Original Article

Antimicrobial resistance among *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates in the United Arab Emirates: 2004-2006

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Abstract

Background: *Streptococcus pneumoniae* and *H. influenzae* represent key aetiological agents in respiratory tract infections showing an increasing trend of antimicrobial resistance. We present the first report on the antimicrobial resistance in *S. pneumoniae* and *H. influenzae* isolated from patients in the United Arab Emirates.

Methods: One hundred *S. pneumoniae* and 102 *H. influenzae* strains were isolated from patients with community acquired respiratory tract infections during the study period (October 2004-March 2006). Susceptibility testing to a panel of antibiotics was conducted using disc diffusion and E test. Minimum inhibitory concentrations were interpreted using CLSI and Pharmacokinetic-pharmacodynamic (PK/PD) breakpoints.

Results: For *S. pneumoniae* isolates, 57% were penicillin susceptible while 98% were susceptible to amoxicillin/clavulanate with both interpretative criteria. Cefaclor was the least effective cephalosporin with only 57% and 43% of isolates showing susceptibility with CLSI and PK/PD breakpoints respectively. Thirty-six isolates were ofloxacin non-susceptible (intermediate and resistant); three resistant isolates were associated with high ciprofloxacin MICs (>8mg/L). There was elevated macrolide resistance with associated high levels of erythromycin/clindamycin cross-resistance (n=22/30) suggesting predominant *erm*(B)-mediated resistance and 21% of isolates demonstrated multidrug resistance. For *H. influenzae*, 18% were beta-lactamase producers. Reduction in cefaclor and cefprozil susceptibility with PK/PD breakpoints (94.1% to 41.2% and 62.7% respectively) was seen and only 1% remained azithromycin and clarithomycin susceptible. For both pathogens, lowest susceptibility was with co-trimoxazole.

Conclusion: These findings indicate a high level of penicillin resistance and continued usefulness of amoxicillin/clavulanate. Elevated macrolide and fluoroquinolone resistance and the occurrence of multidrug resistance indicate a need for continued surveillance.

Key Words: Antimicrobial resistance, *Streptococcus pneumoniae*, *H. influenzae*.

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Introduction

Streptococcus pneumoniae and *H. influenzae* cause a wide spectrum of pediatric and adult infections. These microorganisms represent the two key bacterial aetiological agents in respiratory tract infections such as sinusitis, acute exacerbations of chronic bronchitis and pneumonia worldwide [1]. The global burden of pneumococcal disease is enormous, accounting for about 1 to 2 million deaths annually among children under the age of five years and a similar number of deaths in adults [2]. The virulence of *S. pneumoniae* is associated with the presence of capsular polysaccharides [3] and although the widespread use of the *H. influenzae* type B vaccine has largely eliminated the risk of life-threatening infections due to encapsulated type b strains, localized infections attributable to nonencapsulated strains are still commonly encountered.

The efficacy of beta-lactam antibiotics which have for long been the drug of choice in *S. pneumoniae* and *H. influenzae* infections has been compromised by the rapid emergence and spread of resistant strains [1,4]. For *H. influenzae*, the principal mechanism of resistance is plasmid mediated production of β -lactamase. Penicillin and macrolide resistance in *S. pneumoniae* is high with an overall prevalence of 24.6% and 28% respectively in a recent survey of eight European countries [5]. Higher figures have also been reported from Asia where 44.5% to 77.5% of

Streptococcus pneumoniae isolates are penicillin-resistant and over 70% are erythromycin-resistant [6]. Of additional concern is the upward trend of fluoroquinolone resistance, especially among penicillin- and macrolide-resistant strains. The percentage of fluoroquinolone resistant strains in Hong Kong increased from under 0.5% in 1995 to 13.3% in 2001 [7]. However, there is wide variation in the levels of resistance seen in different countries and regions, thus making it imperative that the trends in geographical variation and the pattern of resistance development should be monitored [8]. This notion is reflected in the increasing number of international and national surveillance studies being conducted.

