

Carbapenems Sparing Antibiotics in the Management of Urinary Tract Infections caused by Multidrug Resistant Gram-Negative Organisms - A New Way to Control Growing Incidences of Carbapenem-Resistant Enterobacteriaceae

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ABSTRACT

Introduction: Urinary tract infections (UTIs) are the most common infection in humans. The retrospective study was aimed to analyze a new AAE (antibiotic adjuvant entity) of ceftriaxone+sulbactam with adjuvant disodium edetate as a carbapenem sparing drug in the management of UTIs caused by *Escherichia coli*. **Methods:** A retrospective review of patients treated for UTIs caused by *Escherichia coli* between January 2014 to April 2015 was conducted. Demographic characteristics, antibiotic therapy, length of hospital stay and clinical and microbiological outcome have been evaluated. **Results:** Data of 322 patients were reviewed. Of these, 112 patients who are diagnosed with UTI and having culture positive with *E. coli* were included in the study. Characterization of these isolates indicated that 48.2% were ESBL positive, 11.6% were MBL positive and 49.0% were found to be non ESBL/MBL. In microbiological evaluation, AAE appeared to be the most active drug against *E. coli* (89.3%) followed by meropenem (62.5%), imipenem plus cilastatin (58.03%) and piperacillin plus tazobactam (52.65%). Clinical success rate was 82.9% in AAE treated patients followed by 76% in meropenem, 71.4% in imipenem plus cilastatin and 63.1% in piperacillin plus tazobactam treated patients. **Conclusion:** The present study advocates that AAE can be considered as a drug of choice to carbapenem. Overall, this study results indicate approximately 6 to 11.5% superiority of

AAE over penems (meropenem and imipenem plus cilastatin) and 19.8% to piperacillin plus tazobactam.

Key words: Ceftriaxone+sulbactam with adjuvant EDTA, AAE, *E. coli*, multidrug resistant, retrospective study, urinary tract infections

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INTRODUCTION

Urinary tract infections (UTIs) are the third most common infection in humans after respiratory and gastro-intestinal infections.^[1] They occur more commonly in women and as many as 50% of women face at least one episode of urinary tract infection in their lives, with 10% developing urinary tract infections yearly.^[2] UTIs are considered as complicated UTI when it is accompanied by calculi, infected cysts, renal/bladder abscesses, certain forms of pyelonephritis, spinal cord injury (SCI), catheters (structural abnormalities), diabetes, pregnancy (metabolic and hormonal abnormalities), transplant recipients (especially renal transplants) and patients with AIDS add to challenges related to impaired host response and sometimes these infections are co-hosted by pathogens like yeast/ fungi.^[3] Clinical presentation may vary from severe obstructive acute pyelonephritis with imminent urosepsis to a catheter-associated post-operative UTI, which might disappear spontaneously as soon as the catheter is removed.^[4,5] The recurrence rate is high and according to studies about 25 % women experienced a second episode of UTI within 6 months of their first UTI.^[6]

In past decade the number of cUTIs due to resistant gram-negative bacteria has risen sharply, mainly due to the spread of ESBL-producing bacteria making treatment of cUTI problematic.^[7,8] To overcome ESBLs resistance, carbapenem drugs have been introduced in clinical settings, although resistance to carbapenem has been reported globally that is mediated through production of carbapenems hydrolyzing enzymes called carbapenemases.^[9-12] As a result of the increasing resistance towards antibiotics and drying antibiotic pipeline compelled us to look into opportunities for improving usage of the existing antimicrobial agents. Among numerous approaches, improvement of the existing antimicrobial agents through antibiotic adjuvant therapy is the most latest and successful.^[13]

Introduction of EDTA as an adjuvant for chelation and catalytic action

to existing antibiotics has been seen as a ray of hope. A new AAE (ceftriaxone, sulbactam with adjuvant EDTA) has been reported to have proven efficacy in a wide range of infections.^[14,15] This retrospective observational study has been performed to evaluate the best choice of antibiotic to be used empirically for the treatment of cUTI as an alternative to carbapenems.

