Original Article

High proportion of drug-resistant isolates in adult community-acquired pneumonia from Northeast India: A hospital-based study

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ABSTRACT

Background: Empirical antibiotic therapy is the mainstay of management of adult community-acquired pneumonia (CAP) globally. Knowledge of prevalent pathogen (bacterial) profile and drug susceptibility pattern is very essential for appropriate management of CAP cases, which again calls for regular update of pathogen profile in a given locality. This study was to identify the bacterial etiology of CAP cases and their antibiotic susceptibility pattern. Methods: This cross-sectional study was done on adult CAP patients from medicine, respiratory medicine, and intensive care unit area in our tertiary care hospital between May 1, 2015, and October 30, 2016. Subjects were enrolled continuously, and expectorated sputum, bronchoalveolar lavage fluid, and blood culture were performed. Urine antigen test was done for Streptococcus pneumoniae and Legionella pneumophila. Three types of ELISA (IgM, IgG, and IgA) were performed for atypical agents (Mycoplasma, Chlamydia, and Legionella) of CAP. Isolates obtained from culture of Sputum/BAL/Blood were further processed for antibiotic susceptibility testing - by disc diffusion as well as E-test method (latter for MIC i.e. minimum inhibitory concentration, determination). Results: About 574 subjects were included, and in 266 (46.3%) cases, bacterial pathogen could be detected. Klebsiella pneumoniae (33.6%) and S. pneumoniae (32.9%) were the predominant agents identified. Atypical agents (Mycoplasma, Legionella, and Chlamydia) were at 15.1%. A high proportion of pneumococci isolates were multidrug resistant (52.6%). Resistance to beta-lactams, macrolide, and other agents was on the higher side, but fluoroguinolones were found to be less resistant (15.8%-21.1%). Extended-spectrum beta-lactamase (among Klebsiella isolates) and methicillin-resistant Staphylococcus aureus were also detected. Conclusion: A moderate-to-high degree of drug-resistant in adult CAP was evident, which is detrimental in effective empirical management of such cases. Urgent implementation of antibiotic stewardship scheme is the need of the hour.

KEY WORDS: Adult community-acquired pneumonia, atypical agents, community-acquired pneumonia, drug-resistant pneumococci, drug-resistant *Streptococcus pneumonia*, macrolide resistance, multidrug resistance, multidrug-resistant *Streptococcus pneumonia*

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INTRODUCTION

Adult community-acquired pneumonia (CAP) is a leading cause of morbidity, often needing hospitalization, and an important cause of mortality, especially in severe cases with sepsis or requiring assisted ventilation.^[1,2] Although multiple pathogens are linked to adult CAP, a few are responsible for most cases, and out of it, bacterial pathogens account for a significant portion of cases. In developed countries, the estimated incidence of CAP is 0.2%-1.1% in adults and the mortality is 2%-14%.^[1,2] The estimated mortality rate in Asia is 7.3%, though incidence and mortality report from India are not available from published studies.^[1-3] Despite the availability of a wide array of diagnostic and management tools, a definitive microbiological etiology usually remains unknown till the first 3 days (or more), and hence, alert clinical evaluation in the first 2 days is strongly advocated.^[4] Overall, in CAP, the early institution of effective presumptive antibiotic therapy is most called for a favorable outcome, and hence, mainstay of treatment is the empirical choice of initial antibiotic therapy.

Widespread use and abuse of antibiotics have led to the rapid emergence and spread of antimicrobial resistance globally, and empirical management of CAP is rendered difficult (for a choice of drug, as most drugs are ineffective) by this phenomenon.^[5] Keeping these facts in view, this study was conducted to identify the bacterial etiology of CAP in adults and their antibiotic susceptibility pattern in our tertiary care teaching hospital herein the northeastern part of India.

METHODS

Data were collected between May 1, 2015, and October 30, 2016, from the indoor and outdoor sections of the department of medicine and respiratory medicine of our tertiary care teaching hospital. Samples from intensive care units (ICUs) and intensive treatment units were also included. The study protocol was approved by the Institutional Ethics Committee of the tertiary care teaching hospital vide letter no. MC/138/2011/pt-III/221.

