Original Research Article

Sensitivity Pattern, Clinical Courses and Outcome of Community Acquired Pneumonia in Bangladesh: A Cross Sectional Prospective Study

Abstract:

Background: Pneumonia acquired outside the hospital by an immune-competent individual is defined as community acquired pneumonia (CAP). It is to be distinguished, on the basis of a wider spectrum of pathogens, from nosocomial pneumonia from pneumonia in an immune-compromised host. Community-acquired pneumonia is associated with a significant mortality and morbidity. Etiology of CAP varies geographically and the understanding of local epidemiology plays an important role in decision making for empirical treatment before test results are available. Primary decisions about empirical antimicrobial treatment required knowledge of predominant microbial patterns and their sensitivities.

Objectives: The aim of this study was to identify the bacterial etiology of CAP, their sensitivity towards empirical therapy and to observe the clinical course as well as short term outcome in hospitalized adult patients.

Methodology: It was one year-long observational prospective study on 87 patients diagnosed with CAP admitted in Chattogram Medical College Hospital, second largest tertiary care hospital during August 2018 to July 2019. Sputum for Gram and Z-N staining, culture and sensitivity, blood for culture, sensitivity and PCR for *Streptococcus pneumonia, Mycoplasma pneumoniae, Legionella pneumophila and Chlamydophila pneumonia* were done. Patients were followed up for in-hospital outcome and 30-day mortality.

Results: The mean age was 49.59 years and male : female ratio was 1.56:1. Most common clinical symptoms were fever, chest pain and cough. *Klebsiella pneumoniae* was identified in the sputum culture of the majority of the patients (39.1%), followed by *Pseudomonas aeruginosa (10.3%), Staphylococcus aureus and Escherichia coli (5.7%)*. The only one sample which was positive in blood culture was *Staphylococcus aureus.* Four samples were positive in PCR and identified *Streptococcus pneumoniae*. The sensitivity to meropenem, levofloxacin and amikacin was highest. The mean duration of hospital stay was 6.34±2.37 along with in-hospital mortality and 30-day mortality was 6.9% and 16.1% respectively.

Conclusion: The bacteriologic profile of community acquired pneumonia revealed Gram-negative bacteria as pre-dominant organism by conventional sputum and blood culture. But need for further serologic tests for atypical and viral pathogens and development of institutional antibiogram to facilitate the choice for empirical therapy is required.

Key words: Community Acquired Pneumonia (CAP), sensitivity, Antibiotic resistance, common pathogens, CURB-65

Background:

Infectious pneumonia is the acute invasion of lung parenchyma by one or more viral, bacterial, fungal or parasitic pathogens. The invasion of the lung is rarely demonstrated in vivo, and is usually substituted by the presence of a new infiltrate on radiological studies[1]. Pneumonia is suspected in a patient presenting with acute cough and at least one suggestive sign or symptom (localized findings on chest examination, fever lasting more than four days, presence of dyspnea or tachypnea). In older patients, cough or fever may be absent and pneumonia manifested by acute confusion or loss of functionality. Evidence of an acute infiltrate on radiological studies differentiates pneumonia from acute bronchitis, a benign, self-resolving condition that does not require antibiotic treatment[2].

Recently, a new category named 'healthcare-associated pneumonia' and including patients living in nursing homes, recently hospitalized, or in frequent contact with the healthcare system (eg. undergoing hemodialysis or ambulatory chemotherapy) has been proposed, but

its relevance is strongly debated and not widely accepted in Europe[3]. Due to major differences in the epidemiology, management, and prognosis, a distinction is made between pneumonia in a patient living at home (CAP), in a patient already hospitalized (hospital-acquired pneumonia), and in a patient with severe immunosuppression.

The community acquired pneumonia (CAP) is generally known as the pneumonia acquired outside the hospital to an immune-competent individual. It differs from nosocomial pneumonia that occurs after 48 hours of admission or within 3 months of discharge from hospital, and from typical pneumonia in an immune-compromised host, on the basis of wider variety of pathogens. Immune-compromised condition implies in the setting of neutropenia, iatrogenic immune-suppression with drugs, status post organ or stem-cell transplantation, HIV infection, or a congenital immune deficiency in a person[4,5].
Chronic obstructive pulmonary disease, conceded immune system, dementia, gastro esophageal reflux disease, etc. increase susceptibility of a patients for pneumonia[6]. Particular forms of antimicrobial resistance of habitual pathogens may also contribute otherwise[7]. The acquaintance of these microbiological characteristics is important and represents the basis for empirical treatments. Serious co-existing illness has been identified as modifying factors of severity of pneumonia[6,8]. On the basis of these obligation, published guidelines on pneumonia advocate specific criteria for antibiotic selection and the management of patients in the presence of co-morbid diseases[9].

