ORIGINAL ARTICLE

Etiological Trends and Antibiotic Susceptibility of Bacterial Strains Causing Respiratory Tract Infections

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ABSTRACT

Background: Lower respiratory tract infections (LTRIs) are emerging as the most common infectious diseases of humans. Antibiotic resistance has increased in all the major pathogens therefore, this project engrossed on defining the current drift of bacterial etiologies of respiratory tract infections among the patients and their antimicrobial susceptibility pattern.

Methods: This cross-sectional study with non-probability consecutive sampling was conducted in the microbiology laboratory of Ziauddin Hospital. Bacterial isolates (163) were recuperated from respiratory sputum specimens obtained from patients with lower respiratory tract infections. The pathogens collected for study were *Streptococcus pneumonia, Haemophilus influenzae,* and *Moraxella catarrhalis.* Frequencies and percentages were computed for categorical variables like microorganism, gender, age, duration of lower respiratory tract infections, etc. Mean and standard deviation were calculated for quantitative variables like age and infection duration. Furthermore, duration of disease was stratified by post stratification Chi Square with p value ≤ 0.05 was considered significant.

Results: Most commonly isolated pathogen is *Moraxella catarrhalis* 72.39% followed by *Haemophilus influenza* 14.72% and *Streptococcus pneumonia* 12.88%. For *Streptococcus pneumoniae* 47% sensitivity showed to Ampicillin, 52% Penicillin, 61.9% Erythromycin and 57% to Ceftriaxone. For *Haemophilus influenzae* 100%, sensitivity showed to Ceftriaxone, 100% Amoxicillin and 62.5% Co-trimoxazole. Similarly, for *Moraxella catarrhalis* 54% sensitivity was showed to Erythromycin, 100% Ceftriaxone and 27% with Levofloxacin.

Conclusion: *Moraxella catarrhalis, Haemophilus influenzae* and *Streptococcus pneumoniae* were the most common bacterial isolates recovered from LTRIs. We found *M. catarrhalis* resistant rate was elevated for Levofloxacin, *Streptococcus pneumonia* for Co-trimoxazole and *Haemophilus influenzae* to all β-lactams.

Keywords: Respiratory Tract Infection; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Streptococcus pneumonia*.

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INTRODUCTION

Lower respiratory tract infection (LRTI) are recognized to be the most widespread and serious infections[1]. According to United Kingdom (UK) studies over all incidence of LRTI in adult population, in general practice is approximately 44 – 84 cases per 1000 population per year[2]. LRTI include Community Acquired Pneumonia (CAP) and Acute Exacerbation of Chronic Bronchitis (AECB)[3]. Etiology of LRTI varies with age, season and geographic region[3]. Bacterial pathogens responsible for typical CAP include *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), *Klebsiella pneumoniae* (*K. pneumoniae*) and *Moraxella catarrhalis* (*M. catarrhalis*) [3,4]. These pathogens are responsible for 85% of CAP cases. Among these, the most common one is *S. pneumoniae*[3].

The increase in antibiotic resistance is a serious health concern which is complicating the management of LRTIs[4,5]. Of particular concern are the appearance and spreading of penicillin resistant *S. pneumoniae*. In *H. influenza* and *M. catarrhalis* principal mechanism of resistance is β-lactamase (BL) production which makes them resistant to all beta-lactams. However, rare β-lactamase negative ampicillin-resistant (BLNAR) *H. influenzae* isolates have also been reported[4].

Due to emergence and dissemination of multidrug resistant pathogens, difference of etiological agent and prevalence of atypical pathogens in different geographical location, it is crucial to frequently update the etiology, predisposing factors and advance laboratory diagnostic facilities to ascertain the infectious cause of LRTI[6].

Usually empirical treatment is adopted for CAP but because of increased frequency of antibiotic resistance isolated respiratory pathogens has complicated the selection process of antimicrobial agents[7]. In developing countries like Pakistan most LRTI are treated empirically, may be due to higher cost of laboratory services or non-availability of standardized laboratories[8]. Ongoing surveillance is essential to update the consultants and general practitioners to choose the appropriate antibiotics in reference to the infected organisms similarly vigilant and shrewd use of antibiotics will minimize the burden of multidrug resistance[4,6]. The purpose of this study was to extract data of the most common bacterial pathogens responsible for LRTI and their antimicrobial susceptibility patterns in tertiary care hospitals setting in Pakistan.

