

Original Research Articles

A new Antibiotic Adjuvant Entity (Ceftriaxone + sulbactam + disodium edetate): a safer alternative to carbapenems for ICU infection management

4

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 carbapenem 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.

28

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)~~ *eliminate brackets + use commas*
 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⁾ *not superscript* 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~~ *a declining* antibiotic pipeline forces us to *would sound better*
 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.~~ *unnecessary sentence*

52 Recent effort to maximize antibiotic activity, ^{and} to overcome drug resistance has led to the search ^{for} ~~of~~
 53 an alternate ^{solution such} ~~perspective~~ called as antibiotic adjuvants. Antibiotic adjuvants are moieties, non-
 54 antibiotic in nature, which in combination with antibiotics, enhance the antimicrobial activity of the
 55 latter [14]. Fixed dose combination of Ceftriaxone + sulbactam + adjuvant disodium edetate is one
 56 such novel Antibiotic Adjuvant Entity (AAE) approved by the Drug Controller General of India
 57 (DCGI) and increasingly used in Indian hospitals. Various reports of the in-vitro susceptibility
 58 studies [14] hints ^{of} the possibility of this AAE to overcome the hurdles of both ESBL (sulbactam
 59 effect) as well as MBL (disodium edetate) producers clinically. If effective in-vivo clinical success

60 is achieved by this AAE, then it can be a potent alternative to treat infections caused by carbapenem
 61 resistant gram negative bacteria. Thus the main goal of this study was to retrospectively analyze the
 62 clinical and microbiological efficacy of this AAE in patients with moderate to severe ^{IAI} ~~intra~~
 63 ~~abdominal~~, LRTI and UTI infections.

64 2. Materials and methods

65 2.1 Patients and antibiotic therapy

66 Study was conducted at ^{200-bed} ~~200 bedded~~ tertiary care IVY hospital Mohali. We retrospectively reviewed
 67 the case reports of 108 patients suffering from different infections and who were treated at IVY
 68 hospital between January 2013 to November 2014. ~~For case of evaluation~~ The population was
 69 categorized into three groups based on the diagnosis and source of infections i.e. intra-abdominal
 70 infections, ^(IAI) urinary tract infections (UTI) and lower respiratory tract infections (LRTI).

71 The patients were administered with either Meropenem (TID) or AAE ~~(ceftriaxone + sulbactam +~~ ^{eliminate this "with"}
 72 ~~EDTA)~~ BID empirically. Meropenem was administered at the dose of 1000 mg thrice ^{daily} ~~a day~~ and
 73 AAE was given at the dose of 1500-3000 mg twice ^{daily depending} ~~a day~~ deepening on the severity of infections.
 74 1500 mg of AAE contains 1000 mg of ceftriaxone, 500 mg of Salbactam and 37 mg of EDTA and
 75 3000 mg of AAE contains 2000 mg of ceftriaxone, 1000 mg of Salbactam and 74 mg of EDTA.
 76 Among these, 84 clinically cured patients, having culture positive infections and showing

77 sensitivity ^{to} ~~towards~~ AAE were considered in the study, while the ^{remaining} ~~rest~~ 24 (98) patients which were
78 resistance to meropenem or AAE, 12 ^{lower case} ~~Patients~~ which were ^{changed} ~~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. ^{Put everything in parentheses after a colon & eliminate parentheses}
81 Case records were analyzed for ^{antimicrobial} ~~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 ^{with} ~~of~~ AAE or meropenem was initially started empirically based on the clinical
87 presentation and treating physician's decision and was continued or ^{modified} ~~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} ~~for meropenem~~ and ^{for} ~~AAE~~, respectively. For colistin
90 therapy, a loading dose of 9 MIU followed by BD doses of 4.5 MIU were used. ^{↳ BID ??}
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]. ^{to} ~~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, ^{In the} ~~AAE was administered empirically.~~ 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 ^{AAE was given to the remaining} ~~to remaining~~ 50% (group G2B), ~~AAE~~
97 ^{the third day} ~~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 ^{on the} ~~with the~~ same
100 antibiotic. Patients ^{who} ~~which~~ failed to respond to meropenem clinically (~~showing no improvement~~),
101 despite microbial sensitivity, ^{to meropenem} ~~were~~ switched to AAE therapy while patients who failed to respond to
^{eliminate coming}

Make sure to spell out if not previously abbreviated

127 Sputum, BAL, ET secretions, urine, ~~Blood, Pus~~ or peritoneal fluids from the patients were ~~tested for~~ ^{to} ~~cultured~~
128 ~~the diagnosis of~~ causative pathogens. Clinical response ~~of the~~ therapy evaluated at the end of the
129 treatment was recorded and classified as cured (complete remission of local and systemic signs and
130 symptoms), improved (improvement of local and systemic signs and symptoms but without
131 complete resolution) or failure (no improvement or deterioration of signs and symptoms).