While many cases of mild to moderate CAP can be successfully managed without identification of the organism, a range of microbiological tests should be performed on patients with severe CAP that required hospitalization. The common etiological agents causing CAP include *Streptococcus pneumonia* (20-60%), *Hemophilus influenza* (3-10%), *Chlamydia pneumonia* (4-6%), *Mycoplasma pneumonia* (1-6%), *Legionella* (2-8%), *Staphylococcus aureus* (3-5%), Gram-negative bacilli (3-5%), viruses (2-13%). In 40-60% cases, no cause is identified and in 2-5% cases, two or more pathogens are identified[10]. However, the epidemiology of bacterial infection varies depending on the geographic location. Petoet al. demonstrated that, in Asia these organisms were identified in a higher proportion of patients[11]. Conversely, although *S. pneumoniae* was commonly identified, it was relatively less important than in most European studies. Also, a substantial proportion of patients presenting with CAP in Asian countries were found to have TB, which is often considered to cause only more chronic pulmonary disease. Finally, *B. pseudomallei* was a major cause of CAP in northeast Thailand and was also reported in other Southeast Asian countries.

Though hospitalization of adult patients with CAP are increasing in Bangladesh, information regarding their clinical presentation, microbiological characteristics, antimicrobial susceptibility pattern that is required for choosing empiric antibiotic treatment and outcome of patients are lacking. Microorganisms causing CAP vary in their susceptibility to antimicrobials from place to place and time to time. Up to date knowledge of the microbial organisms and antibiotic susceptibility pattern of patients with CAP is essential for defining empirical treatment. There is a paucity of recent study regarding these issues in our country especially in our hospital settings, where a large number of CAP patients with different comorbidities are managed routinely.
Hence the present study focuses on the clinico-bacteriological profile in cases of CAP for a better clinical approach.A benchmark data and regular surveillance data regarding bacteriology of CAP and sensitivity pattern is essential to address the problem of CAP among hospitalized patients.These findings will provide clinicians in this region of Bangladesh with a better understanding of the spectrum of pathogens, updated knowledge about their antibiotic susceptibility pattern and in selecting the antibiotic for empirical therapyin hospitalized patients with CAP.

Methodology:

The prospective observational study was conducted from August 2018 to July 2019 in the Department of Medicine of Chattogram Medical College Hospital, the second largest government hospital in the country. Patients of both sexes age above 18 years who were diagnosed as CAP admitted in the Department of Medicine was included in the study as consecutive sampling method. The objective of the study was to isolate and identify the causative bacteria and their sensitivity pattern, describe clinical presentation, in-hospital complication and short term clinical outcome during hospital stay for CAP.
Sputum for Gram and Z-N staining, culture and sensitivity, blood for culture, sensitivity and PCR for *Streptococcus pneumonia, Mycoplasma pneumoniae, Legionella pneumophila and Chlamydophila pneumonia* were done. Patients were followed up for in-hospital outcome and 30-day mortality. Total 85 admitted patients were included after screening of exclusion criteria like chemical pneumonitis, malignancy, radiological evidence of fibrosis, collapse, bronchiectasis, lung abscess and tuberculosis, suspicion of immunosuppression or known immunosuppressive status like HIV, Hematological or lymphoid malignancy. Patient on immunosuppressive drugs- steroids and chemotherapy and getting antibiotic for more than 48 hours were also excluded.
Prior approval for the study was taken from the ethical review committee of Chattogram Medical College. After admission in the indoor, any suspected case of CAP seen by unit doctor was screened by study physician. Evaluation was made by history and physical examination in a structured case record form (CRF) by the study physician. Patients diagnosed clinically as CAP were enrolled in the study. Socio demographic variables (age, sex, residential area, religion, monthly family income), risk factor of pneumonia (smoking habbit, immunization history), clinical parameters (weight, length, height, chief complain, examination findings, CURBE-65 score), complete blood count (TC of WBC, Hb%, ESR), chest X-ray, RBS, Blood urea, blood culture, sputum for Gram staining and culture sensitivity, sputum for AFB for 3 consecutive samples were done. Duration of hospital stay, improvement, referral to ICU, development of complications during the hospital course was recorded besides the short-term outcome of 30-days mortality or survival.
Antibiotic therapy of the enrolled patient was given at the discretion of the treating clinician under the supervision of respective consultant of the medicine unit. The clinical judgment of consultant was ascertained by CURB-65 score by the study physician. During treatment, oral temperature was recorded and frequently physical examinations were performed up to discharge. Patients were asked to report 30 days after discharge for follow up.

