

Effectiveness of Carbapenems in Hospital Acquired Pneumonia and Ventilator Associated Pneumonia against Extended Spectrum β -lactamases Enzyme producing Enterobacteriaceae in a Tertiary Care Hospital

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Abstract: Background: This study aims to find out the prevalence of HAP/VAP, risk factors implicated, organisms involved and their sensitivity patterns. This study was designed to improve morbidity and reduce the hospital stay. **Objective:** The aim was to describe clinical response and microbiologic cure rates associated with carbapenems as first line treatment for infections caused by ESBL-producing organisms.

Methodology: A prospective cohort observational open labelled study was conducted at Owaisi Hospital and Research Center, for patients admitted in the Department of Pulmonology for a period of six months. The demographic data, diagnostic criteria, associated risk factors and laboratory data including culture and antimicrobial susceptibility were collected.

Results: The total in patient population in pulmonology department was 150, out of which 30 were affected by nosocomial pneumonia. Among total patients (i.e n=30) The prevalence of HAP was found to be 19(63.3%) and VAP was found to be 11(36.6%). The incidence of ESBLs Organisms were higher in female patients than in male patients. The culprit ESBLs which are responsible for HAP & VAP were klebsiella (47%), E.coli (17%) citrobacter (23%), pseudomonas (13%). HTN (90%), DM (87%), were most commonly occurring comorbidities. We analyzed the clinical cure rates according to the data collected ie out of 30 pneumonia patients: 25 showed improvement (83%), mortality seen in 3 VAP patients (10%), 2 patients (6.6%) doesn't showed any improvement.

Conclusion: The Prevalence of HAP/VAP was 12.6% (HAP), 7.3%(VAP) out of 150 admissions in pulmonology dept. This study highlights the progressive rise of broad resistance, ever-increasing prevalent and diversity of β -lactamases in Enterobacteriaceae members is driving to the use of carbapenems as a first line therapy

Keywords: ESBL organisms, HAP, VAP

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I. Introduction

Pneumonia is the lower respiratory tract infection which is characterised by acute inflammation of parenchymal cells which are distal to the terminal bronchioles involving alveolar ducts, alveolar sacs and alveoli.^(1, 2) **EPIDEMIOLOGY:** In 2013 , globally 188 countries around the world reported LRTI & it was found to be second cause of death . European countries reported mortality rates ranging from less than 1% - 48% . Incidence of pneumonia increased with increasing patient age (EG – in USA 24.8) cases per 10,000 individuals aged between 65 and 79 years, and 164.3 cases per 10,000 individual reported in adults around 80 years of age. Pneumonia remains the leading infectious disease mostly seen in children under five years of age, and accounted 15% of deaths and in 2015 , 920,000 children are killed ^(3,4) Extended-spectrum β -lactamase (ESBL)-producing bacilli are the generic designation for Gram-negative bacilli producing β -lactamase that have acquired the ability to degrade third- and fourth-generation cephalosporins and monobactams. This class of bacteria includes four species (Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, and Proteus mirabilis) ⁽⁵⁾ The Clinical Laboratory and Standards Institute (CLSI) suggests detection of ESBLs at an earlier stage in order to eradicate them easily. These bacteria may be isolated from various specimens, including urine, sputum, and blood culture ⁽⁶⁾. Pneumonia develops in patients admitted to the hospital for >48 hrs and usually the incubation period is at least 2 days is nosocomial or hospital acquired pneumonia(HAP) ⁽⁷⁾ and that which develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least >48 hrs is Ventilator Associated Pneumonia (VAP) ⁽⁸⁾. Antibiotic choice should be based on culture of sputum that is

noninvasively obtained-spontaneously or by induction of sputum via nasotracheal suctioning or endotracheal aspiration. Blood cultures also serves as a diagnostic tool⁽⁹⁾ Obtaining sputum via non-invasive methods with semi-quantitative cultures is preferred over invasive techniques with quantitative cultures or non-invasive approaches with quantitative cultures. Noninvasive techniques include collection of spontaneously expectorated samples, sputum production, and nasotracheal suctioning, endotracheal aspiration. Invasive approaches include broncho-alveolar lavage, protected specimen brush, and blind bronchial sampling.⁽¹⁰⁾ Carbapenems belongs to the b-lactam class of antibiotics Carbapenems are the drugs of choice for the treatment of infections caused by ESBL-carrying pathogens or MDR Pathogens.⁽¹¹⁾ Carbapenems are generally well tolerated. Allergic reactions are the most common adverse events in treatment with carbapenems; these include rashes, urticaria and immediate hypersensitivity. Major adverse effects such as diarrhoea, pseudomembranous colitis, coagulation abnormalities, nephrotoxicity and hepatotoxicity.⁽¹²⁾

Thus, the aim of the present study is to determine the extent and variation in endemic ESBL producing enterobacteriaceae in different ward environment and to investigate the potential of carbapenems in pneumonia against ESBL-PE to be transferred from environmental isolates to human.

II. Materials and Methods

Study Site:

The study was conducted in the in-patient setup of Pulmonology Department of Owaisi Hospital and Research Centre, a tertiary care teaching hospital in South India, during a period of 6 months. It is a 1000-bedded teaching hospital situated in the heart of the city of Hyderabad, providing specialized health care services to all people.

Plan of work:

- Ethical Committee approval was obtained from Institutional Review Board Committee of a teaching hospital.
- Literature review related to the study was done.
- Designing a data collection form.
- Study procedure was completely explained to patient and a patient informed consent form has been obtained from them.
- Collection of microbial culture.
- Evaluating the effectiveness of carbapenems against ESBL-PE.
- Assessing the patient for improvement in health status against ESBL-PE.
- Review of patients
- Report the data collected.

Study Design:

A hospital based prospective cohort observational open labelled study was conducted on 30 patients. Data were collected from both case records and patients. Study period 6 months.

Sample Size: Approximately 30 samples who took treatment for Pneumonia and Carbapenems are selected according to inclusion and exclusion criteria of the study.

Study Criteria:

The following categories of patients admitted in RICU and MICU ward (inpatients) are enrolled into the study.

Inclusion Criteria:

- Patients of both genders (male and female) above 18 years
- Patients in RICU and MICU who are diagnosed with Pneumonia.
- Patients with HAP
- Patients with VAP

Exclusion Criteria:

- Patients with CAP
- Patients undergoing Bronchiectasis lung study
- Patients with cystic fibrosis
- Patients on immunosuppressants
- Comatose patients
- Pregnant & lactating women are excluded
- Paediatric patients are excluded.