During the acute phase of respiratory tract infections, empirical therapy is often adopted and the clinical impact of these emerging resistant strains has become evident with increasing reports of treatment failures [8-10]. The application of pharmacokinetic (PK) and pharmacodynamic (PD) data in conjunction with minimum inhibitory concentrations (MICs) of antibacterial agents allows for improved selection and appropriate dosing of antimicrobial agents [11]. As surveillance data from various countries continues to show increasing levels of resistance, antimicrobial susceptibility patterns based on the application of PK/PD breakpoints are needed to guide clinician prescribing, thus increasing the likelihood of bacteriologic cure. There are currently no reported data on the pattern or levels of antimicrobial resistance among *S. pneumoniae* and *H. influenzae* isolates in the United Arab Emirates (UAE). This study, which was conducted in conjunction with GlaxoSmithKline as part of the multinational Survey of Antibiotic Resistance (SOAR) Study, provides data on the pattern of antibiotic susceptibility in community acquired *S. pneumoniae* and *H. influenzae* isolates in the UAE.

Materials and Methods

Bacterial isolates and patient data

The study was conducted from October 2004 to March 2006. Specimens including blood, sputum, bronchoalveolar lavage, nasal, throat and ear swabs were obtained from patients with community acquired respiratory tract infections attending healthcare facilities across the UAE. Duplicate isolates from the same patient were not allowed; hence only one isolate was accepted per episode of infection. Relevant patient data such as age, gender, and site of bacterial isolation were recorded. All specimens/isolates were processed at the Al-Qassimi Hospital Microbiology Laboratory (AQHML), Sharjah UAE. Isolates obtained from outside participating centers were re-cultured and re-identified at AQHML. All isolates were stored at -20oC until tested in batches. *S. pneumoniae* identification and speciation was based on colony morphology on blood agar, Gram stain reaction, sensitivity to optochin discs and bile solubility. Both the X and V factors were required for *H. influenzae* determination. *H. influenzae* isolates were also tested for β -lactamase production using the chromogenic cephalosporin (nitrocefin) test (Unipath Ltd., Basingstoke, UK).

Antimicrobial agents and susceptibility testing method

Penicillin, amoxicillin amoxicillin/clavulanate (as co-amoxiclav 2:1), cefuroxime, cefaclor, cefprozil, azithromycin, clarithromycin, ciprofloxacin and ofloxacin were tested using E test strips (AB Biodisk, Solna, Sweden). Susceptibility testing by disc diffusion was conducted for erythromycin, clindamycin, co-trimoxazole, tetracycline and chloramphenicol. The disc diffusion susceptibility testing and determination of inhibition zone diameters were in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [12].

E test

MICs were determined using the E test strips according to the manufacturer's instructions. Briefly, test inocula were prepared from pneumococcal colonies obtained on sheep blood or *H. influenza* colonies obtained on chocolate agar after a 20 to 24 hour culture in 5% CO_2. From these colonies, bacterial suspension in Mueller-Hinton broth (equivalent to 0.5 McFarland) was prepared. For the E test, Mueller-Hinton agar plates (Difco, Detroit, MI, USA) were used for *S. pneumoniae* and Haemophilus Test Medium agar (Oxoid, Basingstoke, United Kingdom) for *H. influenzae*. The inoculated plates with the E test strips were incubated in the inverted position in 5% CO_2 with the exception of azithromycin and clarithromycin where *S. pneumoniae* test plates were incubated in ambient air. The MIC was read

according to the manufacturer's instructions directly from the strip where the elliptical zone of inhibition intersected with the MIC scale. The MICs were interpreted as susceptible, intermediate, or resistant categories in accordance with CLSI guidelines and on the basis of Pharmacokinetic-pharmacodynamic (PK/PD) breakpoints where appropriate (Tables 1A & 1B) [13-15]. For *H. influenzae*, in accordance with manufacturer provided guidelines (E test package insert; AB Biodisk, Solna, Sweden), the standard CLSI and PK/PD breakpoints for azithromycin and clarithromycin were raised by one doubling dilution to account for the adverse effect of CO_2 on macrolide/ azalide antibiotics. *S. pneumoniae* ATCC 49619 and S. aureus ATCC 29213 were included as quality control for S. pneumonia susceptibility testing. For *H. influenzae*, strains of *E. coli* ATCC 35218, *H influenza* ATCC 49247 and *H influenzae* ATCC 49766 were used as quality control.

