ORIGINAL ARTICLE

COMPARISON OF BETA-LACTAM/ BETA-LACTAMASE INHIBITORS WITH CARBAPENEM FOR URINARY BACTEREMIA CAUSED BY CEFTRIAXONE RESISTANT *ESCHERICHIA COLI* AND *KLEBSIELLA SPECIES*

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ABSTRACT

Background: The debate, whether to treat ceftriaxone resistant (CROr) gram negative urinary tract infection with bacteremia (bUTI) with Beta-lactam/beta lactamase inhibitors (BL/BLI) or Carbapenem is going on. Carbapenem are expensive in our part of the world. Our aim was to see the efficacy of BL/BLI in the treatment of bUTI caused by CROr *Escherichia coli* (E-coli) or *Klebsiella species* (spp.) To compare microbiological clearance, clinical failure, new bacteremia and mortality between patients with bUTI who receive BL/BLI or Carbapenem.

Material and Methods: A retrospective chart review was done at a tertiary care hospital of kidney diseases from October 2021 till June 2022. We included all adult patients with bUTI caused by CROr E-coli or *Klebsiella spp*, and they were excluded if bacteremia with no clear source or received antibiotics other than BL/BLI or carbapenems or received for less than 48 hours duration. Demographic characteristics, comorbidities, and clinical outcome were compared between BL/BLI and carbapenem groups.

Results: A total of 41 files were reviewed. The demographics, risk factors and clinical features were comparable. We did not find statistically significant difference in microbiological clearance, clinical failure, and mortality between BL/BLI and Carbapenem groups.

Conclusion: BL/BLI combinations are as efficacious as Carbapenems in CROr bUTI in terms of microbiological clearance. The clinical success and mortality were same in both groups.

Keywords: bUTI, *Klebsiella spp*, Carbapenems, BL/BLI, Mortality, Disease severity, Microbiological clearance.

BACKGROUND

Urinary tract infection (UTI) is one of the most common infections in community as well as in hospital setting. and clinical presentation ranges from simple cystitis to severe pyelonephritis.[1] It has been estimated that around 20 %-30% of patients with complicated UTI or pyelonephritis have bacteremia at the time of presentation.[2] Various risk factors have been identified for bacteremic UTI including diabetes mellitus with poor glycemic control, acute pyelonephritis, solid organ malignancy, elevated neutrophil count or c reactive protein and presence of pyuria.[3,4] *Escherichia coli* and *Klebsiella species*, the members of Enterobacteriaceae family are the predominant pathogens causing UTI.[5] Extended spectrum beta lactamase (ESBLs) and plasmid mediated AmpC beta lactamases production is the most important mechanism of resistance in these pathogens noted worldwide.[6] To treat to ESBL-producing gram negative infections the Carbapenems are the preferred antibiotics of clinicians. MERINO trial has not shown non-inferiority in 30 days mortality with piperacillin-Tazobactam compared to meropenem.[7] The authors recommend against use of piperacillin-Tazobactam for ESBL producing blood stream infection. However, Rodriguez-Bano *et al* in a post MERINO trial commentary concluded that piperacillin-Tazobactam should be considered as an alternative to avoid excessive use

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of Carbapenems in urinary tract infection or non-severe infection.[8] In a retrospective cohort study from Pakistan comparing carbapenem versus BL/BLI for ceftriaxone resistant E.coli bacteremia there was no difference was observed in mortality between two groups and urinary tract infection was found as a protective factor for mortality.[9]

Based on the previous evidence on significantly high mortality in CRO resistance E.coli and *Klebsiella spp* bacteremia other than non-severe infections, we designed our study to see any difference in mortality and clinical response in BL/BLI versus Carbapenems for treatment of ceftriaxone resistant E.coli and *Klebsiella spp* bacteremic urinary tract infections.

