Original Article

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Microbiology Section

Prevalence of Multidrug Resistance in Cases of Lower Respiratory Tract Infection: A Tertiary Care Hospital

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ABSTRACT

Introduction: A rise in antimicrobial resistance makes it imperative to study the bacterial aetiology and antimicrobial susceptibility profiles of commonly isolated organisms causing lower respiratory tract infections from both the community and the hospital setting.

Aim: To study the bacterial aetiology of Lower Respiratory Tract Infections (LRTI) cases from the community and hospital in the present setting and determine the antimicrobial susceptibility profile of the frequently isolated pathogens.

Material and Methods: A prospective observational study was conducted over 15 months at a 1531-bedded tertiary care hospital in Delhi, India. All consecutive sputum, Endotracheal (ET) aspirates and Broncho-Alveolar Lavages (BAL) samples submitted for culture and susceptibility testing were included. Infectious Diseases Society of America (IDSA) definitions were used to categorise the Patients as Community Acquired Pneumonia (CAP) or Hospital-Acquired Pneumonia (HAP) cases. Isolates were identified using conventional methods including colony morphology, gram's staining, motiliy and biochemical reactions and antimicrobial susceptibility was performed as per CLSI guidelines by disk diffusion. Colistin MIC was determined by agar dilution method. E-test strips were used to determine the MICs of penicillin, cefotaxime and ceftriaxone for isolates of *Streptococcus pneumoniae*.

Results: A total of 4748 samples received, 2555 were sputum, 2141 ET aspirates and 52 BAL samples. A total of 792 non-duplicate organisms were isolated of which 316 isolates were from CAP as compared to 476 isolates from HAP. *K. pneumoniae* (31%), *P. aeruginosa* (22%), *E. coli* (16%) and *Acinetobacter* species (16%) were the most common bacteria isolated from the community. Amongst the cases of HAP, *Acinetobacter* species (48%), *P. aeruginosa* (21%), *K. pneumoniae* (16%), *S. aureus* (5%) and *E. coli* (4%) were commonly isolated. Very high rates of resistance to cephalosporins were observed in both CAP and HAP isolates. *K. pneumoniae* isolates from hospital were also significantly (p-value<0.001) more resistant to carbapenems, aminoglycosides, ciprofloxacins as compared to those from the community. *P. aeruginosa* CAP strains showed high rates of susceptibility to all first and second line drugs tested (73-100%). In comparison, HAP strains were significantly more resistant to all classes of antimicrobials tested (p-value<0.001). *A. baumannii* isolates from both community and hospital were highly resistant to all classes of drugs except for colistin. Overall MRSA rate were 60%.

CONCLUSION: High prevalence of resistance to most antibiotics amongst Enterobacteriaceae and non-fermenting GNB isolates was observed in HAP cases with only colistin as a last resort drug. Rational use of antibiotics based on local antibiogram is essential to improve treatment outcomes and reduce antimicrobial resistance.

Keywords: Broncho-alveolar lavages, Endotracheal aspirates, Epidemiology, Pneumonia

INTRODUCTION

LRTI continue to be public health issue globally with an estimated annual incidence of 336 million cases in 2016 [1].Though the exact estimates for LRTI morbidity and mortality among adults are not known, globally pneumonia in children accounts for approximately 120–156 million cases with approximately 1.4 million resulting in death annually [2]. They are the fourth most common cause of disease and disability in India constituting 6.9% of total disease burden [3,4]. Pneumonia is a leading killer of under five children accounting for 16% of total mortality [5]. Besides the burden of CAP, increasing access to better care and treatment facilities has led to emergence of HAP as a major health problem. It is the second most common Hospital Acquired Infection (HAI) and the leading cause of mortality in these patients [6]. Incidence of HAP in various studies in India ranged from 16-54% [7].

A majority of cases of CAP are treated empirically with antibiotics in lieu of exact microbiological diagnosis. It has also been reported that HAP accounts for more than 50% of entire antibiotic prescriptions in ICU patients [7]. In view of increasing antimicrobial resistance with the emergence of Multi-Drug Resistant Organisms (MRDO) and pan-drug resistant organisms, it is imperative to study the aetiology and antimicrobial profile of commonly isolated organisms. Aim of the present study was therefore to ascertain the bacterial aetiology of LRTI cases from the community and the hospital environment in the present setting. The antimicrobial profile of frequently isolated organisms was also determined to facilitate antibiotic therapy choices for the clinicians.