Inclusion and exclusion criteria were set as per the standard guidelines^[1,2]

Inclusion criteria

(i) Adult suspected/diagnosed pneumonia cases (>18 years), (ii) new or progressive pulmonary infiltrate on a chest radiograph obtained within 24 h of presentation, and/or (iii) clinical finding of (a) at least one of the major criteria: cough, sputum production, or temperature >37.8°C, or (b) at least two of the minor criteria: pleuritic chest pain, dyspnea, altered mental status, pulmonary consolidation by physical examination, and white blood cell (WBC) count of >12,000 cells/ μ l.

Exclusion criteria

(i) Earlier hospitalization within the previous3 weeks; (ii) presence of an emerging alternative

diagnosis (e.g., pulmonary or septic emboli, pulmonary edema, or malignancy) during follow-up; (iii) presence of pneumonia caused by tuberculosis (TB) or postobstructive pneumonia due to lung cancer; (iv) presence of severe immunosuppression including severe neutropenia (i.e., $<1.0 \times 10^9$ cells/L), HIV infection, and solid-organ or bone marrow transplantation; receiving corticosteroid treatment with a dosage of >20 mg prednisolone-equivalent per day for >2 weeks.

Subjects underwent a clinical history taking (as per pretested pro forma), physical examinations, and available laboratory reports checks. Relevant findings (X-ray and biochemistry results) were noted down. After a proper demonstration of expectoration of lower respiratory fluids, sputum samples were collected in a clean and sterile container. As far as possible, samples were collected before antibiotic administration. Whenever feasible, in severe CAP cases, bronchoalveolar lavage (BAL) fluid was collected by one pulmonary medicine expert (our last author). Urine sample (spot) was collected in a clean container. For hospitalized subjects (indoor and ICU-admitted cases), up to 5 ml blood was aseptically collected for blood culture bottle (VersaTREK system) and dispatched to the laboratory as early as possible. In addition, we collected another 5 ml of blood, on or after 7th day of initiation of first clinical feature of CAP for serology (ELISA) purpose.

Sputum and BAL samples were homogenized (with dithiothreitol solution); the direct smear was prepared for Gram stain and checked under a microscope for appropriateness (quality) of the samples (number of squamous epithelial cells was <10 and the WBC count was >25/high power field). Samples not fulfilling this criterion were rejected, and re-collection was attempted. Accepted samples (homogenized) were inoculated in three agar media, i.e., Columbia blood agar, MacConkey's agar, and chocolate agar as per description in the standard microbiology textbook/guidelines.^[6-8] All culture media and antibiotic discs were of BD make (Becton Dickinson, Franklin Lakes, USA).

Media were then put inside the incubator for overnight incubation at 37°C. Growth if any was identified by phenotypic methods as per the standard recommendation.^[6-8] Isolates were further processed for antimicrobial susceptibility testing in Mueller–Hinton agar or its modifications (e.g., blood Mueller–Hinton agar) as per relevant Clinical Laboratory Standard Institute (CLSI) guidelines.^[9]

Common isolates were checked for minimum inhibitory concentration (MIC) using E-test as per the CLSI guidelines and manufacturer instructions. For quality control purposes, following reference strains were used.^[9]

Escherichia coli (ATCC 25922), Klebsiella pneumoniae (ATCC 700603), Pseudomonas aeruginosa (ATCC 27853),

Streptococcus pneumoniae (ATCC 49619), and Staphylococcus aureus (ATCC 25923).^[9]

VersaTREK automated blood culture monitoring system (Trek Diagnostics Systems, East Grinstead, West Sussex, UK) was used, and inoculated bottles were kept for 7 days or till a positive growth signal is obtained. Positive growths were subcultured in blood agar, MacConkey's agar, and chocolate agar and subsequently processed as described in sputum culture.