Table 1. A: Breakpoints (mg/L) used to determine *S. pneumoniae* susceptible, intermediate and resistant categories based on PK/PD and CLSI interpretive parameters. B: Breakpoints (mg/L) used to determine *H. influenzae* susceptible, intermediate and resistant categories based on PK/PD and CLSI interpretive parameters.[11.12.13]

A	CSLI breakpoints			PK/PD breakpoints	
Antimicrobial	S	I	R	S	R
Penicillin	≤0.06	0.12-1	≥2	NA	NA
Amoxicillin/clavulanate*	≤2	4	≥8	≤2	≥4
Cefaclor	≤1	2	≥4	≤0.5	≥1
Cefproxil	≤2	4	≥8	≤1	≥2
Cefuroxime	≤1	2	≥4	≤1	≥2
Azithromycin	≤0.5	1	≥2	≤0.12	≥0.25
Clarithromycin	≤0.25	0.5	≥1	≤0.25	≥0.5
Ciprofloxacin	-	-	-	≤1	≥2
Ofloxacin	≤2	4	≥8	≤2	≥4

B	CSLI breakpoints			PK/PD breakpoints	
Antimicrobial	S	I	R	S	R
Ampicillin	≤1	2	≥4	NA	NA
Amoxicillin/clavulanate*	≤4	-	≥8	≤2	≥4
Cefaclor	≤8	16	≥32	≤0.5	≥1
Cefixime	≤1	-	-	≤1	≥2
Cefproxil	≤8	16	≥32	≤1	≥2
Ceftriaxone	≤2	-	-	≤1	≥2
Cefuroxime	≤4	8	≥16	≤1	≥2
Azithromycin**	≤8	-	-	≤0.25	≥0.5
Clarithromycin**	≤16	32	≥64	≤0.5	≥1
Ciprofloxacin	≤1	-	-	≤1	≥2
Ofloxacin	≤2	-	-	≤2	≥4

S: Sensitive; I: Intermediate resistant; R: Resistant ; NA: not applicable.
*Amoxicillin/clavulanate was tested in a 2:1 ratio of amoxicillin to clavulanate; breakpoints are expressed as the amoxicillin component.
**Azithromycin and clarithromycin breakpoints are those provided by AB Biodisk for incubation in CO2 (E test package insert Table 1). Standard CLSI breakpoints are S<4mg/L for azithromycin and for clarithromycin S<8mg/L; I 16mg/L and R>32mg/L. The standard PK/PD breakpoints are azithromycin S<0.12mg/L; R >0.25mg/L and for clarithromycin S<0.25mg/L; R>0.5mg/L.

Results

During the study period, 100 *S. pneumoniae* and 102 *H. influenzae* strains were isolated. About two-thirds of all isolates were obtained from male patients (*S. pneumoniae*: 64/100 and *H. influenzae*: 66/102). Forty (40%) *S. pneumoniae* isolates were obtained from paediatric patients (<12 years) contrasting sharply with *H. influenzae* where 73% (74/102) of isolates were obtained from patients in the same age group. However, for both pathogens, 78% of paediatric patients were under the age of 5 years (*S. pneumoniae*: 31/40; *H. influenzae*: 58/74). For both bacteria, the majority of isolates were from sputum (87/202; 43%). The total numbers of isolates obtained from nasal and ear swabs were similar for both pathogens; however, there was a divergence in the number of isolates obtained from blood and throat swabs. Table 2 shows a comparative distribution of isolation sites for *S. pneumoniae* and *H. influenzae*.

Table 2. Distribution of specimen types from which *S. pneumoniae* and *H. influenzae* were isolated.