Microbiological laboratory tests: Sputum originated from the lower respiratory tract were defined as that containing >25 granulocytes and <10 epithelial cells per low power field microscopic view. Validated sputum was cultured in blood agar, chocolate agar and McConkey's agar media. Isolation and identification of microorganism were done according to the standard method. Blood samples (6-8 ml) were collected aseptically from patients for blood culture. Primary blood cultures were done in Trypticase soya broth and secondary blood cultures were done on blood agar, chocholate agar and McConkey's agar media.

Sputum microscopy and culture: Specimens were classified by Bartlett's Criteria; Bacterial morphological types were screened at oil immersion field. The samples were homogenized with equal volume of N-acetyl cysteine and then vortex and diluted 1 in 100 according to standard microbiological practice and .005 ml of specimen were inoculated in each culture plate. Blood agar media was used for primary isolation and study of hemolytic property of the organism, Chocolate agar media for isolation of fastidious organisms and MacConkey agar media for isolation of Gram negative organisms. For the simplified method, bacteria with almost pure growth with colony numbers of more than twenty-five on the plate were defined as pathogens. Twenty-five colonies in a culture plate was considered equivalent to colony count 10^6/ml. Identification of bacteria were done by colony morphology, Gram stain, biochemical test. Sputum samples were stored at -80˚C for further use.

Susceptibility testing by disc diffusion: Antimicrobial susceptibility was determined by the disc diffusion method of modified Kirby-Baur technique, using Blood agar media (for *Streptococcus pneumonia*), Mueller-Hinton agar media (for *Escherichia coli, Klebsiella* and *Pseudomonas*). The turbidity of the inoculums was standardized to the equivalent to that of 0.5 of McFarland standard. All plates were incubated at 37°C aerobically for Blood agar and Mueller-Hinton agar.
Antimicrobial agents used (CLSI 2017): Following antimicrobials and their concentration per disc were used for susceptibility tests as for i) Gram positive cocci and diplococci: Meropencm (10 microgram), Ceftriaxone (30 microgram), Amoxyclav (30 microgram), Levofloxacin (5 microgram), Azithromycin (1 microgram), Cefexime (30 microgram) and Vancomycin (30 microgram). ii)) For Gram negative bacilli and coccobacilli: Meropenem 10 microgram) Ceftriaxone (30 microgram) Amikacin (10 microgram), Azithromycin (15 microgram), Levofloxacin (5 microgram). Amoxyclav (30 microgram) and Cefixime 30 microgram). The antibiotic sensitivity testing discs were manufactured by Oxoid Ltd, UK.

Polymerase Chain Reaction: PCR was done in the Department of Microbiology of CMCH after collection of all samples for *Streptococcus pneumoniae, Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila.*
Quality control was ensured by testing representative disc from each batch against reference strains of *E. coli* ATCC 25922 and *S. aureus* ATCC 25923; zones of inhibition were tested with standard value (CLSI 2017).
After collection data were entered into Microsoft Xcel data sheet to produce a master sheet. Then they were fed into SPSS version 23 software for the processing and analyses. Continuous variables were reported as means and standard deviation and categorical variables were reported as count and percentages. Between groups comparisons were done either by Chi square test or Fisher exact test for categorical data. Statistical significance was defined as $P < 0.05$ and confidence interval set at 95% level.

Observations and results:
The mean age was 49.59±16.97 years with ranged from 18 to 76 years and maximum number (35.6%) of patients was found in the age group of 40-59 years. There was male predominance with a male to female ration of 1.56:1.
About half of the enrolled patients were either current smoker or ex-smoker. One third (27.8%) of the patients had history of DM and majority of the DM patients had uncontrolled glycemic status (Table II).