METHODS

This descriptive study evaluated the frequency of isolation of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and their susceptibility profile. Study conducted from October 2014 to November 2015 at Department of microbiology, in Ziauddin university hospital (Ref.MIC-2013-201-144). To determine the frequency of bacterial pathogens of LRTI, sample size of patient was calculated with a 0.05 margin of error and 95% confidence level. Prevalence of bacterial pathogens in LRTI is 10.6 % after putting the values in the formula $n = (Z_{1-\alpha,/2})^2 Pq / d^2 = 163$. Specimens were obtained from patients with LRTI and bacterial isolates were recovered from sputum. Isolates from patient of 35-70 years of age were obtained after 48 hours. Patients with diagnosis of ventilator associated pneumonia and health care associated pneumonia were not considered. Clinical laboratory standard institute (CLSI)[10] and the European Committee on Antimicrobial Susceptibility Testing for bacterial identification and antibiotic susceptibility testing[11] was done. Exclusion criteria were strappingly fulfilled. Written approval was taken from the institutional ethical committee Informed consent was also taken from the patients.

Age, gender, source of specimen and visit type were collected and recorded. Samples were inoculated on "sheep blood agar (SBA), chocolate agar and MacConkey agar". Streaking was performed with a sterile wire loop on these media plates following standard procedure. The culture plates were incubated at "35°C in ambient atmosphere" for 24-48 hours and noticed for growth by formation of colonies. Organism grown were identified and their antibiotic susceptibility testing was performed following standard procedures[9-11].

Colonies of *H. influenzae* were identified as "Gram negative rods, tiny, moist, and smooth gray colonies with absence of hemolysis, positive catalase and oxidase test although oxidase test may be variable. However, its oxidase test may be negative due to the presence of growth factors X and V, satellite growth around streaks of Staphylococcus aureus"[12]. Presence of *M. catarrhalis* was identified as "gram negative cocci on gram staining, colony morphology, oxidase test, hockey puck sign, catalase test, and butyrate esterase production, and their inability to ferment sugars"[13]. Identification features of *S. pneumoniae* are defined as "presence of tiny, round, flat, and transparent colonies, with central depression (checker piece and nail head colonies), a hemolysis, catalase negative and oxidase negative, absence of bile-esculin hydrolysis, lysis by bile-salts, susceptibility to optochin and others biochemical characters"[15,18].

The susceptibilities testing of isolated organisms were done by Kirby-Bauer disc diffusion method was used using Mueller Hinton agar plates[10,11]. Twenty-four hours incubated isolated colonies were suspended in normal saline and a suspension of 0.5 McFarland turbidity was made. They were streaked using sterile swabs over the surface of Mueller Hinton agar plates. Antimicrobial discs of different strengths were placed on the surface of the MHA plates and gently pressed. The antimicrobial discs were obtained from Oxoid® (UK) and Bioanalyse® (Turkey). The tested Antimicrobials were "ampicillin (10 μg), co-amoxiclav (amoxicillin/clavulanic acid 20/10 μg), cefadroxil (30 μg), ceftriaxone (30 μg), meropenem (10 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), co-trimoxazole (trimethoprim/ sulfamethoxazole 1.25/23.75μg), erythromycin (15 μg) and clindamycin (2 μg), Vancomycin (30 μg)." The plates were inverted and incubated at 37°C for 16 to 18 hours. The inhibition zone diameters were measured and recorded[10, 11].

For data analysis, Statistical Package for Social Sciences (SPSS) version 17 was used. For variables like microorganism, gender and antibiotic susceptibility frequencies and percentages were calculated. For quantitative variables like age, duration of LRTI, etc., mean and standard deviation was considered. Effect modifiers like age, gender and duration of disease stratified as post stratification Chi-square test applied and *p* value ≤ 0.05 was considered significant.

RESULTS

The average age of the patients (n=163) was 52.61±11.8 (95% CI: 50.78-54.45) years and mean duration of LRTI was 8.55±1.96 months. Histogram (Figure 1) shows the age distribution in different groups. Out of 163 patients, 85(52.15%) were male and 78(47.85%) were female patients.

