

Original Research Articles

A new Antibiotic Adjuvant Entity (Ceftriaxone + sulbactam + disodium edetate): a safer

alternative to carbapenems for ICU infection management

Abstract

Aims: Carbapenem resistant bacteria 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 UTI, LRTI and intra-abdominal infections (IAI) to check the efficacy of novel Antibiotic Adjuvant Entity (AAE); Ceftriaxone + sulbactam + disodium edetate, as an effective alternative for carbapenems in critically ill patients.

Material 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, out of which 18 (72 %) patients achieved clinical success. 24 (75 %) patients out of 32 patients treated with AAE, achieved clinical success and the remaining 8 patients were cured when colistin was given along with AAE. Among 20 multiple bacterial infection patients, 09 (45 %) patients cured with AAE, while the remaining 11 patients cured with AAE and colistin combination therapy.

Conclusion: AAE, displayed adequate efficacy in carbapenem resistant cases and equivalent efficacy in other cabapenem susceptible cases and thus offers encouraging alternative to carbapenem in treating critically ill patients.

Keywords: Ceftriaxone/sulbactam-EDTA, Intra-abdominal infections, Lower respiratory tract

27 infections, Retrospective study, Urinary tract infections.

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29 **1. Introduction**

30 Management of critically ill patients due to increasing antibiotic resistance is a major health-care
 31 problem affecting morbidity and mortality in the intensive care unit [1]. Gram-negative bacteria are
 32 predominantly responsible for severe diseases including those of abdomen (intra-abdominal), lower
 33 respiratory tract (LRTI) and urinary tract (UTI) infections [2]. Beta-lactams are one of the most
 34 frequently used classes of antimicrobials in hospital settings, crucial for the treatment of infections
 35 caused by Gram-negative bacteria [3]. However, on account of the increased resistance towards beta
 36 lactam antibiotics [mainly due to production of extended spectrum beta lactamases (ESBL)],
 37 Carbapenems have become the drug of choice to treat such severe infections [4]. Emergence of
 38 novel beta-lactamases with direct carbapenem-hydrolyzing activity has contributed to an increased
 39 prevalence of carbapenem resistant gram negative bacteria, especially *Enterobacteriaceae* (CRE).

40 CRE are particularly problematic given the frequency with which *Enterobacteriaceae* cause
 41 infections [5], the high mortality associated with infections caused by CRE [6-8], and the potential
 42 for widespread transmission of carbapenem resistance via mobile genetic elements [9,10]. Increase
 43 in carbapenem usage has a direct relationship to increase in carbapenem resistant Gram negative
 44 bacteria [11]. Antibacterial drug discovery and development have slowed considerably in recent
 45 years.^[1] The number of new antibacterial medicines entering the clinic has been declining and, in
 46 view of this fact, new compounds for multi-drug resistant Gram-negative bacteria will unlikely be
 47 available for more than 10 years [12,13]. The problems associated with escalating resistance and
 48 decreased development of antibiotics with novel mechanisms of action has required more research
 49 into existing antibiotics. Scarcity of newer antibiotics and drying antibiotic pipeline forces us to
 50 look for an effective alternate empiric antibiotic therapy equivalent to carbapenems, so as to spare
 51 carbapenem usage and to overcome the resistance due to carbapenamse producing pathogens.

Recent effort to maximize antibiotic activity, to overcome drug resistance has led to the search of an alternate perspective called as 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] hints the possibility of this AAE to overcome the hurdles of both ESBL (sulbactam effect) as well as MBL (disodium edetate) producers clinically. If effective in-vivo clinical success is achieved by this AAE, then it can be a potent alternative to treat infections caused by carbapenem resistant gram negative bacteria. 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 intra-abdominal, LRTI and UTI infections.

2. Materials and methods

2.1 Patients and antibiotic therapy

Study was conducted at 200 bedded tertiary care IVY hospital Mohali. We retrospectively reviewed the case reports of 108 patients suffering from different infections and who were treated at IVY hospital between January 2013 to November 2014 . For ease of evaluations the population was categorized into three groups based on the diagnosis and source of infections i.e. intra-abdominal infections, urinary tract infections (UTI) and lower respiratory tract infections (LRTI).

The patients were administered with either Meropenem (TID) or AAE (ceftriaxone + sulbactam + EDTA) BID empirically. Meropenem was administered at the dose of 1000 mg thrice a day and AAE was given at the dose of 1500-3000 mg twice a day deepening on the severity of infections. 1500 mg of AAE contains 1000 mg of ceftriaxone, 500 mg of Salbactam and 37 mg of EDTA and 3000 mg of AAE contains 2000 mg of ceftriaxone, 1000 mg of Salbactam and 74 mg of EDTA. Among these, 84 clinically cured patients, having culture positive infections and showing

77 sensitivity towards AAE were considered in the study, while the rest 24 (08 patients which were
78 resistance to meropenem or AAE, 12 Patients which were shifted to other antibiotics on discretion
79 of investigator before sensitivity results and 4 patients, who expired during the course of treatment)
80 patients were excluded from the study.

