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ORIGINAL ARTICLE

Treatment outcome of ceftriaxone resistant, *Escherichia-coli* and *Klebsiella spp.* bacteremia comparing carbapenem and Beta-lactam/ Beta-lactamase inhibiters in a tertiary care Hospital

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ABSTRACT

Background: Carbapenem are recommended for the treatment of Ceftriaxone (CRO) resistant *Enterobacterales*, however, there are concerns of cost and resistance. Our aim is to compare the outcome of CRO resistant *E-coli* and *Klebsiella* bacteremia between Carbapenem and Beta-lactam/beta-lactamase inhibitors (BL/BLI).

Material and Methods: This was a prospective cohort study conducted at Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan from October 2021 to June 2022. All adult patients with *E coli* or *Klebsiella spp.* bacteremia, CRO resistant and sensitive to both BL/BLI and Carbapenem were included. The patients were divided into BL/BLI and Carbapenem groups. Demographics, clinical features, comorbidities, laboratory parameters and intensive care unit stay were compared. Outcomes were bacteriological clearance, clinical success and all-cause mortality at day 14 of bacteremia.

Results: A total of 156 patients, 93(59.6%) in BL/BLI and 63(40.0%) in Carbapenem group were included. There was no difference in co-morbidities, risk factors and severity of disease. The 14-day all-cause mortality was 14.1%. No statistically significant difference was found between BL/BLI and Carbapenem group regarding bacteriological clearance (p=0.27) and mortality (p=0.95). The Carbapenem group had less clinical success rate (69.8% vs 82.8%, p=0.057), however not statistically significant.

Conclusion: BL/BLIs were as effective as Carbapenem in microbiological clearance, clinical success and mortality in CRO resistant *E-coli* and *Klebsiella* bacteremia.

Keywords: Bacteremia, Ceftriaxone, Carbapenem, Mortality

BACKGROUND

Ceftriaxone (CRO) resistance can be considered as a marker of extended spectrum beta lactamase (ESBL) production.[1] The primary resistance mechanism found in *Enterobacterales* particularly *Escherichia-coli* and *Klebsiella* species (spp.) is the production of ESBL.[2] ESBL producing organisms are capable of hydrolyzing 3rdgeneration cephalosporin and they also harbor genes conferring resistance to other antimicrobial classes including aminoglycosides, tetracycline, and chloramphenicol.[1,3] Carbapenems are the only option recommended to treat ESBL hydrolyzing organisms.[4] A systemic review and meta-analysis on studies involving patients with bacteremia caused by ESBL producing *Enterobacterales* have demonstrated improved clinical outcome and reduced mortality with the use of Carbapenem.[5] A multi centered randomized controlled trial of patients with *E-coli* or *Klebsiella* bacteremia, which compared Meropenem and Piperacillin-Tazobactam, also demonstrated that Piperacillin-Tazobactam was less effective than Meropenem.[6] Nonetheless, increasing use of Carbapenem in ESBL infections due to cost and development of resistance is concerning.[7] There are studies which did show comparable efficacy of Beta-lactam/beta-lactamase inhibitors (BL/BLI) in the management of CRO resistant *Enterobacterales*.[8] However, the use of BL/BLI combinations for treating CRO resistant bacteremia especially for *Enterobacterales*, remains a topic of debate.

The prevalence of ESBLs producing organisms is significantly elevated, with overall pooled proportion of 0.40.[9] According to Pakistan Antimicrobial Resistance Network (the national antimicrobial resistance data),

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more than 50% of *E-coli* and *Klebsiella* are CRO resistant.[10] To the best of our knowledge, there is a scarcity of data from Pakistan regarding clinical outcome of CRO resistant *Enterobacterales*. A retrospective cohort study by Nasir *et al* comparing in-hospital mortality between Carbapenem with BL/BLI in patients with CRO resistant *E. coli* bacteremia, and found no significant difference in mortality. They advocate for additional studies on the antimicrobial choice in CRO resistant gram negative infection from Pakistan.[11]

Our aim is to evaluate the clinical outcome of CRO resistant *E-coli* and *Klebsiella spp.* in a large public sector hospital, comparing treatment with Carbapenem versus BL/BLI.