MATERIALS AND METHODS

This prospective observational study conducted in the Department of Microbiology, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital. Safdarjung hospital is a 1531-bedded tertiary care multi-specialty facility in Delhi, India with eight ICUs and 41 wards belonging to 21 clinical departments. It receives 2,842,422 out-patients annually. Annual in-patients admissions were 158,331 of which 900 patients were admitted in the ICU. The ethical clearance was obtained from the Institutional Ethics Committee (No. IEC/SJH/VMMC/Project/May-2017/969)

The present study was conducted from August 2016 to October 2017. All consecutive respiratory samples including sputum, Endotracheal (ET) aspirates and BAL received in the Department of Microbiology for culture and susceptibility testing were included in the study. Samples collected in sterile, wide-mouthed, screw-capped containers were accepted for culture. Relevant demographic information was noted for each specimen including age, sex, location of the patient, diagnosis, days of admission,

history of intubation. Infectious Diseases Society of America (IDSA) definitions were used to categorise the patients as community or hospital-acquired pneumonia cases [8]. As no intervention was done and the patient care was not hampered at any stage of the study, patient consent was not required.

The specimens were inoculated on 5% sheep blood agar and MacConkey agar and incubated aerobically at 37°C overnight. Semiquantitative cultures were done for ET aspirates and Bronchoalveolar lavage. These samples were inoculated with a calibrated loop of volume 0.001 mL to determine the colony count in colony forming units/mL (cfu/mL). Sputum sample was homogenised and plated on the blood agar and MacConkeys agar without quantitation. A gram-stained smear was prepared for all specimens and examined microscopically. Sputum samples with more than 25 pus cells or leucocytes and less than 10 squamous epithelial cells per low power field were considered satisfactory for culture interpretation.

After overnight incubation, plates were examined for the growth of respiratory pathogens. In case of ET aspirates and BAL, the colony count was determined on the culture plates. Only the organisms growing as a pure colony with a colony count $\geq 10^5$ (CFU)/mL for ET aspirates and $\geq 10^3$ (CFU)/mL were considered as significant pathogen and processed further for final identification. These isolates were identified using conventional microbiological techniques including colony morphology, Gram's staining and biochemical tests such as catalase, coagulase, oxidase, motility, triple sugar iron test, citrate utilisation, indole test, fermentation of glucose, lactose, sucrose, production of urease, H_2S, phenyl deaminase and others as required.

Antimicrobial Susceptibility Testing (AST) was performed for the pathogenic microorganisms as per CLSI guidelines 2017 [9]. Mueller-Hinton agar (Himedia, India) was used for AST and plates were read at 18-24 hours after incubation at 37°C in ambient air. Aerobic Gram-negative bacilli were tested against cefotaxime (30 µg), ceftazidime (5 µg), amikacin (30 µg), netilmycin (30 µg), piperacillin-tazobactam(100/10 µg), meropenem (10 µg), imipenem (10 µg) and ertapenem (10 µg) using disk diffusion method. Colistin MIC was determined using agar dilution method with concentrations of 0.25, 0.5, 1, 2, 4, 8 and 16 µg/mL. Cefotaxime-cefotaxime/clavulunate and ceftazidime-ceftazidime clavulunate disks were used for detection of Extended Spectrum Beta-Lactamase (ESBL) production.

Staphylococcus aureus isolates was tested against penicillin (10 units), gentamycin (10 µg), erythromycin (15 µg), clindamycin (2 µg), sulfamethaxazole-trimethoprim (1.25/23.75 µg), vancomycin (30 µg), linezolid (30 µg). Cefoxitin (30 µg) disk was used as a surrogate for methicillin. *S. aureus* isolates that tested resistant to cefoxitin by disk diffusion were reported as MRSA. For *Streptococcus pneumoniae* isolates susceptibility to oxacillin (5 µg) by disk diffusion was used as surrogate marker for penicillin susceptibility. Isolates with oxacillin zone ≥20 mm are considered susceptible (MIC≤0.06) to penicillin [9]. Penicillin, cefotaxime and ceftriaxone MICs were determined by E-test strips for isolates with oxacillin zone diameters of <19 mm.