132 3. Results

133 3.1 Patients and demographic characteristics

134 84 clinically cured cases ~~among~~ ^{of the} 108 patients treated in the study period at ~~IVV hospital~~ were
135 diagnosed with ~~the bacterial~~ culture-positive infections, ^{with bacteria sensitive to} ~~showing sensitivity towards~~ AAE. The
136 demographic and baseline characteristics of these 84 patients ~~whose data were analyses in this study~~
137 are given in Table 1. All the patients ~~were having~~ ^{had} moderate to severe infections with mean
138 APACHE II score of 17.84 ± 2.16 ^{and} 26 (30.95 %) ^{had} out of 84 patients ~~were having~~ bacteremia at
139 ~~baseline~~ ^{of} ~~Among~~ these 84 patients, 62 (73.8%) were from ICU population and 22 (26.2%) were
140 from ward populations. Out of 84 evaluable patients, 52 patients were identified with co-
141 morbidities, ^{including} ~~among which~~ hypertension was ~~observed in highest number of cases~~ (26.1 %),
142 ~~followed by~~ ^{and} diabetes (19.0 %), Chronic obstructive pulmonary disease (11.9 %) and ~~least observed~~
143 ~~co-disease was~~ coronary artery disease (CAD) / ischemic heart disease (IHD) (4.7 %) (Table 1).
144 LRTI was the ~~most~~ predominant infection diagnosed ~~contributing a share of~~ (40.47 %) ^(29.76%) among all
145 ~~patients~~ ^(29.76%) LRTI was followed by intra-abdominal ^(29.76%) and urinary tract infections both contributing
146 ~~equally (29.76 %) to the total diagnosed pool of infections~~ (Table 1). Details of the cultures
147 ~~specimens collected from the patients~~ during the study were given in Table 2. 64 cases ^{of} ~~among~~ 84
148 patients were diagnosed with ^{9 monomicrobial} ~~single strain~~ bacterial infections, ^{while} ~~where as~~ 20 were diagnosed
149 with ^{polymicrobial} ~~multiple bacterial~~ infections. ^{44 of monomicrobial} ~~Among the 64 single bacterial infections, 44 (68.75 %) infections~~
150 were caused ^{by} ~~due to~~ pathogens ^{of the} ~~belonging to~~ Enterobacteriaceae family, with *E coli* accounting for
151 ~~68.18 % (30) and Klebsiella sp. for 31.81 % (14) within this family. The remaining 20 (5~~
^{30 (68.18%) cases 14 (31.81%) cases of infection.}

102 AAE mono-therapy were ~~shifted to~~ ^{changed} AAE and colistin ~~combination therapy~~ ^{combination therapy with}. ~~Multi-bacterial~~ ^{In Polymicrobial}
 103 infections caused by pathogens ~~showing sensitivity~~ ^{Sensitive} to AAE and meropenem (Group G3) empirical
 104 treatment was continued and those showing intermediate susceptibility towards AAE and
 105 meropenem (Group G4), were treated with colistin along with the empiric AAE once the
 106 susceptibility report was received.