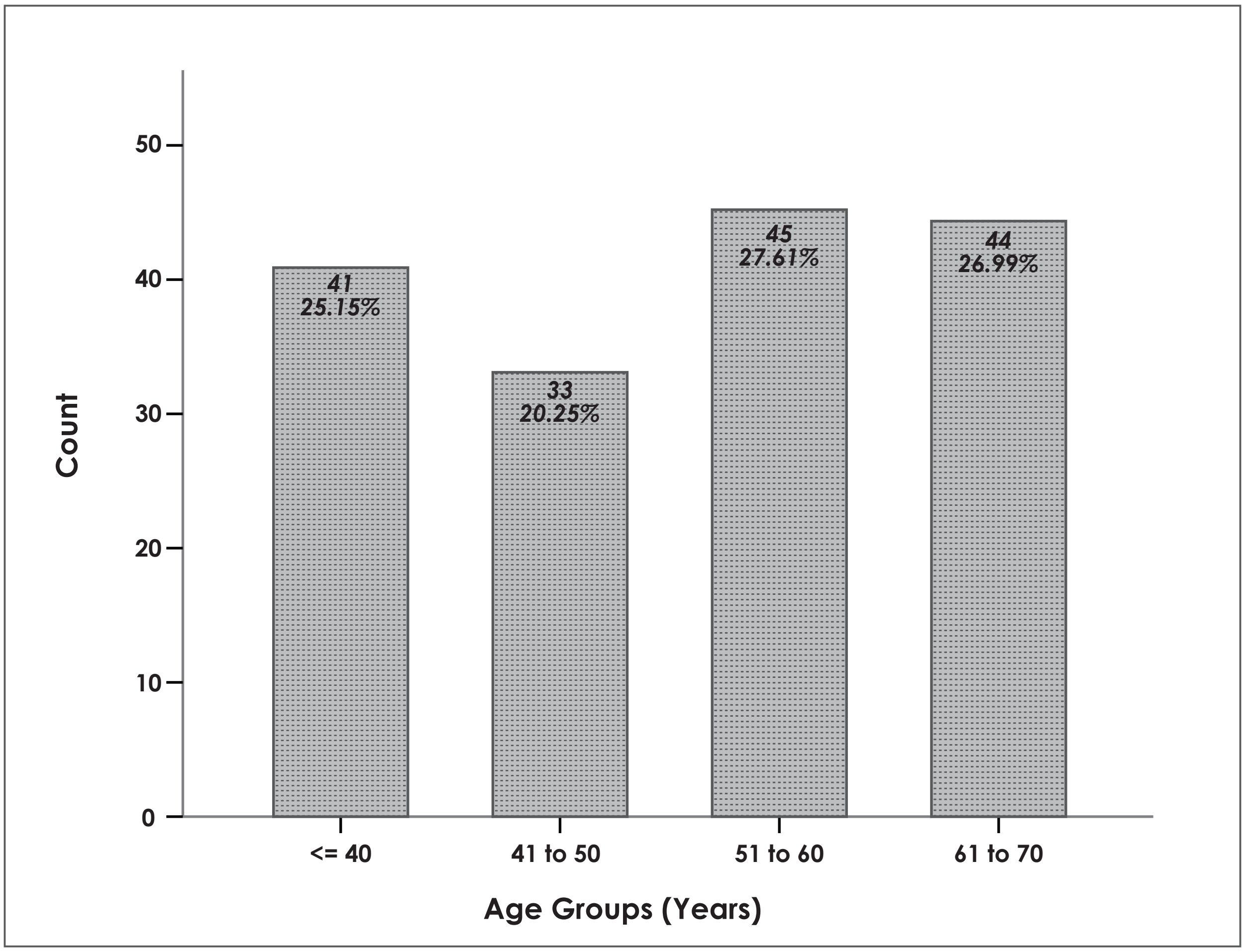

Figure 1: Age distribution of patients in different groups.

Frequency of major pathogen of community acquired lower respiratory tract infection is presented as *Moraxella catarrhalis* organism was commonly observed i.e. 72.39% (118) followed by *Haemophilus influenzae* 14.72% (24) and *Streptococcus pneumoniae* was observed in 12.88% (21) patients. For all three bacteria there were no significant *p*-value found *Streptococcus pneumonia* (0.66), *Haemophilus influenzae* (0.76) and *Moraxella catarrhalis*, (0.92). Sensitivity pattern (Table 1) of these organisms (*Streptococcus pneumonia, Haemophilus influenzae and Moraxella catarrhalis*) were reported and showed that *Streptococcus pneumonia* was 85.7% to 100% sensitive to Levofloxacin, Clindamycin, Linezolid, and Vancomycin. *Haemophilus influenzae* was sensitive to Ampicillin, Ceftriaxone, Co-amoxiclav, Moxifloxacin, Cefixime and Meropenem. *Moraxella catarrhalis* was sensitive to Ceftriaxone and Co-amoxiclav.

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Table 1: Susceptibility pattern of major bacterial pathogens of lower respiratory tract infections (LTRIs).