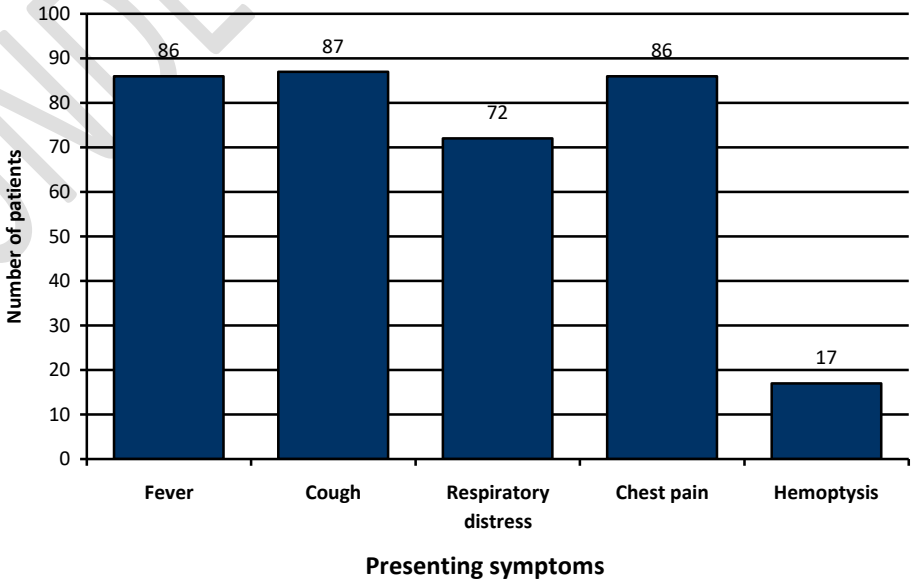

Figure-1: Presenting symptoms of the 87 admitted patients with CAP

Cough was present in all of the study patients. Fever and chest pain were also frequently reported by 86 patients while, respiratory distress was reported by 72 (82.8%) and hemoptysis was reported by 17 (19.5%) patients (Figure 1).

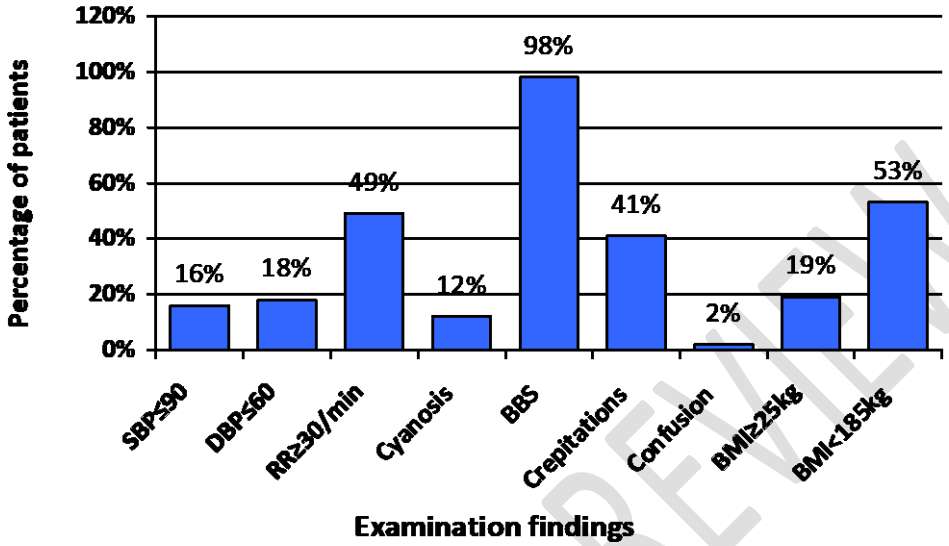

Figure-2: Examination findings of the 87 admitted patients with CAP

(SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; BBS: Bronchial breath sound)**.**

Bronchial breath sound was the most prominent respiratory findings observed in 85 (97.7%) of the patients followed by tachypnea in 43 (49.4%) and crepitation in 36 (41.4%) patients (Figure 2). More than half of the patients were malnourished and one fifth of them were obese as per BMI criteria.

Different laboratory findings of the enrolled CAP patients are presented in Table III. It shows that, sputum gram stain was positive in 55 (63.2%) patients while Z-N stain was negative in entire sample. Sputum culture yield growth in 53 (60.9%) sample while blood culture only in 1 (1.1%) sample. PCR was positive in 4 (4.6%) sample.

