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ORIGINAL ARTICLE

Antimicrobial susceptibility pattern of ceftazidime-avibactam against Eschericia Coli.

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ABSTRACT… Objectives: To identify the susceptibility of Ceftazidime-avibactam against Escherichia coli and their frequency in different clinical specimens. To correlate the susceptibility pattern of ceftazidime-avibactam against Escherichia coli in different age groups and gender. To evaluate susceptibility of drugs among Escherichia coli as compared to traditional antibiotics. **Study Design:** Cross-sectional Study. **Setting:** PNS Shifa Hospital Karachi. **Period:** September 2019 to May 2020. **Material & Methods:** The sample size was 150. The age group 10-50 years. Ethical permission was taken. Informed consent was taken. The specimens were inoculated on Blood and MacConkey's agar culture plates. The culture plate was inoculated at 37℃ in incubator for 24 to 48 hours. Identification of Enterobacteriaceae was done by colony morphology, gram staining, biochemical tests, and API 20E. After identification, the susceptibility profile of conventional antibiotics was identified. Mueller Hinton agar was used to check the antibiotic susceptibility of Ceftazidime-avibactam by disk diffusion method. **Results:** Ceftazidime-avibactam shows sensitivity against 82.7% of the isolates while 17.3 % isolates were resistant. The minimum inhibitory concentration of microorganisms is measured by E-test method that revealed most of the isolate show sensitivity less than 1 μg/mL concentration whereas few of them showed susceptibility on 2-8 μg/mL concentration. We compared our results with other classes of antibiotics used commonly This gives an insight for improved treatment methodologies for future prospects particularly diseases caused by members of Enterobacteriaceae. **Conclusion:** It was concluded that Ceftazidime-avibactam is a novel drug combination that shows high sensitivity against Escherichia coli.

Key words: Antibiotics Resistance, Antibiotics Sensitivity, Ceftazidime-Avibactam, Enterobacteriaceae.

INTRODUCTION

Infections account for a major cause of death throughout the developing world. This is mainly due to the emergence of newer infectious agents and more specifically due to the appearance of antimicrobial resistance. The antimicrobial resistance is recognized as a major problem in the treatment of microbial infections.

The inadequate and inappropriate prescription practices of antibiotic drugs are responsible to develop resistance.[1,2] The high treatment rate and illiteracy are the two important factors that lead to antibiotic resistance.[3] To overcome this scenario, the focus of attention of microbiologists is to develop the drug or introduce the combination of drugs against multi-drug resistance organisms.[1]

The Enterobacteriaceae is the normal flora of human colon and frequently found in large intestine. They are the member of gram-negative rods responsible for urinary tract infection, bloodstream infection, respiratory tract infection, and found frequently in hospital-acquired infections. Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter and Salmonella are the member of Enterobacteriaceae.[4,5,6,7]

Enterobacteriaceae are Gram-negative, facultative anaerobes, that produce lactate and many other ends by-products by fermenting sugar.[8] Escherichia coli is one of the major causes that lead to community-acquired UTI and nosocomial UTI. Around 50% of females experienced at least one episode of UTI.

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Enterotoxigenic E. coli, was found to be the eight-leading reason for diarrheal mortality in 2016, and the frequency of deaths was approximately 3.2%, while it was accounted for 4.2% deaths in less than 5-year children.[9]

The pathogenic factors include enterotoxins, lipopolysaccharide, fimbrial adhesins, cytotoxins, and capsule. Escherichia coli isolates were found 82.8% of resistance to ampicillin, 77.6% to ciprofloxacin[10], and 72.4% to tetracycline.