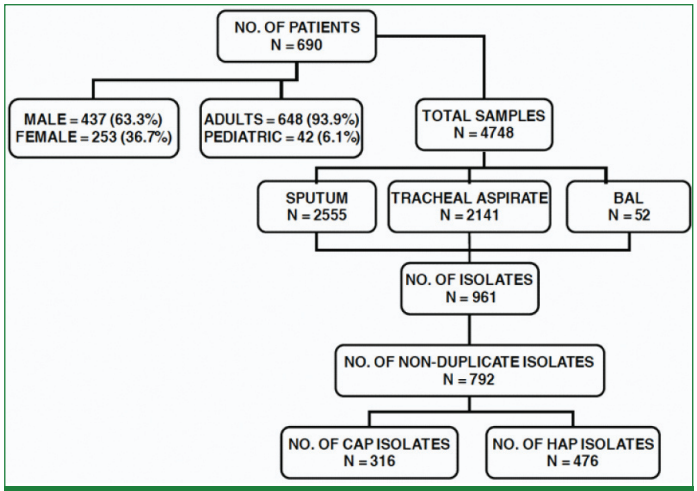
STATISTICAL ANALYSIS

The data was analysed using WHONET 5.6 and Microsoft excel. In case the same organism was isolated within 14 days from the same patient, only the first isolate was analysed for susceptibility profile. Chi-square test was used to calculate statistical significance.p-value<0.05 was considered as statistical significant.

RESULTS

A total of 4748 samples were received for culture and susceptibility testing. Of these 2555 were sputum samples, 2141 ET aspirates and 52 BAL samples [Table/Fig-1].

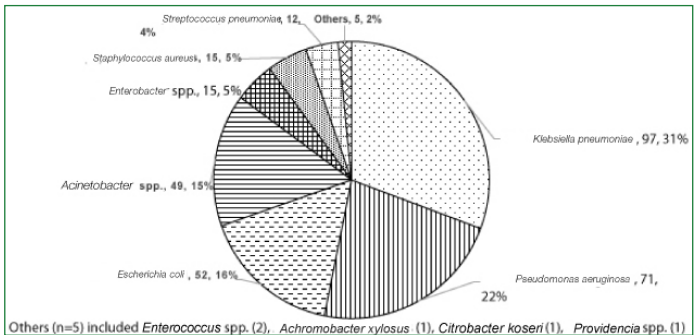
Of the 2555 sputum samples were received, 1824 (71.4%) were from In-Patients Department (IPD) and 731 (28.6%) from the Out-



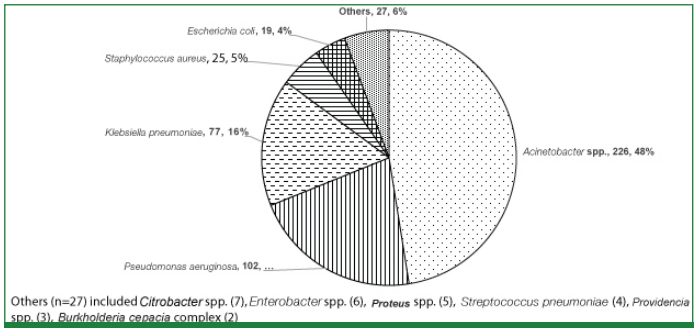
[Table/Fig-1]: Patient, Specimen and isolate characteristics.

Patients Department (OPD). All ET aspirates and BAL samples were received from admitted patients. A total of 961 bacterial isolates were recovered from samples of 690 patients. Of the 690 patients, 437 (63.3%) were male whereas 253 (36.7%) were females. Among these, 648 (93.9%) were adult patients and only 42 (6.1%) were in the paediatric age group. Overall, pathogenic bacteria were recovered from 19.8% of samples with 12.6% (n=322) of sputum samples yielding at least one pathogenic bacteria as compared to 28.5% (n=609) of ET aspirates. Eight of the 52 BAL samples were positive. Only 20 sputum samples (2.7%) were positive among those received from the OPD compared to 302 (16.6%) were from IPD patients.