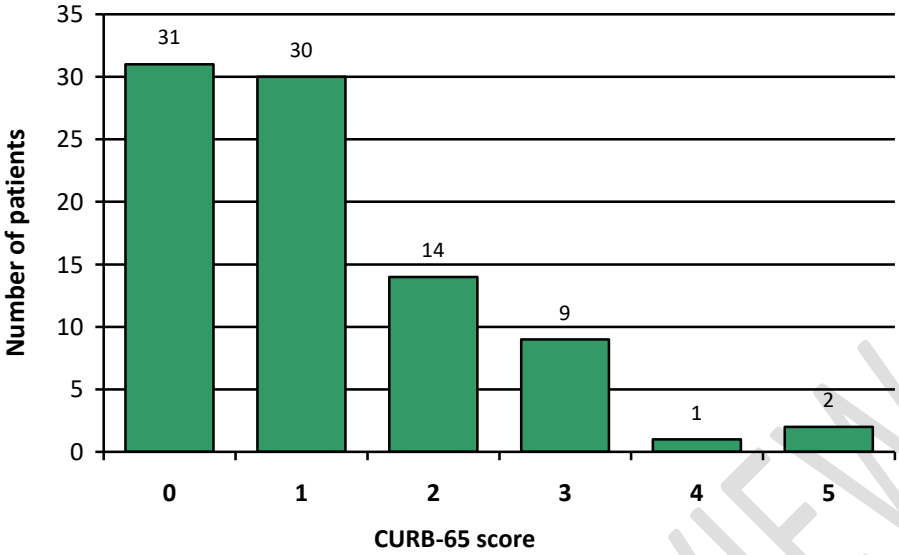

Figure-3: Severity of the 87 admitted CAP patients by CURB-65 score

Out of 87 admitted CAP patients, majority of them either had 0 CURB-65 score (31/87) or 1 CURB-65 score (30/87). Only 11 (13.7%) patients had CURB-65 score 3 or more.
Klebsiella pneumoniae was identified in the sputum culture of the majority of the patients (39.1%), followed by *Pseudomonas aeruginosa (10.3%), Staphylococcus aureus and Escherichia coli (5.7%)*. The only one sample which was positive in blood culture and it was *Staphylococcus aureus. Streptococcus pneumoniae* was identified in all the 4 PCR positive cases.

Table-I: The 30-days outcome of the 87 CAP patients admitted in hospital

Variables	**Frequency (%)**
Develop sepsis	9 (10.3%)
Need ICU	9 (10.3%)
In hospital mortality	6 (6.9%)
Length of hospital stay	6.34±2.37
Re-admission within 30 days	9 (10.9%)
30-day mortality	13(14.1%)

In hospital mortality rate of the CAP patients in this study was 6.9% and 30-day mortality rate was 14.1%. Average length of hospital stay was 6 days. About one tenth of the total patients develop sepsis and need ICU support.

Table-II: Distribution of the isolated organisms according to 30-day mortality

Name of organisms	**30 day outcome**		**P value***
	Survived (n=73)	**Died (n=14)**	
Klebsiella pneumonia	27 (37.0%)	7 (50.0%)	0.384
Pseudomonas aeruginosa	5 (6.8%)	4 (28.6%)	**0.034**
Staphylococcus aureus	5 (6.8%)	0 (0%)	0.588
Escherichia coli	5 (6.8%)	0 (0%)	0.588
Streptococcus pneumonia	3 (4.1%)	1(7.1%)	1.0
No organisms	28 (38.4%)	3 (21.4%)	0.362

*P value derived from Chi-square test or Fisher's exact test.

Table II shows that, patients who died within 30 days, majority had either *Klebsiella pneumonia or Pseudomonas aeruginosa.* Among survivors in addition of these two organisms *Staphylococcus aureus, Escherichia coli* and *Streptococcus pneumonia* were identified.

Table-III: Distribution of the isolated organisms according to severity by CURB-65

Name of organisms	**CURB-65 score**	
	≤2 (n=75)	**>2 (n=12)**
Klebsiella pneumonia	29 (38.7%)	5 (41.7%)
Pseudomonas aeruginosa	9 (12.0%)	0 (0%)
Staphylococcus aureus	4 (5.3%)	1 (8.3%)
Escherichia coli	5 (6.7%)	0 (0%)
Streptococcus pneumonia	3(4%)	1 (8.3%)
No organisms	26 (34.7%)	5 (41.7%)

During admission severity of pneumonia was assessed by CURB-65 score. Patients with severe disease (CURB-65 >2) and with less severe disease (CURB-65 ≤2) have almost similar bacteriological pattern.