81 Case records were analyzed for parameters like age, sex, APACHE II score, co-morbadities,
82 duration of treatment, total leukocyte count, neutrophil count, liver function tests, renal function
83 test, culture sensitivity, serum electrolytes, radiological imaging, reason for the change of
84 antibiotics, dose, duration and route of administration of AAE or Meropenem and final
85 microbiological and clinical outcome.

86 The antibiotic therapy of AAE or meropenem was initially started empirically based on the clinical
87 presentation and treating physician's decision and was continued or shifted based on the *in-vitro*
88 microbiological susceptibility tests and clinical outcome. The antibiotic doses used in the therapy
89 were, 1 g/ 8 hrs, and 1.5 g or 3.0 g / 12 hours for meropenem and AAE respectively. For colistin
90 therapy, a loading dose of 9 MIU followed by BD doses of 4.5 MIU were used.

91 On retrospective evaluation, patients were divided into two main groups. i.e. Group A-Single
92 bacterial infection [64 (76.2 %) patients] and Group B-multiple bacterial infections [20 (23.8 %)
93 patients]. Out of 64 patients in group A, 14 (21.9%) patients (Group G-1) with infection caused by
94 meropenem resistant and AAE susceptible bacteria, AAE was administered empirically. A 50
95 (78.1%) patients (Group G-2) with meropenem and AAE susceptible bacterial infections,
96 meropenem was administered to 50% cases (group G2A) and to remaining 50% (group G2B) AAE
97 was administered. On day 03 of treatment, along with bacteriological evaluations, the progress of
98 the therapy (measured in terms of the improvement in the symptoms) was also recorded and the
99 patients showing improvement with respective empiric therapies were continued with the same
100 antibiotic. Patients which failed to respond to meropenem clinically (showing no improvement),
101 despite microbial sensitivity, were switched to AAE therapy while patients who failed to respond to

AAE mono-therapy were shifted to AAE and colistin combination therapy. Multi bacterial infections caused by pathogens showing sensitivity 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 pathogens isolated from the patients was done by Kirby–Bauer disk diffusion method as recommended by the Clinical Laboratory Standards Institute.^[15] meropenem disk (10 µg), piperacillin+tazobactam disk (100/10 µg), Amoxycillin+Clavulinic acid (20/10 µg), cefoperazone+sulbactam (75/30 µg) and ceftriaxone+sulbcatam+EDTA disk (55 µg) were procured from Himedia (Mumbai, India) and used in the study. Inoculum of 0.5 McFarland standards turbidity was prepared in a Mueller-Hinton broth from isolated colony of pathogens selected from 18–24 hour agar plates. Within 15 minutes, a sterile cotton swab was dipped into the inoculum suspension. The swab was rotated several times and pressed firmly against the inside wall of the tube above the fluid level and inoculated on the dried surface of a Mueller-Hinton agar (MHA) plate by streaking the swab over it. For even distribution of inoculum, the swab was streaked two more times at 60° C over the agar surface. After 3–5 minutes, antibiotic discs were applied and pressed down to ensure complete contact with agar surface. The discs were distributed evenly to ensure a minimum distance of 24 mm from center to center. The plates are then inverted and incubated for 16-18 hrs aerobically at 37° C within 15 minutes of disc application. Sensitivity of isolated organisms against antibiotics were reported as sensitive (S), Intermediate (I) or resistant (R) based on the breakpoints.

2.3 Clinical analysis of patients

Clinical signs and symptoms associated with infection (like abdominal infections, LRTI or UTI) were re-evaluated initially after 3 days of empirical antibiotic therapy and also at the end of therapy.

Sputum, BAL, ET secretions, urine, Blood, Pus or peritoneal fluids from the patients were tested for the diagnosis of causative pathogens . Clinical response of the 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 among 108 patients treated in the study period at IVY hospital were diagnosed with the bacterial culture positive infections, showing sensitivity towards AAE. The demographic and baseline characteristics of these 84 patients whose data were analyses in this study are given in Table 1. All the patients were having moderate to severe infections with mean APACHE II score of 17.84 ± 2.16 and 26 (30.95 %) out of 84 patients were having bacteremia at baseline. Among these 84 patients, 62 (73.8%) were from ICU population and 22 (26.2%) were from ward populations. Out of 84 evaluable patients, 52 patients were identified with co-morbidities, among which hypertension was observed in highest number of cases (26.1 %), followed by diabetes (19.0 %), Chronic obstructive pulmonary disease (11.9 %) and least observed co-disease was coronary artery disease (CAD) / ischemic heart disease (IHD) (4.7 %) (Table 1) . LRTI was the most predominant infection diagnosed contributing a share of 40.47 % among all patients. LRTI was followed by intra-abdominal and urinary tract infections both contributing equally (29.76 %) to the total diagnosed pool of infections (Table 1). Details of the culture specimens collected from the patients during the study were given in Table 2. 64 cases among 84 patients were diagnosed with single strain bacterial infections, where as rest 20 were diagnosed with multiple bacterial infections. Among the 64 single bacterial infections, 44 (68.75 %) infections were caused due to pathogens belonging to *Enterobacteriaceae* family, with *E coli* accounting for 68.18 % (30) and *Klebsiella sp.* for 31.81 % (14) within this family. The remaining 20 (5