Specimen from which bacteria was isolated	Number of isolates obtained from specimen type	
	***S. pneumoniae* (N=100)**	***H. influenzae* (N=102)**
Sputum	52	35
Blood	16	2
Nasal swab	10	14
Throat swab	2	28
Ear swab	19	22
Bronchoaleveolar lavage	0	1
Pleural fluid	1	0

For *S. pneumoniae*, 57% of isolates were penicillin susceptible, 38% were intermediate resistant, and 5% were resistant. There was a high level of susceptibility to amoxicillin/clavulanate with 98% of isolates being sensitive to this antibiotic irrespective of the interpretive criteria applied. In general, the penicillin-resistant isolates showed lower sensitivity to other antibiotics compared to penicillin sensitive isolates; i.e. almost half of the penicillin non-susceptible (full and intermediate resistance) isolates were non-susceptible to azithromycin (21/43) and clarithromycin (20/43). Susceptibility to cefprozil and cefuroxime was 92% and 87% respectively in contrast to 57% seen with cefaclor (MIC90 64mg/L) (Table 3).

Table 3. Susceptibility of *S. pneumoniae* to antimicrobial agents based on CLSI and PK/PD breakpoints.

			CLSI breakpoints			PK/PD breakpoints	
Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	S (%)	R (%)
Penicillin	0.032	1	57	38	5	-	-
Amoxicillin-clavulanate	0.016	1	98		2	98	2
Cefaclor	0.5	64	57	11	32	43	57
Cefproxil	0.125	2	92	3	5	82	18
Cefuroxime	0.064	2	87	9	4	87	13
Azithromycin	0.125	>256	67.4	1.1	31.5	48.3	51.7
Clarithromycin	0.064	>256	68.5	-	31.5	68.5	31.5
Erythromycin*	-	-	69	1	30	-	-
Clindamycin*	-	-	77	1	22	-	-
Ciprofloxacin	-	2	-	-	-	63	37
Ofloxacin	2	4	64	33	3	64	36
Co-trimoxazole*	-	-	3	20	77	-	-
Tetracycline*	-	-	81.4	1.7	16.9	-	-
Chloramphenicol*	-	-	97	-	3	-	-

*Data based on disk susceptibility testing
S: Sensitive; I: Intermediate resistant; R: Resistant.

When the PK/PD breakpoints were applied, the proportion of cefaclor and cefprozil sensitive *S. pneumoniae* isolates reduced to 43% and 82% respectively with no change in percentage of cefuroxime-sensitive isolates. Resistance to the macrolides was high, ranging from 30.0%-31.5% of isolates with the CLSI breakpoints (Table 3). For azithromycin, MIC90 was >256mg/L with 31.5% of isolates being resistant when CLSI interpretive breakpoints were applied and rising to 51.7% of isolates with PK/PD breakpoint. Based on disk diffusion data, we found that the level of cross-resistance between erythromycin and clindamycin was 73% (n=22/30). Only 64% of isolates were ofloxacin sensitive, 3% were resistant, and 33% were intermediate resistant. The three ofloxacin-resistant isolates showed ciprofloxacin MICs of >8mg/L. Lowest level of susceptibility was observed with co-trimoxazole where only 3% of isolates showed sensitivity to this drug (Table 3). Multidrug resistance (resistance to >3 antimicrobial classes) was high with 21% of isolates demonstrating co-resistance to erythromycin, co-trimoxazole, and tetracycline.

For *H. influenzae*, there was over 80% susceptibility (CLSI breakpoints) for most of the antimicrobials tested. The notable exception was co-trimoxazole where only 62.7% of strains isolated were susceptible to this antibiotic. Table 4 shows the proportion of resistant and sensitive strains based on CLSI breakpoints and PK/PD breakpoints. However, application of PK/PD breakpoints resulted in reduction of the sensitivity for cefaclor and cefprozil from 94.1% to 41.2% and 62.7% respectively (Table 4).

Table 4. Susceptibility of *H. influenzae* to antimicrobial agents based on CLSI and PK/PD breakpoints.