107 2.2 In-vitro microbial antibiotic susceptibility testing

108 Antimicrobial susceptibility testing of the pathogens isolated from the patients was done by Kirby-
 109 Bauer disk diffusion method as recommended by the Clinical Laboratory Standards Institute.^[15]
 110 meropenem disk (10 µg), piperacillin+tazobactam disk (100/10 µg), Amoxycillin+Clavulanic acid
 111 (20/10 µg), cefoperazone+sulbactam (75/30 µg) and ceftriaxone+sulbactam+EDTA disk (55 µg)
 112 were procured from Himedia (Mumbai, India) and used in the study. Inoculum of 0.5 McFarland
 113 standards turbidity was prepared in a Mueller-Hinton broth from isolated colony of pathogens
 114 selected from 18–24 hour agar plates. Within 15 minutes, a sterile cotton swab was dipped into the
 115 inoculum suspension. The swab was rotated several times and pressed firmly against the inside wall
 116 of the tube above the fluid level and inoculated on the dried surface of a Mueller-Hinton agar
 117 (MHA) plate by streaking the swab over it. For even distribution of inoculum, the swab was
 118 streaked two more times at 60° C over the agar surface. After 3–5 minutes, antibiotic discs were
 119 applied and pressed down to ensure complete contact with agar surface. The discs were distributed
 120 evenly to ensure a minimum distance of 24 mm from center to center. The plates are then inverted
 121 and incubated for 16-18 hrs aerobically at 37° C within 15 minutes of disc application. Sensitivity
 122 of isolated organisms against antibiotics were reported as sensitive (S), Intermediate (I) or resistant
 123 (R) based on the breakpoints.

This is excellent. If editor needs to save publication space it could be reduced to "standard CLSI techniques"

124 2.3 Clinical analysis of patients

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

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~~ *classified by* susceptibility pattern towards
 161 meropenem and AAE

This Table needs to be simplified to make more readable.
 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 ^{for} ~~among~~ these
182 12 patients ^{who were} cured with AAE therapy was $6.91 \text{ days} \pm 1.08 \text{ (SD)}$ (Table 5). 25 ~~patients out~~ of 50 ^{patients}
183 ^{with} carbapenem and AAE susceptible ^{organisms} ~~patients~~ were treated with meropenem. ^{of} ~~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 ^{on} ~~with the~~ carbapenem therapy. For the remaining 7 patients,
186 ^{treatment changed} ~~the therapy was shifted~~ to AAE. ^{of} ~~Among~~ these, 4 patients showed clinical cure. The mean treatment
187 duration for these 4 cured patients with AAE therapy was $5.75 \text{ days} \pm 0.5 \text{ (SD)}$. 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 $5.8 \text{ days} \pm 1.36 \text{ (SD)}$. ^{I the} ~~And in~~ 5 patients who did not show
192 clinical improvement after initial 3 days of AAE therapy, colistin was added ^{to the} ~~in~~ treatment regimen.
193 The administration of colistin resulted ⁱⁿ clinical cure of all the patients (Table 7). ~~Out of~~ 20 patients
194 ^{polymicrobial infection} ~~with multiple bacterial infections~~, 12 patients ^{with} ~~having~~ infection ^{due to} ~~with~~ AAE and meropenem sensitive
195 strains, were continued ^{on} ~~with the ongoing~~ empirical AAE treatment. ^{of} ~~Among~~ these 12 patients, ^{nine} ~~of~~
196 ~~patients~~ were cured ^{In the} ~~and for remaining~~ 3 patients, colistin was ^{added to} ~~given along with~~ the ongoing AAE
197 therapy. The mean treatment duration for these ⁹ ~~09~~ patients cured with AAE was $9.88 \text{ days} \pm 1.69$
198 (SD) (Table 8). However, ⁸ ~~08~~ patients with cultures showing intermediate resistance towards both
199 AAE and carbapenem, clinical success was achieved with addition of ^{the} ~~colistin~~ to ongoing AAE
200 treatment ^{regimen} ~~regime~~ after ³ ~~03~~ days of treatment. The mean treatment duration for the AAE and colistin
201 therapy was $9.87 \text{ days} \pm 2.64 \text{ (SD)}$ (Table 9).

202 None ^{of} ~~among~~ the 84 patients had any serious side effect ^{therapy-related} ~~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~~

^{in lab parameters} ~~therapy-related~~ ^{were}
9 No untoward therapy-related changes in lab parameters were observed