Antibiotics	*Streptococcus pneumonial* (n=21)		*Haemophilus influenza* (n=24)		*Moraxella catarrhalis* (n=118)	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Ampicillin	10[47.6%]	11[52.4%]	24[100%]	0[0%]	NT	NT
Penicillin	11[52.4%]	10[47.6%]	NT	NT	NT	NT
Erythromycin	13[61.9%]	8[38.1%]	NT	NT	64 [54.2%]	54[45.8%]
Ceftriaxone	12[57.1%]	9[42.9%]	24[100%]	0[0%]	118[100%]	0[0%]
Levofloxacin	19[90.5%]	2[9.5%]	NT	NT	32[27.1%]	86[72.9%]
Co-amoxiclav	10[47.6%]	11[52.4%]	24[100%]	0[%]	118[100%]	0[0%]
Co-trimoxazole	3[14.3%]	18[85.7%]	15[62.5%]	9[37.5%]	18[15.3%]	100[84.7%]
Moxifloxacin	NT	NT	20[83.3%]	4[16.7%]	41[34.7%]	77[65.3%]
Ciprofloxacin	NT	NT	NT	NT	77[65.3%]	41[34.7%]
Tetracycline	NT	NT	NT	NT	41[34.7%]	77[65.3%]
Cefixime	NT	NT	24[100%]	0[0%]	NT	NT
Meropenem	NT	NT	24[100%]	0[0%]	NT	NT
Clindamycin	18[85.7%]	3[14.3%]	NT	NT	NT	NT
Linezolid	21[100%]	0[0%]	NT	NT	NT	NT
Vancomycin	21[100%]	0[0%]	NT	NT	NT	NT

NT= Not Tested.

Table 2: Frequency of major pathogen of community acquired lower respiratory tract infection (LRTI) with respect to age groups, gender and duration of disease.

Bacterial Strains	Age Groups (Years)					Gender			Duration of Disease		
	≤40 n=41	41-50 n=33	51-50 n=45	61-70 n=44	*p-Value*	Male n=85	Female n=78	*p-Value*	≤8 days n=86	>8 days n=77	*p-Value*
Streptococcus pneumoniae	4 (9.8%)	4 (12%)	5 (11%)	8 (18%)	0.65	14 (16.5%)	7 (9%)	0.15	12 (14%)	9 (11.7%)	0.66
Haemophilus influenzae	5 (12%)	2 (6%)	8 (17.8%)	9 (20.5%)	0.30	13 (15.3%)	11 (14%)	0.83	12 (14%)	12 (15.6%)	0.76
Moraxella catarrhalis	32 (78%)	27 (81.8%)	32 (71%)	27 (61.4%)	0.18	58 (68.2%)	60 (76.9%)	0.21	62 (72%)	56 (72.7%)	0.92
Chi-Square test applied.											

Stratification analysis (Table 2) was performed and *Moraxella catarrhalis* was observed highest (81.8%) among 41-50 age group and in females (76.9%). However, all three bacteria (*Streptococcus pneumonia, Haemophilus influenza; Moraxella catarrhalis)* showed no significant results among different age groups, gender and duration of disease.

DISCUSSION

Lower respiratory tract infection (LRTIs) is in the midst of the most common infectious diseases globally[14]. Bacterial agents responsible for of LRTIs are different in different areas, so the susceptibility profile will also vary between geographical locations. Current information of the bacteria responsible for LRTIs and their sensitivity profile are therefore essential for the selection of appropriate therapy[4-6]. This study was conducted to ascertain the antimicrobial resistance pattern among microorganisms isolated from patients with an innovative approach toward developing antibiotic policies in association with the clinicians[15].

Sputum Gram stains and culture are considered as a simple test for the diagnosis of LRTI[16]. In our study, *M catarrhalis* was the most predominant isolate recovered from patients with LRTIs. However, another study conducted in Pakistan reported *S. aureus* as the most dominant bacteria followed by *S. pneumoniae*[17]. In another study conducted in Pakistan most common cause of LRTI was *Streptococcus pneumoniae* followed by *H influenza*, whereas *M. catarrhalis* was on sixth position[18]. In last 20 to 30 years; the *M. catarrhalis* has arisen as a pathogen and is now considered as a principal cause of upper respiratory tract infections in healthy kids and elderly people[19].

All the isolated of *S. pneumoniae* in our study displayed erratic sensitivity to linezolid and vancomycin. Similar results were gathered from various studies conducted in other parts of the world[4,21,22]. In *S. pneumoniae* resistance to penicillin is of special concern. Guèye Ndiaye observed 1% *S. pneumoniae* resistance to penicillin[22]. In the early 1990, a study conducted in Greece, evaluated the antimicrobial susceptibilities of *S. pneumonia* isolated from patients with CAP. That study showed 14% resistance to penicillin[4] while we observed 47% resistance.