152 *Acinetobacter* sp. + 15 *Pseudomonas* sp.) isolates were of *non-Enterobacteriaceae* family which
 153 caused infections in 31.25 % patients. Different combinations of either *E coli*, *Klebsiella* sp.,
 154 *Acinetobacter* sp., *Pseudomonas* sp and *Neisseria gonorrhoeae* were identified in mixed bacterial
 155 infections.

156 3.2 *In-vitro* microbial antibiotic susceptibility testing

157 The results of the *In-vitro* microbial antibiotic susceptibility testing carried out for isolated
 158 pathogens against meropenem and AAE showed different susceptibility patterns, yielding four
 159 groups as follows (Table 3)

160 **Table 3:** Isolated pathogen groups, separated based on the susceptibility pattern towards
 161 meropenem and AAE

Single bacterial infection (n=64, 76.2%)	
Group-1 (G1)	Patients with Meropenem Resistant and AAE susceptible single bacterial infection and in whom AAE was used empirically (n=14, 21.87 %)
Group-2 (G2)	Patients with Meropenem and AAE susceptible single bacterial infection (n=50, 78.13 %)
Group-2A (G2A)	Patients with Meropenem and AAE susceptible single bacterial infection and in whom Meropenem used empirically (n=25 , 39.06%)
Group-2B (G2B)	Patients with Meropenem and AAE susceptible single bacterial infection and in whom AAE used empirically (n=25 , 39.06%)

Multiple bacterial infection (n=20, 23.8%)

Group-3 (G3) Patients with Meropenem and AAE susceptible multiple bacterial infection and in whom AAE was used empirically (n=12, 60.0%)

Group-4 (G4) Patients with Meropenem and AAE intermediate multiple bacterial infection and in whom AAE was used empirically (n=8, 40.0%)

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 (Figure 1). Out of 64 bacteria isolated from patients with single strain bacterial infections, 50 (78.13 %) showed susceptibility towards carbapenem and the remaining 14 (21.87 %) were resistant to it. Where as all the 64 (100 %) isolates showed showed susceptibility towards AAE. However all the tested pathogens showed low non significant (< 10 %) susceptibilities towards the other tested antibiotics. The susceptibility test carried out for bacterial samples isolated from patients with multi bacterial infections, 12 samples showed sensitivity towards AAE and meropenem, where as the remaining 08 (40%) samples showed intermediate susceptibility towards both cabapenem and AAE. From *Enterobacteriaceae* family *E. coli*, and *K. pneumoniae* were isolated while *Neisseria gonorrhoea*, *S. Pneumoniae*, *Acinetobacter sp.* and *P. aeruginosa* were also amongst the most common non-enterobacterial pathogens isolated. The overall susceptibility of all the isolated pathogens were 83.01 % and 69.81 % for AAE and meropenem respectively (Table 4).

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. And for 2 Patients, which failed to respond to AAE clinically (showing no improvement clinically),

181 were switched to AAE and colistin combination therapy. The mean treatment duration among these
 182 12 patients cured with AAE therapy was (6.91 days $\pm$ 1.08 (SD)) (Table 5). 25 patients out of 50
 183 carbapenem and AAE susceptible patients were treated with meropenem. Among these patients, 18
 184 patients showed the clinical improvement (measured in terms of disease symptoms) after initial 3
 185 days of treatment and were continued with the carbapenem therapy. For the remaining 7 patients,
 186 the therapy was shifted to AAE. Among these, 4 patients showed clinical cure. The mean treatment
 187 duration for these 4 cured patients with AAE therapy was (5.75 days $\pm$ 0.5 (SD)). For the remaining
 188 3 patients, the clinical success was achieved after the administration of colistin with AAE (Table 6).
 189 Among 25 Similar patients (having infections with carbapenem and AAE susceptible bacterial
 190 cultures) but treated with AAE, 20 patients showed satisfactory clinical cure. The mean treatment
 191 duration for these 20 cured patients was (5.8 days $\pm$ 1.36 (SD)). And in 5 patients who did not show
 192 clinical improvement after initial 3 days of AAE therapy, colistin was added in treatment regime.
 193 The administration of colistin resulted clinical cure of all the patients (Table 7). Out of 20 patients
 194 with multiple bacterial infections, 12 patients having infection with AAE and meropenem sensitive
 195 strains, were continued with the ongoing empirical AAE treatment. Among these 12 patients, 09
 196 patients were cured and for remaining 03 patients, colistin was given along with the ongoing AAE
 197 therapy. The mean treatment duration for these 09 patients cured with AAE was (9.88 days $\pm$ 1.69
 198 (SD)) (Table 8). However, 08 patients with cultures showing intermediate resistance towards both
 199 AAE and carbapenem, clinical success was achieved with addition of colistin to ongoing AAE
 200 treatment regime after 03 days of treatment. The mean treatment duration for the AAE and colistin
 201 therapy was (9.87 days $\pm$ 2.64 (SD)) (Table 9).