MATERIALS AND METHODS

Study design

This retrospective study has been performed to evaluate and compare the use of new AAE in management of cUTI and co-relate its clinical efficacy with meropenem to support its use as carbapenem sparing drug. The study was performed at the tertiary care hospitals from January 2014 to April 2015. Being a retro-respective, it was not required to take approval of hospital ethics committee. Patient's hospital case sheets and sample culture registers of the microbiology department were reviewed to short list all culture positive cases of cUTI. Only those cases of cUTI caused by Gram-negative microorganisms constituted the study population. Patient were classified as complicated UTIs if there were certain predisposing factors present. These factors include:

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obstructed urinary flow due to congenital causes, prostatic obstruction or urinary stones; incomplete bladder emptying due to anatomic (prostatic or urethral) or neurogenic (congenital or acquired spinal cord abnormalities) reasons; vesicoureteral reflux, foreign bodies in the urinary tract (instruments, catheters, drainage tubes); systemic illness such as diabetes; pregnancy and males participating in anal intercourse.

Culture identification and susceptibility testing

E. coli identification and susceptibility study was conducted as reported earlier.^[16,17]

Screening of isolates for extended spectrum beta-lactamases (esbl) and metallo beta-lactamases (mbl) production has been performed as reported earlier.^[16,18]

Demographic analysis and antibiotic therapy

The detailed demographic and baseline characteristics of all patients including number of evaluable patients, age, weight, types of infections, severity which are analyzed in this study are given in [Table 1]. The patients have been treated with either meropenem (1.0 g, every 8 h), new any therapy (ceftriaxone sulbactam with adjuvant EDTA, 3.0 g every 12 h), imipenem plus cilastatin (500 mg QID) and piperacillin plus tazobactam (4.5 g every 8 hrs) intravenously. For those patients who has failed to respond to AAE, colistin therapy with a loading dose of 9 MIU followed by BD doses of 4.5 MIU has been used along with Flores..

The antibiotic therapy of all the patients included in this study has been initially started empirically based on the clinical symptoms and treating physicians decision and was continued or shifted to other therapy based on the *in vitro* microbiological susceptibility tests and clinical outcomes.

Clinical evaluation of patients

The clinical efficacy of the therapy was evaluated and classified as cured (resolution of clinical signs and symptoms or improvement not requiring further antibacterial therapy), or failure (persistence of clinical signs and symptoms or worsening in signs and symptoms that required alternative antimicrobial therapy after 72 h of treatment). The overall efficacy rate was defined as the proportion of the patients cured. Bacterial efficacy was evaluated based on the following four categories: complete eradication if elimination of the original causative pathogens, persistence if the original causative pathogens were repeatedly isolated, substitution if new organisms were isolated on repeated culture and re-infection if reappearance of the original causative pathogens after eradication and with clinical symptoms of infection.

RESULTS

Study design and demographic analysis

During this retrospective evaluation data of 322 patients having Gram-negative organisms in urine culture was reviewed. Of which, 114 culture were found to be of *E. coli* and meeting other criteria of the of study. The remaining culture (n=208) were of other pathogens and were excluded. On evaluation of susceptibility testing of these 114 isolates, only 112 isolates were observed to be susceptible to all drugs and were included in the study. There were chances of anaerobic associated infections (not detected in current study), hence metronidazole has been administered in patients of all groups as additional cover. All the 112 patients have been treated empirically by either AAE, meropenem, imipenem plus cilastatin or piperacillin plus tazobactam. The average age of patients was 55.23 ± 11.21 years [Table 1]. Acute pyelonephritis was reported in 33.0 % (n=37) cases, asymptomatic bacteriuria 16.9 % (n=19) cases, chronic prostatitis in 17.8 % (n=20), hydroureteronephrosis in 32.1 % (n=36). Diabetes mellitus was found to be the most common co-factor for complication in 24.1% cases and was handled as per standard of care.

