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Medicine

# ANTIBIOTIC SUSCEPTIBILITY PATTERNS IN PATIENTS WITH GRAM NEGATIVE SEPSIS

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**ABSTRACT** Gram Negative Sepsis is an important cause of morbidity and mortality in hospital intensive care units all over the world, especially in developing countries like India. Increasing rates of antibiotic drug resistance has been noted in recent times and this adversely affects the prognosis and outcomes of patients. This study was undertaken to provide some insights into this important problem because there are very few studies on antibiotic susceptibility patterns on patients with gram negative sepsis (with positive blood cultures) in India, especially Southern India.

A prospective hospital based observational study was carried out to determine the antibiotic susceptibility patterns in patients with gram negative sepsis. Patients with positive blood cultures were included in the study. Outcome (in-hospital mortality) was noted. Presence of risk factors and comorbidities were also studied, including diabetes mellitus, CKD on chronic hemodialysis, HIV, COPD and Malignancy In our study, Diabetes mellitus was the most common risk factor. Mortality was higher in patients with one or more comorbidities. Age was an independent risk factor. Klebsiella pneumoniae was the most common organism isolated followed by Acinetobacter baumanii, Escherichia coli and Pseudomonas aeruginosa. Mortality was more in patients with Acinetobacter baumanii followed by Pseudomonas and Klebsiella, followed by E.coli. Mortality in patients with cultures resistant to Meropenem was higher

Among commonly used first line antibiotics in MICU, resistance to Fluoroquinolones (Ciprofloxacin) was highest overall (two thirds were resistant). Resistance to beta lactam antibiotic (Cefoperazone sulbactam) was seen in almost half of the patients. Among 'last resort' broad spectrum antibiotics, Carbapenem (Meropenem) resistance was seen in approximately one third of the patients. Colistin resistance was seen in 1 in 10 patients. High resistance patterns to Meropenem, Tigecycline and Colistin is an alarming and worrisome trend.

**KEYWORDS :** Gram negative sepsis, Antibiotic susceptibility patterns, Antibiotic sensitivity, Antibiotic drug resistance, Intensive care unit

## INTRODUCTION

Bloodstream infection is a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive therapy. Bacteremia due to gram negative bacilli is a significant problem in both hospitalized and community dwelling patients. These organisms pose serious therapeutic problems because of the increasing incidence of multidrug resistance. Gram negative bacillary sepsis with shock has a mortality rate of 12 to 38 percent.

Approximately two-thirds of the cases occur in patients with significant underlying illness. Sepsis related mortality rates increase with age and pre-existing comorbidity like diabetes mellitus, chronic liver disease, patients on hemodialysis, malignancy, recipients of solid organ transplant and bone marrow transplant, HIV, COPD etc. The widespread use of immunosuppressive drugs, indwelling catheters and mechanical devices also play a role.

Gram-negative bacteria cause a wide spectrum of diseases, including urinary tract, bloodstream, airway, venereal, and health care-associated infections. Recently Gram-negative bacteria with resistance to commonly used antibiotics, including quinolones, colistins (polymyxins), carbapenems, cephalosporins, and other β-lactam antibiotics, have been isolated from humans with increasing frequency.

Medical Intensive care units (MICUs) are an important source of infections, especially bacterial infections. Bloodstream infection is a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive therapy. This study was taken up to determine demographic and clinical risk factors, bacteriological profile, drug sensitivity patterns and focuses on current patterns of bacteriological isolates at a tertiary care hospital in Telangana. There was no previous data available from this part of the country.

## METHODOLOGY

A prospective observational study was performed on patients satisfying the inclusion and exclusion criteria as mentioned below. The study was carried out in Medical Intensive Care Unit of a tertiary care hospital and was done over a period of 18 months. Non-probability consecutive sampling technique was used where all patients meeting the inclusion criteria within the study duration were selected till the sample size was reached.

150 adult patients who met clinical criteria for Sepsis and Septic shock and were admitted to Medical Intensive Care Unit were included in the study. Included patients had blood culture results positive for gram negative bacilli and coccobacilli (included clinically important gram-negative isolates: Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumanii). Patients who were transferred to palliative care or to other hospitals were not included in this study. Post-surgical patients were also excluded.

The protocol was approved by Institutional Ethics Committee. Consent was obtained from the hospital administration and academic and research committee of the hospital for use of anonymized data of the patients. Informed consent was taken from the patient or their immediate relatives.

Patient details were obtained including age, sex, clfinical history, primary diagnosis, risk factors, bacteriological profile, and in-hospital mortality and necessary investigations are done including HBA1c.