202 None among the 84 patients had any serious side effect related to drug. Nothing significant was
 203 observed at the end of therapy when the liver function test, renal function test and serum
 204 electrolytes were evaluated keeping in view of disease pathology and comparison with baseline
 205 values. No untoward changes caused by the drug was observed in any lab parameters. All the

206 patients had a good clinical response and were stable and discharged.

207 **4. Discussion**

208 We present the retrospective study of 84 patients diagnosed with either of LRTI, UTI and intra-
 209 abdominal infections and treated with carbapenem or/and AAE. Carbapenems are a class of broad-
 210 spectrum antibiotics which possess stability against hydrolysis by ESBL and *AmpC* chromosomal
 211 β -lactamase enzymes and are often reserved to treat the most serious infections [16-18]. Thus,
 212 carbapenems have been effectively used to treat serious infections caused by ESBL producing
 213 bacteria. Carbapenems are the choice of drugs to treat infections like bacterial meningitis, skin, soft
 214 tissue, bone and joint infections, gastrointestinal infections, septicemia, febrile neutropenia,
 215 nosocomial pneumonia, cystic associated respiratory infections and urinary tract infections
 216 [16,19,20]. However in past few years, carbapenem resistance among gram negative bacteria has
 217 been reported increasingly throughout the world and India [21-26]. This carbapenem resistance is
 218 mainly attributed to the ability of the bacteria to produce MBL enzymes (carbapenamases). In
 219 India, the prevalence of MBLs range from 8% to 79% [27-30]. However, in the absence of
 220 carbapenem hydrolyzing MBLs, carbapenem resistance is usually multi-factorial. Increased
 221 production of *AmpC* chromosome-encoded cephalosporinase, reduced outer membrane porin *OprD*
 222 expression, over expression of efflux pumps and associated factors are known to contribute to
 223 carbapenem resistance [31-33].

224 In view of this increased resistance towards carbapenems, many researchers from Indian sub-
 225 continent have recommended the use of beta lactamase and beta lactamase inhibitor combinations
 226 (BL + BLI) in place of carbapenems [27,34]. However, these treatments with BL + BLI
 227 combinations do not fully solve the problem to kill both ESBL and MBL producers. Hence we
 228 have used an adjuvant antimicrobial FDC, a novel combination of
 229 Ceftriaxone+sulbactam+disodium edetate to treat the patients with infections caused by
 230 carbapenem resistant bacteria.

231 *In-vitro* microbial antibiotic susceptibility testing of the bacteria isolated from the 84 patients
 232 yielded 4 group of bacteria; G1 - with carbapenem resistant and AAE susceptible, G2 - both
 233 carbapenem and AAE susceptible G3 – multiple Pathogens showing susceptibility to both
 234 meropenem and AAE and G4 – multiple Pathogens showing intermediate sensitivity to AAE and
 235 meropenem. Out of 14 patients, 12 (85.7 %) patients from group G1, which were treated with AAE
 236 achieved clinical success. This advocates the consistency in *in-vitro* and *in-vivo* results for the AAE
 237 treatment and justifies the selection of AAE to treat infections caused by carbapenem resistant
 238 bacteria. Among the 25 patients in group G2A, to whom carbapenem treatment was given, 18 (72
 239 %) cases have achieved success. This highlights the significantly high percentage of either false *in-*
 240 *vitro* susceptibility results and/or failure of the drug to eradicate the bacterial infection *in-vivo*. The
 241 results of the present study, are in accordance with the previous study by Chytra et al., who
 242 reported similar clinical cure rates (74.3%) of critically ill patients by carbapenem (meropenem)
 243 [1]. This increased clinical failure rates may be attributed to the rise of carbapenem resistant
 244 bacteria, resulted from various resistance mechanism along with carbapenamases (MBL)
 245 production. One such resistance mechanism is over-expression of efflux pumps like like *MexAB-*
 246 *OprM* efflux system in *Pseudomonas sp.* (specific to meropenem resistance) [35], *AcrB* efflux
 247 pumps in *E coli* [36], *AcrAB* efflux pumps in *Klebsiella sp.*[37] and *AdeABC* type efflux pumps
 248 identified in *Acinetobacter sp.*[38] However among the remaining 7 patients from group two, 4
 249 patients (57.14 %) have achieved clinical success with AAE treatment, advocating the superiority
 250 of AAE over carbapenem. Similar trends were observed in group G2B 25 patients treated with
 251 AAE, with 80 % (20) patients achieving clinical success. The superior efficacy of AAE over
 252 meropenem may be attributed to the different ways through which AAE target various resistance
 253 mechanism in bacteria. The various mechanisms including, inhibition of conjugal spreading of
 254 resistant gene from one bacteria to another. AAE does this by chelating Mg^{2+} ions required for the
 255 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. The adjuvant present in AAE chelates the divalent ions (Zn^{2+}) required the activity of MBLs and thus deactivate the MBLs activity which in turn increase activity of 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, opening the new therapeutic option in these failure cases. And in 20 patients from the group G3 and group G4 (multi bacterial infections with strains showing either AAE and meropenem sensitive or intermediary resistance) clinical success was achieved with in 09 (45 %) patients with AAE treatment and in remaining 11 patients, AAE and colistin therapy was needed to achieve the clinical success. This antibiotic combination therapy opens up an efficient option to treat the mono drug resistant multi bacterial 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 to reach the site of action.

