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A New Antibiotic Adjuvant Entity (Ceftriaxone + Sulbactam + Disodium Edetate): An Alternative to Carbapenems for the Management of Intensive Care Unit Infection

Sachin Verma[1*]

[1]*Internal Medicine and Critical Care, Ivy Hospital, Mohali, Chandigarh, India.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: Carbapenem resistant bacterial infections have limited treatment options and are associated with high mortality. Here we present a retrospective analysis of treatment and outcome for ICU patients suffering from moderate to severe urinary tract infection (UTI), lower respiratory tract infection (LRTI) and intra-abdominal infections (IAI) to assess the efficacy of novel antibiotic adjuvant entity (AAE); ceftriaxone + sulbactam + disodium edetate, as an effective alternative for carbapenems in critically ill patients.
Materials and Methods: A retrospective study was conducted to evaluate efficacy of AAE in 84 patients showing sensitivity to AAE with UTI, LRTI and IAI treated at IVY hospital, Mohali, India between January 2013 to November 2014. The antibiotic therapy was initiated empirically and continued based on the results of the microbiological susceptibility testing and clinical outcome.
Results: 64 (76.19%), patients were diagnosed with single-organism infections, among which, 14 (16.16%) bacteria were resistant to meropenem and all the bacteria were susceptible to AAE. Empirical meropenem treatment was given to 25 patients, of which 18 (72%) patients achieved clinical success. 24 (75%) patients of 32 patients treated with AAE, achieved clinical success and

**Corresponding author: E-mail: sachinverma.265@rediffmail.com;*

the remaining 8 patients were cured when colistin was given with AAE. 20 (23.80%), patients were diagnosed with polymicrobial infections. Among 20 polymicrobial infectious patients, bacterial samples of 12 patients showed sensitivity towards AAE and meropenem, where as the remaining 8 (40%) samples showed intermediate susceptibility towards both cabapenem and AAE. 9 (45%) patients were cured with AAE, while the remaining 11 patients were cured with AAE and colistin combination therapy.

Conclusion: From the above study, it can be concluded that patients experience similar rates of clinical response in carbapenem susceptible cases and in some cases where patients failed to respond to carbapenem therapy but responded to AAE treatment. Hence, AAE can be used as an alternative to carbapenems in the treatment of moderate and severe infections caused by Gram negative organisms.

Keywords: Ceftriaxone/sulbactam-EDTA; intra-abdominal infections; lower respiratory tract infections; retrospective study; urinary tract infections.

1. INTRODUCTION

Management of critically ill patients infected with antibiotic resistant organisms is a major health-care problem affecting morbidity and mortality in the intensive care unit [1]. Gram-negative bacteria are predominantly responsible for these severe infections [2]. Beta-lactams are one of the most frequently used classes of antimicrobials in hospital settings, and are crucial for the treatment of infections caused by Gram-negative bacteria [3]. However, because of increasing beta lactam resistance primarily due to production of Extended Spectrum Beta Lactamases (ESBL), carbapenems have become the choice of drug class to the treatment of severe infections [4]. Emergence of novel beta-lactamases with direct carbapenem-hydrolyzing activity has contributed to an increased prevalence of carbapenem-resistant Gram negative bacteria, especially *Enterobacteriaceae* (CRE).

CRE are particularly problematic given the frequency with which *Enterobacteriaceae* cause infections [5]. The high mortality associated with infections caused by CRE [6-8], and the potential for widespread transmission of carbapenem-resistance via mobile genetic elements [9,10]. Increase in carbapenem usage has a direct relationship to an increase in carbapenem resistant gram negative bacteria [11]. Antibacterial drug discovery and development have slowed considerably in recent years [1]. The number of new antibacterial medicines entering clinical practice has been declining and, in view of this fact, few compounds for multi-drug resistant gram-negative bacteria will be available for more than 10 years [12,13]. The problems associated with escalating resistance and decreased antimicrobial development has required more research into the use of available antibiotics for alternate empiric therapy of severe infections.