			CLSI breakpoints			PK/PD breakpoints	
Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	S (%)	R (%)
Ampicillin	0.125	4.0	81.4		15.7	-	-
Amoxicillin-clavulanate	0.25	0.5	100	-	-	100	0
Cefaclor	1.0	4.0	94.1	4.9	1.0	41.2	58.8
Cefproxil	1.0	4.0	94.1	4.9	1.0	62.7	37.3
Cefuroxime	0.25	0.5	100	-	-	62.7	37.3
Azithromycin	2.0	4.0	97.1	2.9	-	1	99.0
Clarithromycin	4.0	8.0	98.0	2.0	-	1.0	99.0
Ciprofloxacin	-	0.008	100	-	-	100	-
Ofloxacin	0.023	0.064	100	-	-	100	-
Co-trimoxazole*	-	-	62.7	-	37.3	-	-
Tetracycline*	-	-	88.2	5.9	5.9	-	-
Chloramphenicol*	-	-	92.2	1.9	5.9	-	-

*Data based on disk susceptibility testing
S: Sensitive; I: Intermediate resistant; R: Resistant.

For azithromycin and clarithromycin sensitivity was only 1% with PK/PD breakpoints. Nineteen (18%) *H. influenzae* isolates were beta-lactamase producers. Over half (58%; 11/19) of these isolates were from patients in the paediatric age group. With the exception of two strains with intermediate resistance (MIC 2mg/L), the remaining 17 isolates showed full resistance to ampicillin. All the β-lactamase negative strains were sensitive to ampicillin (MIC range: 0.023 -1.0mg/L) and no β-lactamase negative ampicillin resistant (BLNAR) strains were identified. Susceptibility to amoxicillin-clavulanate, cephalosporins, macrolides/azalides and fluoroquinolones was unaffected by the β-lactamase status of the isolates (data not shown). Susceptibility to co-trimoxazole, tetracycline and chloramphenicol was found to be lower in the β-lactamase producers.

Discussion

S. pneumoniae and *H. influenzae* have been reported to account for 18.6% and 10% respectively of isolates obtained from sputum of patients with community acquired pneumonia in

the UAE [16]. There are, however, no reports describing the susceptibility pattern of these pathogens to commonly used antimicrobial agents in this setting. In this study, the majority of the *H. influenzae* isolates were obtained from paediatric patients. Although the successful introduction of the *H. influenzae* type b vaccine as part of the routine childhood immunization schedule in the UAE in 1999 has resulted in a dramatic decline in the incidence of *H. influenzae* meningitis [17], data presented here indicates that *H. influenza* remains a major aetiological agent in community acquired childhood upper respiratory tract infections. Additionally, the findings demonstrate a considerable degree of penicillin resistance in *S. pneumoniae* isolates in the UAE with just 57% of isolates showing susceptibility to this antibiotic. Although this observation is lower compared to 95.5% and 88.5% susceptibility reported for Austria and Belgium [5], it is still much higher compared to data from the United States and Asian countries [6,18]. Relative to recent regional data, Saudi Arabia has lower susceptibility levels (44.6%) [19], while it is much higher in Qatar with 68% of isolates being penicillin susceptible [20].

For *H. influenzae*, β-lactamase production remains a critical mechanism of resistance to the aminopenicillins. β-lactamase production among *H. influenzae* ranges from approximately 4% in Russia to 26% in the United States, 31% in France, 35% in Qatar and as high as 45% in Thailand [20-22]. In our study, the finding of 18% of isolates being β -lactamase producers appears to be on the lower end of the spectrum, comparable to 18.7% described for the United Kingdom [22] and no BLNAR strains were identified. However, the majority of our *S. pneumoniae* (98%) and *H. influenzae* (100%) isolates remain sensitive to amoxicillin-clavulanate. Penicillin resistance in *S. pneumoniae* is a pharmacokinetic issue and can be overcome with appropriate dosing regimens such as high-doses of amoxicillin/clavulanate (875/125 mg tid and 2000/125 mg bid). Remarkably, in this study the high level of susceptibility to amoxicillin-clavulanate remained consistent even with the application of PK/PD criteria, thus indicating the continued usefulness of the present regimen of this drug in the management of community acquired respiratory tract infections caused by these pathogens in our setting. In contrast, co-trimoxazole appears to be of limited use showing the least in vitro activity against both pathogens.