Source of Data

- Patient data collection form.
- Patient interaction.
- Treatment charts.
- Culture sensitivity reports
- Microbiology reports.

Novelty of the study:

Due to the limited studies on effectiveness of carbapenems against ESBL-PE in HAP/VAP patients , this research work is being carried out. Moreover, this studies are done in abroad countries like Europe , USA and limited studies has been done in South Indian tertiary care hospitals (Hyderabad, Telangana) thus, aiming us to isolate organisms at Owaisi hospital, Hyderabad as well as isolating the culture sensitivity profiles .

This study helps to improve morbidity , to reduce hospital stay and to reduce hospital cost to the patients due to the increased prevalence of infection with ESBL-PE. Thus helps in clinical improvement.

Expected outcomes:

- Positive culture becomes negative
- Clinical improvement.
- Improvement in inflammatory markers like CRP , Sr. procalcitonin.
- Improvement in leucocyte count
- Improvement in chest X-ray.

Statistical Analysis:

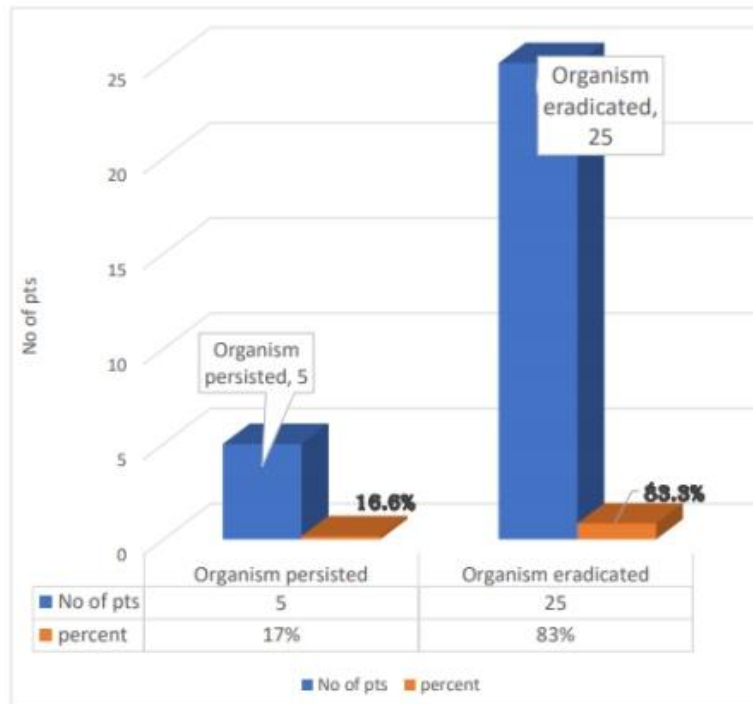
A sample size of 30 pateints , 19 pateints in HAP and 11 in VAP were collected during a period of 6 months based upon the inclusion and exclusion criteria of the study .The parameters recorded include :

- WBC count
- Serum Procalcitonin
- ESR
- CRP
- Temperature Profile
- Chest X-ray

The results were depicted in the form of tables and graphs. Microsoft Word and MS Excel are used to generate graphs and tables. Data was analysed using statistical method independent t- test with the help of graph pad 3.0 version (quickcalcs).

III. Results

After treatment with carbapenem therapy in total n=30 pts ; among them 5 organisms(17%) had persisted and 25(83%) had eradicated.

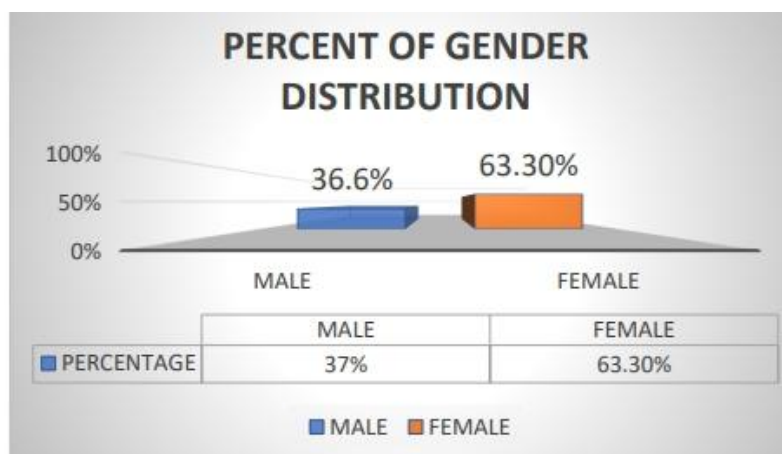


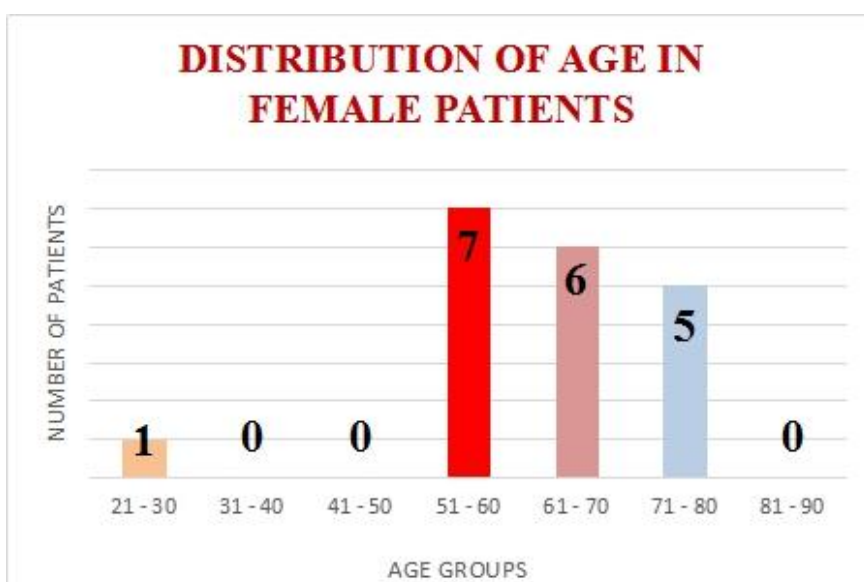
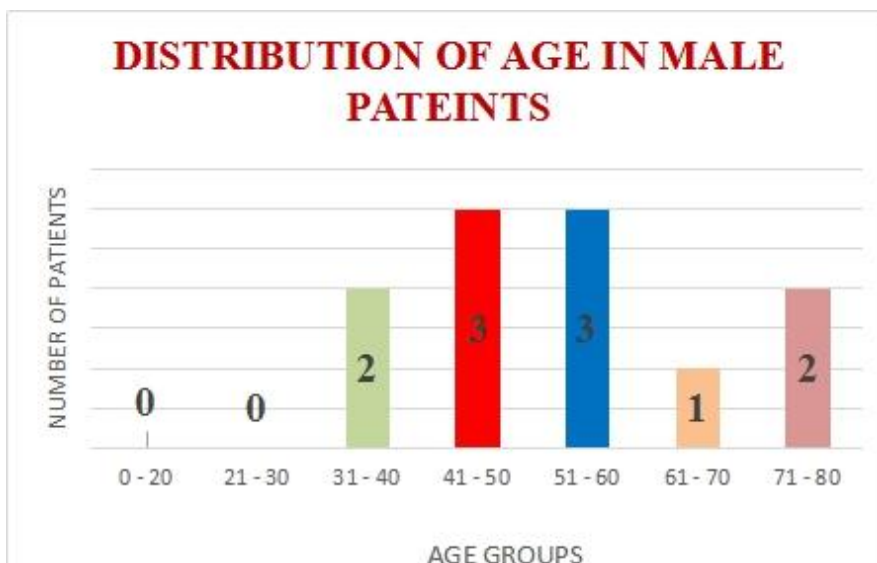
Showing better microbiological and clinical cure rates upon treatment with carbapenems. Out of total (n = 30), we achieved 83 % (n= 25) of microbiologic and clinical cure rates by eradicating Gram - ve organisms in 25 patients.