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,~~ ^{The}
 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~~ ^{unnecessary sentence}
 216 [16,19,20]. However in past few years, carbapenem resistance among gram negative bacteria has
 217 been reported increasingly throughout the world ^{including India} and India [21-26]. This carbapenem resistance is
 218 ^{primarily} ~~mainly~~ attributed to the ^{production of} ~~ability of the bacteria to produce~~ MBL enzymes (carbapenemases). In
 219 India, the prevalence of MBLs range from 8% to 79% [27-30]. ~~However,~~ ^{often} ~~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 ^{the} 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, ^{treatment} ~~these treatments~~ with BL + BLI
 227 combinations ^{may not effectively eradicate} ~~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 groups 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. ^{12 of 14 group G1} Out of 14 patients, 12 (85.7%) patients from group G1, which were treated with AAE
 236 achieved clinical success. This ^{establishes correlation of} ~~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. ^{of group G2A} Among the 25 patients in group G2A, ^{receiving} to whom carbapenem treatment was given, 18 (72
 239 %) ^{Eliminate this sentence} ~~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 ^{The} 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 ^{using} by carbapenem (meropenem) ^{therapy}
 243 [1]. ^{These} This increased clinical failure rates may be attributed to the rise of carbapenem resistant
 244 bacteria, ^{resulting} ~~resulted~~ from various resistance mechanisms ^{together} 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] ^{of} However among the remaining 7 patients from group two, 4
 249 patients (57.14 %) ^{suggesting} ~~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 20 of} ~~with 80 % (20) patients~~ achieving clinical success. The superior efficacy of AAE over
 252 meropenem may be attributed to the different ways ⁱⁿ through which AAE target various resistance
 253 mechanisms in bacteria. ^{The} ~~The various~~ mechanisms ^{include} 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

256 the AAE down-regulates the expression of *MexAB-OprM* and *AcrAB-tolC* efflux pumps [40].
 257 Sulbactam prevents inactivation of beta-lactam antibiotics by binding to the beta- lactamases. ~~The~~
 258 ~~EDTA the adjuvant in AAE,~~ ~~adjuvant present in AAE~~ chelates the divalent ions (Zn^{2+}) required the activity of MBLs and thus
 259 deactivates the MBLs activity which in turn increases activity of β -lactam towards microorganisms
 260 [41]. Further, AAE is believed to disorganize the EPS and make the cell wall more porous, thus
 261 enhancing its entry into the bacterial cells . It has also been found to inhibit curli formation and
 262 bacterial adhesion [42]. The remaining patients were successfully treated when colistin was
 263 administered with AAE, ~~opening the~~ ^{presenting us with a} new therapeutic option in ~~these failure cases~~ ^{the patients who failed} ~~And in 20~~ ^{AAE treatment}
 264 patients from the group G3 and group G4 (~~multi-bacterial infections with strains showing either~~
 265 ~~AAE and meropenem sensitive or intermediary resistance~~) clinical success was achieved with in 09
 266 (45 %) patients with AAE treatment, ~~and in~~ ^{the} remaining 11 patients, AAE and colistin therapy was
 267 ~~needed to achieve the~~ ^{required} clinical success. This antibiotic combination therapy ~~opens up~~ ^{provides us with} an efficient
 268 option to treat the ~~mono drug~~ ^{single drug-} resistant ~~multi-bacterial~~ ^{polymicrobial} infections. The efficacy of this combination
 269 might be due to the proven effect of AAE as an efflux pump inhibitor [40] which may be helping
 270 colistin ~~to reach~~ ^{its} the site of action.

271 5. Conclusion

272 In conclusion, the present retrospective study generated a representative status of the carbapenem
 273 susceptibility among gram negative pathogens isolated from LRTI, UTI and intra-abdominal
 274 infections and its representative efficacy ~~monitored in terms of~~ clinical cure rates. The ~~major~~
 275 ~~aspects emerged from the present study are~~ ^{Results of the present study suggest a} the rise of the carbapenem resistance, ~~incidences, rise of~~
 276 ~~false susceptibility results for the carbapenems,~~ ^{not proven} ~~rise in the carbapenem clinical failure rates in~~ ^{an increase} the incidence of
 277 severe infections and efficacy of AAE at par with with meropenem ~~thus AAE is a carbapenem~~ ^{providing us with}
 278 alternative or ~~sparing to tackle the~~ ^{in the treatment of} moderate and severe infections caused by resistant gram negative
 279 bacteria. This study also sheds light on ~~an alternative option to use AAE along~~ ^{provides us with an alternative option} with colistin to
 280 successfully treat ~~the~~ patients with infections caused by ~~bacteria~~ ^{organisms} with intermediate resistance to

Eliminate this sentence

Not really proven by paper results.