Prevalence of ESBLs and MBLs

Our results showed that 48.2 % (54/112) isolates of *E. coli* were ESBL positive and 11.6% (13/112) were MBL positive.

In vitro antibiotic susceptibility

On evaluation of culture and sensitivity reports, only patients infected with *E. coli* were involved in the study. The results of *in vitro* antimicrobial susceptibility of AAE, imipenem plus cilastatin, meropenem and piperacillin plus tazobactam are presented in Table 3. According to the susceptibility results, AAE seemed to be the most active drug against *E. coli* with 89.3 % susceptibility followed by meropenem (62.5%), imipenem plus cilastatin (58.03%) and piperacillin plus tazobactam (52.65%).

Antibiotics treatment and their efficacy evaluation

A total of 112 patients have been included in this analysis out of which 47 have received AAE (G1), 25 meropenem (G2), 21 imipenem plus cilastatin (G3) and 19 piperacillin plus tazobactam (G4). Indication wise cure rates of different drugs are depicted in Table 2. In line with the hospital protocol, on third day of therapy, progress of the therapy has been evaluated in terms of the improvement in the clinical signs and symptoms and microbiological results. Patients with susceptible pathogens and clinical improvement has been continued on respective empirical therapies. Patients in AAE group showing no clinical improvement have been put on add on (dual) therapy with colistin. Patients of other groups with no improved clinical response have been shifted to AAE and observed for clinical signs of improvement. Those showed improvement have been retained on the therapy and those showing poor response were put on dual therapy with addition of colistin along with AAE.

Table 1: Demographics characteristics of 112 evaluable patients treated during the study period

Characteristic	G1	G2	G3	G4
Age (y) mean (SD)	55.32 (± 6.52)	54.68 (± 7.25)	53.10 (± 6.60)	55.89 (± 6.77)
Sex (n) Male (%)	24 (51.06%)	12 (48.0%)	11 (52.38%)	10 (52.63%)
Sex (n) Female (%)	23 (48.94%)	13 (52.0%)	10 (47.62%)	9 (47.37%)
Weight (kg) mean (SD)	57.62 (± 7.90)	58.2 (± 8.95)	59.52 (± 6.41)	60.37 (± 8.39)
BMI (SD)	21.01(± 1.71)	21.89 (± 1.72)	21.83 (± 1.82)	22.63 (± 2.17)
Diabetes duration (y) mean (SD)	4.03 (± 1.23)	4.15 (± 1.23)	4.00 (± 1.49)	4.00 (± 1.67)