Blood cultures (2 samples of 10ml each) were obtained using sterile, aseptic precautions, either immediately when sepsis was suspected or within 24hrs of admission to the hospital before starting treatment.

All samples were processed using standard microbiological techniques. Blood samples were inoculated into Bact /Alert pf plus bottles as soon as they were collected and incubated in automated machine for 7 days. The interpretation was based on the recommendations of Clinical Laboratory Standards Institute (CLSI).Outcomes included in hospital mortality or recovery.

All statistical analysis was done using SPSS software version 20 and MS Excel 2016. Numerical data are reported as mean ± 1 SD when variables were normally distributed and median and interquartile

intervals (IQR) when skewed. Categorical variables were reported as percent. Intergroup comparisons were performed with Chi-square test for categorical variables.

P values less than 0.05 were considered significant.

## RESULTS

**TABLE 1: Organism Isolated**

| Organism isolated | Number | Percentage |
|---|---|---|
| Klebsiella pneumonia | 51 | 34% |
| Acinetobacter baumannii | 41 | 27.3% |
| Escherichia coli | 39 | 26% |
| Pseudomonas aeruginosa | 19 | 12.7% |

In present study Klebsiella Pneumoniae was the most common organism isolated followed by Acinetobacter Baumanii, Escherichia Coli, and Pseudomonas Aeruginosa.

**Figure 1: ORGANISM ISOLATED**

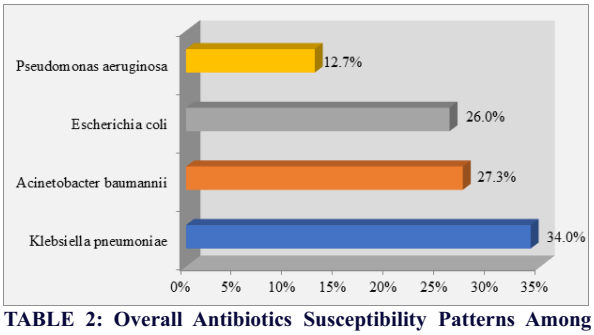


**TABLE 2: Overall Antibiotics Susceptibility Patterns Among Gram Negative Bacteria**

| Overall sensitivity to antibiotics | Number | Percentage |
|---|---|---|
| Ciprofloxacin | 49 | 32.7% |
| Amikacin | 93 | 62% |
| Cefoperazone-sulbactam | 79 | 52.7% |
| Piperacillin-tazobactam | 77 | 51.3% |
| Meropenem | 94 | 62.7% |
| Colistin | 133 | 88.7% |

In present study there was high resistance to commonly used antibiotics like Ciprofloxacin, Cefperazone-sulbactam and Piperacillin-Tazobactam.

**FIGURE 2: Overall Antibiotics Susceptibility Patterns Among Gram Negative Bacteria**

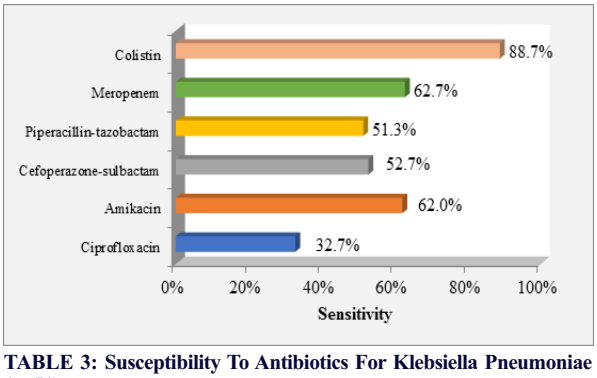


**TABLE 3: Susceptibility To Antibiotics For Klebsiella Pneumoniae (n=51)**

| Type of antibiotic | Sensitive to Klebsiella | Resistant to Klebsiella |
|---|---|---|
| Ciprofloxacin | 18 (35.3%) | 33 (64.7%) |
| Amikacin | 36 (70.6%) | 15 (29.4%) |
| Ceftriaxone | 13 (25.5%) | 38 (74.5%) |
| Cefoperazone-sulbactam | 26 (50.9%) | 25 (49.1%) |
| Piperacillin-tazobactam | 23 (45.1%) | 28 (54.9%) |
| Meropenem | 30 (58.8%) | 21 (41.2%) |
| Tigecycline | 45 (88.2%) | 06 (11.8%) |
| Colistin | 43 (84.3%) | 08 (15.7%) |

In present study there was high resistance of Klebsiella pneumoniae to Ceftriaxone, Ciprofloxacin and resistance to Colistin and Tigecycline was seen in around one tenth of patients.