IV. Discussion

In this study , the no. of patients included are 30, involving prospective cohort observational open labelled study assessing the safety and efficacy of Carbapenems in pts with ESBL producing enterobacteriaceae. Our data suggests that treatment with carbapenems is associated with good clinical and microbiological outcome.

Among the total population i.e; n=30; number of male subjects = 11 (37%), number of female subjects =19(63.3%).

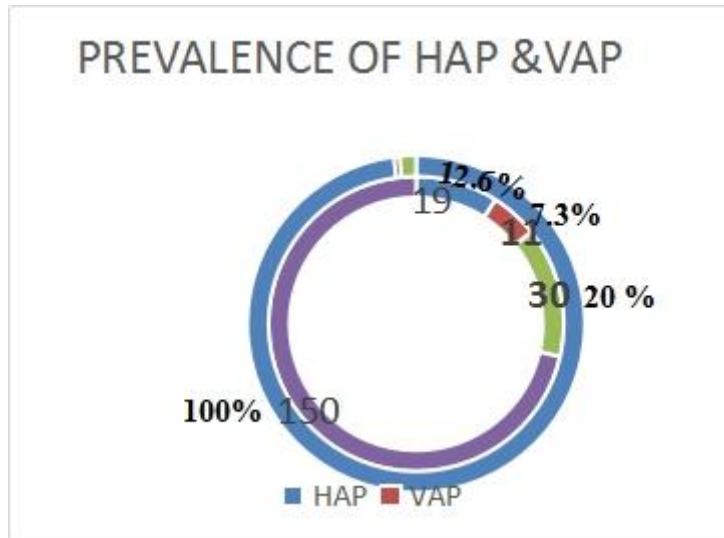




Accounting majority of cases in females in the age group of 51-60 yr (23%) and male 41-60 (20%).

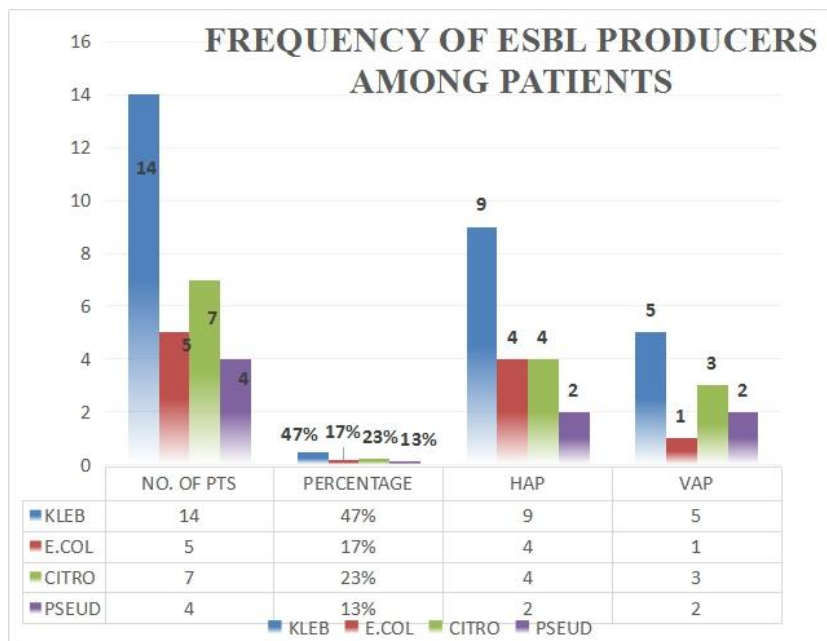
AGE GROUPS (YRS)	MALE (n=11)		FEMALE (n=19)	
21 - 30	0	0%	1	3.3%
31 - 40	2	7%	0	0%
41 - 50	3	10%	0	0%
51 - 60	3	10%	7	23%
61 - 70	1	3.3%	6	20%
71 - 80	2	6.6%	5	17%

Thus, The incidence of ESBLs Organisms were higher in female patients than in male patients. Among total patients (i.e n=30).