Table-IV: Overall sensitivity pattern of the tested organisms

Name of antibiotic	**number**	**Sensitivity pattern**		
		Resistance	**Intermediate sensitive**	**Sensitive**
Amoxicillin-Clavulanate	52	43 (82.7%)	1 (1.9%)	8 (15.4%)
Clarithromycin	52	34 (65.4%)	13 (25.0%)	5 (9.6%)
Azythromycin	52	15 (28.8%)	7 (13.5%)	30 (57.7%)
Vancomycin	5	0 (0%)	1 (20.0%)	4 (80.0%)
Meropenem	52	2 (3.8%)	0 (0%)	50 (96.2%)
Cotrimoxazole	52	23 (44.4%)	4 (7.7%)	25 (48.1%)
Ceftazidime	51	26 (51.0%)	6 (11.8%)	19 (37.2%)
Ceftriaxone	52	20 (38.5%)	2 (3.8%)	30 (57.7%)
Cefuroxime	52	36 (69.2%)	7 (13.5%)	9 (17.3%)
Cefixime	52	38 (73.1%)	3 (5.8%)	11 (21.2%)
Levofloxacin	52	5 (9.6%)	1 (1.9%)	46 (88.5%)
Amikacin	52	0 (0%)	2 (3.8%)	50 (96.2%)

Overall the isolated organisms in the study were found to be highly sensitive for Meropenem (96.2%), Amikacin (96.2%), Levofloxacin (88.5%) and Vancomycin (80.0%).

Discussion:

The maximum numbers of cases of CAP (70%) were aged more than 40 years with a mean age of around 50 years. According to the earlier studies by Naik et al. the average age was around 53 years[12] but differ with the study of Salam et al. conducted in Bangladesh where the corresponding figure was comparatively lower (39 years)[13]. However, in a study conducted among the adult population of USA reported that the median age of the patients was 57 years[14]. This variation in their study may be due to higher life expectancy in their population.

The microbial diagnosis of CAP was confirmed in 65.5% of patients with standard sputum culture, blood culture and PCR test (53/87 were sputum culture positive and 4/87 were PCR positive). However, this rate varies in different studies. With different laboratory testing the etiological diagnosis could be confirmed in 29%, 49% and 75.6% cases in different studies among Indians respectively[12,15]. Comparatively high incidence of the etiological diagnosis in the present study is probably explained by the strict inclusion criteria. Patients with a history of getting antibiotic for more than 48 hours were excluded from the present study. However, no causative organisms were identified in a significant proportion of patients (34.5%) in the

present study. The possible causes for the inability to determine etiology in these patients were lack of sensitivity of laboratory investigations, prior antibiotic treatment and lack of more sophisticated investigations which are expensive and require highly trained personnel. Other prospective studies for evaluating the causes of CAP in adults have failed to establish an etiologic diagnosis in 40 - 60% of cases even with extensive diagnostic testing[14,16].

Fever and cough were most common symptoms whereas bronchial breath sound on affected side and crepitation were the commonest signs observed in the present study. Almost similar observations regarding the clinical presentations were also reported by other studies among hospitalized patients[13,17]. Sign of consolidation like bronchial breath sound was found in 98% cases in the present study and similarly Salam et al. found consolidation in almost all study patients.

The mean duration of hospital stay (*6.34 ± 2.37 days)* was similar to few other studies where the mean duration of hospital stay was 5.0±1.7 days and 5±1.2 days[13,18]. The in-hospital mortality rate during index admission and 30-day mortality was 6.9% and 16.1% respectively in the present study but the mortality rate of CAP in various hospital-based studies is variable, being 2% in a population of USA[14] to a higher mortality of 25% in Europe in earlier studies[19].

Prognosis of the patient was seen in hospitalized patient through CURB score. Out of 87 patients 61 patients in this study had CURB-65 score within score-1. Only 13.7% patients had CURB-65 score 3 or more in this study. Nine CAP cases in present study were needed to be shifted to ICU as they developed sepsis.

It was observed that isolated *Klebsiella* strain was mostly resistant to commonly used antibiotics for CAP like amoxiclav, cefixime, cefuroxime, clarithromycin and ceftazidime in present study. Other isolated organisms like *S. aurius*, *Pseudomonas*, *Escherichia coli*, were also resistant to β-lactamase inhibitor, macrolides and third generation cephalosporin. This study also revealed meropenem, amikacin and levofloxacin were the most sensitive antibiotics for the organisms identified form the CAP patients. However, meropenem is costly and not recommended by the guideline published by American thoracic society and infectious disease society of America[20].

Frequently used β-lactam antiobiotic and macrolides for the treatment CAP are first line regimens but emerging strain are more resistant to these conventional antibiotics. Multi drug resistant to β-lactamase, macrolides and fluroquinolone is an emerging problem and complicating the management of CAP[21]. In a study in Dhaka Medical College Hospital reported that, the sensitivity pattern of isolated strain of bacteria from CAP patients was alarming and the resistant bacteria were emerging[13].