Ceftazidime-avibactam is combination which includes ceftazidime, which is a well conclusively proved antipseudomonal cephalosporin along with avibactam, The medical benefit of avibactam has potential to prevent enzymes of narrow-spectrum β-lactamases, ESBLs, AmpC β-lactamases (as found in Enterobacteriaceae family.[11] It has been a matter of serious concern since antimicrobial resistance of Enterobacteriaceae isolates has gradually and constantly increased to an alarming level leading to very limited therapeutic options. Therefore rationale of this study is to introduce the new combination of antibiotics that act against Enterobacteriaceae like Escherichia coli and provide new antimicrobial combination.

MATERIAL & METHODS

This is a cross-sectional study was done by taking the clinical samples of patients from urine, blood, CSF, pus and respiratory specimens of patients admitted in PNS Shifa Hospital from September 2019 to May 2020. The Gram stain of the samples was performed to identify the gram-negative rods by the pink color of the colonies. All specimens like urine, blood, pus, and respiratory specimen were inoculated on Blood agar and MacConkey's agar. Culture plates were incubated at 37º C in ient air for 24 to 48 hours. On blood agar, circular, grey and moist colonies were observed, while on MacConkey's agar circular, pink and lactose fermenting colonies were found. Further identification of organisms was done for biochemical tests. API 20E system and Triple sugar iron (TSI) was used to biochemical identification of E. col the data was entered into a specially designed Subject Evaluation Form. Permission was taken from Hospital Ethical Committee (ERC/08/2020). Informed consent from all the 150 patients was taken for this study. Age, gender and hospital identity number of patients were recorded on specially designed proforma.

Inclusion Criteria

Escherichia coli was collected from different clinical specimens of patient. Clinical specimens include urine and blood. The specimens of age group from 10 to 50 years of age and both genders were received from different wards at PNS Shifa hospital.

Exclusion Criteria

Repeated samples from same patient. All the other members of Enterobacteriaceae were excluded except Escherichia coli.

RESULTS

In our study it is shown that susceptibility pattern of ceftaxidime-avibactam shows 90% (136) (samples) sensitivity against E.Coli as shown Table-I. Table-II shows the minimum inhibitory concentration of microorganisms is measured by E-test method that revealed most of the isolate show sensitivity less than 1 μg/mL concentration whereas few of them showed susceptibility on 2-8 μg/mL concentration our next focus was to identify the antimicrobial activity of the commercially available antimicrobial drugs as shown in Table-III. From the analysis of the data followed by exposing E.Coli with the commonly used antibiotics we found that combination of Piperacillin-tazobactam- (100/10ug), Amoxicillin-clavulanate (20/10ug) (b-lactam b-lactamase inhibitors) has 80% and 82 % resistance against E. coli.as shown in Table-V. these finding consistent with previously reported findings.[19,20,21,22] It is shown the decreased sensitivity or high resistance of Amoxicillin-clavulanate, ceftriaxone, ceftazidime, piperacillin/ tazobactam and meropenem with respect to ceftaxidime-avibactam. Our findings are consistent with the previously conducted studies against E.coli.[23,24,25]

In terms of gender among our samples included 52.4% males and 47.6% females as shown in Table-V and average age is 30yrs as shown in Table-

IV. Followed by the identification of pathogens, ceftazidime-avibactam was used to identify its antimicrobial activity in male and female patients. We identified susceptibility of ceftazidime-avibactam (30/20 μg/mL) combination by disk-diffusion test in male shown 86% susceptibility for E. coli ie 61 patient as shown in Table-VI where as in female it shows that 95% (75 sample) shows sensitivity as shown in Table-VII.

Antimicrobial Susceptibility	Escherichia Coli (%)
Sensitive	136 (90%)
Resistant	14 (10%)
Total	150

Table-I. Antimicrobial susceptibility pattern of ceftazidime-avibactam by disk diffusion method in E coli positive sample. (n=150)

MIC Distribution	Escherichia Coli (n=150)
≤1μg/ml	82(55%)
2-8μg/ml	53(35%)
16μg/ml	15(10%)
≥μg/ml	0
Total	150

Table-II. MIC distribution pattern of ceftazidime-avibactam.

