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Determination of Microbiological Spectrum and Antimicrobial Resistance Trend among Patients with Respiratory Tract Infection in Pakistan

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[ZK]Conception and design, [MBA, HI] Collection and assembly of data, [SG]Analysis and interpretation of the data, Statistical expertise, [SS, ZK] Final approval and guarantor of the article

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A B S T R A C T

Background: The most reported infections in humans are respiratory tract infections (RTIs). Some of these infections are mostly mild, temporary lasting and sometimes self-limiting due to which many infected persons tend to ignore these infections. Respiratory infections occur in all age group but most of the time male are commonly affected.

Objectives: To determine the prevalence of various bacterial pathogens associated RTIs and identify the member of pathogenic organisms in respiratory tract infection and their antibiotic susceptibility in health care centres.

Methodology: Sputum sampling was done from 227 patients and the specimens go through microbiology examination. Antibiotic susceptibility profiling was carried out by Kirby Bauer's disc diffusion method.

Results: Patients having the URTIs and LRTIs infections belong to both genders according to age groups. Total number of female and male patients was 80 and 147, respectively. Age group of ranged 40-60 years was at a high risk of respiratory tract infections. The most prevalent microorganism was Pseudomonas aeruginosa (n=51, 22.4%) and least was Citrobacter farmeri (n= 4, 1.8%). Highly effective drugs were meropenem and levofloxacin, while high resistance was observed against amikacin and cefepime.

Conclusion: Pseudomonas aeruginosa was found the most prevalent organisms in respiratory tract infection patients. The patients within the age range of 40-60 years were observed at high risk of getting respiratory tract infection. Among all the tested antibiotics meropenem and levofloxacin were the most effective drugs.

Key words: Respiratory tract infection, pathogenic bacteria, antimicrobial susceptibility.

Introduction

The invasive treatments are more common in hospitals; nosocomial infections are now experienced by a greater percentage of hospitalized patients. Such infections increase the length of a hospital stay, use extra hospital resources, increase the risk of microorganisms infecting health care workers, burden the health care system and allow for the rapid transmission of the infection.[1,2] Basically, the top causes of common hospital-acquired infections are not the same as those of community-acquired infections.[2] On the other hand, antimicrobial susceptibility in each type of organism is determined by infection origin, possible changes over time and the local epidemiological trends for that area. [3]

Two of the most common in-hospital infections, found in the urinary and respiratory tracts, use a lot of health resources. Also, such infections can seriously harm and even kill many people who have been hospitalized. [4] When a HAI is diagnosed, the therapy should depend on what antibiotics are known to be effective against the pathogen causing the infection. [5]

A microbial infection occurs when pathogenic microbes enter the human body through different paths and cause the body to respond with symptoms.[6] Most of these pathogens are generally cleared out by the immune system, so the result is either no signs of sickness or minor infection on the cell tissue.[7] Yet, when there is heightened toxicity, a lot of microorganisms or the immune system is not working well, these pathogens can make tissues ill, causing illnesses with symptoms including fever, rash and diarrhoea.[8] An effective immune response to

some microbes can quickly eliminate them, whereas when the response is weak, an infection can grow into a lasting, untreated problem.[9] Still, using antibiotics too much and for a long time can cause the development of resistance in microbes. [10] If pathogens become tolerant to antibiotics after some changes, antibiotic resistance occurs which can hinder successful patient outcome. [11]

For now, treating infections caused by bacteria mostly depends on using cephalosporin antibiotics.[12] But since resistance to antibiotics is increasing, they are becoming less useful, so there is a growing need to explore other treatments. Excessive and unsuitable use of antibiotics often leads to resistance, so health practitioners tend to prefer personalized therapy protocols. Experts are proposing to use drugs known as glycopeptide antibiotics, increase infection control efforts and create new antimicrobial treatments to deal with rising antibiotic resistance. [13 14 15]

Respiratory tract infections (RTIs) which cause many serious health problems, are some of the most prevalent infections globally. [16] Where a person lives, their age and the setting of their healthcare play a role in which pathogens cause respiratory infections. [17] It has become very concerning for public health that respiratory infections can become resistant to drugs. [18] Having antimicrobial resistance can make it difficult to treat an infection, take a long time for illness to be gone and cause additional expenses.[19] Understanding the spread of pathogens causing RTIs and knowing which ones are resistant to certain drugs is important for choosing and using correct treatments and establishing good infection control steps. [20]