Recent effort to maximize antibiotic activity and overcome drug resistance has led to the search for an alternate solution such as the use of antibiotic adjuvants. Antibiotic adjuvants are moieties, non-antibiotic in nature, which in combination with antibiotics, enhance the antimicrobial activity of the latter [14]. Fixed dose combination of Ceftriaxone + sulbactam + adjuvant disodium edetate is one such novel Antibiotic Adjuvant Entity (AAE) approved by the Drug Controller General of India (DCGI) and increasingly used in Indian hospitals. Various reports of the in-vitro susceptibility studies [14] suggest the possibility of AAE as a method for overcoming the hurdles of both ESBL (sulbactam effect) as well as Metallo Beta Lactamases (MBL) (disodium edetate) producers clinically. Two recently published retrospective studies support the use of this AAE in septicaemia and sepsis [15,16]. Thus the main goal of this study was to retrospectively analyze the clinical and microbiological efficacy of this AAE in patients with moderate to severe IAI, LRTI and UTI.

2. MATERIALS AND METHODS

2.1 Patients and Antibiotic Therapy

This study was conducted at the 200 bed tertiary care IVY hospital Mohali, Chandigarh. We retrospectively reviewed the case reports of 108 critical care patients suffering from different infections (IAI, LRTI, UTI) and who were treated at IVY hospital between January 2013 to November 2014. Of 108 patients, 84 patients

were included in the study of which 34 patients were diagnosed with LRTI and each of 25 patients were diagnosed with IAI and UTI. These 84 clinically cured patients had both culture positive infection and sensitivity of organisms to AAE with 0% mortality. Of 84 patients, 59 patients (IAI=17, LRTI=25 and UTI=17) were treated with AAE and 25 patients (IAI=8, LRTI=9 and UTI=8) were treated with meropenem. The remaining 24 patients were excluded from the study: 8 patients had bacteria resistant to meropenem or AAE. 12 patients which were changed to other antibiotics on the discretion of the investigator before sensitivity results. 4 patients died during the course of treatment.

The patients were administered either meropenem or AAE empirically. Meropenem was administered at the dose of 1000 mg *t.i.d.* and AAE was given at the dose of 1500-3000 mg *bis in die (b.i.d.)* depending upon the severity of infections. Patients receiving additional colistin therapy (not responding to single therapy) were given a loading dose of 9 (million international units) MIU followed by *b.i.d.* doses of 4.5 MIU.

Case records were analyzed for age, sex, APACHE II score, co-morbidities, duration of antimicrobial treatment, total leukocyte count, neutrophil count, liver function tests, renal function tests, culture and sensitivity of isolated organisms, serum electrolytes, radiological imaging, reason for the change of antibiotics, dose, duration and route of administration of AAE or meropenem and final microbiological and clinical outcome.

Antibiotic therapy with AAE or meropenem was initially begun empirically based on the clinical presentation and treating physician's decision. It was continued or modified based on the *in-vitro* microbiological susceptibility tests and clinical outcome.

On retrospective evaluation, patients were divided into two main groups. i.e. group A mon-omicrobial infection [64 (76.2%) patients] and group B poly-microbial infections [20 (23.8%) patients]. AAE was administered empirically to 64 patients in group A, 14 (21.9%) patients (group G-1) with infection caused by meropenem resistant and AAE-susceptible bacteria. In 50 (78.1%) patients (group G-2) with meropenem and AAE-susceptible bacterial infections, meropenem was administered to 50% cases (group G2A) and AAE was given to the remaining 50% (group G2B). On the third day of treatment, together with bacteriological evaluations, the progress of the therapy (improvement in the symptoms) was also recorded and the patients showing improvement with respective empiric therapies were continued on the same antibiotic. Patients who failed to respond to meropenem clinically despite microbial sensitivity to meropenem were switched to AAE therapy while patients who failed to respond to AAE mono-therapy were changed to combination therapy with AAE and colistin. In poly-microbial infections caused by pathogens sensitive to AAE and meropenem (group G3) empirical treatment was continued and those showing intermediate susceptibility towards AAE and meropenem (group G4), were treated with colistin along with the empiric AAE once the susceptibility report was received.