**FIGURE 3: Susceptibility To Antibiotics For Klebsiella Pneumoniae**

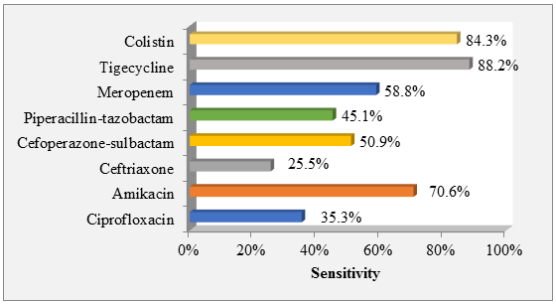


**TABLE 4: Susceptibility To Antibiotics For Acinetobacter Baumannii (n=41)**

| Type of antibiotic | Sensitive to Acinetobacter | Resistant to Acinetobacter |
|---|---|---|
| Ciprofloxacin | 13 (31.7%) | 28 (68.3%) |
| Amikacin | 19 (46.3%) | 22 (53.7%) |
| Cefoperazone-sulbactam | 20 (48.8%) | 21 (51.2%) |
| Piperacillin-tazobactam | 21 (51.2%) | 20 (48.8%) |
| Meropenem | 23 (56.1%) | 18 (43.9%) |
| Tigecycline | 38 (92.7%) | 03 (7.3%) |
| Colistin | 39 (95.1%) | 02 (4.9%) |

In present study there was high resistance of Acinetobacter to ciprofloxacin, ceftriaxone and around half of patients were resistant to cefperazone-sulbactam, piperacillin-tazobactam and meropenem.

**FIGURE 4: Susceptibility To Antibiotics For Acinetobacter Baumanni**

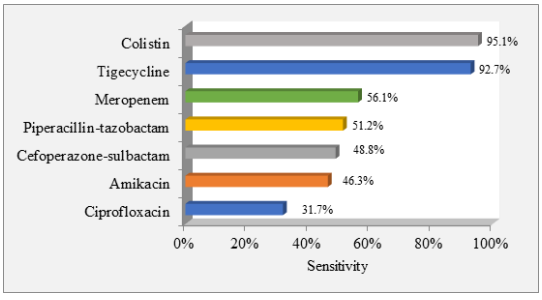


**TABLE 5: Susceptibility To Antibiotics For Escherichia Coli (n=39)**

| Type of Antibiotic | Sensitive to E.Coli | Resistant to E.Coli |
|---|---|---|
| Ciprofloxacin | 10 (25.6%) | 29 (74.4%) |
| Amikacin | 26 (66.7%) | 13 (33.3%) |
| Ceftriaxone | 11 (28.2%) | 28 (71.8%) |
| Cefoperazone-sulbactam | 22 (56.4%) | 17 (43.6%) |
| Piperacillin-tazobactam | 23 (59%) | 16 (41%) |
| Meropenem | 30 (76.9%) | 09 (23.1%) |
| Tigecycline | 37 (94.9%) | 02 (5.1%) |
| Colistin | 37 (94.9%) | 02 (5.1%) |

In present study there was high resistance of Escherichia coli to ciprofloxacin and ceftriaxone.

**FIGURE 5: Susceptibility To Antibiotics For Escherichia Coli**

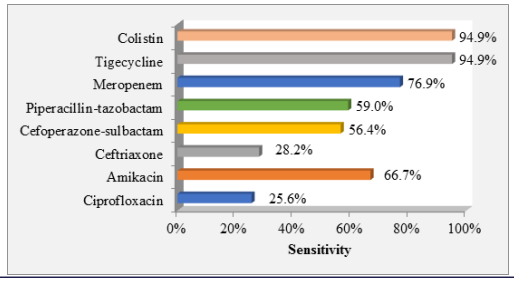

**TABLE 6: Susceptibility To Antibiotics For Pseudomonas Aeruginosa (n=19)**

| Type of antibiotic | Sensitive to Pseudomonas | Resistant to Pseudomonas |
|---|---|---|
| Ciprofloxacin | 8 (42.1%) | 11 (57.9%) |
| Amikacin | 12 (63.1%) | 09 (36.9%) |
| Cefoperazone-sulbactam | 09 (47.4%) | 10 (52.6%) |
| Piperacillin-tazobactam | 10 (52.6%) | 09 (47.4%) |
| Meropenem | 11 (57.9%) | 08 (42.1%) |
| Colistin | 14 (73.7%) | 05 (26.3%) |

In present study there was high resistance to commonly used antibiotics and around one fourth of patients were resistant to colistin.