BinaxNOW urinary antigen test for *Legionella pneumophila* and BinaxNOW *S. pneumoniae* (both Alere Inc., Waltham, MA, United States) were used for urinary antigen detection. These kits are highly rated by the FDA with level I evidence of being better than ELISA.^[2]

Multiple ELISA kits (all from NovaTec Immundiagnostica GmbH, Dietzenbach, Germany) were used for *Mycoplasma pneumoniae* (IgG, IgA, and IgM), *Chlamydia pneumoniae* (IgG, IgA, and IgM), and *L. pneumophila* (IgG, IgA, and IgM) in each serum sample (9 ELISAs in total) in a Thermoscientific's MultiScan FC Elisa Reader (Ratastie, Finland). Two ELISA-positive results out of three (IgM, IgG, and IgA) were considered as acute infection by a particular agent.

Data generated were analyzed by SPSS version 23 for Windows (SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used to express continuous variables, while categorical variables were denoted by frequencies and percent. The relationship between categorical variables was examined by Chi-square and Fisher's exact tests, taking P < 0.05 as a significant level in all tests.

RESULTS

As per the inclusion and exclusion criteria, a total of 606 subjects were selected. However, 31 of the subjects were excluded [Figure 1] due to multiple reasons leaving us, with 574 study subjects finally. Basic demographics, clinical presentation, laboratory data, and risk factors are presented in Table 1.

PATHOGEN PROFILE

Out of 574 subjects, we had respiratory sample (in all 574), blood for culture (in 217), urine for antigen detection (in 528), and serum for ELISA (in 329). Overall, we had 304 agent detections from 266 positive subjects (out of 574 subjects, i.e., 46.3% detection) with single agent in 228 (85.7%) cases and double agents in 38 (14.3%) cases [Tables 2 and 3].

Hence, overall, we had *K. pneumonia* in 102 cases (33.6%; 89 single infections, 13 dual infections), *S. pneumoniae* in 100 cases (32.9%; 91 single infections, 9 dual infections), *S. aureus* in 38 cases (12.5%; 29 single infections, 9



Figure 1: Flow diagram of the study

dual infections), *M. pneumoniae* in 24 cases (7.9%; 21 single infections, 3 dual infection), *L. pneumophila* in 15 cases (4.9%; 14 single infection, 1 dual infection), *Moraxella catarrhalis* in 14 cases (4.6%; 11 single infection, 3 dual infection), *Chlamydia pneumoniae* in 7 cases (2.3%; all single infection), *Staphylococcus* group in 2 cases (0.2%; all single infection), and *Acinetobacter* sp. in 2 cases (0.2%; all single infection).

There was a complete absence of an important agent - *Haemophilus influenzae*, despite best efforts from our side.

The distribution of culture isolates growing in various media includes *S. pneumoniae* 57, *Klebsiella pneumonia* 102, *S. aureus* 38, *M. catarrhalis* 14, *Staphylococcus* group (non-*aureus*) 2, and *Acinetobacter* sp. 2, i.e., a total of 215 isolates.

DISCUSSION

The current study was carried on 574 adult patients diagnosed with CAP from a tertiary care teaching hospital. A predominance of male over female was observed [Table 1]. Elderly populations were more with 43% of subjects being above 60 years age bracket (mean age: 57.2 \pm 17.2). About 52.1% of cases [Table 1] were smokers, and the association of smoking and CAP development is