2.2 *In-vitro* Microbial Antibiotic Susceptibility Testing

Antimicrobial susceptibility testing of the isolated pathogens was done by Kirby–Bauer disk diffusion method as recommended by the Clinical Laboratory Standards Institute [17].

2.3 Clinical Analysis of Patients

Clinical signs and symptoms associated with these infections were evaluated upon initiation of therapy, after 3 days of empirical antibiotic therapy, and at the end of therapy. Clinical improvement was determined by physicians. Sputum, bronchoalveolar lavage (BAL), endotracheal (ET) secretions, urine, blood, pus or peritoneal fluids from the patients were cultured for causative pathogens. Clinical response to therapy evaluated at the end of the treatment was recorded and classified as cured (complete remission of local and systemic signs and symptoms), improved (improvement of local and systemic signs and symptoms but without complete resolution) or failure (no improvement or deterioration of signs and symptoms).

3. RESULTS

3.1 Patients and Demographic Characteristics

84 clinically cured cases of the 108 patients treated in the study period were diagnosed with culture- positive infections with bacteria sensitive to AAE. All patients had moderate to severe

infections with mean APACHE II score of 17.84±2.16; 26 (30.95%) of 84 patients had bacteremia. 52 of 84 evaluable patients had co-morbid conditions including hypertension (26.1%), diabetes (19.0%), chronic obstructive pulmonary disease (11.9%) and coronary artery disease (CAD) / ischemic heart disease (IHD) (4.7%). LRTI was the predominant infection diagnosed (40.47%), followed by intra-abdominal (29.76%) and urinary tract infections (29.76%). 64 of 84 patients were diagnosed with a mono-microbial infection, while 20 were diagnosed with poly-microbial infection. 44 of 64 mono-microbial infections, 44 were caused by pathogens of the *Enterobacteriaceae* family, with *E. coli* accounting for 30 (68.18%) cases and *Klebsiella sp.* for 14 (31.81 %) cases of infection. The remaining 20 (5 *Acinetobacter sp.* + 15 *Pseudomonas sp.*) isolates were of *non-Enterobacteriaceae* family. Different combinations of either *E. coli, Klebsiella sp., Acinetobacter sp., Pseudomonas sp. and Neisseria gonorrhoeae* were identified in mixed bacterial infections.

3.2 *In-vitro* Microbial Antibiotic Susceptibility Testing

The results of *in-vitro* microbial antibiotic susceptibility testing carried out for isolated pathogens were classified into 4 groups: G1 – single pathogen susceptible to AAE and resistant to meropenem, G2 – single bacteria susceptible to both AAE and meropenem, G3 – multiple pathogens showing sensitivity to both AAE and meropenem and G4 – multiple pathogens showing intermediate resistance to both AAE and meropenem (Fig. 1). Of 64 bacteria isolated from patients with mono-microbial infections, 50 (78.13%) showed susceptibility towards carbapenem and the remaining 14 (21.87%) were resistant. All 64 (100%) isolates showed showed susceptibility towards AAE. In susceptibility tests carried out for bacteria isolated from patients with polymicrobial infections, 12 strains were sensitive to AAE and meropenem, while the remaining 8 (40%) strains showed intermediate susceptibility to both cabapenem and AAE. From the *Enterobacteriaceae* family, *E. coli*, and *K. pneumoniae* were most commonly isolated. *Neisseria gonorrhoeae, S. pneumoniae, Acinetobacter sp.* and *P. aeruginosa* were the most common non-*Enterobacteriaceae* pathogens isolated. The overall susceptibility of all the isolated pathogens were 83.01% and 69.81% for AAE and meropenem respectively (Table 1).

