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Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: a new way to spare carbapenems

Prashant Bhatia

Correspondence: prashantb_34@rediffmail.com

Department of Respiratory Medicine, Asian Institute of Medical Sciences, Faridabad, Haryana, India.

Abstract

Background: Increasing prevalence of carbapenem resistance in Gram negative bacteria due to excessive and indiscriminate use of carbapenems has forced the medical fraternity to find out ways to spare carbapenems. This retrospective study was aimed to explore a new fixed dose combination (FDC) of ceftriaxone+sulbactam with adjuvant disodium edetate as a carbapenem sparing drug in the management of moderate to severe bacterial infections of lower respiratory tract infections (LRTIs), urinary tract infections (UTIs) and intra-abdominal infections (IAIs).

Methods: A retrospective analysis involves those patients in whom FDC or meropenem was used empirically for the management of these infections caused by multidrug resistant pathogens.

Results: The average age of evaluated patients was 58.17±13.98 years. Out of 107 patients, 95 patients selected for the evaluations in which LRTIs, UTIs and IAIs were diagnosed in 43 (45.26%), 32 (33.68%) and 20 (21.05%) patients, respectively. The most common pathogen was *Escherichia coli* (38.94%), followed by *Klebsiella species* (26.31%), *Pseudomonas species* (18.94%) and *Acinetobacter species* (15.78%). According to the susceptibility results, FDC appeared as the most active antibacterial agent against *E. coli* (94.54%) followed by *Acinetobacter species* (93.33%), *Pseudomonas species* (88.88%) and *Klebsiella species* (84%). On the other hand, meropenem susceptibility to *E. coli* was 86.47% followed by *Acinetobacter species* (78.57%), *Pseudomonas species* (66.66%) and *Klebsiella species* (64%). Further our results revealed that FDC has >75% clinical success compared to meropenem (~61% clinical success).

Conclusion: These results depict non-inferiority of new FDC in the treatment of moderate to severe Gram negative bacterial infections caused by carbapenem resistant organisms and therefore, it should be considered as an alternative to carbapenem for treating LRTIs, UTIs and IAIs.

Keywords: Ceftriaxone/sulbactam-EDTA, lower respiratory tract infections, urinary tract infections, retrospective study

Introduction

Hospital acquired or nosocomial infections (HAIs) are infections occurring during a stay in hospital that are not present at the time of hospital admission. Lower respiratory tract infections (LRTIs), urinary tract infections (UTIs) and intra-abdominal infections (IAIs) are amongst the most prevalent HAIs [26,36]. LTRIs are thought to be leading cause of death all over the world (WHO, 2008). UTIs are the most common infections among the women, particularly under 50 years of age [27]. IAIs, especially complicated IAIs, represent an important cause of morbidity and are frequently associated with poor prognosis [35]. A wide variety of bacterial pathogens are accounting for such infections including *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter spp.*, and coagulase-negative *Staphylococci* [21,27]. Empiric antibiotic therapy is commonly used for the treatment of these infections and is usually presumptive and instituted before knowledge of the etiology of specific disease. Among various classes of drugs, β-lactams are one of the most frequently prescribed empirical antimicrobial drugs for the treatment of such infections [24]. However, in recent years, rise in resistance to β-lactam drugs has been noticed because of the extended spectrum

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β-lactamases (ESBLs) enzymes which hydrolyse most of the β-lactam antibiotics [10,22,23].

To cater the antibiotic resistance due to extended spectrum beta-lactamases (ESBLs), carbapenem drugs have been introduced in clinical settings. Although, carbapenem drugs play a vital role in the management of the infections caused by ESBLs producing organisms due to their broad spectrum activity and stability to hydrolysis against ESBLs [31], carbapenem resistance among the members of the *Enterobacteriaceae, Pseudomonas* and *Acinetobacter* has been reported globally [11,15,22,30]. The common mechanisms of carbapenem resistance are carbapenem hydrolyzing enzymes, changes in outer membrane proteins, over expression of efflux pumps [32]. Carbapenem resistant organisms are associated with high mortality and morbidity rates and have the potential to spread widely [37]. Increasing use of carbapenem drugs has also a direct alliance with carbapenem resistant Gram negative bacteria [18]. Until recently, most of the older antibiotics have become less useful due to the spread of such carbapenem resistant bacteria. As a result of the increasing resistance towards antibiotics over the past few years, it is no wonder that we are now facing the prospect of losing the battle against many bacterial diseases. Although the new antibiotics have to come along to take their place, the drug development pipeline for new antibiotics has been drying out. The drying antibiotic pipeline particularly against Gram negative bacteria has forced us to look into opportunities for improving usage of the existing antimicrobial agents.