Table 1: Baseline data

Table 1. Dasellile uata	
Characteristics	n (%)
Demographic data	
Number of subjects	574
Age (years), mean±SD	57.2±17.2
Sex	
Female	153 (26.66)
Male	421 (74.34)
Smoker	299 (52.1)
Nonsmoker	275 (47.91)
Alcohol user	85 (14.81)
>60 years age	247 (43)
Clinical data	
Fever	506 (88.15)
Dyspnea	306 (53.31)
Cough	473 (82.40)
Expectoration	417 (72.65)
Hemoptysis	146 (25.43)
Chest pain	279 (48.61)
Laboratory data	
WBC $\times 10^{9}$ /L	14.8±10.7
Platelet $\times 10^{9}/L$	230±26.1
CRP (mg/dL)	180.8 ± 3.32
CURB-65 severity rate	
CURB 2	404 (70.4)
CURB 3-5	170 (29.6)
Severity of illness	
Mild CAP (outdoor)	307 (53.5)
Moderate CAP (indoor)	141 (24.4)
Severe CAP (ICU admitted)	126 (22.1)
Comorbidities	
Diabetes	213 (37.1)
HT	141 (24.6)
IHD	53 (9.2)
Liver disease	22 (3.8)
COPD	121 (21.1)
Number of subjects with one modifying and risk factors*	71 (12.4)
Number of subjects with ≥ 2 modifying and risk factors*	318 (55.4)

*Modifying and risk factors include age >60 years, severe pneumonia, diabetes, HT, IHD, liver disease, COPD, existing pneumonia (transferred from other hospital) etc. Values are mean±SD or *n* (%). SD: Standard deviation, CRP: C-reactive protein, CURB-65 severity score: (C: Mental confusion, U: Blood urea >7 mmol/l, R: Respiratory rate ≥30/min, B: Low blood pressure [diastolic ≤60 mmHg or systolic <90 mmHg]; age ≥65 years), WBC: White blood cells, COPD: Chronic obstructive pulmonary disease, IHD: Ischemic heart disease, HT: Hypertension, CAP: Community-acquired pneumonia, ICU: Intensive care unit

a fact.^[10] Comorbid conditions such as diabetes (37.1%), hypertension (24.6%), and chronic obstructive pulmonary disease (21.1%) were seen and similar comorbidities were reported earlier.^[11,12]

Bacterial agent was found in 52.96%, with *K. pneumonia* being maximum (31.6%) closely followed by *S. pneumoniae* at 31.0%. Other identified pathogens were *S. aureus* (11.8%) and atypical agents (*M. pneumonia* 10.5%, *L. pneumophila* 5.6%, *C. pneumoniae* 4%), *M. catarrhalis* in 4.3%, etc. These findings are slightly different from a recent adult CAP study from North India (Kashmir) where *S. pneumoniae* emerged as a major agent (30.5%) followed by *L. pneumophila* (17.5%), influenza viruses (15.4%), *M. pneumoniae* (7.2%), *C. pneumoniae* (5.5%), *K. pneumonia* (4.8%), etc.^[13] A study from Shimla earlier reported predominance of *S. pneumoniae* (35.8%) along

with Klebsiella (22%), S. aureus (17%), Mycoplasma (15%), E. coli (11%), etc.^[3] One systematic review on CAP on Indian adolescent and adult population found predominantly S. pneumoniae (19%), M. pneumoniae (15.5%), Klebsiella (10.5%), and Legionella (7.3%).^[14] A study from Bhopal found an almost equal number of S pneumoniae and GNB (like our study) and another from New Delhi reported S. pneumoniae (35.3%) S. aureus (23.5%), K. pneumoniae (20.5%), and H. influenzae (8.8%).^[15,16] From South India (Mangalore), another report found S. pneumoniae at 31% followed by Pseudomonas (15%), K. pneumoniae (13%), etc.^[17] Majority of these works found S. pneumoniae as a major pathogen followed by agents such as Klebsiella. Peto et al. in a recent systematic review opined that S. pneumoniae may not be a significant agent in CAP cases from Asian countries unlike in western countries.^[18] Conventional culture technique's sensitivity to the isolation of fastidious organisms such as S. pneumoniae is considered low, which can explain our isolation of 57 isolates despite total detection of 100.^[19] M. pneumoniae was detected in 10.5% of our subjects, which was somewhat similar to few previously conducted studies from India.^[20,21] This moderate positivity rate was attributed to low socioeconomic conditions and crowding.^[20,21]