3.3 Efficacy of Antibiotic Therapy

14 patients with carbapenem-resistant and AAE-susceptible bacterial infections were treated with AAE. Bacteriological eradication with successful clinical response was observed in 12 patients. 2 patients who failed to clinically respond to AAE were switched to AAE and colistin combination therapy. The mean treatment duration for the 12 patients who were cured with AAE was 6.91 days ±1.08 (SD). 25 of 50 patients with carbapenem and AAE-susceptible organisms were treated with meropenem. 18 of these patients showed clinical improvement (measured in terms of disease symptoms) after 3 days of treatment and were continued on carbapenem therapy. For the remaining 7 patients, treatment was changed to AAE. Of these, 4 patients showed clinical cure. The mean treatment duration for these 4 cured patients with AAE therapy was 5.75 days ±0.5 (SD). For the remaining 3 patients, clinical success was achieved after the administration of colistin with AAE. Of 25 patients having infections with carbapenem and AAE-susceptible organisms and treated with AAE (as penem sparer option), 20 showed satisfactory clinical cure. The mean treatment duration for these 20 cured patients was 5.8 days ±1.36 (SD). In the 5 patients who did not show clinical improvement after 3 days of AAE therapy, colistin was added to the treatment regimen. The administration of colistin resulted in clinical cure of all 5 patients. Of 20 patients with polymicrobial infection, 12 patients with infection due to AAE and meropenem sensitive strains, were continued on empirical AAE treatment (as penem sparer option). Of these 12 patients, nine were cured. In the remaining 3 patients, colistin was added to the ongoing AAE therapy. The mean treatment duration for these 9 patients cured with AAE was (9.88 days ±1.69 (SD)). However, 8 patients with cultures showing intermediate resistance towards both AAE and carbapenem, clinical success was achieved with the addition of colistin to ongoing AAE treatment regimen after 3 days of treatment. The mean treatment duration for the AAE and colistin therapy was (9.87 days ±2.64 (SD)).

None of the 84 patients had any serious treatment-associated side effects or changes in lab parameters. All the patients had a good clinical response and were stable at the time of hospital discharge.