A total of 792 non-duplicate organisms were isolated during the study period. Among these, 316 isolates were from patients diagnosed with CAP and 476 isolates were from cases of HAP. Gram-negative Bacteria (GNB) constituted 90.9% of the isolates from CAP and 93.9% of the isolates from HAP. *Klebsiella pneumoniae* (n=97, 31%), *Pseudomonas aeruginosa* (n=71, 22%), *Escherichia coli* (n=52, 16%) and *Acinetobacter* species (n=49, 16%) were the most common bacteria isolated from the community [Table/Fig-2]. Only 15 isolates of *Staphylococcus aureus* and 12 isolates of *Streptococcus pneumoniae* were recovered during the study period. Amongst cases of HAP, *Acinetobacter* species (n=226) was the most common organism isolated [Table/Fig-3]. Other organisms



[Table/Fig-2]: Distribution of organisms from CAP cases.



[Table/Fig-3]: Distribution of organisms from HAP cases.

frequently isolated included *P. aeruginosa* (n= 102), *K. pneumoniae* (n=77), *S. aureus* (n=25) and *E. coli* (n = 19) [Table/Fig-3]. Four isolates of *S. pneumoniae* were recovered from HAP cases.

The antimicrobial susceptibility profile for most frequently isolated gram negative bacilli from the community and hospital are summarised in [Table/Fig-4,5].

	Klebsiella pneumoniae		*Escherichia coli*	
Antibiotic	CAP (n=97)	HAP (n=77)	CAP (n=52)	HAP (n=19)
Cefotaxime	14.43	0	3.84	5.26
Piperacillin/Tazobactam	32.29	7.01	12.12	21.42
Imipenem	53.6	18.18	61.53	84.21
Meropenem	58.76	18.18	71.15	89.47
Ertapenem	55.67	14.28	65.38	73.68
Amikacin	56.7	23.37	65.38	84.21
Netilmycin	67.01	20.77	69.23	84.21
Ciprofloxacin	21.64	5.33	7.69	11.11
Colistin	100	100	100	100

[Table/Fig-4]: Antimicrobial susceptibility profile of Enterobacteriaceae isolates (Percentage susceptibility).

	Acinetobacter baumannii		*Pseudomonas aeruginosa*	
Antibiotic	CAP (n=49)	HAP (n=226)	CAP (n=71)	HAP (n=102)
Ceftazidime	0	0.89	76.05	40.19
Piperacillin/ Tazobactam	12.24	1.76	72.72	36.9
Imipenem	6.12	3.09	87.32	33.33
Meropenem	8.16	2.21	83.09	35.64
Amikacin	8.16	2.65	88.7	43.13
Netilmycin	22.44	26.1	88.7	40.59
Ciprofloxacin	10.63	1.81	78.57	37.62
Colistin	100	100	100	100

[Table/Fig-5]: Antimicrobial susceptibility profile of Non-fermenting GNB isolates (Percentage susceptibility).

Enterobacteriaceae: *Klebsiella pneumoniae* demonstrated high rate of resistance to third generation cephalosporins (3GCs). Other β-lactam drugs had significantly greater activity (p <0.001) against CAP isolates in comparison with HAP isolates with a percentage susceptibility of 32.29% vs 7.01% (CAP vs HAP) for piperacillin-tazobactam, 53.6% vs 18.18% (CAP vs HAP) for imipenem, 58.76% vs 18.18% for meropenem and 55.67% vs 6.49% (CAP vs HAP) for ertapenem. Similarly, for aminoglycosides and ciprofloxacin, susceptibility of CAP isolates was significantly higher (p-value <0.001) than in HAP cases. *E. coli* (n=52) isolates from community as well as the hospital (n=19) demonstrated extremely high rates of resistance to cefotaxime {96.16% (CAP) and 94.74% (HAP)} and piperacillin/tazobactam {87.88% (CAP) and 78.58% (HAP)}. In contrast with *K. pneumoniae* strains, carbapenems were active against majority of *E. coli* isolates both from CAP and HAP cases. ESBL production could be demonstrated in 21.15% of CAP and 15.78% of HAP isolates of *E. coli*. Susceptibility to aminoglycosides, ciprofloxacin and colistin did not differ significantly between community and hospital strains.