Another feature of our study was the nonisolation of *H. influenzae*, which is considered a significant CAP agent worldwide. This is even though we put up best efforts possible (using chocolate agar media enriched with factor X and factor V as one of the primary plates, putting laboratory workers experienced in Haemophilus isolation, etc.).^[8] Widespread availability and use of antibiotic in the backdrop of drug-sensitive fastidious H. influenzae in our population could be an explanation of nonisolation. Of late hospital agents, GNBs (P. aeruginosa, K. pneumoniae, and E. coli) have emerged as causes of CAP.^[22,23] Our results [Tables 2, 3 and Figure 2] are very much in tune with this fact, attributable to the ever-increasing number of elderly CAP patients harboring colonizers (mainly GNBs), as well as suffering severe forms of disease requiring hospitalization, ICU admission, etc.[19,23]

K. pneumonia isolates showed [Supplementary Table 1] high resistance to penicillin/beta-lactamase inhibitors (43.2%–40.1%). Third and fourth-generation cephalosporins resistance ranged from 60% to 37%. On the other hand, carbapenems showed full susceptibility [see Supplementary Table 1]. About 39.2% and 36.6% were resistant to ciprofloxacin and levofloxacin, respectively. E-test-based extended-spectrum beta-lactamase (ESBL) phenotypic confirmation detected 40.2% of isolates producing ESBLs. The level of drug resistant in CAP-related *Klebsiella* is higher than earlier reported from India.^[15,16,21]

Our study found 54.4% of *S. pneumonia*e isolates to be resistant to oxacillin and 50.9% with penicillin MIC>8ug/ ml [Supplementary Table 1 and 2]. Resistant range macrolide MIC (>1 ug/ml) was detected among 50.9% isolates while about 40.4% of isolates were resistant to

Table 2: Distribution of single pathogen

Name of pathogen	Culture					UA test out of 558 samples			ELISA (IgM, IgA, or IgG) out of 329 samples		
identified	Respiratory sample i.e.,	BC (ou	t of 217 sa	amples)	UA+	UA+	Total	ELISA	ELISA	Total	detected
	sputum/BAL positive cases (out of 574 samples)	BC + RC+	BC + RC-	Total BC+	C+	С-	UA+	+ UA+	+ UA-	(ELISA+)	
K. pneumoniae	89	13	0	13							89
S. pneumoniae	52	15	5	20	23	31	54				91
S. aureus	28	5	1	6							29
M. pneumonae										21	21
C. pneumonia										7	7
L. pneumophilia						12	12	3	2	5	14
H. influenza	0	0	0	0							0
Moraxella sp.	11	0	0	0							11
Staphylococcus	2	1	0	1							2
group (non <i>aureus</i>)											
Acinetobacter sp.	2	0	0	0							2
Total											266

C+/C-: Culture positive/culture negative, RC+/RC-: Respiratory sample culture positive/respiratory sample culture positive, BC+/BC-: Blood culture positive/blood culture negative, UA+/UA-: Urinary antigen positive/urinary antigen negative, ELISA+/ELISA-: ELISA reactive/ELISA nonreactive, ELISA: Enzyme linked immunosorbent assay, *K. pneumoniae: Klebsiella pneumoniae, S. pneumonia: Streptococcus pneumoniae, S. aureus: Staphylococcus aureus, M. pneumonae: Mycoplasma pneumonae, C. pneumonia: Chlamydia pneumonia, L. pneumophilia: Legionella pneumophilia, H. influenza: Hemophilus influenza, BAL: Broncho-alveolar lavage*

Table 3: Distribution of multiple pathogen

Combination of pathogen detected (method in parenthesis)	Number of cases
Klebsiella and S. aureus (RC and RC)	6
Klebsiella and S. pneumoniae (RC and UA)	7
M. pneumonia and Legionella (ELISA IgM and UA)	1
S. pneumoniae and M. pneumonia (UA and ELISA IgM)	2
Moraxella and S. aureus (RC and RC)	3