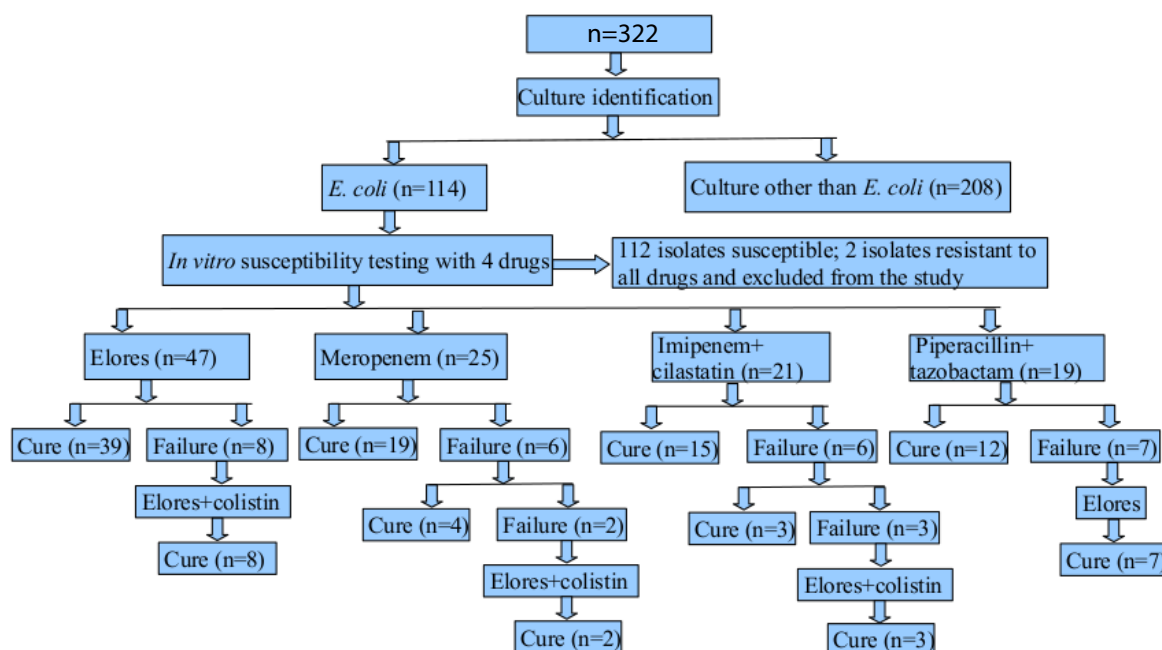


Figure 1: Overview of the study design

In G1, 39 patients (82.9 %) have been clinically cured with complete bacteriological eradication. The mean duration of antimicrobial therapy for these patients is 6 days. While 8 patients (17.0%) did not respond to AAE on day 3 have been shifted to AAE+colistin combination therapy and all these have achieved clinical success. The average length of antibiotic treatment is 9 days.

With regard to G2, where 25 patients received meropenem, 19 patients (76%) were cured with average treatment duration of 8 days whereas 6 patients (24%) did not show response has been shifted to FDC from which 2 got cured and 4 have been put on dual therapy with average treatment duration 11 days. In G3, of 21 patients, 15 patients (71.4%) showed satisfactory clinical cure with imipenem plus cilastatin. The average treatment duration is 9 days while 6 patients (28.6%) who did not show clinical response at 3rd day have been shifted to AAE that resulted in clinical cure of 3 while remaining 3 have been put on dual therapy leading to increase in cure time to 12 days. In G4, for 19 patients who received piperacillin plus tazobactam, 12 patients (63.1%) responded well to achieve clinical cure. The average treatment duration is 9 days. On the other hand, 7 patients (36.8%) who did not show any clinical improvement on day 3 have been shifted to AAE and these patients get cured. The mean treatment duration for these 7 cured patients is 12 days [Table 4]

DISCUSSION

Carbapenems are a class of beta-lactam antibiotics with broad spectrum of antibacterial activity and have been considered last resort antibiotics for many bacterial infections caused by ESBL-producers.^[19] However, in past few years, carbapenem-resistant due to carbapenemases and *OprD* expression have emerged among **Enterobacteriaceae** family.^[10,20,21]

In order to combat carbapenem resistance, combination of beta-lactam and beta lactamase inhibitors have received much consideration as a carbapenem alternative drug.^[22-24] However, only BL+BLI combinations did not exhibit significant activity against some ESBLs and MBL

producing Gram negative organisms. Hence, AAE supplemented with antibiotic resistance breaker (proven for efficacy and safety) is in use at multiple multispecialty centers to treat the patients with infections caused by such organisms.^[25,26] The retrospective evaluation has been carried out to collect adequate in support of this new AAE when used as carbapenem sparer.

In the current investigation, 112 patients of cUTI infected with *E. coli* and treated with AAE, meropenem, imipenem plus cilastatin and piperacillin plus tazobactam have been retrospectively analyzed for correlation between type of resistance (ESBL/MBL) and the clinical response. In UTI, *E. coli* has been reported to be most common^[27,28] which corroborates with current investigation where 114/322 (35.4%) patients are found to be positive to *E. coli*.