A variety of ways in which bacteria can use their genes lets them become resistant to drugs that were once effective against them. Resistance of S. pneumoniae to penicillin and beta-lactam antibiotics usually develops because the bacterium alters its PBPs which play an essential role in building and keeping the wall around the bacterial cells. Changes to the cell wall because of PBP mutations make the beta-lactam ring bind less effectively to its active PBP site. Although one change in a single amino acid can give a strain resistance to beta-lactam antibiotics, strains that are most resistant to penicillin (MIC ≥ 2 µg/ml) have more changes in PBP proteins than those with minor resistance (MIC 0.12 to 1 µg/ml). [21]

When penicillin becomes less susceptible, third-generation cephalosporins and amoxicillin show a greater risk of failure. Beta-lactam drugs can overcome PBP-related resistance when enough medicine stays at the infection site for an adequate time. Pneumococcal infection treatment is effective if the unbound concentration of beta-lactams in the blood is kept above the MIC of the invading pneumococcus for about half the time between doses. [22]

Antimicrobial resistance is occurring at rising rates all over the world, but its nature and level of progress vary from one region to another. It has been very valuable to use surveillance to track changes in resistance to different antimicrobial agents by respiratory tract infections at the national and international level. The Alexander Project collected and reported on how sensitive *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* are to antimicrobials in adults from 1992 onward and included centers in 26 countries between 1998 and 2001. [23]

Various risk factors for infection with a strong bacterial pathogen are well established such as antimicrobial medication, being less than 24 months old, infections in the upper respiratory tract (including sinus or middle ear), attending day care and nasopharyngeal carriage. During the late 1800s, the first descriptions of pneumococcus colonizing healthy individuals became available. [24] Many children around the world, sick or otherwise, commonly carry S. pneumoniae in their nose. [25]

Nowadays high rate of mortality in patients with acute infections of respiratory disorder is due to non-efficacy of antibiotics against bacteria has been at distressing stage throughout the world, so more studies to search for novel bacterial strains against different agents is required. The current study is aimed to determine the prevalence of various bacterial pathogens associated RTIs (respiratory tract infection) from sputum samples and throat swabs, determine the antimicrobial resistance pattern of the isolated bacterial agents and to identify and differentiate the member of pathogenic microorganisms in respiratory tract infection.

Materials and Methods

A total of 227 sputum and throat swabs samples were collected from the patients who visited Jinnah Hospital, Mayo Hospital and Services Hospital Lahore. The patients with respiratory tract infection were included irrespective of the patient's age and gender. A written consent was obtained from the patients or their guardians. The patients suffering from any serious disease including tuberculosis, AIDS, hepatitis and/or cancer were excluded. The patients who were on antibiotic therapy were also excluded. Samples were collected by using sterile container wide mouth glass bottles with screw caps. The samples were transported to the laboratory in sterile containers of Amie's medium (oxoid). Containers were completely labelled with name, sex, age, and time of collection. Throat was rubbed with a sterile cotton swab tanking possible sample make sure sample were not contaminated with saliva. For every sample

new swab was used and gloves were changed each time to avoid contamination. Swabs were dropped in the transport medium (Amies medium) and safely send to the laboratory for examination. Cultures were identified on the base of their culture characteristics and pattern of biochemical reactions.

The antibiotics sensitivity was determined by Kirby-Bauer's disc diffusion method on MHA agar plates and the results were interpreted as per standard CLSI guidelines 2022 and European Committee on Antimicrobial Susceptibility Testing (EUCAST). The basic purpose of Kirby-Bauer's disc method was to identify the pattern of specific organisms against specific drugs.