This study was conducted over a short period of over nine months and it is possible that less common pathogens were not detected during the study. A larger multi-center study is needed to obtain accurate information on the epidemiology of CAP in this area of Bangladesh. Moreover, the etiology remained undetermined in 21.4% of patients who died during hospitalization. This emphasizes the need of further investigations in patients in whom the bad prognostic factors are present at the time of admission so as to establish the etiology, start early treatment and thereby reducing mortality.

Conclusion:

The present study revealed that the Gram-negative bacilli like *Klebsiella pneumonia, Escherichia coli and Pseudomonas aeruginosa* were common organism for CAP identified by sputum culture. *Staphylococcus aureus* was found by PCR test. For CAP that required hospitalization sensitivity results were in favor of meropenem, amikacin and levofloxacin. Overall mortality of in-hospital and 30-day were high.

Recommendations:

Regional differences in bacteriological profile as well as their sensitivity pattern should be considered during selecting the best and sensitive drugs for treating CAP. Institutional antibiogram should be developed to facilitate the choice for empirical therapy. To determine

the full etiological spectrum of CAP future studies incorporating large sample with serologic tests for atypical and viral pathogens from different center is essential.

.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

References:

1. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014 Oct 23; 371 (17): 1619-28. doi: 10.1056/NEJMra1312885. https://www.nejm.org/doi/10.1056/nejmra1312885
2. Lodise TP, Anzueto AR, Weber DJ, Shorr AF, Yang M, Smith A, Zhao Q, Huang X, File TM. Assessment of time to clinical response, a proxy for discharge readiness, among hospitalized patients with community-acquired pneumonia who received either ceftaroline fosamil or ceftriaxone in two phase III FOCUS trials. Antimicrob Agents Chemother. 2015 Feb;59(2):1119-26. doi: 10.1128/AAC.03643-14. Epub 2014 Dec 8. PMID: 25487791; PMCID: PMC4335888. https://pubmed.ncbi.nlm.nih.gov/25487791/
3. Julio Alberto Ramirez and Antonio R. Anzueto, Changing needs of community-acquired pneumonia, *Journal of Antimicrobial Chemotherapy*, 2011; 66 (3): iii3–iii9, doi:10.1093/jac/dkr094 https://academic.oup.com/jac/article/66/suppl_3/iii3/668789
4. Ewig, S, Welte, T, Chastre, J. and Torres, A. Rethinking the concepts of community-acquired and health-care-associated pneumonia. The Lancet Infectious Diseases, 2010; 10(4), 279–287. doi:10.1016/s1473-3099(10)70032-3 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(10)70032-3/fulltext?refissn=0272-5231&refuid=S0272-5231%2811%2900051-7
5. Waterer GW, Self WH, Courtney DM, Grijalva CG, Balk RA, Girard TD, Fakhran SS, Trabue C, McNabb P, Anderson EJ, Williams DJ, Bramley AM, Jain S, Edwards KM, Wunderink RG. In-Hospital Deaths Among Adults With Community-Acquired Pneumonia. Chest. 2018 Sep;154(3):628-635. doi: 10.1016/j.chest.2018.05.021. Epub 2018 May 30. PMID: 29859184; PMCID: PMC6859251. https://pubmed.ncbi.nlm.nih.gov/29859184/
6. Ruiz, M., Ewig, S., Marcos, M. A., Martinez, J. A., Arancibia, F., Mensa, J., & Torres, A. (1999). Etiology of Community-Acquired Pneumonia: American Journal of Respiratory and Critical Care Medicine, 160(2), 397–405. doi:10.1164/ajrccm.160.2.9808045 https://www.atsjournals.org/doi/full/10.1164/ajrccm.160.2.9808045
7. Arancibia F, Bauer TT, Ewig S, et al. Community-Acquired Pneumonia Due to Gram-Negative Bacteria and Pseudomonas aeruginosa: Incidence, Risk, and Prognosis. *Arch Intern Med.* 2002;162(16):1849–1858. doi:10.1001/archinte.162.16.1849. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/212617
8. Benisy R, Bayatmakoo Z, Mobaiyen H. Prognostic factors and outcome of patients hospitalized with community acquired Pneumonia. J Anal Res Clin Med, 2018; 6(2): 86-92. https://jrcm.tbzmed.ac.ir/Article/JARCM_904_20180221112428
9. Niederman M S, Mandell L A, Anzueto A, Bass J. B, Broughton W A, Campbell G D et al. Guidelines for the Management of Adults with Community-acquired Pneumonia. American Journal of Respiratory and Critical Care Medicine, 2001; 163 (7), 1730–1754. doi:10.1164/ajrccm.163.7.at1010 https://www.atsjournals.org/doi/full/10.1164/ajrccm.163.7.at1010
10. Bartlett, J.G., and Mundy, L.M. Community-acquired pneumonia. N Engl J Med, 1995; 333:1618-24. https://www.nejm.org/doi/full/10.1056/NEJM199512143332408
11. Peto L, Nadjm B, Horby P, Ngan TT, van Doorn R, Van Kinh N, Wertheim HF. The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. Trans R Soc