RC: Respiratory culture, UA: Urinary antgen, ELISA: Enzyme linked immunosorbent assay, *S. aureus: Staphylococcus aureus, S. pneumonia: Streptococcus pneumonia, M. pneumonia: Mycoplasma pneumoniae*

clindamycin – hinting toward the possible existence of MLS_B type resistance.^[24] This is in tune with the global trend of increasing resistance of *S. pneumoniae* to beta-lactams and macrolides.^[19,25-28] Resistance to quinolones was found to be comparatively less; e.g., 21.1% of isolates were resistant to Levofloxacin [Supplementary Table 1]. For moxifloxacin, it was even lesser at 15.8% perhaps attributable to the fact that this drug has an additional target, i.e., GyrA subunit of DNA gyrase compared to a single target (mutation-prone ParC subunit of the enzyme topoisomerase IV) for older fluoroquinolones (levofloxacin, ciprofloxacin).^[19] Ideal pharmacodynamics and adequate tissue penetration are additional advantages of moxifloxacin over levofloxacin in pneumococcal CAP.^[29]

Our results found that 5.3% (2/38) strains of *S. aureus* were methicillin-resistant *S. aureus* (MRSA) S pneumoniae [Supplementary Table 1]. This is comparable to the finding of 3.5% of MRSA in adult CAP cases from a recent study done in North India.^[13] Vancomycin and linezolid had 100% susceptibility. Macrolide resistance was recorded at 10.5% (confirmed by MIC test), while quinolone resistance was detected in 10/38 (26.3%) isolates (MIC confirmed in 9/38) [Supplementary Table 2]. About 94.7% of isolates were penicillin resistant.



Figure 2: Pie depicting various pathogens of adult community-acquired pneumonia subjects

Multidrug resistance (MDR) in *S. pneumoniae* is defined as resistance to three or more antibiotic classes.^[24] *S. pneumoniae* MDR generally involves reduced susceptibility to β -lactams, macrolides, tetracyclines, and sulfonamides; resistance to quinolones in MDR *S. pneumoniae* is fewer frequent.^[24] Data from the current study indicate that about 30/57 (52.6%) strains were resistant to three or more antibiotic groups, i.e., MDR *S. pneumoniae*. Lynch and Zhanel earlier opined that more than 30% of *S. pneumoniae* worldwide are MDR.^[30] Van Bambeke *et al.* too observed above 40% of pneumococci may display MDR phenotypes, with highly variable distribution among different countries.^[31]