Antibiotic	Sensitive	Resistant
Amoxicillin-clavulanate	26(17%)	82(83%)
Ceftazidime	23(15%)	127(85%)
Ceftriaxone	20(13%)	130(87%)
Cefepime	33(22%)	117(77%)
Cefotaxime	32(21%)	118(79%)
Ciprofloxacin	72(48%)	78(52%)
Imipenem	98(65%)	52(35%)
Meropenem(10ug)	105(70%)	45(30%)
Piperacillin-tazobactam	30(20%)	120(80%)
Gentamicin (10ug)	44(29%)	106(71%)
Amikacin(30ug)	96(63%)	104(37%)
Levofloxacin	51(34%)	99(66%)
Cotrimoxazole	26(17%)	124(83%)

Table-III. Antimicrobial susceptibility pattern of Escherichia Coli. (n=150)

Descriptive Statistics	Escherichia Coli (n=150)
Mean Age (years)	30.56
SD	9.93
Median	28.50
Range	37
Minimum	13
Maximum	50

Table-IV. Descriptive statistics of samples by age (years). (n=150)

Gender	Escherichia coli (%)
Male	79 (52.4%)
Female	71 (47.6%)
Total	150

Table-V. Frequency distribution of gender in E coli positive sample. (n=150)

Antimicrobial Susceptibility	Escherichia Coli	
Sensitive	61 (86%)	75 (95%)
Resistant	10 (14%)	4 (5%)
Total	71	79

Table-VI. Antimicrobial susceptibility pattern of microorganisms for male and female patient's susceptibility pattern of ceftazidime-avibactam against Escherichia coli.

DISCUSSION

An ever increasing problem around the world is antimicrobial resistance to an alarming level, thus making it difficult to obtain treatment options for various infections.[12,13] Choices for various reliable and effective therapeutic options are seriously limited.[14,15,16] Evidence suggests that an alarming proportion of all bacteria isolated throughout the world shows gram-negative bacteria having ESBL enzymes.[17,18] Therefore, the current study was designed to address the susceptibility and frequency of ceftazidime-avibactam antimicrobial activity in commonly prevalent Enterobacteriaceae like E. coli.

The brake points were categorized according to CLSI guidelines of 2020 by using the disk diffusion method that showed values ≤ 20mm were found to be resistant and values ≥ 21 represented sensitivity. This finding is consistent with study done by García-Castillo et al in 2011.[26,27,28,29]

In summary it is concluded that ceftazidime-avibactam combination in the present study observed effective in-vitro antimicrobial activity and broad antimicrobial spectrum for variable strains isolated from the patients at PNS Shifa hospital our results indicated that a combination of ceftazidime-avibactam presents as an effective and promising treatment option to treat infections that are caused by E.coli. The drug also shows promising results against those infections which are resistant to most of the antimicrobial drugs

that are currently available for clinical use. We concluded that ceftazidime-avibactam is highly effective on ceftazidime resistant microorganism.

Ceftazidime avibactam combination is promising therapy for treatment of E. coli The study is being conducted at only one setting, it should be multicentered. Sample size is small. Susceptibility pattern and frequency of other members of Enterobacteriaceae is being evaluated.

CONCLUSION

It was concluded that Ceftazidime-avibactam is a novel drug combination that shows high sensitivity against Escherichia coli. Ceftazidime/avibactam, therefore, presents as an additional treatment option against the multidrug-resistant gram-negative bacteria. It is worth mentioning, no other antibiotic tested has come up with better overall coverage than Ceftazidime-avibactam against resistant Escherichia coli.

REFERENCES

1. Ayukekbong JA, Ntemgwa M, Atabe AN. **The threat of antimicrobial resistance in developing countries: Causes and control strategies.** Antimicrobial Resistance & Infection Control. 2017 Dec; 6(1):1-8.