MATERIAL AND METHODS

This was a prospective cohort study conducted at Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan from October 2021 to June 2022. SIUT is the largest public sector hospital especially for renal diseases and solid organ transplantation, also providing care for patients in urology, oncology, hepatobiliary, gastroenterology and general surgery.

All admitted patients ≥18 years of age with at least one positive blood culture for *E coli* or *Klebsiella spp.*, non-susceptible to Ceftriaxone but susceptible to both BL/BLI and Carbapenem were included. Those patients who had poly-microbial growth, who received antibiotics other than BL/BLI or Carbapenem and who received less than 48 hours of antibiotics were excluded from the study. The patients were stratified into two groups BL/BLI and Carbapenem group. Those who initially received BL/BLI then switched to Carbapenem within 48 hours, were included in Carbapenem group and vice versa.

All positive blood samples were Gram stained and sub-cultured on Chocolate agar (Oxoid) and Mac-Conkey agar (Oxoid) plates then incubate overnight at 35°C. Identification of bacterial growth was performed using Gram staining, colony morphology and relevant biochemical tests.

Antibiotics susceptibility testing was performed on Muller Hinton Agar (Oxoid) by Kirby-Bauer disc diffusion method with results interpreted according to the Clinical and Laboratory Standards Institute criteria for the corresponding year. The sensitivity plates were incubated overnight at 35°C.[12]

Data were collected with informed consent and included demographics, clinical features and laboratory parameters, recent hospitalization and recent antibiotics exposure, empirical antibiotic choice and intensive care unit (ICU) stay. We calculated the Charlson comorbidity index, Pitt bacteremia score and qSOFA score for all patient on arrival. For patients admitted to ICU, duration of ICU stay, duration of mechanical ventilation and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were documented. The most likely source of bacteremia was identified based on clinical and laboratory evaluation. The presence of a central line, site and duration, peripheral vascular catheter, urethral catheter, nephrostomy tubes, drains, endotracheal intubation, parenteral nutrition, any recent surgical procedure and hemodialysis were noted. Patients were followed up on day 3 with repeat blood culture to document bacterial clearance. Fever, total leucocyte count, and hypotension were recorded. Patients were followed at day14 to assess all-cause mortality. If patients were discharged by the primary team before the end of 14 days, telephone contact was made to ascertain their survival status.

Outcomes were recorded as bacteriological clearance at day 3 of treatment, clinical success and all-cause mortality at day 14 following the positive blood culture.

Operational definitions:

Bacterial clearance or microbiological cure: defined as blood cultures sent after 72 hours of appropriate treatment was negative or no growth.

Clinical Success: defined as resolution of signs and symptoms like fever, hypotension, altered level of consciousness, ICU stay.

Disease Severity: defined as Pitt's bacteremia score of >4, high APACHE II score and qSOFA score of 2.

Appropriate empirical antibiotics: Defined as antibiotics which were started at the time of culture taken and later found to be susceptible on sensitivity report.

The sample size was calculated using Openepi sample size calculator OpenEpi: Sample Size for X-Sectional, Cohort, and Clinical Trials free accesses on internet. Total population of ceftriaxone resistant *E. Coli* and *Klebsiella, spp.* bacteremia in 6 months was approximately 200. Based on the previous estimate of mortality rate 21% with margin of error 3% and 95%

confidence level, a total sample size was 156 patients was calculated.[11]

All the data was entered in MS Excel then transferred into SPSS version 22.0 for analysis. Normally distributed continuous measures were presented as mean and standard deviation while non-normally as median. Their mean difference or median were compared using unpaired "t" or Mann Whitney U test as appropriate. Categorical variables were reported as frequency and percentages and proportion difference were compared using Chi-squire or Fisher' Exact tests. p-value 0.05 was considered as statistically significant.