One recently introduced approach to improve the existing antimicrobial agents is the use of antibiotic adjuvant therapy, which potentiates the activity of antibiotics. Adjuvant therapies include antibiotic combinations, synergy between antibiotics and non-antibiotics, inhibition of resistance by altering the physiology of antibiotic-insensitive cells, such as those in biofilms.

Introduction of a novel AAE (antibiotic adjuvant entity) with use of EDTA as adjuvant for chelation and catalytic action to existing antibiotics has been seen as a ray of hope. A new FDC (ceftriaxone, sulbactam with adjuvant EDTA) a novel antibiotic adjuvant entity (AAE) has been reported to have proven efficacy in a wide range of infections [7,8].

This retrospective observational study was aimed to explore a new Fixed Dose Combination (FDC) of Ceftriaxone+Sulbactam with adjuvant Disodium edetate as a carbapenem sparing drug in the management of moderate to severe bacterial infections of LRTIs, UTIs and IAIs.

Methods

Study design

This retrospective study was designed to evaluate the efficacy of new FDC in comparison to meropenem in the treatment of the patients who are diagnosed with moderate to severe Gram negative hospital acquired bacterial infections. It was conducted at Asian institute of medical sciences, Faridabad for a period of 18 months between June 2013 to December 2014. All patients admitted to the hospital for more than 48 hours with single pathogen infection and showing sensitivity towards new FDC or Meropenem were considered eligible for the study.

Hospital case sheet files of all the patients were reviewed to collect the necessary data like clinical signs and symptoms at the time of admission of patients and during the course of treatment and finally at the end of therapy. All the necessary lab investigations like sputum, bronchoalveolar lavage (BAL), endotracheal (ET) secretions, urine and blood culture and sensitivity reports, hematology, biochemistry and other relevant investigations carried out at baseline and end of treatment were evaluated from all the enrolled patients.

Bacterial identification

Identification of bacteria was carried out according to the methods described by Cheesbrough (2000).

Demographic analysis and antibiotic therapy

The detailed demographic and baseline characteristics of all patients including number of evaluable patients, age, types of infections who were analyzed in this study are given in **Table 1**. The patients were assigned to receive either meropenem (1.0 g, every 8 h) or new Elores, (ceftriaxone+sulbactam with adjuvant EDTA, 1.5 g or 3.0 g, every 12 h) through intravenous administration. For those patients who were more severe or failed to respond to FDC, colistin with a loading dose of 9 MIU followed by BD doses of 4.5 MIU were used along with previous antibiotic.

The antibiotic therapy of both of the drugs (FDC or meropenem) was initially started empirically based on the clinical symptoms and treating physicians decision and was continued or shifted to other therapy based on the *in vitro* microbiological susceptibility tests and clinical outcomes. Based on the *in vitro* antibiotic susceptibility, all the patients were divided into 3 groups for ease of evaluations:

Group-I (G1): Patients with meropenem intermediate and FDC susceptible culture in whom FDC was used (n=20, 21.05%).

Group-2 (G2): Patients with meropenem and FDC susceptible culture (n=65, 68.42%).

Table 1. Demographics characteristics of the patients treated during the study period.

Characteristic	Value
Evaluable patients	95
Age, mean year SD	58.17±13.98
Type of infection (%)	
UTI	32 (33.68%)
LRTI	43 (45.26%)
IAIs	20 (21.05%)
Number of Infections with *Enterobacteriaceae* family pathogens	62 (65.26%)
Number of Infections with non-*Enterobacteriaceae* family pathogens	33 (34.73%)

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Group-2A (G2A): Patients with meropenem and FDC susceptible culture in whom Meropenem used empirically (n=31, 32.63%).
Group-2B (G2B): Patients with meropenem and FDC susceptible culture in whom FDC used empirically (n=34, 35.78%).
Group-3 (G3): Patients with meropenem and FDC intermediate culture in whom FDC was used empirically along with colistin (n=10, 10.52%).