Turbidity of the inoculum was compared to the 0.5 McFarland. The turbidity of inoculum was adjusted in such a way to matched to the turbidity of standard, as 0.5 McFarland. Bacterial suspension was spread on MHA plates, the standard antibiotic discs was used to identify the susceptibility pattern against the microorganisms including 30µg Ceftazidime, 30µg Amikacin, 25µg Co-Trimoxazole, 10µg Erythromycin, 10µg Gentamicin, 10µg Ampicillin, 10µg Chloramphenicol, 5µg Ceftriaxone, 5µg Ciprofloxacin, 5µg Cefixime, 5µg Levofloxacin and Colistin 10µg were placed to check the sensitivity and incubated the plates for 12-16 hours at 37°C. The zone of inhibition was appeared after the incubation was measured.

Data were analyzed by Statistical Package for Social Sciences (SPSS) version 25 (IBM, USA). Categorical variables were calculated as frequency and percentage. The categorical variables were compared by Chi-square test at 95% confidence interval. A two-tailed *p*-value of less than 0.05 was described as statistically significant.

Results

A total of 13 bacterial species, 5 (38.46%) Gram positive and 8 (61.53%) Gram negative, were identified (Table I). *P. aeruginosa* was found to be the most prevalent (n=51, 22.4%), while C*itrobacter farmer* (n=4, 1.8%) was the least prevalent. Gram negative bacteria included *P. aeruginosa* (n=51, 22.4%), *K. pneumonia* (n=43, 18.9%), *E. coli* (n=36, 15.8%), *Providencia spp* (n=7, 3.1%), (n=6, 2.6%), *Acinetobacter baumanii* (n=5, 2.2%), *Citrobacter farmeri* (n=4, 1.8%), *Serralia liquefaciens* (n=12, 5.2%), and *Stenotrophomonas maltophilia* (n=10, 4.4%). Among Gram positive bacterial species, *S. pyogenes* (n=18, 7.4%) was the most prevalent followed by *Staphylococcus aureus* (n=15, 6.6%), *Streptococcus viridians* (n=10, 4.4%), *Staphylococcus spp* (n=6, 2.6%), and *Streptococcus pneumonia* (n=6, 2.6%). *Candida albicans* (n=6, 2.6%) was the only fungus detected in the isolated samples.

Table I: Frequency Distribution of Isolated Bacterial Species.

Sr.No	Bacterial Agents	Gram Staining	N	%
1	Pseudomonas aeruginosa	-ve	51	22.4%
2	Klebsiella pneumonia	-ve	43	18.9%
3	Escherichia coli	-ve	36	15.8%
4	Streptococcus pyogenes	+ve	18	7.4%
5	Staphylococcus aureus	+ve	15	6.6%
6	Providencia spp	-ve	7	3.1%
7	Staphylococcus spp	+ve	6	2.6%
8	Streptococcus pneumonia	+ve	6	2.6%
9	Candida albicans		6	2.6%
10	Acinetobacter baumanii	-ve	5	2.2%
11	Citrobacter farmeri	-ve	4	1.8%
12	Serralia liquefaciens	-ve	12	5.2%
13	Stenotrophomonas maltophilia	-ve	10	4.4%
14	Streptococcus viridians	+ve	10	4.4%

The total number of infected patients was found to be 227 whereas the number of infected female patients was 80 and male was 147. The infection rate was found higher in the patients of age group 3 (41-60 years) and lowest in age group 5 in between (81-100 years) as shown in **(**Figure 1**)**. The age group 2 (21- 40 years) female mostly has respiratory tract infection as compared to man on the other hand, males ranging (41-60 years) mostly have respiratory infection as compared to female.

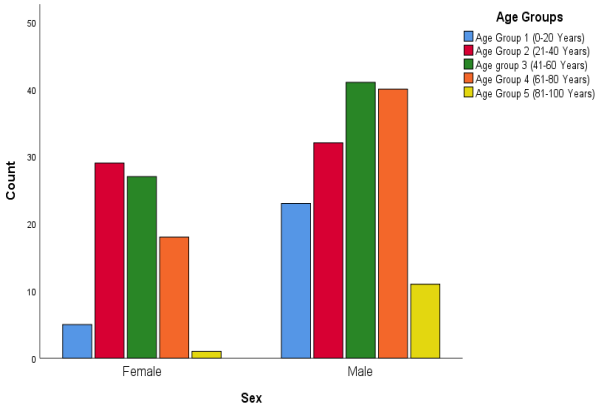

Figure 1. Prevalence of Infection Rate According To Age Group.