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

possibly
decreased

such

result because of this

we recommend the

288 Consent

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

290 Ethical Approval

291 Not applicable

292

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411 **Legends to Figures**

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

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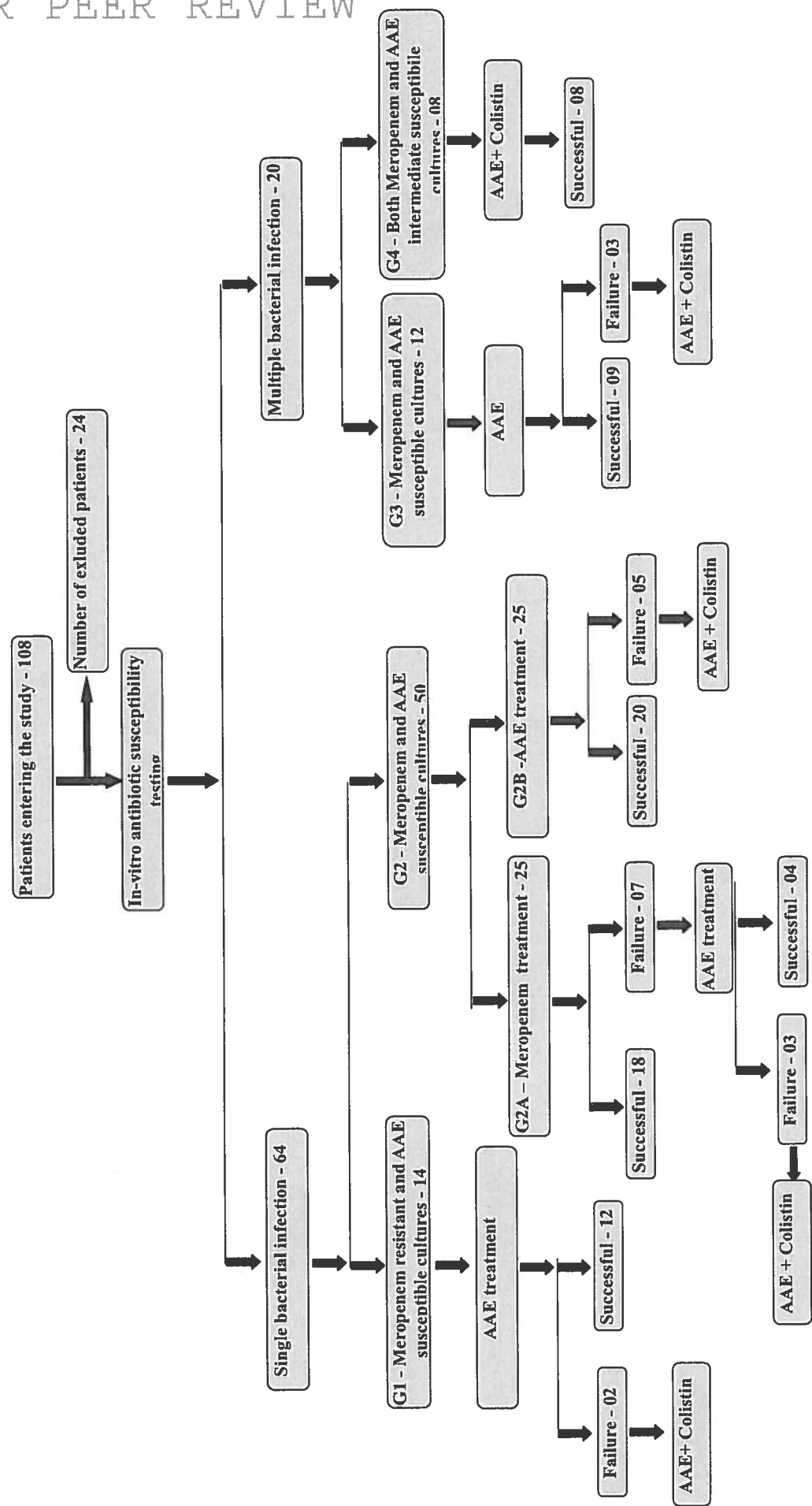


Figure 1

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

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)

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 pathogens	Number of individual isolates	Susceptibility/ Resistance %					
				AAE			Meropenem		
				S	I	S	S	I	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

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

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

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

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

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

Note: NA – Not applicable

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

meropenem and AAE

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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

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