2. Parsonage B, Hagglund PK, Keogh L, Wheelhouse N, Brown RE, Dancer SJ. **Control of antimicrobial resistance requires an ethical approach.** Frontiers in microbiology. 2017 Nov 2; 8:2124.

3. Chokshi A, Sifri Z, Cennimo D, Horng H. **Global contributors to antibiotic resistance.** Journal of global infectious diseases. 2019 Jan; 11(1):36.

4. S, Kapoor RK, Virdi JS, Gulati P. **Integrons in Enterobacteriaceae: diversity, distribution and epidemiology.** International journal of antimicrobial agents. 2018 Feb 1; 51(2):167-76.

5. Dos Santos, G.S., Solidônio, E.G., Costa, M.C.V.V., Melo, R., de Souza, I.F.A.C., Silva, G. and Sena, K.X.F.R., 2015. **Study of the Enterobacteriaceae group CESP (Citrobacter, Enterobacter, Serratia, Providencia, Morganella and Hafnia): A review.** The battle against microbial pathogens: basic science, technological advances and educational programs, 2, pp.794-805.

6. Ahmed M, Moremi N, Mirambo MM, Hokororo A, Mushi MF, Seni J, Kamugisha E, Mshana SE. **Multi-resistant gram negative enteric bacteria causing urinary tract infection among malnourished underfives admitted at a tertiary hospital, northwestern, Tanzania.** Italian journal of pediatrics. 2015 Dec; 41(1):1-5.

7. Scott LJ. **Eravacycline: A review in complicated intra-abdominal infections.** Drugs. 2019 Feb; 79(3):315-24.

8. Ammar EM, Wang X, Rao CV. **Regulation of metabolism in Escherichia coli during growth on mixtures of the non-glucose sugars: Arabinose, lactose, and xylose.** Scientific reports. 2018 Jan 12; 8(1):1-1.

9. Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, Brewer TG, Engmann CM, Houpt ER, Kang G, Kotloff KL. **Morbidity and mortality due to shigella and enterotoxigenic Escherichia coli diarrhoea: The Global Burden of Disease Study 1990–2016.** The Lancet Infectious Diseases. 2018 Nov 1; 18(11):1229-40.

10. Hariharan P, Bharani T, Franklyne JS, Biswas P, Solanki SS, Paul-Satyaseela M. **Antibiotic susceptibility pattern of Enterobacteriaceae and non-fermenter Gram-negative clinical isolates of microbial resource orchid.** Journal of natural science, biology, and medicine. 2015 Jan; 6(1):198

11. Van Duin D, Bonomo RA. **Ceftazidime/avibactam and ceftolozane/tazobactam: Second-generation β-lactam/β-lactamase inhibitor combinations.** Clinical Infectious Diseases. 2016 Jul 15; 63(2):234-41.

12. Bhardwaj, N., Khurana, S., Kumari, M., Malhotra, R. and Mathur, P., 2018. **Pattern of antimicrobial resistance of gram-negative bacilli in surgical site infections in in-patients and out-patients at an apex trauma center: 2013–2016.** Journal of laboratory physicians, 10(4), p.432.

13. Ruppé É, Woerther PL, Barbier F. **Mechanisms of antimicrobial resistance in Gram-negative bacilli.** Annals of intensive care. 2015 Dec; 5(1):1-5.

14. Arendrup MC, Patterson TF. **Multidrug-resistant Candida: Epidemiology, molecular mechanisms, and treatment.** The Journal of infectious diseases. 2017 Aug 15; 216(suppl_3):S445-51.

15. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, Laxminarayan R, Klein EY. **The mortality burden of multidrug-resistant pathogens in India: A retrospective, observational study.** Clinical Infectious Diseases. 2019 Aug 1; 69(4):563-70.

16. Lim C, Takahashi E, Hongsuwan M, Wuthiekanun V, Thamlikitkul V, Hinjoy S, Day NP, Peacock SJ, Limmathurotsakul D. **Epidemiology and burden of multidrug-resistant bacterial infection in a developing country.** elife. 2016 Sep 6; 5:e18082.