All identified isolates of upper and lower respiratory tract infections were screened for antibiotics susceptibility test against different antibiotics (Table II). Antibiotics used were Aztreonam, Ampicilline, Optochin, Cefoperazone / Sulbactam, Norfioxacin, Rifampicin, Vancomycin, Moxifloxacin,

Chloremphenicol, Polymyxin, Pencililin, Erythomycin, Co-Triamoxazole, Clindamycin, Bactitracin, Amikacin, Tobramycin, Gentamicin, Ciprofloxacin, Imipenem, Levofloxacin, Meropenem, Amoxicillin/Clavulanic Acid, Ceflexin, Cefotaxime, Ceftazidime, Ceftriax One, Cefepime, Piperacillin/Tazobactam, and Doxycycline.

Table II: Overall Antibiotic sensitivity pattern of isolated bacteria.

Antibiotics Class	Antibiotics	Disk contents	Resistant Isolates
Aminogyleasides	Gentamicin	10µg	8
	Tobramycin	10µg	55
	Amikacin	30µg	56
Antipseudomonal -fluoroquinolones	Ciprofloxacin	5µg	42
	Levofloxacin	5µg	43
	Gatifloxacin	5µg	0
Antipseudomonal carbapenem	Imipenem	10µg	70
	Meropenem	10µg	43
	Doripenem	10µg	0
Antipseudomonal penicillin+β lactam inhibitors	Piperacillin	100µg	11
	Ticarcillin-clavulanic acid	75/10µg	1
Extended spectrum cephalosporins	Ceftazidime	30µg	52
	Cefepime	30µg	17
	Ceftoxime	30µg	22
	Ceftriaxone	30µg	48
Folate pathway inhibitors	Trime/Sulpha methoxazole	1.25/23.75µg	20
Penicillin+β lactam inhibitors	Ampicillin-Sulbactam	10/10µg	35
	Piperacillin-tazobactam	100/10µg	51
Tetrcyclines	Doxycycline	30µg	40
	Tigecycline	30µg	11
	Minocycline	30µg	36

Antibiogram analysis of gram-positive bacteria showed least resistance towards different antibiotics as compared to gram negative bacteria. Best activities were showed by Levofloxacin towards *Citrobacter farmeri* (100%), *Klebsiella pneumonia* (90%), *Streptococcus pyogens* and *Acinetobacter baumanii* (88%), *Staph. aureus* (86%), followed by *Pseudomonas aeruginosa* (85%), and least sensitivity was shown by *E. coli* (81%). Meropenem was highly effective towards *Acinetobacter baumanii* (83%), *Klebsiella pneumonia* (80%), *S. aureus* (78%), *Streptococcus pyogens* (76%), *Pseudomonas spp.* (71%), whereas *E. coli* (67%) were moderately sensitive. *Streptococcus pyogens* (70%) and *Klebsiella pneumonia*e (60%) were moderately sensitive. *E. coli* showed high resistance (72%) towards Ceftazidime and Ciprofloxacin and 70% resistivity towards Amikacin and Cefepime. Similarly, *Pseudomonas spp.* showed high resistance (71%) towards Amikacin and Cefepime. *S. aureus* also showed high resistance towards Piperacillin- Tazobactam and Cefipime (65%).

Discussion

Respiratory Tract Infections (RTI) is the most prominent infectious in Respiratory Tract unit (RTU). The most reported infections in humans are respiratory tract infections (RTIs). Some of these infections are mostly mild, temporary lasting and sometimes self-limiting due to which many infected persons tend to ignore these infections. A total of 227 samples were collected from different hospitals. The infection rate was found in higher in males than females. Age group (41-60 years) male was count high infection rate due to smoking and dust that cause respiratory infection high.