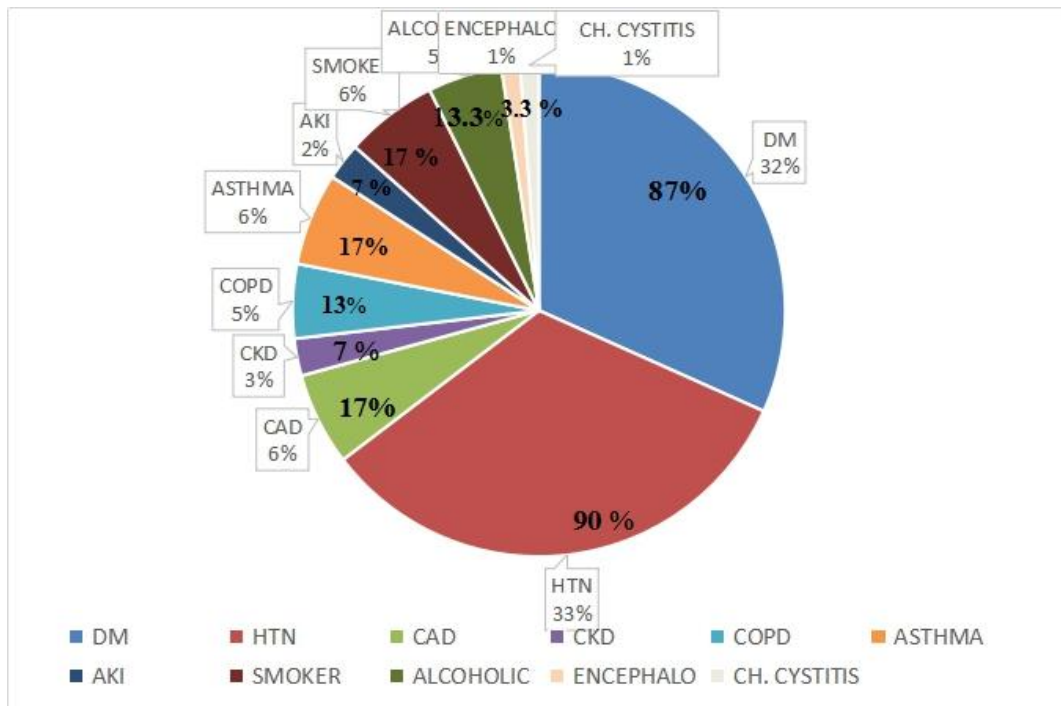


	NO.OF PT.	PERCENTAGE
HAP	19	12.6 %
VAP	11	7.3 %
TOTAL	30	20 %
NO. OF ADMISSIONS	150	100%

The prevalence of HAP was found to be 19 (12.6%) and VAP was found to be 11(7.3%).

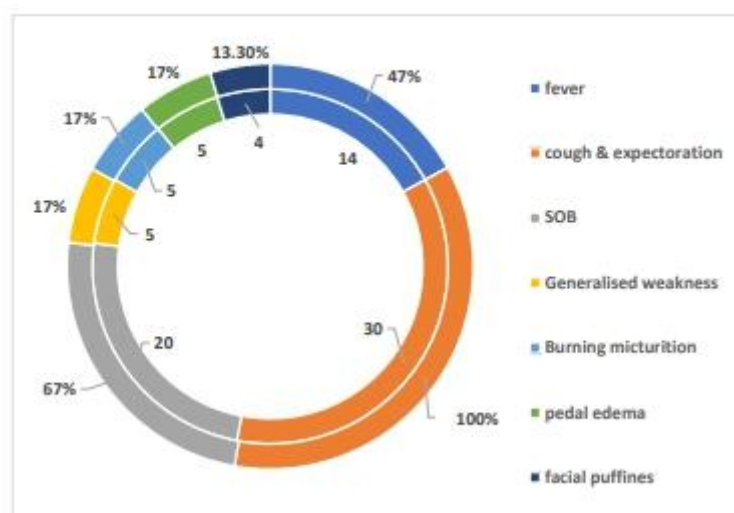


The culprit ESBLs which are responsible for HAP and VAP were klebsiella (47%) in which 9 pts are HAP and 5 pts are VAP, followed by citrobacter (23%) in which 4 pts has HAP and 1 pt has VAP, e.coli (17%) in which 4 pts has HAP and 3 pts has VAP, pseudomonas (13%) in which 2 pts has HAP and 2 pts has VAP.

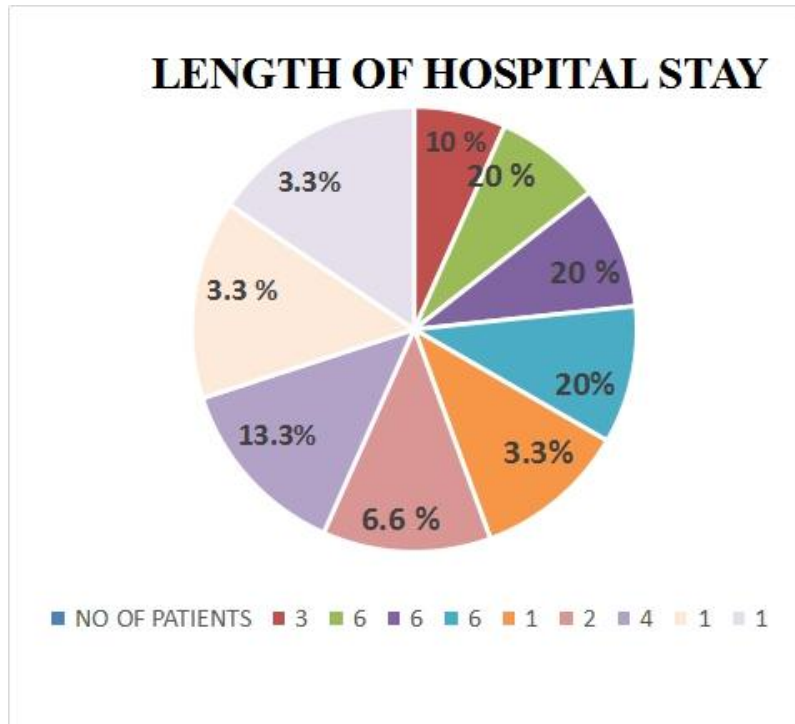


The study conducted observed that the risk factors for HAP and VAP are hypertension.(90%),diabetes (87%) ,asthma (17%) ,COPD (13.3%)and others are CAD (17%) followed by smoking(17%) and alcohol (13.3%). Thus, diabetes and hypertensions were most commonly encountered comorbidities.