MATERIAL AND METHODS

This retrospective cohort study was conducted at Sindh Institute of Urology and Transplantation (SIUT) Karachi Pakistan the data was collected from October 2021 till June 2022. All adult patients with ceftriaxone resistant *E.coli* and *Klebsiella species (spp.)* bacteremia secondary to urinary tract infection were included in analysis. Positive blood cultures of above-mentioned pathogens during this period were collected from microbiology laboratory and medical record was reviewed of those patients who were admitted due to bacteremia originating from urinary source (bUTI) defined below and received either BL/BLI or carbapenem. Only one episode of bacteremia per person was included. Polymicrobial bacteremia and patients who received less than 48 hours of antibiotics were excluded.

Data was collected retrospectively from patient's file for baseline characteristics, clinical features and laboratory results, any recent antibiotics use, ICU stay, Charlson co morbidity index and Pitt bacteremia score were calculated for all patients at baseline.

Follow up on day 3 was recorded for bacterial clearance and clinical failure (Persistence of fever, leukocytosis and hypotension). New episode of bacteremia and all-cause mortality was noticed on day 14 and day 28.

The primary end point was all-cause mortality at day 14 and 28. The secondary end point were bacteriological clearance, clinical failure and new episode of bacteremia. Patients were divided into two groups. Those who received imipenem, meropenem or ertapenem were kept in Carbapenem group and who received piperacillin-Tazobactam, amoxicillin-clavulanate or cefoperazone-salbactum as BL/BLI group.

All blood cultures were performed at microbiological laboratory of SIUT, as per CLSI protocols. Susceptibility test was conducted by disc diffusion method. The results were analyzed as per CLSI break points.[10]

Bacteremia originating from urinary source (bUTI) is defined as blood culture showing growth of ceftriaxone resistant *E coli* or *Klebsiella spp* and symptoms/signs suggestive of UTI with or without positive urine culture of same organism and sensitivity.

If the patient presented with sign and symptoms of lower urinary tract (frequency, urgency, dysuria, decrease urine output) or with pyelonephritis (fever, vomiting, flank pain) or any radiological evidence of renal, perirenal collection or emphysematous pyelonephritis with or without renal failure and or requirement of hemodialysis.

All the data was entered and analyzed using SPSS version 22 for the results. The data was reported as mean and standard deviation for continuous variables if data were normally distributed while reported as median (IQR) if it was not normally distributed. Their mean difference or median were compared using unpaired "t" or Mann Whitney U test as appropriate. Categorical variables were reported as count while percentages and proportion difference were compared using Chi-squire or Fisher' Exact tests. P-value 0.05 was considered as statistically significant.

RESULTS

Among all files total 41 patients were found eligible for having *E.coli* and *Klebsiella spp* bacteremia originating from urinary tract and were analyzed. Of those 41 patients, 16 were received Carbapenem and 25 BL/BLI combinations. Mean age (SD) of study population was 51 ± 14.61 versus 43.76 ± 17.19 (Carbapenem and BL/BLI groups respectively) A total of 12 (29.2%) patients were diabetic and 25(60.9%) had renal failure in both groups. Clinical parameters at the onset of bacteremia including fever, leukocytosis, hypotension and altered mental status were comparable between groups (Table-1). We have found overall 28-day mortality of 14.6% (6.3% in Carbapenem and 11% in BL/BLI group) with no statistically significant difference between two groups (*p*=value 0.228). None of patient after 14 days of onset of bacteremia died within Carbapenem group, in contrast 5(11%) patients died in comparative group although did not reached statistical difference. Repeat blood cultures after 72 hours showed microbiological clearance 91.6% in Carbapenem group versus 88% in BL/BLI group (*p*=value 0.570). Other secondary outcomes (clinical failure and new episode of bacteremia) were also found to be comparable between the groups (Table-2).