Neethu Mariyam Johny et al. (2020) highlighted that the most common pathogen that cause respiratory tract infection was *Klebsiella pneumonia* (n=31, 58.5%), 17% *S. aureus*, and 17% *Pseudomonas Aeruginosa, (Klebsiella pneumoniae* was the most prevalent causative agent in this study and found this organism susceptible to Amikacin (87.10%), Meropenem (84.62%), Gentamicin (87.10%) and Ofloxacin (66.6%). More resistant to Amoxicillin, Linezolid, Azithromycin and Ampicillin.[26]

Chawla et al. isolated a total of 830 pathogens from respiratory tract including 56.7% *P. aeruginosa*, 39.3% *Acinetobacter* spp. 45.5% S*tenotrophomonas maltophilia*, and 12.1% *Burkholderia cepacia*. Most effective drug was Cefoperazone-Sulbactam (75.9%), followed by Piperacillin-Tazobactam (71.4%) and meropenem (73.3%).[27]

Taura *et al.* reported that *S. pneumoniae* (25.6%) had the highest rate of occurrence, followed by *Klebsiella spp* (20.8%), *E. coli* (20.9%) and *S. aureus,* (16.3%). Other bacteria like *Proteus spp* (4.7%), *P. aeruginosa* (4.7%), *H. influenzaae* (4.7%) and *Serratiae species* (2.3%) were also identified.[28]

Soma *et al.* reported that most of the isolates were found resistant to piperacillin/tazobactam. *P. aeruginosa, K. pneumoniae, E. coli, Citrobacter*, and Shigella showed 100% resistance to Piperacillin. A higher resistance to *Pseudomonas aeruginosa* isolates was observed with Piperacillin/tazobactam and Cefepime i.e. 42% and 40%, respectively.[29] Same work was conducted by Akcay *et al*. (2014) in turkey to know about resistance rate of different antibacterial drugs against *A. baumannii.* The resistance pattern of Imipenem and Meropenem in *A. baumannii* were isolates from markedly dropped from 79.1% and 76.6% to 7.1% and 5.8%. Similar susceptibility pattern was observed for some other antibiotics like these Amikacin, Gentamicin and Fluoroquinolone which are highly effective among other antimicrobial drugs.[30]

Antibiogram analysis of gram-positive bacteria showed least resistance towards different antibiotics as compared to gram negative bacteria. Best activities were showed by Levofloxacin towards *Citrobacter koseri* (100%), *Klebsiella pneumonia* (90%), *Streptococcus pyogens* and *Acinetobacter baumanii* (88%), *S. aureus* (86%), and followed by *Pseudomonas spp* (85%), and least sensitivity was shown by *E. coli* (81%). Meropenem was highly effective towards *Acinetobacter baumanii* (83%), *Klebsiella pneumonia* (80%), *S. aureus* (78%), *Streptococcus pyogens* (76%), *Pseudomonas spp* (71%), whereas *E. coli* (67%) were moderately sensitive. *Streptococcus pyogens* (70%), and *Klebsiella pneumonia* (60%) were moderately sensitive. *E. coli* showed high resistance towards Ceftazidime and Ciprofloxacin that is (72%), and (70%) resistivity towards Amikacin and Cefepime. Similarly, *Pseudomonas* spp showed high resistance towards Amikacin and Cefepime that is (71%). *S. aureus* also showed high resistance towards Piperacillin- Tazobactam and Cefipime that is (65%). These results are in good agreement with the findings of Toh *et al*. who concluded that Imipenem and Amikacin were the most effective drugs being used against *Enterobacteriaceae*.

Conclusions

Respiratory tract infection is one of the most common illnesses found in most health care setups. In the current study it was concluded that Gram- negative bacteria were more prevalent compared to Gram-positive organism. *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *E. coli* were the most predominant organism in this study. The patients with age range 40-60 years were at a higher risk of bacterial infection. Most isolates showed antibiotic resistance level associated with misuse of antibiotic. Highly effective drugs against almost all isolates were meropenem and levofloxacin, while high resistance was observed against amikacin and cefepime. Infection rate was high in male group due to smoking and dust that cause respiratory tract infection. Respiratory tract infection is the leading cause of death and disability. A misuse of the antibiotics is the main cause of the high resistance against many antibiotics in Pakistan. It is suggested that patient with respiratory tract infection or suspected case should take proper treatment and follow their physician instruction while choosing antibiotics during treatment.

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