Non-Fermenters: *Pseudomonas aeruginosa* was the second most frequently isolated GNB from both CAP (n=71) and HAP (102) cases. Strains from the community showed high rates of susceptibility to all first and second line drugs tested with percentage susceptibility ranging from 73% for piperacillin/tazobactam to 100% for colistin. In comparison, the HAP strains were significantly more resistant to all classes of antimicrobials tested (p-value <0.001) except for colistin (percentage susceptibility =100%). *Acinetobacter baumannii* was the most frequently isolated organism from HAP cases (n=226) and fourth most commonly from CAP cases (n=49). Isolates from both community and hospital environment were highly resistant to all classes of drugs except for colistin (100% susceptible and netilmycin (22.44% vs 26.10% - CAP vs HAP).

Gram-Positive Cocci: Less than 10% of all isolates were gram positives. *Staphylococcus aureus* was isolated in 40 cases, 15 from community and 25 from HAP cases. Overall, 24 strains (60%) were methicillin resistant (MRSA) with an 80% (n=12) MRSA rate from the community [Table/Fig-6]. Susceptibility profile of community and hospital isolates was similar except for trimethoprim/sulfamethaxazole which was significantly less active against CAP isolates (33.33% vs 80% - CAP vs HAP). No resistance to vancomycin or linezolid was detected. Of the 16 isolates of *Streptococcus pneumoniae* recovered, one isolate was resistant of penicillin. Only two isolates were susceptible to erythromycin and clindamycin susceptibility was 71.4%. No resistance to ceftriaxone or cefotaxime was detected.

Antibiotic	CAP (n=15)	HAP (n=25)
Penicillin	0	0
Gentamycin	26.67	44
Clindamycin	60	56
Erythromycin	20	24
Ciprofloxacin	0	4
Sulfamethoxazole/Trimethoprim	33.33	80
Vancomycin	100	100
Linezolid	100	100
MRSA (n)	12	12

[Table/Fig-6]: Antimicrobial susceptibility profile of *Staphylococcus aureus* isolates (Percentage susceptibility).

DISCUSSION

Laboratory identification of LRTI aetiology is paramount for accurate diagnosis and treatment of patients both from the community and hospital settings in view of rampant antimicrobial resistance. In the present study, a bacterial aetiology could be determined in overall 19.8% of all respiratory specimens with 12.6% of sputum, 15.4% and 28.5% of ET aspirates and BAL samples yielding a microbiological diagnosis. Previous studies from Northern India have reported a culture positive rate ranging from 17.3% to 75.6% for cases from the community [10-12]. Many of these studies were conducted on a smaller sample size of few hundred samples as compared to the present study where 4748 samples were analysed [12-14]. Viral and Mycobacterial aetiology could account for cases where no bacteria were isolated.

Gram-negative bacilli accounted for 90.9% of all isolates from the community. This is in concurrence with studies from India and other developing countries which have reported a predominantly gram-negative aetiology (77.8% to >90%) in CAP cases [11,14-16]. *K. pneumoniae* (31%) was the most frequently isolated organisms followed by *P. aeruginosa* (22%), *E. coli* (16%) and *A. baumannii* (16%). Earlier studies from different regions of India have also reported *K. pneumoniae* and *P. aeruginosa* as most commonly isolated causes of CAP [10,15]. Similarly, studies from both developed and developing countries have reported a comparable isolation pattern from these patients [15-17]. Gram-positive cocci, primarily *S. aureus* (5%) and *S. pneumoniae* (4%) constituted less than 10% of CAP isolates.

As has been reported previously, *Acinetobacter baumannii* (48%) was the most common agent causing HAP in our study [18-20]. Findings of a review conducted with perspectives and data from 10 Asian countries suggest a predominantly Gram-negative aetiology for HAP in all these countries [21]. *A. baumanni* and *P. aeruginosa* were the most common pathogens isolated in all countries with members of family Enterobacteriaceae and *S. aureus* being other frequently identified pathogens [21].