RESULTS

A total of 156 patients were inducted in the study. Enrolment of patients in BL/BLI and Carbapenem groups are shown in Figure 1. Over all 45 (28.8%) were switched from BL/BLI to Carbapenem group. No patient was switched from Carbapenem to BL/BLI group. Overall 93(59.6%) were analyzed in BL/BLI group and 63(40.0%) in Carbapenem group.

Table-I shows the comparison of demographic characteristics between BL/BLI and Carbapenem groups. The age and gender were comparable. There was no significant difference between the two groups in term of co-morbidities, risk factors and severity of the disease. The most common comorbidity in our patient population is being on hemodialysis.

There were 103(66.0%) *E-coli* bacteremia, 64 (68.8%) in BL/BLI and 39 (61.9%) in Carbapenem group. Similarly, 53 (34.0%) *Klebsiella spp*. bacteremia with 29 (31.0%) in BL/BLI and 24 (38.0%) in Carbapenem group. Both organisms were equally distributed in both groups. (p=0.37)

The overall all-cause mortality at day14 was 14.1%. No statistically significant difference was observed between BL/ BLI and Carbapenem group in terms of bacteriological clearance (90%vs 83% p=0.27) and mortality (14.3% vs 14.0% p=0.95). The Carbapenem group had a lower clinical success rate (69.8% vs 82.8%, p=0.057) compared to BL/BLI group, however the difference was not statistically significant. (Table-II)

Table-III shows the comparison of non-survivors between BL/BLI and Carbapenem group. There was no statistically significant difference between sources of bacteremia, comorbidities, clinical characteristics and bacteriological clearance. However, if we look into percentages, higher percentage of non-survivors on BL/BLI had Pitt bacteremia score ≥ 4 and high qSOFA score.

We compared the mortality between patients who were switched to Carbapenem group at 48, 72 and 96 hours. We compared between those who remain in one group throughout the treatment with those who were switched. There was no statistically significant difference in mortality between the groups.

Table-I: Comparison of demographics, risk factors and source of bacteremia between BL/ BLI and Carbapenem group n=156.

Characteristics	**Beta lactam/beta lactamase inhibitor group** 93(60%) **n (%)**	**Carbapenem group** 63(40%) **n (%)**	**p-value**
Age Median (IQR)	48.0 (34-62)	50.0 (36-64)	0.34
Female	41 (44)	24 (38)	0.45
Comorbidities			
CCI (median)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.02
CCI >3 (%)	13 (14)	9(14)	0.95
Diabetes Mellitus	29 (31)	22 (35)	0.62
Malignancy	1 (1.1)	4 (6.3)	0.159
Renal Failure	61 (65.6)	40 (63.5)	0.78
Hemodialysis	52 (55.9)	40 (63.5)	0.34
HIV	2 (2.2)	2 (3.2)	1.00*
Transplant recipient	6 (6.5)	0 (0)	0.08*
COVID-19	1 (1.1)	2 (3.2)	0.56*
Risk factors			
ICU stay (n=31)	15 (16.1)	16 (25.4)	0.15
Central Line	40 (43)	35(55.6)	0.12
Foleys	28 (30.1)	26 (41.3)	0.15
Percutaneous nephrostomy tube	4 (4.3)	4 (6.3)	0.71*

Mechanical ventilation	4 (4.3)	7 (11.1)	0.12*
Cardiac Arrest within 48 hrs.	1 (1.1)	0 (0)	1.00*
Recent antibiotics in 1 month	32 (34.4)	22 (34.9)	0.94
Surgeries	15(16)	7(11)	0.37
Clinical features			
Fever	57 (61.3 %)	40 (63.5)	0.78
Hypotension	15 (16.1)	06 (9.5)	0.23
Altered mental status	09 (9.7)	10 (15.9)	0.24
Total leucocyte count (TLC) Median (IQR)	13.0 (8.65-21.0)	15.70 (9.80-24.05)	0.10
Leukocytosis (TLC≥12)	44 (47.3)	37 (58.7)	0.16
Disease severity			
APACHE Score Median (IQR)	22.0 (15.75-26.5)	20.5 (16.25-27.25)	0.86
qSOFA score >2	13(14)	8(12.7)	0.81
Pitt's bacteremia score ≥ 4	5 (5.4)	7 (11.1)	0.22*
Source of bacteremia			
Central Line	38 (40.9)	33 (52.4)	0.15
Urinary tract	25 (26.9)	16 (25.4)	0.83
Skin and Soft Tissue	2 (2.2)	2 (3.2)	1.00*
Abdomen	8 (8.6)	4 (6.3)	0.43*
Surgical Site Infections	2 (2.2)	1 (1.6)	0.64*
Pneumonia	2 (2.2)	1(1.6)	1.0
No clear source identified	16 (17.2)	6 (9.5)	0.17