17. Eichenberger EM, Thaden JT. **Epidemiology and mechanisms of resistance of extensively drug resistant Gram-negative bacteria.** Antibiotics. 2019 Jun; 8(2):37.

18. Kaye KS, Pogue JM. **Infections caused by resistant gram□negative bacteria: epidemiology and management.** Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2015 Oct; 35(10):949-62.

19. Kim HS, Chon JW, Kim YJ, Kim DH, Kim MS, Seo KH. **Prevalence and characterization of extended-spectrum-β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in ready-to-eat vegetables.** International Journal of Food Microbiology. 2015 Aug 17; 207:83-6.

20. Najjuka CF, Kateete DP, Kajumbula HM, Joloba ML, Essack SY. **Antimicrobial susceptibility profiles of Escherichia coli and Klebsiella pneumoniae isolated from outpatients in urban and rural districts of Uganda.** BMC research notes. 2016 Dec; 9(1):1-4.

21. Rizwan M, Akhtar M, Najmi AK, Singh K. **Escherichia coli and Klebsiella pneumoniae sensitivity/ resistance pattern towards antimicrobial agents in primary and simple urinary tract infection patients visiting University Hospital of Jamia Hamdard New Delhi.** Drug research. 2018 Jul; 68(07):415-20.

22. Yaseen M, Rashid S, Naqvi S. **Urinary tract infection in pregnant females attending antenatal clinics among middle socioeconomic settings.** The Professional Medical Journal. 2020 Aug 10; 27(08):1636-41.

23. Liao CH, Lee NY, Tang HJ, Lee SS, Lin CF, Lu PL, Wu JJ, Ko WC, Lee WS, Hsueh PR. **Antimicrobial activities of ceftazidime–avibactam, ceftolozane–tazobactam, and other agents against Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa isolated from intensive care units in Taiwan: Results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan in 2016.** Infection and drug resistance. 2019; 12:545.

24. Ramalheira E, Stone GG. **Longitudinal analysis of the in vitro activity of ceftazidime/avibactam versus Enterobacteriaceae, 2012–2016.** Journal of global antimicrobial resistance. 2019 Dec 1; 19:106-15.

25. Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. **Ceftazidime/avibactam tested against Gram-negative bacteria from intensive care unit (ICU) and non-ICU patients, including those with ventilator-associated pneumonia.** International journal of antimicrobial agents. 2015 Jul 1; 46(1):53-9.

26. García-Castillo M, García-Fernández S, Gómez-Gil R, Pitart C, Oviaño M, Gracia-Ahufinger I, Díaz-Regañón J, Tato M, Cantón R, Bou G, Rodríguez JG. **Activity of ceftazidime-avibactam against carbapenemase-producing Enterobacteriaceae from urine specimens obtained during the infection-carbapenem resistance evaluation surveillance trial (iCREST) in Spain.** International journal of antimicrobial agents. 2018 Mar 1; 51(3):511-5.

27. King M, Heil E, Kuriakose S, Bias T, Huang V, El-Beyrouty C, McCoy D, Hiles J, Richards L, Gardner J, Harrington N. **Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections.** Antimicrobial agents and chemotherapy. 2017 Jul 1; 61(7).

28. Krapp F, Grant JL, Sutton SH, Ozer EA, Barr VO. **Treating complicated carbapenem-resistant enterobacteriaceae infections with ceftazidime/ avibactam: A retrospective study with molecular strain characterization.** International journal of antimicrobial agents. 2017 Jun 1; 49(6):770-3.

29. Tuon FF, Rocha JL, Formigoni-Pinto MR. **Pharmacological aspects and spectrum of action of ceftazidime–avibactam: A systematic review.** Infection. 2018 Apr; 46(2):165-81.

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