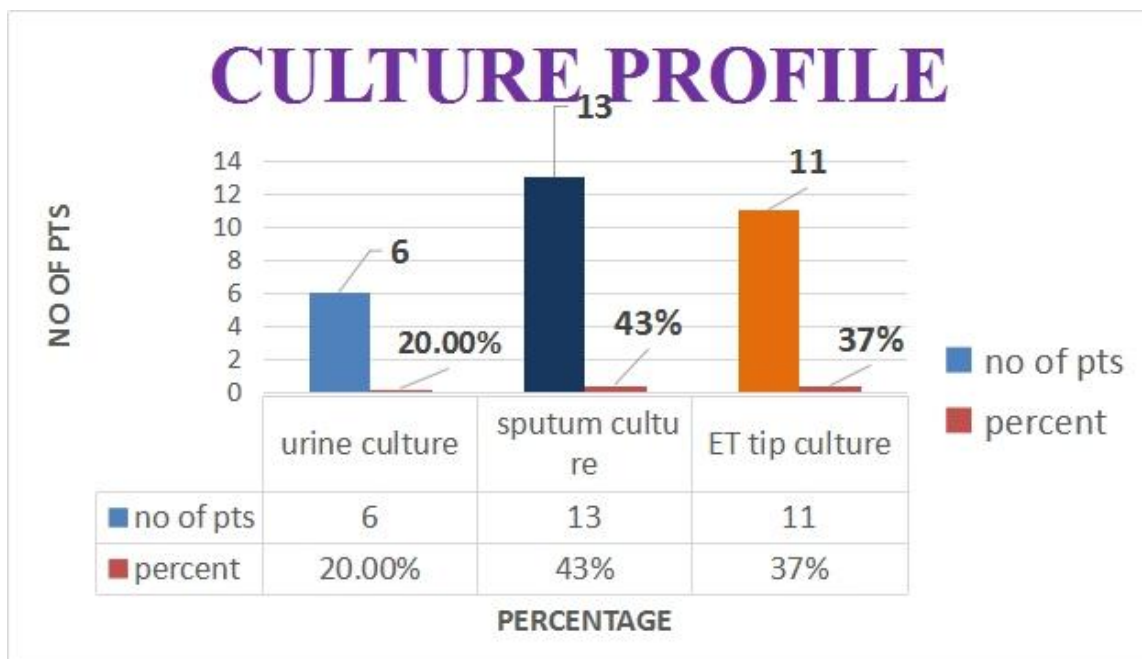
CLINICAL FEATURES:



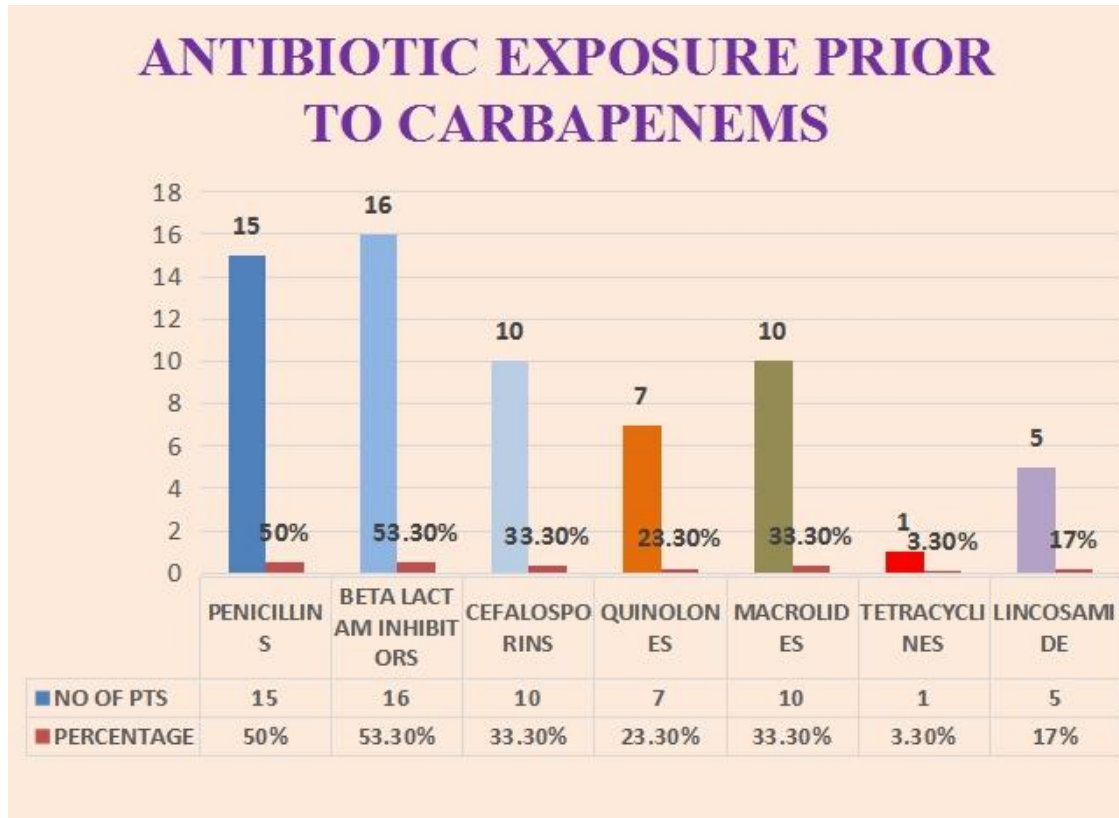
The clinical features associated in our study included fever (47%),cough with expectorion (100%), SOB(67%) ,generalised weakness(17%) burning micturition (17%), pedal oedema(17%) , facial puffiness(13.30%).



NO. OF PTS- HAP(n=19)	NO. OF PTS- VAP(n=11)	LENGTH OF STAY(DAYS)
3	-	6 days
6	-	7days
5	-	8days
3	2	9days
1	1	10days
1	2	11days
-	4	12days
-	1	13days
-	1	14days



Among total n=30 pts 6 pts (20.00%) performs urine culture, 13 pts (43%) performs sputum culture and 11 pts (37%) performs endotracheal aspiration tip culture.