5. Conclusion

In conclusion, the present retrospective study generated a representative status of the carbapenem susceptibility among gram negative pathogens isolated from LRTI, UTI and intra-abdominal infections and its representative efficacy monitored in terms of clinical cure rates. The majors aspects emerged from the present study are, the rise of the carbapenem resistance incidences, rise of false susceptibility results for the carbapenems, rise in the carbapenem clinical failure rates in severe infections and efficacy of AAE at par with with meropenem thus AAE is a carbapenem alternative or sparing to tackle the moderate and severe infections caused by resistant gram negative bacteria. This study also sheds light on an alternative option to use AAE along with colistin to successfully treat the patients with infections caused by bacteria with intermediate resistance to

AAE and carbapenems. Use of broad spectrum antibiotic with optimal microbial efficacy, good penetration at site of infection can help in preventing antimicrobial resistance by sparing carbapenems. During the last two years the AAE has been used as a carbapenem sparing drug at our centre. The in-house susceptibility pattern of pathogens towards the carbapenems has significantly improved due to less exposure of carbapenem to pathogens. This is quite an encouraging sign and is highly recommendable to use AAE as a carbapenem sparing drug, to keep hold on the growing rate of carbapenem resistance.

Consent

Due to the retrospective study design, informed consent was not deemed necessary.

Ethical Approval

Not applicable

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411 **Legends to Figures**

412 **Figure 1:** Overview of the study design

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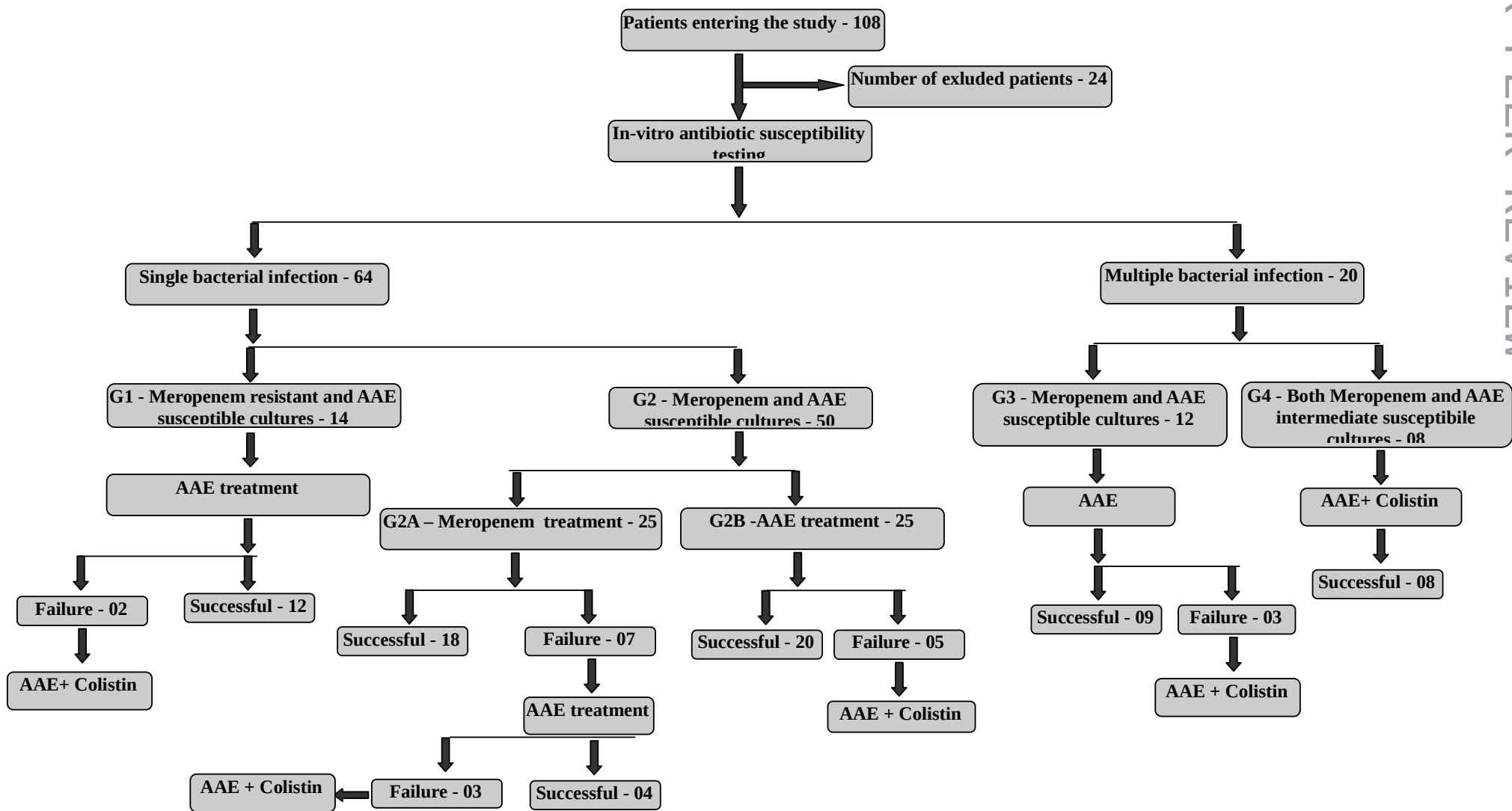