**FIGURE 6: Susceptibility To Antibiotics For Pseudomonas Aeruginosa**

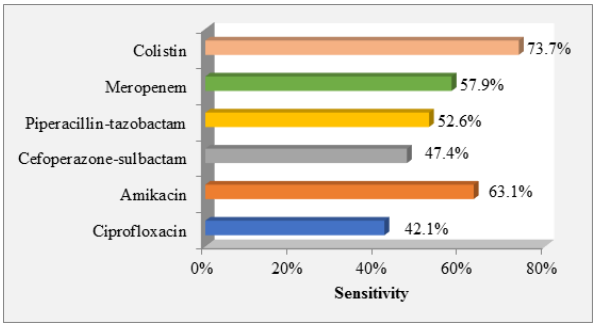


**TABLE 7: RISK FACTORS OF GRAM NEGATIVE SEPSIS**

| Risk factors | Number | Percentage |
|---|---|---|
| Diabetes | 64 | 42.7% |
| Malignancy | 15 | 10% |
| Chronic Obstructive Pulmonary Disease (COPD) | 17 | 11.3% |
| Chronic Kidney Disease (CKD) | 09 | 6% |
| HIV | 09 | 6% |

In present study Diabetes mellitus was the most common risk factor in Gram negative patients with sepsis.

## DISCUSSION

Gram Negative Sepsis is an important cause of morbidity and mortality in hospital intensive care units all over the world, especially in developing countries like India. Increasing rates of antibiotic drug resistance has been noted in recent times and this adversely affects the prognosis and outcomes of patients. This study was undertaken to provide some insights into this important problem because there are very few studies on antibiotic susceptibility patterns on patients with gram negative sepsis (with positive blood cultures) in India, especially Southern India.

A prospective hospital based observational study was carried out to determine the antibiotic susceptibility patterns in patients with gram negative sepsis. Patients with positive blood cultures were included in the study.

In our present study majority of patients were between age group of 60-80 which were 40%. Mean age of patients in present study was 54.86±15.9. Presence of risk factors and comorbidities were also studied, including diabetes mellitus, CKD on chronic hemodialysis, HIV, COPD and Malignancy. In our study, Diabetes mellitus was the most common risk factor. Mortality was higher in patients with one or more comorbidities. Age was an independent risk factor.

Klebsiella pneumoniae was the most common organism isolated followed by Acinetobacter baumanii, Escherichia coli and Pseudomonas aeruginosa. Mortality was more in patients with Acinetobacter baumanii followed by Pseudomonas and Klebsiella, followed by E.coli (not statistically significant). Mortality in patients with cultures resistant to Meropenem was higher(statistically significant)

Antibiotic susceptibility patterns were studied for Ciprofloxacin, Ceftriaxone, Amikacin, Cefperazone-sulbactam, Piperacillin-Tazobactum, Meropenem,Tigecycline and Colistin in present study. Ceftriaxone was not tested for Pseudomonas aeruginosa and Acinetobacter baumanii as these bacteria are inherently resistant for Ceftriaxone. Tigecycline was not tested for Pseudomonas aeruginosa as it is intrinsically resistant to it. There was high resistance of gram negative bacteria to commonly used antibiotics like ciprofloxacin and ceftriaxone. Around half of the patients were resistant to cefperazone-sulbactam and piperacillin-tazobactam.

Among commonly used first line antibiotics in MICU, resistance to Fluoroquinolones (Ciprofloxacin) was highest overall (two thirds were resistant). Resistance to beta lactam antibiotic (Cefoperazone-sulbactam) was seen in almost half of the patients. Among 'last resort' broad spectrum antibiotics, Carbapenem (Meropenem) resistance was seen in approximately one third of the patients. Colistin resistance was seen in1 in 10 patients.

High resistance patterns to Meropenem, Tigecycline and Colistin (12% resistant to colistin) is an alarming and worrisome trend.

## LIMITATIONS OF THE STUDY

Study was performed at a tertiary care, non-governmental hospital, hence the patient population may not be representative of all socio-economic strata. Large proportion of patients were transferred from other hospitals and had already received antibiotics, which may have influenced the antibiotic susceptibility patterns. The study results were from patients admitted only to Medical Intensive Care Unit (MICU) and does not represent patients admitted to other ICU's or wards. We did not test for molecular mechanisms of resistance, which might have yielded valuable insight into reasons behind emergence of resistance.

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