CONCLUSION

Regular update of the pathogen profile of CAP is essential as erstwhile nosocomial agents (e.g., GNBs, MRSA) have emerged as community agents. To avoid inadequate therapy, resistance pattern and prevalence of MDR agents are necessary. It is very crucial for choosing empirical antimicrobials in seriously ill patients. As our study proves that there is widespread drug resistance in CAP cases – implementation of an antibiotic stewardship program is needed, with steps such as de-escalation, shifting to oral therapy, early ambulation, and discharge, and a short course of antimicrobials. Further studies on molecular aspects of drug resistant (e.g., macrolide resistant in pneumococci to confirm MLS_R or erm) will be essential.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary T ⁱ	ible 1: Drug	3 sensitivit	y testing ru	esult										
Antibiotic	S. pneu	monia (n=57)	, n (%)	Klebsiel	<i>la</i> sp.(<i>n</i> =102)	і, <i>п</i> (%)	S. aur	eus (n=38), n	(%)	Moraxella s n (⁹	ip. (<i>n</i> =14), %)	Acinetoba	cter sp. (n=	2), n (%)
	s	I	R	s	I	R	S	I	R	s	R	S	I	R
ESBL	I	I	I			41 (40.2)	ı					,		,
Oxacillin*	26 (45.6)	ı	31 (54.4)											
Erythromycin	23 (40.4)	4(7)	30 (52.6)				29 (76.3)	5 (13.2)	4(10.5)	12 (85.7)	2 (14.3)			
Azithromycin	22 (38.6)	5 (8.8)	30 (52.6)				31 (81.6)	4(10.5)	3 (7.9)	14(100)	0			
Clarithromycin	24 (42.1)	4(7)	29 (50.9)											
Co-trimoxazole	12 (21.1)	2 (3.5)	43 (75.4)	15 (17.7)	19 (18.6)	68 (66.7)	4(10.5)	2 (5.3)	32 (84.2)	8 (57.1)	6 (42.9)	0	0	2 (100)
Clindamycin	21 (36.8)	13 (22.8)	23 (40.4)				28 (73.7)	4(10.5)	6 (15.8)					
Doxycyline	24 (42.1)	9 (15.8)	24 (42.1)	50 (49)	13 (12.7)	39 (38.2)	27 (71.1)	1 (2.6)	10 (26.3)	10 (71.4)	4 (28.6)	0	0	2(100)
Ciprofloxacin				54 (52.9)	8 (7.8)	40 (39.2)	24 (63.2)	4(10.5)	10 (26.3)	11 (78.6)	3 (21.4)	0	2(100)	0
Levofloxacin	38 (50.9)	11 (28.1)	8 (21.1)	57 (55.9)	8 (7.8)	37 (36.3)	27 (71.1)	2 (5.3)	9 (23.7)	12 (85.7)	2 (14.3)	1(50)	1(50)	0
Moxifloxacin	43 (57.9)	8 (26.3)	6 (15.8)	61 (59.8)	11 (10.8)	30 (29.4)	27 (71.1)	3 (7.9)	8 (21.1)	14(100)	0	1 (50)	1 (50)	0
Offoxacin	33 (49.1)	15 (31.6)	9 (19.3)											
Vancomycin	57 (100)	0	0				38 (100)		0					
Linezolid	55 (96.5)	0	2 (3.5)				38 (100)	ı	0					
Chloramphenicol	18 (31.6)	0	39 (68.4)	8 (7.8)	23 (22.5)	71 (69.6)	11 (28.9)	5 (13.2)	22 (57.9)	2 (14.3)	12 (85.7)			
Amoxiclav				51 (50)	4 (3.9)	47 (46.1)				12 (85.7)	2 (14.3)			
Cefazolin				38 (37.3)	4 (3.9)	60 (58.8)								
Gentamicin				37 (36.3)	14 (3.7)	51 (50)	18 (47.4)	10 (26.3)	10 (26.3)			0	1 (50)	1 (50)
Tobramycin				40 (39.2)	14 (3.7)	48 (47.1)						0	1 (50)	1 (50)
Amikacin				46 (45.1)	15 (14.7)	41 (40.2)						1(50)	1(50)	0
Pipercillin-Tazo				55 (53.9)	6 (6.9)	41 (40.2)						1(50)	0	1 (50)
Ticarcillin -clav				51 (50)	7 (6.7)	44 (43.1)						0	1(50)	1 (50)
Cefuroxime (oral)				36 (35.3)	7 (6.7)	59 (57.8)								
Cefotaxime				52 (50.9)	7 (6.7)	43 (42.1)				12 (85.7)	2 (14.3)	2(100)	0	0
Ceftriaxone				52 (50.9)	9 (8.8)	41 (40.2)				12 (85.7)	2 (14.3)	2(100)	0	0
Cefepime				53 (52)	12 (1.8)	37 (36.4)				14(100)	0	2 (100)	0	0
Cefioxitin				41 (40.2)	4 (3.9)	57 (55.9)	36 (94.7)		2 (5.3)	9 (64.3)	5 (35.7)			
Meropenem				98 (96.1)	4 (3.9)	0				14(100)	0	2 (100)	0	0
Ertapenem				99 (97.1)	3 (2.9)	0				14(100)	0			
Azteronam				50 (49)	8 (7.8)	44 (43.1)								
Tetracycline				41 (40.2)	10 (9.8)	51 (50)	21 (55.3)	5 (13.2)	12 (31.6)	8 (57.1)	6 (42.9)	0	0	2(100)
Minocycline				43 (42.2)	15 (14.7)	44 (43.1)								
Penicillin 10U							2 (5.3)	,	36 (94.7)					
Tiecoplanin							38 (100)	0	0					
Cefixime										11 (78.6)	3 (21.4)			
Cefuroxime										8 (57.1)	6 (42.9)			
Ceftazidime				53 (52)	7 (6.7)	42 (413)						1(50)	1(50)	0
Ampicillin-sulbactam												0	0	2(100)
Imipenem												2(100)	0	0
S. aureus: Staphylococ is used and zone of inh	ibition 19 mm	pneumonia: . or less in S p	Streptococcus neumoniae is	<i>pneumonia,</i> E suggestive of	ESBL: Extend Penicillin res	ded spectrum istance. (Suri	beta-lactama rogate marker	se producing for Penicilli	strains, S: Se 1). Earlier it v	nsitive, I: Int was used for I	ermediate, R: MRSA detect	: Resistant, (ion but curr	Oxacillin* :	ug disc les prefer
cefoxitin 30 ug disc foi	 Staphylococc 	us aureus (Mi	ec A/PBP2b)	resistance det	ection.		5						5	-