Figure 1

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425 **Table 1:** Demographics and other baseline characteristics of the patients treated during the study period
426

Characteristic	Value
Evaluable patients	84
Age, mean year SD	59.66 ± 17.16
No. male:female	48:36 (57.14 %: 42.85 %)
Mean Apache II score	17.84 ± 2.16
Bacteremia incidences	26 (30.95 %)
Type of infection (%)	
Intra -Abdominal infections	25 (29.76 %)
UTI	25 (29.76 %)
LRTI	34 (40.47 %)
Type of Co-morbidities (%)	
Hypertesion	22 (26.1%)
Diabities	16 (19.0)
Coronary artery disease (CAD) / Ischemic heart disease (IHD)	04 (4.7%)
Chronic obstructive pulmonary disease (COPD)	10 (11.9)

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Table 2 : Details of culture Specimens of the patients treated during the study period

Type of infection	Culture specimen	No of Patients(%)
Intra -Abdominal infections	Blood	14 (56%)
	Ascitic/Peritoneal fluid	11 (44%)
LRTI	Sputum	10 (29.4%)
	Endotracheal secretions	14 (41.1%)
	Broncho alveolar lavage	5 (14.7%)
	Blood	5 (14.7%)
UTI	Urine	18 (72.0%)
	Blood	7 (28.0%)

Table 4: In-vitro antibiotic susceptibility testing for bacteria isolated from single/multiple organism infections

S. No.	Diagnosis	Isolated pathoges	Number of individual isolates	Susceptibility/ Resistance %			
				AAE		Meropenem	
				S	I	S	I
1	Intra-abdominal infection	<i>E coli</i>	15	86.7	13.3	60	40
		<i>Klebsiella sp.</i>	6	83.4	16.6	83.33	16.77
		<i>Acinetobacter sp.</i>	2	100.0	0.0	100	0
		<i>Pseudomonas sp.</i>	8	75.0	25.0	62.5	37.5
		<i>N. Gonorrhoea</i>	1	0.0	100	0	100
2	LRTI	<i>E coli</i>	6	100.0	0.0	100	0
		<i>Klebsiella sp.</i>	12	91.7	8.3	75	25
		<i>Acinetobacter sp.</i>	4	100.0	0.0	25	75
		<i>Pseudomonas sp.</i>	15	80.0	20.0	60	40
		<i>S. Pneumoniae</i>	04	50.0	50.0	50	50
3	UTI	<i>E coli</i>	21	85.7	14.3	80.95	19.05
		<i>Klebsiella sp.</i>	4	75.0	25.0	75	25
		<i>Pseudomonas sp.</i>	3	100.0	0.0	100	0
		<i>N. Gonorrhoea</i>	4	75.0	25.0	75	25
		<i>Acinetobacter sp.</i>	1	0.0	100.0	0	100
Total			106				

S: Susceptibility, I: Intermediate resistance

Table 5: Summary of antibiotic therapy for the group G1 patients with cultures with resistance to meropenem and susceptible to AAE