It has been shown that the value of the antibacterial MIC90 of a bacterial species in determining which drug should be used for a specific infection can be increased by interpreting the MIC90 in conjunction with the in vivo PK/PD data for the agent [11,15]. Both human and animal studies have shown that antibiotic breakpoints based on PK/PD data show significantly better correlation with clinical and bacteriologic success. As in vitro MIC and PK/PD breakpoints may differ substantially, breakpoints for the latter have been published for several antimicrobial agents against selected bacteria [14,22,23]. In light of clinical and PK/PD data, the CLSI revised the recommended MIC breakpoints for oral β -lactams against *Streptococcus pneumoniae* in 2000. In this study, we have interpreted the MICs on the basis of both CLSI and PK/PD breakpoints. Based on the PK/PD breakpoints, cefaclor was the least effective cephalosporin. However, using CLSI breakpoints, 94.1% of *H. influenzae* isolates were classified as sensitive versus 41.2% by PK/PD breakpoints; and for *S. pneumoniae*, 57% were sensitive versus 43% when PK/PD breakpoints were applied. Antibiotic therapy in respiratory tract infections is usually aimed at bacterial eradication in a bid to maximize clinical cure and minimize the development and spread of resistance. Such an increase in antimicrobial resistance when the clinically relevant PK/PD breakpoints are applied reduces the probability of achieving these targets and increases the probability of clinical failure. A knowledge of the resistance pattern in terms of the PK/PD breakpoints as described in this study is therefore of significant clinical relevance.

Recent reports indicate a trend for decreasing susceptibility of *S. pneumoniae* to fluoroquinolones [7,22]. The finding that 24% of isolates were non-susceptible (intermediate and resistant) to ofloxacin with elevated ciprofloxacin MIC90 in these resistant isolates is of concern. Although *H. influenzae* isolates show 100% susceptibility to these antimicrobial agents, their use as empirical therapy in respiratory tract infection may be affected by increasing *S. pneumoniae* resistance. The susceptibility of *S. pneumoniae* to the macrolides we studied, namely erythromycin, azithromycin, clarithromycin and clindamycin, was under 80% irrespective of interpretive criteria

applied. This high level of macrolide resistance coupled with the finding that almost half of the penicillin resistant isolates were also resistant to azithromycin and clarithromycin is of concern. The picture was even more disturbing for *H. influenzae* where only 1% of isolates were sensitive to azithromycin and clarithromycin using PK/PD breakpoints. This finding is consistent with clinical data indicating bacteriological failures associated with macrolide therapy in otitis media. [8,24]. The findings from this study indicate that macrolide antimicrobials might not be appropriate for the empirical therapy of respiratory tract infection in the UAE.

Erythromycin resistance in *S. pneumoniae* arises as a result of modification of the drug-binding site which is regulated by the *erm*(B) gene (MLSB-phenotype) and is associated with high-level resistance (MICs of >64 mg/L) [25,26]. Low-level erythromycin resistance also occurs with MICs of 1-32 mg/L, and is due to the active efflux of the drug which is regulated by the *mef*(A) gene [25]. Cross resistance between erythromycin and clindamycin can be used to approximate the prevalence of the *erm*(B) mediated methylation mechanism versus *mef*(A) efflux mediated mechanism [27]. In North America, macrolide-resistance in pneumococci is predominantly mediated by *mef*(A) gene, while *erm*(B)-mediated ribosomal methylation has been found in over 80% of erythromycin-resistant *S. pneumoniae* isolates in most European countries [25,28]. On the basis of the high rate of cross-resistance to clindamycin in this study, the *erm*(B) mediated (MLSB phenotype) resistance appears to be predominant among the isolates in our setting.

It has been said with the global increase in antimicrobial resistance, agents and doses providing drug concentrations that exceed the magnitude of the PK/PD breakpoints required should be selected to limit the emergence and spread of bacterial resistance [29]. The findings of this study provide data which can give relevant prescribing guidance for clinicians. Based on PK/PD breakpoints, amoxicillin/clavulanate had the best overall activity of the antimicrobial products tested and cefalcor was the least effective cephalosporin for both of these pathogens. The high levels of resistance to macrolides in both pathogens, the elevated fluoroquinolone resistance in *S. pneumoniae*, and the occurrence of multidrug resistant isolates are all cause for concern and indicate an urgent need for continued surveillance.

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