BL/BLI: β lactam/β lactamase inhibitor, CCI: Charlson comorbidity index, APACHE: Acute physiology and chronic health evaluation, qSOFA: Quick sepsis related organ failure assessment; *Fisher exact test

Table-II: Comparison of outcome between BL/BLI and Carbapenem group.

Outcomes	BL/BLI n (%)	Carbapenem n (%)	p-value
Microbiological Clearance	60/ 67 (89.5)	43/52 (82.6)	0.27
Clinical success	77(82.8)	44 (69.8)	0.057
Mortality at day 14	9(14.3)	13 (14.0)	0.957

BL/BLI: β lactam/β lactamase inhibitor

Table-III: Comparison of non-survivors between BL/BLI and Carbapenem group.

Characteristics	BL/BLI n/total (%)	Carbapenem n/total (%)	p-value
Source of bacteremia			
Central line	3/38 (10)	05/33 (15)	0.752
UTI	5/25 (20)	0/16 (0)	0.13
Co-morbidities			
CCI ≥3	3/13 (23)	1/9 (11)	0.61
Renal failure	9/61 (14.7)	8/40 (20)	0.49
Clinical			
ICU stay	7/15 (46.7)	5/16 (31)	0.37
Mechanical ventilation	3/4 (75)	3/7 (43)	0.54
On ionotropic support	6/15 (40)	1/6 (16.7)	0.61
qSOFA score >2	8/13 (61.5)	3/8 (37.5)	0038
Pitt's score≥4	5/5 (100)	3/7 (42.9)	0.08
Bacterial clearance	5/60 (13)	5/43 (11.6)	0.79

BL/BLI: β lactam/β lactamase inhibitor, CCI: Charlson comorbidity index, qSOFA: Quick sepsis related organ failure assessment