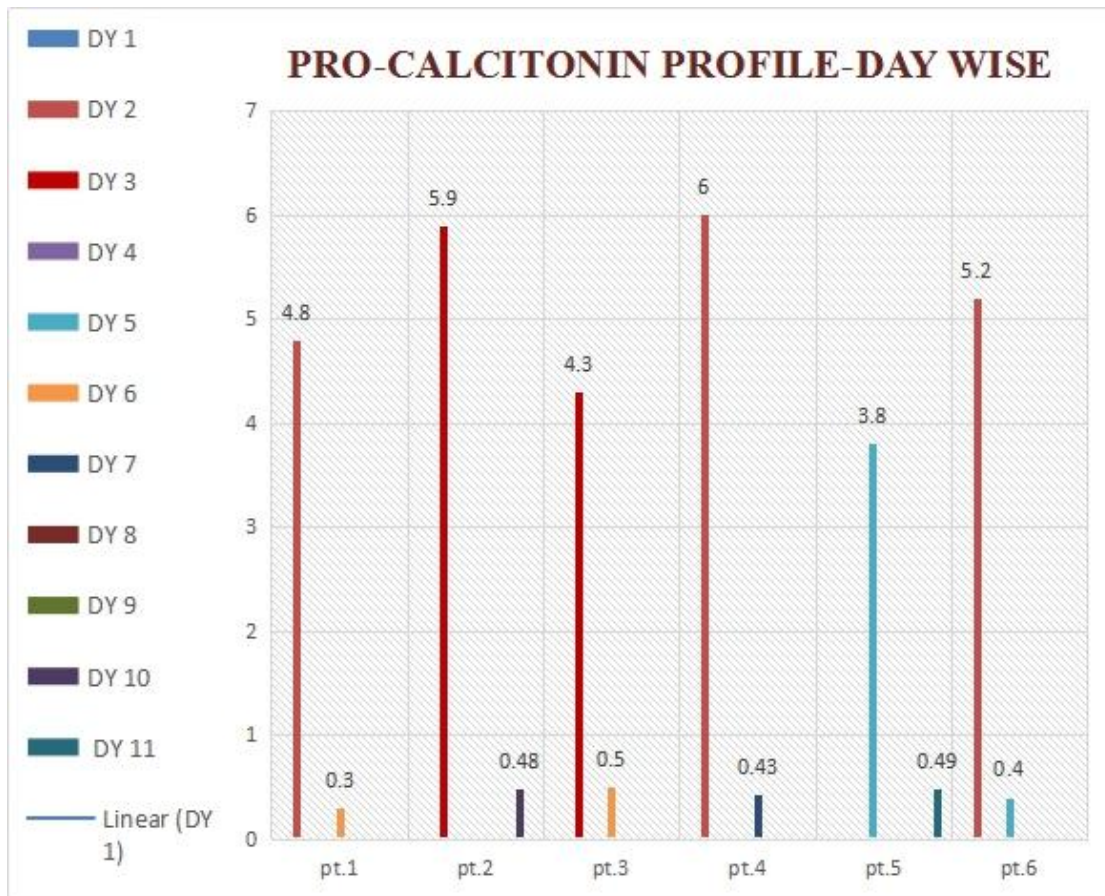
The most frequently used antibiotics prior to carbapenem therapy were penicillins (50%), beta lactamase inhibitors (53.30%) cephalosporins (33.30%) , quinolones (23.30%), macrolides (33.30%) tetracyclins (3.30%) ,lincosamide (17%) .



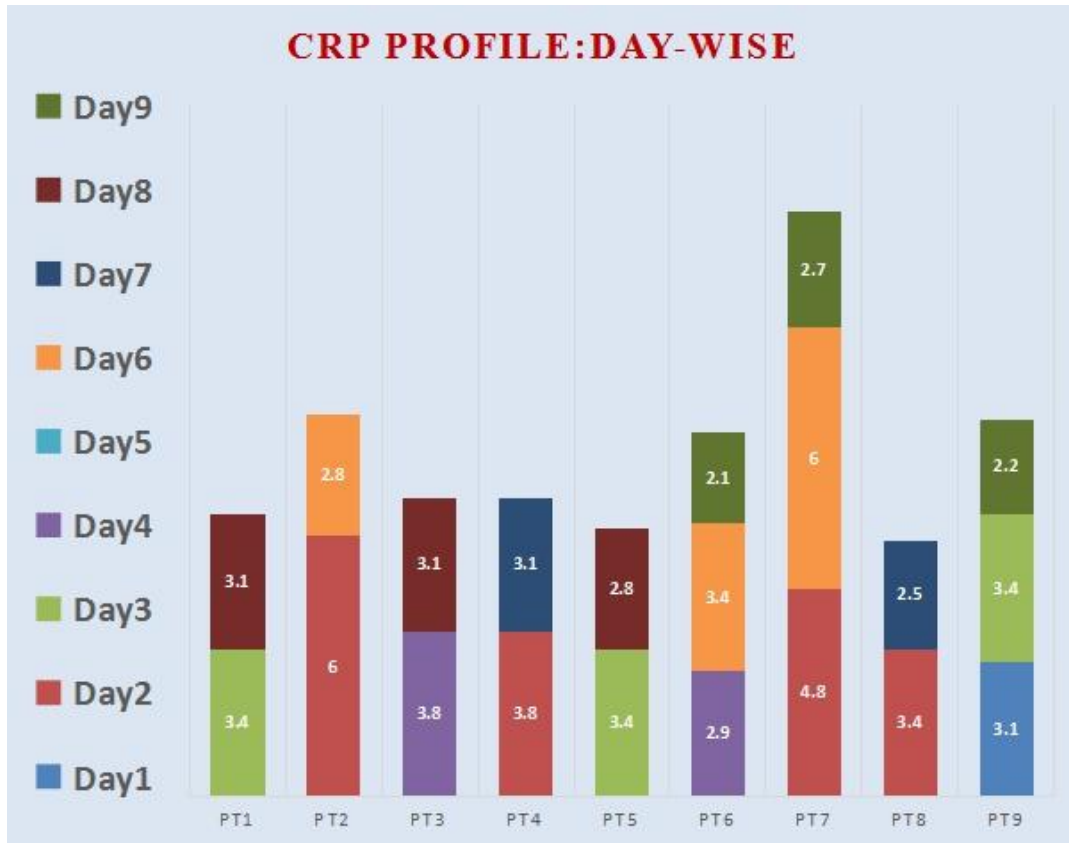
Out of total (n=30) patients , In WBC profile ,29 (96.6%) patients showed improvement



