients for S. pneumoniae: Twenty-four percent of the patients belonged to the paediatric age group (<18 years), 16% were between 18–35 years, 37% were adult (35–65 years) and 24% were old age (>65) groups.

Age distribution for H. influenzae: Forty-seven percent of patients belonged to paediatric age (<18 years), 26% of patients from younger age (18–35), 31% were adults (35–65) and 19% patients were of older age (>65) group. Over all 64% of S. pneumoniae was isolated from male and 36% from female, while for H. influenzae, 57% were from male and 43% were from female. The patient clinical histories for S. pneumoniae and H. influenzae are displayed in Table-1. One hundred and sixty-five (82%) of isolates collected were from out patients clinics of which 78 (78%) were S. pneumoniae and 87 (87%) were H. influenzae. Total number of isolates collected from the patients hospitalized for <48 hrs were 35 (18%) of which 22 (22%) were S. pneumoniae and 13 (13%) were H. influenzae. Immune statuses of all patients were unknown.

ANTIBIOTIC SUSCEPTIBILITY

Disk Diffusion:

The results of the disc susceptibility testing are given in Table-2. Seventy-two percent of S. pneumoniae were found susceptible to erythromycin and to clarithromycin and 97% to levofloxacin. Susceptibility of S. pneumoniae against ampicillin, amoxicillin, co-amoxiclavate and cefixime was tested by E test method only. Ninety-seven percent of H. influenza were found susceptible to ampicillin. All isolates of H. influenzae were sensitive to co-amoxiclavate, cefixime and levofloxacin.

Minimum Inhibitory Concentration (MIC)

The results of MIC tests are shown in Table-3. All S. pneumoniae were found susceptible to ampicillin with MIC range 0.016–0.25, amoxicillin 0.016–0.5, co-amoxiclavate 0.016–0.5 µg/ml. About two third isolates were found susceptible to erythromycin and clarithromycin with MIC range of 0.032–0.5 µg/ml. Ninety-seven percent of the isolates were susceptible to levofloxacin with MIC range 0.2–2 µg/ml. All H. influenzae were found susceptible to co-amoxiclavate with MIC range of 0.094–1 and cefixime 0.023–0.064 µg/ml. Ninety-eight percent of isolates were found

sensitive to ampicillin with MIC range 0.019–1, 98% isolates were susceptible to clarithromycin with MIC range of 0.125–8 and 99% of the isolates were susceptible to levofloxacin with MIC range of 0.004–0.016 µg/ml.

Table-1: Overall distribution of pathogens according to Type of Infection & Specimen Source

		<i>S. pneumoniae</i>	<i>H. influenzae</i>
Infection	Acute exacerbation of chronic bronchitis	3	1
	Acute exacerbation of chronic obstructive airways disease.	-	1
	Acute otitis media	6	7
	Bacterial infection of Acute bronchitis	1	4
	Community acquired pneumoniae	90	87
Specimen Source	Blood culture	7	2
	Bronchial brush	5	1
	Broncheal alveolar Lavage.	10	2
	Endotracheal aspiration	-	7
	Middle ear pus (paracenteses)	6	7
	Sputum	72	81

Table-2: Comparison of Disc diffusion and MICs (µg/ml) values of sensitive strains of S. pneumoniae against selected antibiotics (n=100)

Antibiotic	%S	%R	MIC Range (µg/ml)
Ampicillin	-	-	0.016-.25
Amoxicillin	100	-	0.016-0.5
Co-amoxiclavate	100	-	0.016-0.5
Erythromycin	72	28	0.032-0.5
Clarithromycin	72	28	0.032-0.5
Levofloxacin	97	3	0.064-2

Table-3: Comparison of Disc diffusion and MICs (µg/ml) values of sensitive strains of H. influenzae against selected antibiotics (n=100)

Antibiotic	%S	%I	%R	MIC Range (µg/ml)
Ampicillin	97	-	3	0.019–1
Co-amoxiclavate	100	-	-	0.094–1
Cefixime	100	-	-	0.023–0.064
Clarithromycin	98	2	-	0.125–8
Levofloxacin	99	-	1	0.004–0.016

DISCUSSION AND CONCLUSIONS

ACTIVE data was collected during the period of 2006–2007. This study evaluated the antimicrobial susceptibility of community-acquired lower respiratory tract bacterial isolates. The results show that antibiotic resistance among these isolates in Pakistan is relatively low compared with other countries and regions throughout the world, as determined by recent global surveillance studies.⁶

In this study, the macrolide class of antimicrobials showed poor potency against S. pneumoniae. Pneumococcal resistance to antimicrobials,

including the commonly used penicillins, macrolides and co-trimoxazole, has been increasing in most countries over the last decade, with many isolates now resistant to multiple antibiotics. Resistance to erythromycin and other macrolides among *S. pneumoniae* is increasingly being noticed in Pakistan as well, finding that is consistent with other countries.⁷

Our results showed 28% *S. pneumoniae* were resistant to erythromycin and clarithromycin. Beta lactams; ampicillin, amoxicillin, co-amoxiclavate, cephalosporin cefixime, showed excellent MIC results and none of the isolate was resistant to these antibiotics. Resistance to levofloxacin was detected in 3% of *S. pneumoniae* tested in this study. Similarly, fluoroquinolones and cephalosporins were found to be consistently active against *H. influenzae* tested in this study. β -lactamase producing *H. influenzae* is an emerging problem all over the world.^{8,9} However, our results suggest that β -lactamase producing strains of *H. influenzae* are less prevalent in our community as all the isolates were sensitive to β -lactams, macrolides, cephalosporins with very low level resistance to ampicillin (3%).

Although standard parameters of antimicrobial activity such as MIC and minimal bactericidal concentration are useful, they do not provide information about the time course or rate of kill relative to concentration or whether post-antibiotic effects on leukocytes contribute to activity. Antibiotics can be divided into two major groups: those that exhibit concentration-dependent killing and prolonged persistent effects and those that exhibit time-dependent killing and minimal-to-moderate persistent effects. With drugs that fall into the former group, the area under the concentration-time curve (AUC) and peak levels are the major parameters correlating with efficacy. The ratio of peak concentration to MIC is a measure of potency that also indicates the efficacy of the drug.¹⁰

Levofloxacin demonstrates concentration-dependent bactericidal activity most closely related to the pharmacodynamic parameters of the ratio of AUC to MIC and the ratio of peak plasma concentration (C_{max}) to MIC. Increasing the dose of levofloxacin exploits these parameters by increasing peak drug concentrations, allowing for a shorter course of treatment without diminishing its therapeutic benefit.¹¹ The Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria, as well as the World Health Organization recommendations, emphasize the importance of choosing the best possible drug for the optimal duration to prevent the further emergence of resistant bacterial strains.¹² Other potential benefits of a

short-course, higher-dose therapy include less total drug exposure, avoidance of adverse effects, enhanced patient and healthcare worker convenience, adherence, and improved cost-effectiveness.¹³

CONFLICT OF INTEREST

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