S. No	Age	Diagnosis	Organism	AAE dose	Duration (days)	Clinical Response	Therapy shifted to AAE + Colistin	Duration (days)	Clinical Response
1	52	Intra abdominal infection	<i>E coli</i>	1.5 g BID	8	Cured	NA	NA	NA
2	53	Intra abdominal infection	<i>E coli</i>	1.5 g BID	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
3	64	Intra abdominal infection	<i>Pseudomonas sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
4	45	Intra abdominal infection	<i>E.coli</i>	1.5 g BID	7	Cured	NA	NA	NA
5	71	Intra abdominal infection	<i>E.coli</i>	1.5 g BID	6	Cured	NA	NA	NA
6	60	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
7	49	LRTI	<i>Acinetobacter sp.</i>	1.5 g BID	8	Cured	NA	NA	NA
8	70	LRTI	<i>Acinetobacter sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
9	64	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	8	Cured	NA	NA	NA
10	22	LRTI	<i>Klebsiella sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
11	21	LRTI	<i>Klebsiella sp.</i>	1.5 g BID	7	Cured	NA	NA	NA
12	12	LRTI	<i>Acinetobacter sp.</i>	1.5 g BID	9	Cured	NA	NA	NA
13	82	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	5	Cured
14	56	UTI	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA

Note: NA – Not applicable

Table 6: Summary of antibiotic therapy for the group G2A patients with cultures showing susceptibility to both AAE and meropenem

S. No	Age	Diagnosis	Organism	Meropenem dose	Duration (days)	Clinical Response	Therapy shifted to AAE/ AAE + Colistin	Duration (days)	Clinical Response
1	50	Intra abdominal infection	<i>E coli</i>	1 g TID	7	Cured	NA	NA	NA
2	47	Intra abdominal infection	<i>E coli</i>	1 g TID	6	Cured	NA	NA	NA
3	56	Intra abdominal infection	<i>Klebsiella sp.</i>	1 g TID	6	Cured	NA	NA	NA
4	90	Intra abdominal infection	<i>Pseudomonas sp.</i>	1 g TID	7	Cured	NA	NA	NA
5	57	Intra abdominal infection	<i>E coli</i>	1 g TID	7	Cured	NA	NA	NA
6	76	Intra abdominal infection	<i>Acinetobacter sp.</i>	1 g TID	3	Cured	NA	NA	NA
7	54	Intra abdominal infection	<i>E coli</i>	1 g TID	6	Cured	NA	NA	NA
8	68	Intra abdominal infection	<i>Pseudomonas sp.</i>	1 g TID	3	Cured	NA	NA	NA
9	70	LRTI	<i>Klebsiella sp.</i>	1 g TID	5	Cured	NA	NA	NA
10	71	LRTI	<i>Pseudomonas sp.</i>	1 g TID	6	Cured	NA	NA	NA
11	56	LRTI	<i>Klebsiella sp.</i>	1 g TID	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
12	29	LRTI	<i>Klebsiella sp.</i>	1 g TID	7	Cured	NA	NA	NA
13	27	LRTI	<i>E coli</i>	1 g TID	3	Failure	1.5 g BID	5	Cured
14	23	LRTI	<i>E coli</i>	1 g TID	8	Cured	NA	NA	NA
15	57	LRTI	<i>Klebsiella sp.</i>	1 g TID	3	Failure	3.0 g AAE +	10	Cured

							colistin (9 MIU loading and 4.5 MIU BID)		
16	62	LRTI	<i>E coli</i>	1 g TID	3	Failure	1.5 g BID	6	Cured
17	67	LRTI	<i>E coli</i>	1 g TID	7	Cured	NA	NA	NA
18	66	UTI	<i>Klebsiella sp.</i>	1 g TID	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	13	Cured
19	71	UTI	<i>E coli</i>	1 g TID	3	Failure	1.5 g BID	6	Cured
20	77	UTI	<i>Pseudomonas sp.</i>	1 g TID	6	Cured	NA	NA	NA
21	71	UTI	<i>E coli</i>	1 g TID	7	Cured	NA	NA	NA
22	91	UTI	<i>E coli</i>	1 g TID	3	Failure	1.5 g BID	6	Cured
23	71	UTI	<i>Pseudomonas sp.</i>	1 g TID	3	Cured	NA	NA	NA
24	55	UTI	<i>E.coli</i>	1 g TID	3	Cured	NA	NA	NA
25	22	UTI	<i>E coli</i>	1 g TID	6	Cured	NA	NA	NA

Note: NA – Not applicable

483 **Table 7:** Summary of antibiotic therapy for the group G2B patients with cultures showing susceptibility to both AAE and meropenem
484

S. No	Age	Diagnosis	Organism	AAE dose	Duration (days)	Clinical Response	Therapy shifted to AAE + Colistin	Duration (days)	Clinical Response
1	48	Intra abdominal infection	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA
2	79	Intra abdominal infection	<i>Pseudomonas sp.</i>	3 g BID	5	Cured	NA	NA	NA
3	69	Intra abdominal infection	<i>Klebsiella sp.</i>	3.0 g BID	2	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
4	55	Intra abdominal infection	<i>Acinetobacter sp.</i>	1.5 g BID	5	Cured	NA	NA	NA
5	54	Intra abdominal infection	<i>Klebsiella sp.</i>	3.0 g BID	7	Cured	NA	NA	NA
6	53	Intra abdominal infection	<i>E coli</i>	1.5 g BID	5	Cured	NA	NA	NA
7	54	Intra abdominal infection	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA
8	80	LRTI	<i>Klebsiella sp.</i>	1.5 g BID	1	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
9	63	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
10	71	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	10	Cured	NA	NA	NA
11	64	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
12	89	LRTI	<i>Klebsiella sp.</i>	3.0 g BID	2	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
13	35	LRTI	<i>Pseudomonas sp.</i>	1.5 g BID	6	Cured	NA	NA	NA
14	73	LRTI	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA