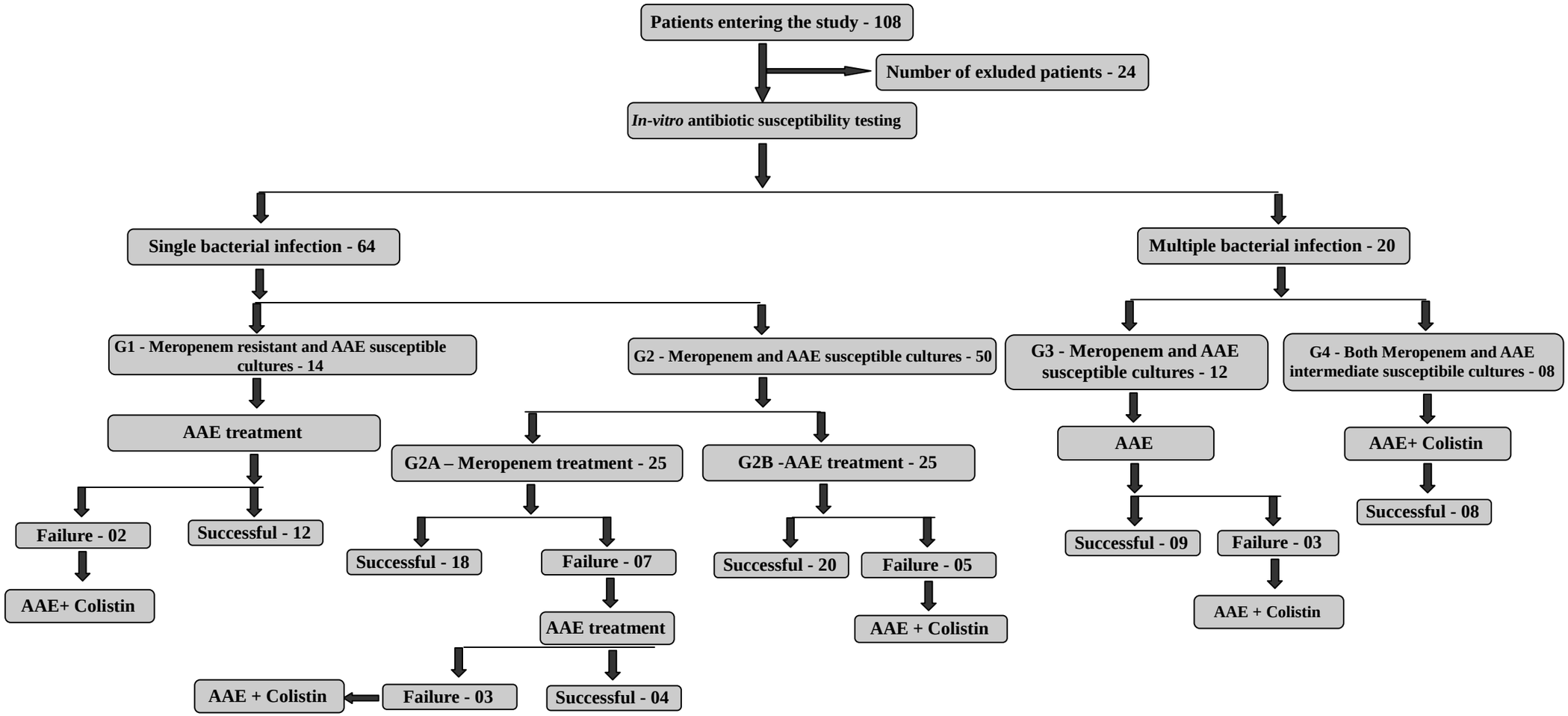

Fig. 1. Overview of the study design

Table 1. *In-vitro* antibiotic susceptibility testing for bacteria isolated from single/multiple organism infections

Diagnosis	Isolated pathoges	Number of individual isolates	Susceptibility/Resistance %			
			AAE		Meropenem	
			S	I	S	I
Intra- abdominal infection	*E. coli*	15	86.7	13.3	60	40
	Klebsiella sp.	6	83.4	16.6	83.33	16.77
	Acinetobacter sp.	2	100.0	0.0	100	0
	Pseudomonas sp.	8	75.0	25.0	62.5	37.5
	N. gonorrhoea	1	0.0	100	0	100
LRTI	*E. coli*	6	100.0	0.0	100	0
	Klebsiella sp.	12	91.7	8.3	75	25
	Acinetobacter sp.	4	100.0	0.0	25	75
	Pseudomonas sp.	15	80.0	20.0	60	40
	S. pneumoniae	04	50.0	50.0	50	50
UTI	*E. coli*	21	85.7	14.3	80.95	19.05
	Klebsiella sp.	4	75.0	25.0	75	25
	Pseudomonas sp.	3	100.0	0.0	100	0
	N. gonorrhoea	4	75.0	25.0	75	25
	Acinetobacter sp.	1	0.0	100.0	0	100
Total		106				

S: Susceptibility, I: Intermediate resistance

4. DISCUSSION

Carbapenems are broad-spectrum antibiotics which possess stability against hydrolysis by ESBL and AmpC chromosomal β-lactamase enzymes and are often reserved to treat the most serious infections [18-20]. The carbapenems have been effectively used to treat serious infections caused by ESBL producing bacteria [21,22]. However in recent years, carbapenem-resistance among Gram negative bacteria has been reported increasingly throughout the world including India [21-26]. This carbapenem resistance is attributed to various factors including production of MBL enzymes (carbapenamases), production of AmpC chromosome-encoded cephalosporinase, reduced outer membrane porin OprD expression, over expression of efflux pumps and other associated factors known to contribute to carbapenem resistance [27-30]. Several studies have demonstrated the role of EDTA in MBL inhibition and efflux pump down-regulation. However, the role of EDTA in OprD and AmpC is not well reported [31-33].