In-vitro antibiotic susceptibility testing

All isolates, recovered from all cultures were subjected to susceptibility testing for FDC, meropenem and colistin using the disk diffusion method according to the recommendations of CLSI (2013). The discs of meropenem (10 µg), FDC (45 µg) and colistin (10 µg) were obtained from Himedia (Mumbai, India). The zones of inhibition surrounding the various antibiotic discs were measured and compared with CLSI. Sensitivity of isolated organisms against antibiotics were reported as sensitive (S) and intermediate (I) based on the breakpoints.

Clinical evaluation of patients

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

Results

Study design and demographic analysis

A total of 107 patients data were evaluated retrospectively in this study. Variables of each patient such as age, causative agents, dosage and regime of antibiotic therapy were recorded. Out of these 107 patients, 95 patients with single bacterial infection were treated either FDC or meropenem. Twelve patients who were either culture negative or treatment failure or expired during course of study were excluded from the study. The average age of patients was 58.17±13.98 years.

In vitro antibiotic susceptibility

On evaluation of culture and sensitivity data, it was observed that clinical samples of the patients were cultured on an appropriate medium, and significant growth was found in 95 samples (88.78%) which yielded clinically significant pathogen that could be implied as a causative agent. Among bacterial infections, the most common pathogen that was isolated was *E. coli* which was isolated from 37 patients (38.94%), followed by *Klebsiella spp*. (n=25 patients, 26.31%), *Pseudomonas spp*. (n=18 patients, 18.94%) and *Acinetobacter spp*. (15 patients, 15.78%). Overall, 62 (65.26%) pathogens caused infections belonging to the *Enterobacteriaceae* family while 33 (34.73%) pathogens belonging to non-*Enterobacteriaceae* family.

The results of *in vitro* antimicrobial susceptibility test of FDC and meropenem are presented in **Table 2**. All the pathogens showed different susceptibility patterns towards FDC and meropenem. According to the susceptibility results, FDC appeared as the most active antibacterial agents against *E. coli* (94.54%) followed by *Acinetobacter spp*. (93.33%), *Pseudomonas spp*. (88.88%) and *Klebsiella spp*. (84%). On the other hand, high rates of susceptibility to meropenem were demonstrated by *E. coli* (86.47%) followed by Acinetobacter spp. (78.57%), *Pseudomonas spp*. (66.66%) and *Klebsiella spp*. (64%). Overall, out of 95 pathogens, majority of pathogens (n=85, 89.47%) were susceptible to FDC and the remaining 10 pathogens (10.52%) showed intermediate response to it.

Antibiotics treatment and their efficacy evaluation

On day 3 of treatment, progress of the therapy was measured in terms of improvement in the clinical signs and symptoms and microbiological results. Patient with susceptible pathogens with clinical improvement were continued on respective empirical therapies. Patients who were not showing response towards FDC, colistin was given as an add on therapy.

In G1, out of 20 patients which received FDC, 15 patients (75%) were clinically cured with complete bacteriological eradication within 7-8 days whereas 5 patients who failed to respond to FDC on day 3 were shifted to FDC+colistin combination therapy and all these patients got cured in additional 8 days therapy making a total of 11 days. The duration of antibiotic treatment in these 15 patients treated with FDC was 7.2±1.01 days (**Table 3**). In G2, among 65 patients whose pathogens were susceptible to both FDC and meropenem, 31 patients received meropenem (G2A) and 34 received FDC (G2B). The clinical assessment of meropenem receiving group (G2A) showed cure in 19 patients (61.29%) while 12 patients (38.70%) did not show any clinical improvement therefore colistin was added to ongoing therapy. On day 3,

Table 2. *In-vitro* antibiotic susceptibility testing for bacteria isolated from single organism infections.