15	86	LRTI	<i>Klebsiella sp.</i>	1.5 g BID	1	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	10	Cured
16	81	LRTI	<i>Klebsiella sp.</i>	3 g BID	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	12	Cured
17	21	LRTI	<i>E coli</i>	1.5 g BID	4	Cured	NA	NA	NA
18	52	UTI	<i>E coli</i>	1.5 g BID	7	Cured	NA	NA	NA
19	68	UTI	<i>Pseudomonas sp.</i>	1.5 g BID	5	Cured	NA	NA	NA
20	57	UTI	<i>E coli</i>	1.5 g BID	5	Cured	NA	NA	NA
21	64	UTI	<i>E coli</i>	1.5 g BID	4	Cured	NA	NA	NA
22	69	UTI	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA
23	66	UTI	<i>E coli</i>	1.5 g BID	4	Cured	NA	NA	NA
24	53	UTI	<i>E coli</i>	1.5 g BID	6	Cured	NA	NA	NA
25	78	UTI	<i>E coli</i>	1.5 g BID	7	Cured	NA	NA	NA

Note: NA – Not applicable

501 **Table 8:** Summary of antibiotic therapy for the group G3 patients with multi-pathogen infection, showing meropenem and AAE susceptibility
502

S. No	Age	Diagnosis	Organism	AAE dose	Duration (days)	Clinical Response	Therapy shifted to AAE + Colistin	Duration (days)	Clinical Response
1	79	Intra abdominal infection	<i>Pseudomonas sp. + E coli</i>	3.0 g AAE	12	Cured	NA	NA	NA
2	52	Intra abdominal infection	<i>Klebsiella sp. + Pseudomonas sp.</i>	3.0 g AAE	3	Failure	NA	NA	NA
3	77	Intra abdominal infection	<i>Klebsiella sp. + E coli</i>	3.0 g AAE	8	Cured	NA	NA	NA
4	70	LRTI	<i>S. Pneumoniae + Pseudomonas sp.</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	8	cured
5	52	LRTI	<i>Acinetobacter sp. + Pseudomonas sp.</i>	3.0 g AAE	8	Cured	NA	NA	NA
6	75	LRTI	<i>Klebsiella sp. + Pseudomonas sp.</i>	3.0 g AAE	10	Cured	NA	NA	NA
7	45	LRTI	<i>S. Pneumoniae + Pseudomonas sp.</i>	3.0 g AAE	11	Cured	NA	NA	NA
8	58	UTI	<i>Neisseria gonorrhoea + E coli</i>	3.0 g AAE	12	Cured	NA	NA	NA
9	80	UTI	<i>Klebsiella sp. + E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	7	cured
10	55	UTI	<i>Neisseria gonorrhoea + E coli</i>	3.0 g AAE	9	Cured	NA	NA	NA
11	85	UTI	<i>Klebsiella sp. + E coli</i>	3.0 g AAE	8	Cured	NA	NA	NA
12	62	UTI	<i>Neisseria gonorrhoea + E coli</i>	3.0 g AAE	11	Cured	NA	NA	NA

503 Note: NA – Not applicable

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505 **Table 9:** Summary of antibiotic therapy for the group G4 patients with multi-pathogen infection, showing intermediate susceptibility to both

meropenem and AAE

S. No	Age	Diagnosis	Organism	AAE dose	Duration (days)	Clinical Response	Therapy shifted to AAE + Colistin	Duration (days)	Clinical Response
1	62	Intra abdominal infection	<i>Neisseria gonorrhoea</i> + <i>Pseudomonas sp.</i> + <i>E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
2	46	Intra abdominal infection	<i>Klebsiella sp.</i> + <i>Pseudomonas sp.</i> + <i>E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	9	Cured
3	21	LRTI	<i>S. Pneumoniae</i> + <i>Pseudomonas sp.</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	12	Cured
4	52	LRTI	<i>Klebsiella sp.</i> + <i>Pseudomonas sp.</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
5	67	LRTI	<i>S. Pneumoniae</i> + <i>Pseudomonas sp.</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
6	67	UTI	<i>Klebsiella sp.</i> + <i>E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	4	Cured
7	53	UTI	<i>Acinetobacter sp.</i> + <i>E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	4	Cured
8	56	UTI	<i>Neisseria gonorrhoea</i> + <i>E coli</i>	3.0 g AAE	3	Failure	3.0 g AAE + colistin (9 MIU loading and 4.5 MIU BID)	6	Cured

Note: NA – Not applicable