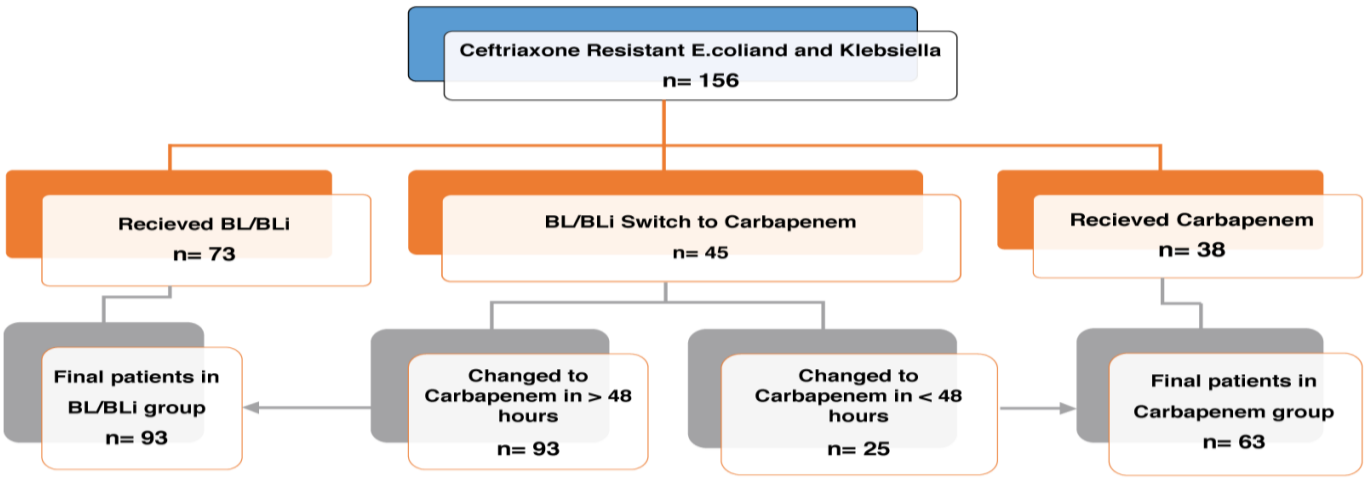

Figure-I: Enrollment of patients in BL/BLI and carbapenem group.

DISCUSSION

We prospectively compared the outcome of Ceftriaxone resistant *E-coli* and *Klebsiella spp.* bacteremia in patients treated with either BL/BLI or Carbapenem. Both groups in our cohort were similar regarding baseline characteristics and risk factors. We found no any difference in bacteriological clearance, clinical success and all-cause 14-day mortality between BL/BLI and Carbapenem treatment groups. Our findings endorse a similar study from Pakistan where Nasir *et al* did not find any significant difference in mortality between Pipericillin-tazobactum and Carbapenem treatment groups.[11] In 2012, an analysis of 6 published prospective cohort studies came to the conclusion that BL/BLI were a suitable alternative to Carbapenem in ESBL producing *E-coli* blood stream infections.[8] A systematic review and meta-analysis of 25 observational studies published in 2018 also reported no significant difference in 30 days mortality between BL/BLI and Carbapenem either with empirical or definitive treatment.[14] However the landmark randomized controlled trial (MERINO trail) published in 2018, recommended that Piperacillin/Tazobactam should be avoided owing to higher mortality (risk difference 8.6%).[6] In 2021, post MERINO trail, Rodriguez-Bano *et al* published a commentary argued that treating CRO resistant gram negative organisms with only Carbapenem may lead to increase resistance and cost. They emphasized that Carbapenem sparing antibiotics can be used particularly in patients without severe sepsis or shock.[15] Recently Zhang *et al* did a systematic review of 26 studies, 1 randomized trail, 3 prospective cohort study and 22 retrospective cohort studies. They looked into therapeutic response in addition to all-cause mortality and found BL/BLI were equivalent to Carbapenem, with numerically higher rates of therapeutic response with BL/BLI.[16]

We analyzed the risk factors for mortality between BL/BLI and carbapenem in order to assess the severity of infection between the groups. We found that although there was no statistically significant difference, but numerically there were higher number of patients in BL/BLI group who had severe disease with higher APACHE, Pitt's bacteremia and q-SOFA score. We can conclude that those patients who had severe infections and treated with BL/BLI had similar outcome as compared to patients treated with Carbapenem.

The primary limitations of our study is its observational design, which did not allow for control over changes in the antibiotic therapy during the course of treatment. We infer that the primary physicians may change treatment to Carbapenem more readily in sicker patients. However, when we look into patients' characteristics, more sick patients were receiving BL/BLI. Secondly, for ESBL production we use Ceftriaxone resistance as a marker which may not be a robust method to detect ESBL. Thirdly we rely on disc diffusion methods did not have MICs for isolates, we can argue that this represents a real-life scenario in a resource poor setting.

CONCLUSION

In conclusion, BL/BLI therapy appears to be effective in achieving microbiological clearance, clinical success and reduced mortality in patients with ESBL producing *E-coli* and *Klebsiella* bacteremia.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Beena Rani, Sunil Kumar Dodani: Concept and design of study, drafting, final approval, agreement to be accountable for all aspects of the work

Zaheer Udin Babar, Sanjay Badlani, Mehreen Fatima: Developed study methodology, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Maryam Mushtaq: Data **c**ollection, data analysis and interpretation of data, final approval, agreement to be accountable for all aspects of the work

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