The antibiotic resistance patterns of *Streptococcus pneumoniae* isolates vary widely from one country to another. Data from the Sofia Maraki project stated ceftriaxone resistance levels in *S. pneumoniae* 0% in Greece[4] to 30% in south India in 2013[21]. Similarly, Ndiaye et al., in Dakar observed negligible resistance against Co-amoxiclav and ceftriaoxone[23] while we observed high antimicrobial resistance to ampicillin (47%), ceftriaxone (42%), and Co-amoxiclav (47%).

Within context to the present study, *H. influenzae* seems to be surprisingly susceptible to numerous classes of antibiotics, including the β-lactams and b-lactamase inhibitor combinations. The prevalence rate of co-amoxiclav, ceftriaxone, cefixime, and meropenem is 100% sensitive. The same picture is observed to other studies conducted in different parts of world[4,24,25]. Although, the cotrimoxazole resistance cases (26%) were reported in the research study conducted in Kuala Lumpur [26]. A significant reduction in the resistance to cotrimoxazole is observed in *H. influenzae* when the results of our study were compared with those from Ethiopia, where 66% of the isolates were resistant to cotrimoxazole[27]. In *H. influenza*, fluoroquinolone resistance has only rarely been observed in Greece[4] and in different parts of Pakistan[24]. However, we have noticed 16% isolates of *H. influenzae* resistant to moxifloxacin, which comes in the family of fluoroquinolone.

M catarrhalis has emerged as a significant pathogen responsible for LRTI in recent years. Since, 90% of *M. catarrhalis* isolates produce beta lactamase enzyme making them resistant to ampicillin. β-lactam/ β-lactamase inhibitor combinations, such as amoxicillin-clavulanate have therefore considered as a treatment of choice for *M. catarrhalis* infections[28]. All isolates of *M. catarrhalis* were 100% sensitive to amoxicillin/clavulanate and ceftriaxone, which is comparable to other recent studies conducted in Karachi[29]. Similarly, Ramana et al., also noticed 100% sensitivity to amoxicillin/clavulanate[30]. However, in the current study, *Moraxella* isolates displayed maximum resistance to levofloxacin (27%) tracked by moxifloxacin (34%) and tetracycline (34%).

Over the past ten to twenty years, *M. catarrhalis* has progressed to a well-recognized pathogen. Indeed, beta-lactamase producing strains appear to be more prevalent, and this may play a vital role in the therapy of infections. British Thoracic Society and American Thoracic Society guidelines suggest empirical antibiotic treatment with amoxicillin or a macrolide for outpatients in case of first use of antibiotic. For in patients not requiring ICU, treatment recommended is a respiratory fluoroquinolone or a beta lactam plus macrolide. For patients requiring ICU, a beta lactam plus either clarithromycin or a respiratory fluoroquinolone is advised[24]. In addition to this, it is important to collect information on the local resistance pattern, which could contribute, to some knowledge for selection of appropriate empirical antibiotic therapy. Although prevalence and antibiotic susceptibility profile of these bacteria vary from area to area, continuous surveillance at indigenous and national levels remains imperative to notice any auxiliary changes in frequency of pathogens and observe any fluctuations in their sensitivity profile. Therefore, this may help physicians and doctors to select appropriate antimicrobial options for the management of LRTI. Furthermore, it may also curtail the antimicrobial resistance in the community as well as in health care setup.

CONCLUSION

The most prevalent bacterial agents of LRTIs are *M. catarrhalis* followed by *Haemophilus influenzae and*

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Streptococcus pneumoniae. Similarly, the isolates collected in our setup *M. catarrhalis* resistant rate was elevated for levofloxacin, *Streptococcus pneumonia* for Co-trimoxazole. However, *Haemophilus Influenzae* showed minimum resistant and remained susceptible to all β-lactams. Thus, vigilant use of antimicrobial agents will reduce the load of multidrug resistance and thereby enabling improved patient management and limiting the resultant morbidity and mortality arising from LRTI's.

CONFLICT OF INTEREST

The authors would like to acknowledge the Ziauddin laboratory staff and the supervisor for their immense contribution.

CONFLICT OF INTEREST

The authors declare no conflict of interest

ETHICS APPROVAL

Ethics review committee of Ziauddin University Pakistan approved this study (Ref.MIC-2013-201-144).

PATIENT CONSENT

Verbal and written signed consent were taken from patients.

AUTHORS' CONTRIBUTION

FA analyzed and interpreted the patient data; FIA reviewed the manuscript while NK majorly contributed in the manuscript writing.

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