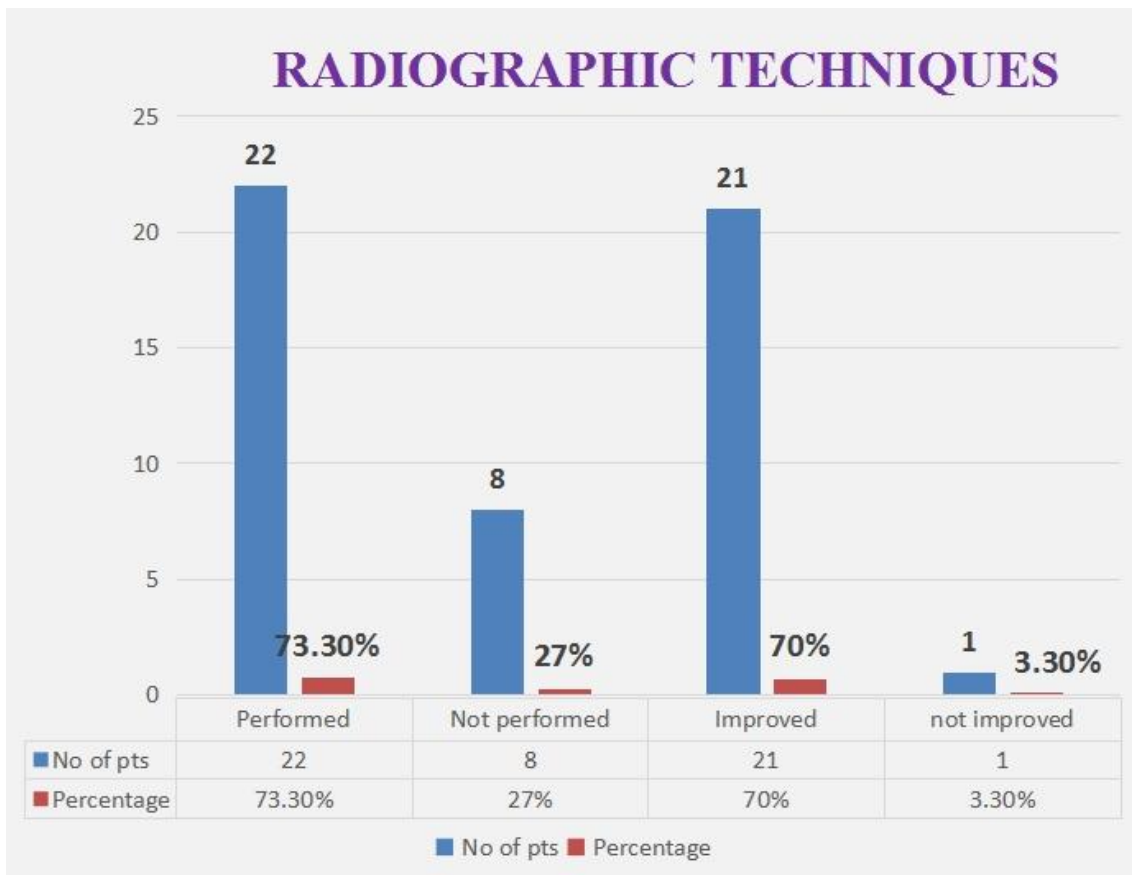
Out of 30 pts, 14 patients (46.6%) became Afebrile.



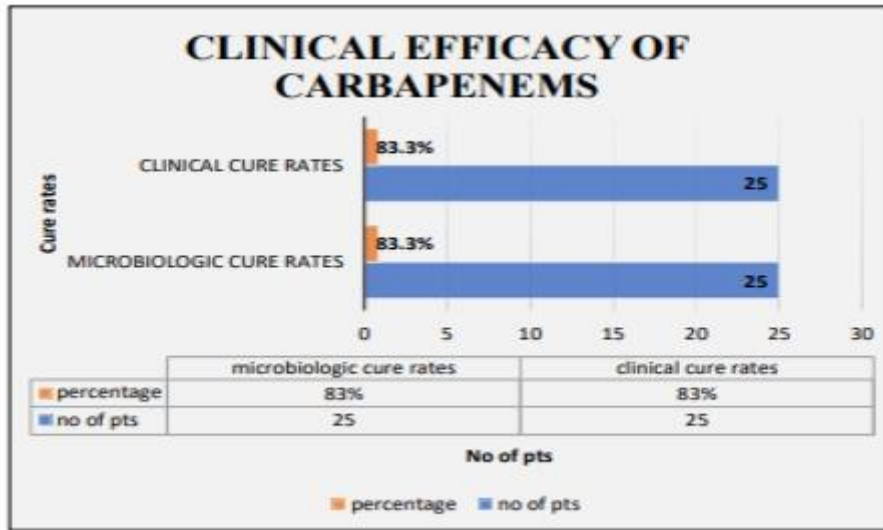
Out of 30 pts, 6 (20%) patients attained normal procalcitonin levels



Out of 30 pts, 9 patients (30%) attained normal CRP levels



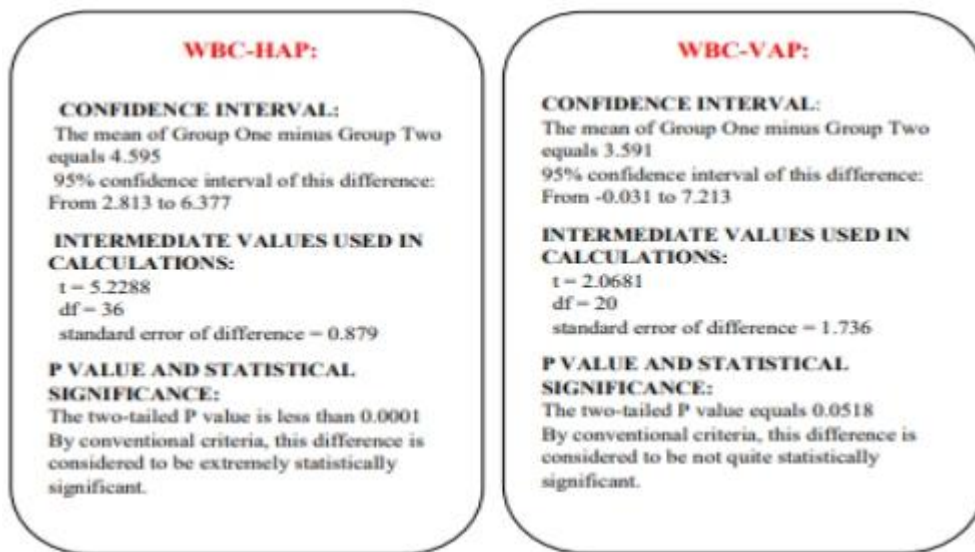
Out of 30, only 22 performed x-ray procedure due to financial constraints, 21 patients (70%) showed improvement in chest X-ray after the treatment with carbapenems.



Out of total (n = 30) , we achieved 83 % (n=25) of microbiologic and clinical cure rates by eradicating Gram – ve organisms in 25 patients.

We analyzed the clinical cure rates according to the data collected ie out of 30 pneumonia patients improvement was seen in 25 (83%) patients and mortality 3 (10%) and 2 doesn't showed any improvement (6.6%).