Antibiotic	S. pnet	umonia	K. pneu	moniae	S. at	ıreus
	MIC range/ interpretation	Number of isolate, <i>n</i> (%)	MIC range/ interpretation	Number of isolate, <i>n</i> (%)	MIC range/ interpretation	Number of isolate, <i>n</i> (%)
Penicillin	<0.06 0.06–2	8 (14) 16 (28.1)			<0.12 >0.25	3 (7.9) 35 (92.1)
	4	4(7)				(/=)
	>8	29 (50.9)				
Cefotaxime	<1	13 (22.8)	<1	56 (54.9)		
	2	12 (21.1)	2	5 (4.9)		
	>4	32 (56.1)	>4	41 (40.2)		
Meropenem	< 0.25	54 (94.7)	<1	97 (95.1)		
1	0.5	3 (5.3)	2	5 (4,9)		
	>1	0	>4	0		
Vancomycin	<1	57 (100)			<2	38 (100)
5		· · · ·			4-8	0
					>16	0
Erythromycin	< 0.25	25 (43.9)			< 0.5	30 (78.9)
5 5	0.5	3 (5.3)			1-4	4 (10.5)
	>1	29 (50.9)			>8	4 (10.5)
Levofloxacin	<2	40 (70.2)	<2	63 (61.8)		
	4	9 (15.8)	4	0		
	>8	8 (14)	>8	35 (34.3)		
Linezolid	<2	57 (100)			<4	38 (100)
					>8	0
Doxycycline	< 0.25	28 (49.1)	<4	51 (50)	<4	25 (65.8)
5.5	0.5	7 (12.3)	8	11 (10.8)	8	11 (28.9)
	>1	22 (38.6)	>16	40 (39.2)	>16	2 (5.3)
Azithromycin	< 0.5	24 (42.1)				
5	1	4(7)				
	>2	29 (50.9)				
Ceftazidime		× /	<4	56 (54.9)		
			8	6 (5.9)		
			>16	40 (39.2)		
Ciprofloxacin			<1	60 (58.9)	<1	24 (63.2)
Cipiolioxaciii			2	4 (3.9)	2	5 (3.2)
			>4	38 (37.2)	>4	9 (23.7)
Gentamicin			<4	37 (36.3)	<4	20 (52.6)
			8	15 (14.7)	8	9 (23.7)
			>16	50 (49)	>16	9 (23.7)
Cotrimoxazole			<2/38	31 (30.4)	<2/38	3 (7.9)
			>4/76	71 (69.6)	>4/76	35 (92.1)
Oxacillin				× /	<2	36 (94.7)
					>4	2 (5.3)

Supplementary Table 2: E-test results

K. pneumoniae: Klebsiella pneumonia, S. aureus: Staphylococcus aureus, S. pneumonia: Streptococcus pneumonia, MIC: Minimum inhibitory concentration