In view of this increased resistance of Gram-negative bacteria to carbapenems, many researchers from the Indian sub-continent have recommended the use of beta lactamase and beta lactamase inhibitor combinations (BL + BLI) in place of carbapenems [27,34]. However, treatment with BL + BLI combinations may not effectively eradicate both ESBL and MBL producers. Hence we have used an adjuvant antimicrobial FDC, a novel combination of Ceftriaxone + sulbactam + disodium edetate to treat the patients with infections caused by carbapenem resistant bacteria.

In-vitro microbial antibiotic susceptibility testing of the bacteria isolated from the 84 patients yielded 4 groups of bacteria: G1 - with carbapenem resistant and AAE susceptible, G2 - both carbapenem and AAE susceptible G3 – multiple pathogens showing susceptibility to both meropenem and AAE and G4 – multiple pathogens showing intermediate sensitivity to AAE and meropenem. 12 of 14 group G1 patients treated with AAE achieved clinical success. This established correlation of *in-vivo* results for the AAE treatment and justifies the selection of AAE to treat infections caused by carbapenem resistant bacteria. Of the 25 group G2A patients receiving carbapenem treatment 18, (72%) achieved success. The results of the present study are in accordance with the previous study by Chytra et al., who reported similar clinical cure rates (74.3%) of critically ill patients using carbapenem (meropenem) therapy [1]. These clinical failure rates may be attributed to the rise of carbapenem resistant bacteria, resulting from various resistance mechanisms together with carbapenamase (MBL) production. One such resistance mechanism is over-expression of efflux pumps

like MexAB-OprM efflux system in *Pseudomonas sp.* (specific to meropenem resistance) [35], AcrB efflux pumps in *E. coli* [36], AcrAB efflux pumps in *Klebsiella sp.* [37] and AdeABC type efflux pumps identified in *Acinetobacter sp.* [38]. Of the remaining 7 patients from group two, 4 patients (57.14%) achieved clinical success with AAE treatment suggesting the treatment success with AAE over carbapenem. Similar trends were observed in group G2B with 20 of 25 patients treated with AAE achieving clinical success. The enhanced efficacy of AAE over meropenem may be attributed to the different ways in which AAE targets various resistance mechanisms in bacteria. The mechanisms include the inhibition of conjugal spreading of a resistant gene from one bacteria to another. AAE does this by chelating Mg^{2+} ions required for the activity of relaxases and thereby inhibiting conjugation process [39]. It has also been reported that the AAE down-regulates the expression of MexAB-OprM and AcrAB-tolC efflux pumps [40]. Sulbactam prevents inactivation of beta-lactam antibiotics by binding to the beta-lactamases. EDTA, the adjuvant in AAE, chelates the divalent ions (Zn^{2+}) required the activity of MBLs and thus deactivates the MBLs activity which in turn increases activity of the β-lactam towards microorganisms [41]. Further, AAE is believed to disorganize the EPS and make the cell wall more porous, thus enhancing its entry into the bacterial cells. It has also been found to inhibit curli formation and bacterial adhesion [42]. The remaining patients were successfully treated when colistin was administered with AAE, thereby providing us with a new therapeutic option in the patient who failed AAE treatment. In 20 patients from the group G3 and group G4 clinical success was achieved in 9 (45%) patients with AAE treatment. In the remaining 11 patients, AAE and colistin therapy was required to achieve clinical success. This antibiotic combination therapy provides us with an efficient option to treat the single-drug resistant poly-microbial infections. The efficacy of this combination might be due to the proven effect of AAE as an efflux pump inhibitor [40] which may be helping colistin reach its site of action.

5. CONCLUSION

AAE provides us with a carbapenem alternative in the treatment of moderate and severe infections caused by resistant Gram negative bacteria. The results of this retrospective study provide us with an alternative regimen (AAE with colistin) to successfully treat patients with infections caused by organisms with intermediate resistance to both AAE and carbapenems. We, therefore, recommended the use AAE as a carbapenem alternative antimicrobial agent.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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