Widespread resistance to cefotaxime was observed amongst Enterobacteriaceae isolates both from CAP (*K. pneumoniae*, 85.6% and *E. coli*, 96.2%) and HAP cases (*K. pneumoniae*, 100% and *E. coli*, 94.74%). This is in concordance with earlier reports of high prevalence of resistance to 3GCs from India and other developing countries [10,16,17]. Carbapenems demonstrated significantly greater activity against CAP isolates of *K. pneumoniae* with approximately 56% susceptibility to imipenem, meropenem and ertapenem. In comparison, less than 20% of HAP isolates were sensitive to either of the carbapenems tested. Susceptibility to carbapenems amongst *E. coli* isolates was higher ranging from 61.53% to 89.47% in all LRTI cases. Higher rates of resistance to carbapenems were observed in our setting as compared to other studies where resistance rates of <10% from the community and 10-60% from hospitalised patients has been reported for *K. pneumoniae* [11,18,19]. No resistance to colistin was observed which remains the last resort drug for HAP cases in our setting.

Near total resistance to 3GCs was also observed amongst the isolates of *A. baumannii* in the present study similar to previous reports [10,17]. *A. baumannii* isolates also demonstrated extremely high level resistance to most other classes of antimicrobials. Although the resistance rates for CAP were much greater than previously reported [10], earlier studies from Asia have also observed high level of resistance to carbapenems, ciprofloxacin and aminoglycosides amongst *A. baumanii* complex [19,22]. In contrast to other GNBs, *P. aeruginosa* strains from CAP cases demonstrated >70% sensitivity to ceftazidime, pipercillin/tazobactam and ciprofloxacin. Ahmed SM et al., also reported similar susceptibilities to ceftazidime (60%) and ciprofloxacin (76%) [10]. Carbapenems and aminoglycosides were similarly effective in >85% of CAP isolates tested as has been reported earlier [10,23]. In comparison, resistance rates amongst HAP isolates to most of the drugs tested was 60-70%, while no resistance was noted to colistin in concordance with reported rates from studies from India and other Asian countries [19,22,24].

Overall, MRSA accounted for 60% of all isolates of *Staphylococcus aureus* in the present study while no resistance to vancomycin or linezolid was observed. Chung DR et al., in a review of HAP in Asia have reported more than 80% MRSA rates in various Asian countries although no vancomycin resistance was observed [25]. Studies from India have reported varied MRSA rates ranging from 16% to 50% amongst pneumonia isolates [24,26]. In the present study, very high rate of resistance to carbapenems was observed in the community for *K. pneumoniae* and *A. baumannii*. MRSA isolation was also greater than previously reported [24,26]. Our hospital is a tertiary care centre catering to a large population from Delhi as well as neighbouring states. A sizable number of patients attending our OPD are referred from primary and secondary care centres and have already been exposed to antibiotics contributing to isolation of drug resistant organisms from CAP cases.

Antimicrobial resistance is an enormous challenge in resource poor settings in India. In the present report, detection of significantly higher rates of resistance in GNB isolates of HAP as compared to those from the community conforms to earlier reports [17-19,21]. Hospital environment have proven to be reservoirs of Multi-Drug Resistant Organisms (MDROs) which are often associated with higher mortality, longer period of stays and resource utilisation in the ICUs [27,28]. On the other hand, appropriate antibiotic therapy was associated with better ICU survival [28]. Therefore, it is imperative to study bacterial aetiology and antimicrobial susceptibility profile of LRTIs. This can facilitate in formulating facility specific antibiotic policy for both CAP and HAP cases and improving patient outcomes.

LIMITATION

As the study was conducted over a single period of time, the trend of antimicrobial resistance could not be adequately determined. Further studies are required to ascertain the increasing prevalence of antibiotic resistance in LRTI cases as well as its effect on patient outcome.

CONCLUSION

The present study was conducted to evaluate the bacteriological profile of LRTIs from community and hospital setting in a large tertiary care setting in India. Gram-negative bacilli were the predominant cause of both CAP and HAP in our setting. High prevalence of resistance to most antibiotics amongst Enterobacteriaceae and non-fermenting GNB isolates was observed in HAP cases with only colistin as a last resort drug. Carbapenem resistance was also rampant in *K. pneumoniae* and *A. baumannii* in the community. The study underlines the need for rational use of antibiotics based on local antibiogram to improve treatment outcomes and reduce antimicrobial resistance.

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