On antimicrobial susceptibility data evaluations 89.3 % of *E. coli* were found to be sensitive to AAE, followed by meropenem (62.5%), imipenem plus cilastatin (58.03%) and piperacillin plus tazobactam (52.6%). The greater susceptibility of *E. coli* to AAE and lesser susceptibility of comparator drugs is consistent with previous studies.^[14, 29]

With regard to clinical success rate, the overall clinical success rate in AAE treated patients is 82.3% compared to 76% in meropenem, 71.4% in imipenem plus cilastatin and 63.1% in piperacillin plus tazobactam. Overall, AAE is showing 6 to 11.5 % higher clinical success rates compared to penems (meropenem and imipenem plus cilastatin) and 19.8 % to piperacillin plus tazobactam. The greater cures rates with this new AAE is likely to be associated with efflux over expression and MBL genes in pathogens to which other drugs fail to respond. AAE has been shown to be more effective against MBLs and AcrAB-tolC efflux positive isolates and mixed isolates.^[29-31] All these factors may contribute to make it more efficacious against multi-drug resistant pathogens. The clinical success rates achieved with AAE is similar to a phase III study conducted^[15] where clinical cure rates with AAE was 83.33%. Several animal studies also indicated promising *in vivo* efficacy of AAE.^[32,33]

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Table 2: Indication wise cure rates of drugs

Therapy		Indications		
			Pyelonephritis (n,%)	Complicated urinary Tract infections (n,%)
Single therapy	AAE	Empiric	20 (54.0)	19 (25.3)
		Shifted	4 (10.8)	10 (13.3)
	Meropenem		6 (16.2)	13 (17.3)
	Imipenem plus cilastatin		3 (8.1)	12 (16.0)
Dual therapy	Piperacillin plus tazobactam		1 (2.7)	11 (14.7)
	AAE+colistin		3 (8.1)	10 (13.3)
Total			37	75

Table 3: *In vitro* antibiotic susceptibility testing for *E. coli*

Name of drugs	Susceptibility	
	No of isolates	%
AAE	100/ 112	89.3
Meropenem	70 / 112	62.5
Imipenem+cilastatin	65 /112	58.03
Piperacillin+tazobactam	59 /112	52.6

Table 4: Summary of the clinically cured patients and reasons of failure of therapy

Drug regimen opted	No of patients	Clinically cured (percentage)	Reason for failure identified	Average treatment time	Mortality
Mono therapy with metronidazole					
Ceftriaxone+sulbactam	47	39 (82.9)	MBL positive+	6	nil
with adjuvant EDTA (AAE)			ESBL		
Meropenem	25	19 (76)	MBL positive	8	nil
Imipenem cilastatin	21	15 (71.4)	MBL positive	9	nil
Piperacillin tazobactam	19	12 (63.1)	Mixed ESBL+	9	nil
			MBL positive		
Dual therapy					
Ceftriaxone+sulbactam	14	14 (100)	MBL positive	3+6	nil
with adjuvant EDTA (AAE)					
Ceftriaxone+sulbactam	13	13 (100)	Mixed ESB+MBL	3+6	nil
with adjuvant EDTA (AAE)+colistin					

In contrast, lesser cure rates of comparator drugs may be probably due to less activity of these drugs against biofilm producing MBLs, AcrAB-tolC positive isolates.^[29,34] This retrospective study revealed 24 % failure cases with meropenem, 28.5% in imipenem plus cilastatin and 36.8 % in piperacillin plus tazobactam treated group which can be co-related with failure of these drugs to respond to efflux, biofilm and MBL genes along with false susceptibility reported earlier.^[35]

In conclusion, our data advocates that AAE of ceftriaxone + sulbactam with adjuvant disodium edetate can be considered as an alternate option for Carbapenem as sparing drug. Overall, our results indicate around 6 to 11.5 % superiority of new AAE alone over penems (meropenem and imipenem plus cilastatin) and 19.8 % to piperacillin plus tazobactam.

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Conflicts of interest

None.

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