Table-1: Demographics and clinical characteristics of bUTI due to ceftriaxone resistant *E.coli* and *Klebsiella spp* in Carbapenem vs BL/BLI group

Demographics Characteristics	Carbapenem n= 16(%)	BL/BLI n= 25(%)	P Value
Age Mean ± SD	51 ± 14.61	43.76 ± 17.19	0.172
Female	8 (50)	15 (60)	0.529
Diabetes Mellitus	6 (37.5)	6 (24)	0.281*
Renal Failure	9 (56.3)	16 (64)	0.620
On Hemodialysis	3 (18.8)	6 (24)	0.646
Transplant recipient	-	2 (8)	0.366*
Charlson Comorbidity Index>3	2 (12.5)	5 (11)	0.431*
Risk Factors			
Foleys	12 (75)	18 (72)	0.544*
PCNs	4 (50)	4 (16)	0.374*
Central Line	1 (6.3)	2(8)	0.666*
Recent antibiotics usage in last 1 month	5 (31.3)	10 (40)	0.375
Clinical and Lab Parameters			
Fever	8 (50)	16 (64)	0.375
Leukocytosis	10 (62.5)	12 (48)	0.364
Hypotension	2 (12.5)	5 (11)	0.431*
Altered mental status	1 (6.3)	1(4)	0.341*
ICU stay(n=6)	3 (18.8)	3 (12)	0.434*
Mechanical ventilation	1 (6.3)	1 (4)	0.634*
Pitt's≥ 4	-	2 (8)	0.366*

*-Fischer exact Test

Table 2: Comparison of primary and secondary Outcome between Carbapenem and BL/BLI groups.

Outcomes	Carbapenem N= 16 (%)	BL/BLI N= 25 (%)	P-value
Primary Objective			
14 Day mortality	-	5 (11)	0.071*
28-day Mortality	1 (6.31)	5 (11)	0.228*
Secondary Objective			
Microbiological clearance	11/12 (91.6)	15/17 (88)	0.570
Clinical Failure	4 (25)	7 (28)	0.564*
New Bacteremia in 28 days	2 (12.5)	2 (8)	0.512*

*-Fischer exact Test

DISCUSSION

Carbapenem use for ESBL producing Enterobacteriaceae has been subject of discussion for a long time because of risk of developing Carbapenem resistance.[12] In this cohort of ceftriaxone resistant *E.coli* and *Klebsiella spp* bacteremia originating from urinary source have shown no significant difference in terms of mortality, clinical failure and microbiological clearance.

Our findings are similar to post hoc analysis done by Rodriguez-Bano *et al* where no difference was found in mortality and length of hospital stay in Carbapenem or BL/BLI group. The authors therefore recommended using amoxicillin-clavulanate or piperacillin-Tazobactam as suitable alternatives to Carbapenems with blood stream infection due to ESBL Enterobacteriaceae.[13] Our findings are in concordance with Nasir *et al* showing urinary tract infection as protective effect on mortality in contrast to higher Pitt bacteremia score with BL/BLI combination for ceftriaxone resistant *E.coli* bacteremia.[9]

We have found overall mortality of 14.6% at day 28 with no difference between Carbapenem or BL/BLI group. Mortality caused by urosepsis has shown variable results. Tocut *et al* in a retrospective cohort of urosepsis have shown mortality of 6.3% - 12.7% in sensitive and resistant *E.coli* strain respectively.[14] Another retrospective study done by Tal *et al* in elderly patients with bacteremic UTI found in hospital mortality of 33%.[15] There is scarce data to the best of our knowledge on head to head comparison of bacteremic versus non bacteremic UTI in terms of mortality. This study is adding evidence to controversy about use of BL/BLI as an acceptable Carbapenem sparing option in ceftriaxone resistant *E.coli* and *Klebsiella* bacteremia of urinary origin. Our study has several caveats. Firstly, due to rare presentation of disease and included only one medical centre, we could able to obtain limited and small sample size. Secondly, due to retrospective data collection clinical information was limited to physician's note. Lastly this data cannot be generalized to other non-Enterobacteriaceae organisms.

CONCLUSION

In conclusion, our study shows no difference in mortality, clinical failure and microbiological clearance treated with either BL/BLI combination or Carbapenem. We recommend randomized controlled trial addressing use of BL/BLI and Carbapenems for bacteremia of urinary source.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTION:

Beena Rani: Study design, data collection, data interpretation, data analysis, literature search

Zaheer Udin Babar: Literature search, questionnaire design and research writing.