The results generated through independent unpaired t-test were statistically significance , thus rejecting null-hypothesis (H_0) and accepting alternate hypothesis (H_a).



The result generated through independent unpaired t-test (n = 30) in: WBC in HAP (n=19) the two tailed p-value < 0.0001 , in VAP (n=11) the two tailed p-value =0.0518

TEMPERATURE-HAP

Confidence interval:
The mean of Group One minus Group Two equals 2.500
95% confidence interval of this difference:
From 1.853 to 3.147

Intermediate values used in calculations:
t = 8.1120
df = 18
standard error of difference = 0.308

P value and statistical significance:
The two-tailed P value is less than 0.0001
By conventional criteria, this difference is considered to be extremely statistically significant.

TEMPERATURE-VAP

Confidence interval:
The mean of Group One minus Group Two equals 2.050
95% confidence interval of this difference:
From 0.199 to 3.901

Intermediate values used in calculations:
t = 2.7094
df = 6
standard error of difference = 0.757

P value and statistical significance:
The two-tailed P value equals 0.0351
By conventional criteria, this difference is considered to be statistically significant.

FEVER (n = 10) in HAP the two tailed p – value < 0.0001 , in VAP (n=4) the two tailed p-value =0.035

CRP-HAP

Confidence interval:
The mean of Group One minus Group Two equals 1.680
95% confidence interval of this difference:
From 0.371 to 2.989

Intermediate values used in calculations:
t = 2.9597
df = 8
standard error of difference = 0.568

P value and statistical significance:
The two-tailed P value equals 0.0182
By conventional criteria, this difference is considered to be statistically significant.

CRP-VAP:

Confidence interval:
The mean of Group One minus Group Two equals 0.575
95% confidence interval of this difference:
From 0.238 to 0.912

Intermediate values used in calculations:
t = 4.1761
df = 6
standard error of difference = 0.138

P value and statistical significance:
The two-tailed P value equals 0.0058
By conventional criteria, this difference is considered to be very statistically significant.

CRP (n = 5) in HAP the two tailed p-value =0.0182 , in VAP (n=4) the two tailed p-value =0.058

PROCALCITONIN-HAP

Confidence interval:
The mean of Group One minus Group Two equals 4.8180
95% confidence interval of this difference:
From 4.0678 to 5.5682

Intermediate values used in calculations:
t = 14.8093
df = 8
standard error of difference = 0.325

P value and statistical significance:
The two-tailed P value is less than 0.0001
By conventional criteria, this difference is considered to be extremely statistically significant.

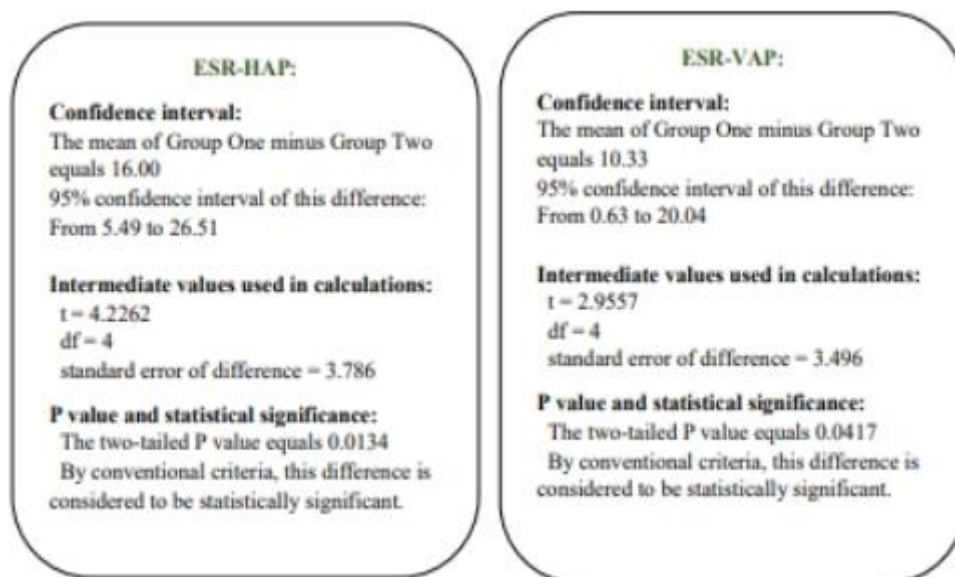
PROCALCITONIN-VAP

Confidence interval:
The mean of Group One minus Group Two equals 4.3967
95% confidence interval of this difference:
From 3.0119 to 5.7814

Intermediate values used in calculations:
t = 8.8155
df = 4
standard error of difference = 0.499

P value and statistical significance:
The two-tailed P value equals 0.0009
By conventional criteria, this difference is considered to be extremely statistically significant.

PROCALCITONIN (n=5) in HAP the two tailed p – value = 0.0001 , in VAP (n=3) the two tailed p – value =0.0009



ESR (n= 3) in HAP the two tailed p – value =0.0134 , in VAP (n=3) the two tailed p – value =0.0417. Thus the above results the differences are considered to be statistically significant except statistical analysis of WBC in VAP patients to be not quite statistically significant.

V. Conclusion:

By determining prevalence and by performing appropriate culture, radiographic techniques and examination of inflammatory markers we have eradicated the Gram negative organisms thereby improving clinical status of patients thereby reducing length of hospital stay and cost associated with the stay. We observed that Patients treated with carbapenems achieved favorable clinical response and microbiologic cure rates. This conclusion seems relevant not only from the patient’s perspective (such as improvement of clinical conditions), but also from a societal perspective. Thus, our data suggest that carbapenems are considered as first line agents in treatment of nosocomial pneumococcol infection caused by caused by ESBL-producing gram negative organisms and helps in improving morbidity.

Acknowledgements

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Conflict of Interest:

Authors state that there are no conflict of interests.

Abbreviations

- ✓ CAP – Community Aquired Pneumonia
- ✓ HAP – Hospital Acquired Pneumonia
- ✓ HAP – Healthcare Associated Pneumonia
- ✓ VAP – Ventilator Associated Pneumonia
- ✓ ESBL – Extended Spectrum Beta Lactamase
- ✓ ESBL-PE – Extended Spectrum Beta Lactamases Producing Enterobacteriaceae
- ✓ CRP – C reactive Protein
- ✓ ESR – Erythrocyte Sedimentation Rate

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