Trop Med Hyg. 2014 Jun;108(6):326-37. doi: 10.1093/trstmh/tru058. Epub 2014 Apr 29. PMID: 24781376; PMCID: PMC4023908. https://pubmed.ncbi.nlm.nih.gov/24781376/
12. Shah BA, Singh G, Naik MA, Dhobi GN. Bacteriological and clinical profile of Community acquired pneumonia in hospitalized patients. Lung India 2010; 27:54-7. https://www.lungindia.com/article.asp?issn=0970-2113;year=2010;volume=27;issue=2;spage=54;epage=57;aulast=Shah
13. Salam, M. A., Amin, M. R., & Islam, Q. (2017). Clinical Presentation and Bacterial Etiology of Adult Community Acquired Pneumonia. *Journal of Bangladesh College of Physicians and Surgeons*, *34* (3), 128-134. https://doi.org/10.3329/jbcps.v34i3.32343 https://www.banglajol.info/index.php/JBCPS/article/view/32343
14. Jain, S., Self, W.H., Wunderink, R.G., Fakhran, S., Balk, R., Bramley, A.M., Reed, C., Grijalva, C.G., Anderson, E.J., Courtney, D.M., et al. Community-Acquired pneumonia requiring hospitalization among U.S. adults. N. Engl. J. Med. 2015, 373, 415–427. https://www.nejm.org/doi/pdf/10.1056/NEJMoa1500245
15. Bansal S, Kashyap S, Pal LS, Goel A. Clinical and bacteriological profile of community acquired pneumonia in Shimla, Himachal Pradesh. Indian J Chest Dis Allied Sci. 2004 Jan-Mar;46(1):17-22. PMID: 14870864. https://pubmed.ncbi.nlm.nih.gov/14870864/
16. Hooi LN, Looi I, Ng A J. A Study on Community Acquired Pneumonia in Adults Requiring Hospital Admission in Penang, Med J Malaysia, 2001; 56 (3): 274-277. http://www.e-mjm.org/2001/v56n3/Community_Acquired_Pneumonia.pdf
17. Lamb, A., and Patil, A.H. (2018) Epidemiology and clinical features of community acquired pneumonia: hospital based study. Int J Res Med Sci,6(7):2260-3. http://dx.doi.org/10.18203/2320-6012.ijrms20182427 https://www.msjonline.org/index.php/ijrms/article/view/5071
18. Falguera, M., Pifarre, R., Martin, A., Sheikh, A., & Moreno, A. Etiology and Outcome of Community-Acquired Pneumonia in Patients With Diabetes Mellitus. Chest, 2005; 128(5), 3233–3239. doi:10.1378/chest.128.5.3233 https://journal.chestnet.org/article/S0012-3692(15)52883-3/abstract
19. Ortqvist A, Hedlund J, Grillner L, Jalonen E, Kallings I, Leinonen M, Kalin M. Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. Eur Respir J. 1990 Nov;3(10):1105-13. PMID: 2090471. https://pubmed.ncbi.nlm.nih.gov/2090471/
20. Lee MS, Oh JY, Kang CI, Kim ES, Park S, Rhee CK, Jung JY, Jo KW, Heo EY, Park DA, Suh GY, Kiem S. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia. Infect Chemother. 2018 Jun;50(2):160-198. doi:10.3947/ic.2018.50.2.160 https://icjournal.org/DOIx.php?id=10.3947/ic.2018.50.2.160
21. Shah P B, Giudice JC, Griesback R Jr., Morley TF, Vasoya A. The newer guidelines for the Management of Community-acquired pneumonia. Journal of infectious diseases, 2004; 104(12):521-26. https://jaoa.org/article.aspx?articleid=2092910