Sunil Kumar Dodani: Data interpretation analysis methodology study design questionnaire design

Asma Nasim: Study design, literature search data analysis

Sanjay Badlani: Participate in data analysis, literature search methodology questionnaire format.

REFERENCES

1. Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi FJFiPH. Disease burden and long-term trends of urinary tract infections: A worldwide report. Front Public Health. 2022; 10: 888205. DOI: 10.3389/fpubh.2022.888205
2. Bai AD, Bonares MJ, Thrall S, Bell CM, Morris AMJBID. Presence of urinary symptoms in bacteremic urinary tract infection: a retrospective cohort study of *Escherichia coli* bacteremia. BMC Infect Dis 20, 781 (2020). DOI: 10.1186/s12879-020-05499-1
3. Lalueza A, Sanz-Trepiana L, Bermejo N, Yaiza B, Morales-Cartagena A, Espinosa M, et al. Risk factors for bacteremia in urinary tract infections attended in the emergency department. Intern Emerg Med. 2018; 13(1): 41-50. DOI: 10.1007/s11739-016-1576-6
4. Varma M, Peravali SK, Vandana K, Kamath A, Singh R. A study of risk factors for bacteremia caused by urinary tract infections. Asian Journal of Medical Sciences, 2018;9(5):25-30. DOI: 10.3126/ajms.v9i5.19907
5. Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo CJP. Urinary Tract Infections: The Current Scenario and Future Prospects. 2023;12(4):623. DOI: 10.3390/pathogens12040623
6. Bedenic B, Mestrovic T. Mechanisms of Resistance in Gram-Negative Urinary Pathogens: From Country-Specific Molecular Insights to Global Clinical Relevance. Diagnostics (Basel). 2021 Apr 28;11(5):800. DOI: 10.3390/diagnostics11050800
7. Harris PN, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E.coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018 Sep 11;320(10):984-94. DOI: 10.1001/jama.2018.12163. Erratum in: JAMA
8. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Pascual AJJ-AR. CON: Carbapenems are NOT necessary for all infections caused by ceftriaxone-resistant Enterobacterales. JAC Antimicrob Resist. 2021; 3(1): dlaa112. DOI: 10.1093/jacamr/dlaa112
9. Nasir N, Ahmed S, Razi S, Awan S, Mahmood SFJBRN. Risk factors for mortality of patients with ceftriaxone resistant E. coli bacteremia receiving carbapenem versus beta lactam/beta lactamase inhibitor therapy. BMC Res Notes. 2019; 12(1): 611. DOI: 10.1186/s13104-019-4648-7
10. Clinical, M100 LSIJCs. Performance standards for antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute Wayne, PA; 2017. p. 106-12.
11. Wayne PJ. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing: 20th informational supplement. 2010.

12. Durante-Mangoni E, Andini R, Zampino RJCM, Infection. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect. 2019; 25(8): 943-50. DOI: 10.1016/j.cmi.2019.04.013.
13. Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A, Diseases E-SB-LREdIePIGdEdIHGJCI. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase–producing *Escherichia coli*: A post hoc analysis of prospective cohorts. Clin Infect Dis. 2012; 54(2): 167-74. DOI: 10.1093/cid/cir790
14. Tocut M, Zohar I, Schwartz O, Yossepowitch O, Maor YJBID. Short-and long-term mortality in patients with urosepsis caused by *Escherichia coli* susceptible and resistant to 3rd generation cephalosporins. BMC Infect Dis. 2022;22 (1): 571. DOI: 10.1186/s12879-022-07538-5
15. Tal S, Guller V, Levi S, Bardenstein R, Berger D, Gurevich I, et al. Profile and prognosis of febrile elderly patients with bacteremic urinary tract infection. J Infect. 2005; 50(4): 296-305. DOI: 10.1016/j.jinf.2004.04.004