Isolated pathogens	Number of individual isolates	Susceptibility %			
		FDC of Ceftriaxone+ Sulbactam+Disodium edetate		Meropenem	
		S	I	S	I
E. coli	37	94.54	5.4	86.47	23.53
Klebsiella sp.	25	84	16	64	36
Pseudomonas sp.	18	88.88	11.11	66.66	33.34
Acinetobacter sp.	15	93.33	6.66	78.57	21.43
Total	95	--	--	--	--

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Table 3. Summary of antibiotic therapy for the group G1 patients with cultures with intermediate resistance to meropenem and susceptible to FDC.

S. No	Age	Organism	FDC dose	Duration (days)	Clinical response	Colistin add on	Duration (days)	Clinical response
1	46	*E. coli*	1.5 g BID	6	Cured	NA	NA	NA
2	55	*E. coli*	3.0 g BID	7	Cured	NA	NA	NA
3	71	*Klebsiella sp.*	3.0 g BID	8	Cured	NA	NA	NA
4	68	*Klebsiella sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
5	49	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
6	71	*Pseudomonas sp.*	3.0 g BID	7	Cured	NA	NA	NA
7	63	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
8	52	*Pseudomonas sp.*	3.0 g BID	8	Cured	NA	NA	NA
9	54	*Pseudomonas sp.*	3.0 g BID	8	Cured	NA	NA	NA
10	59	*Klebsiella sp.*	3.0 g BID	9	Cured	NA	NA	NA
11	62	*E. coli*	1.5 g BID	5	Cured	NA	NA	NA
12	81	*Klebsiella sp.*	1.5 g BID	8	Cured	NA	NA	NA
13	72	*Pseudomonas sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
14	66	*Acinetobacter sp.*	3.0 g BID	7	Cured	NA	NA	NA
15	50	*E. coli*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
16	41	*Klebsiella sp.*	3.0 g BID	8	Cured	NA	NA	NA
17	76	*Pseudomonas sp.*	1.5 g BID	7	Cured	NA	NA	NA
18	39	*E. coli*	3.0 g BID	6	Cured	NA	NA	NA
19	54	*Acinetobacter sp.*	1.5 g BID	2	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
20	70	*E. coli*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured

Note: NA: Not applicable

of these 12 patients, 7 patients (58.33%) were cured whereas 5 (41.66%) patients failed to respond and were shifted to combination therapy of FDC+colistin and all the patients achieved clinical success. The average duration of treatment was 8.58±0.96 days (**Table 4**). For 34 patients who received FDC, 26 patients (76.47%) showed satisfactory clinical cure while in 8 patients (23.52%) who did not show clinical response at 3 day, colistin was added to the treatment regime that resulted in clinical cure of all patients after additional 7 days. The mean treatment for these 26 cured patients was 8.58±0.9 days. The average treatment duration was 7.46±1.24 days for patients in the FDC treated group (**Table 5**).

Among those patients who did not respond to either meropenem or FDC, colistin was added to ongoing therapy and complete clinical success was observed treatment duration 8.67±0.71 days (**Table 6** and **Figure 1**).

Discussion

Carbapenems are β-lactam antimicrobial agents that are relatively resistant to hydrolysis by most β-lactamases including Amp-C and have been considered as the last resort drugs all over the world for the management of serious infections [**1**,**39**]. However, increasing carbapenem resistance among Gram negative bacteria has been documented greatly in recent years [**16**,**17**,**22**]. Amongst various mechanism of carbapenem resistance, acquired metallo-β-lactamases (MBL) have recently emerged as one of the most worrisome resistance mechanisms owing to their capacity to hydrolyze all β-lactams, including carbapenems [**13**].

To combat such increasing carbapenem resistance, novel beta-lactam and beta lactamase inhibitor combination (BL+BLI) has received much attention as a carbapenem alternative drug in recent past [**9**,**12**,**15**,**20**,**33**]. However, only BL+BLI combinations did not exhibit significant activity against some ESBLs and majority of MBL producing Gram negative organisms. Hence a novel antibiotic combination of ceftriaxone+sulbactam with adjuvant disodium edetate (proven for efficacy and safety to treat the patients with infections caused by such organisms has been used in current investigations.

In the present study, 95 culture positive patients in ICU with

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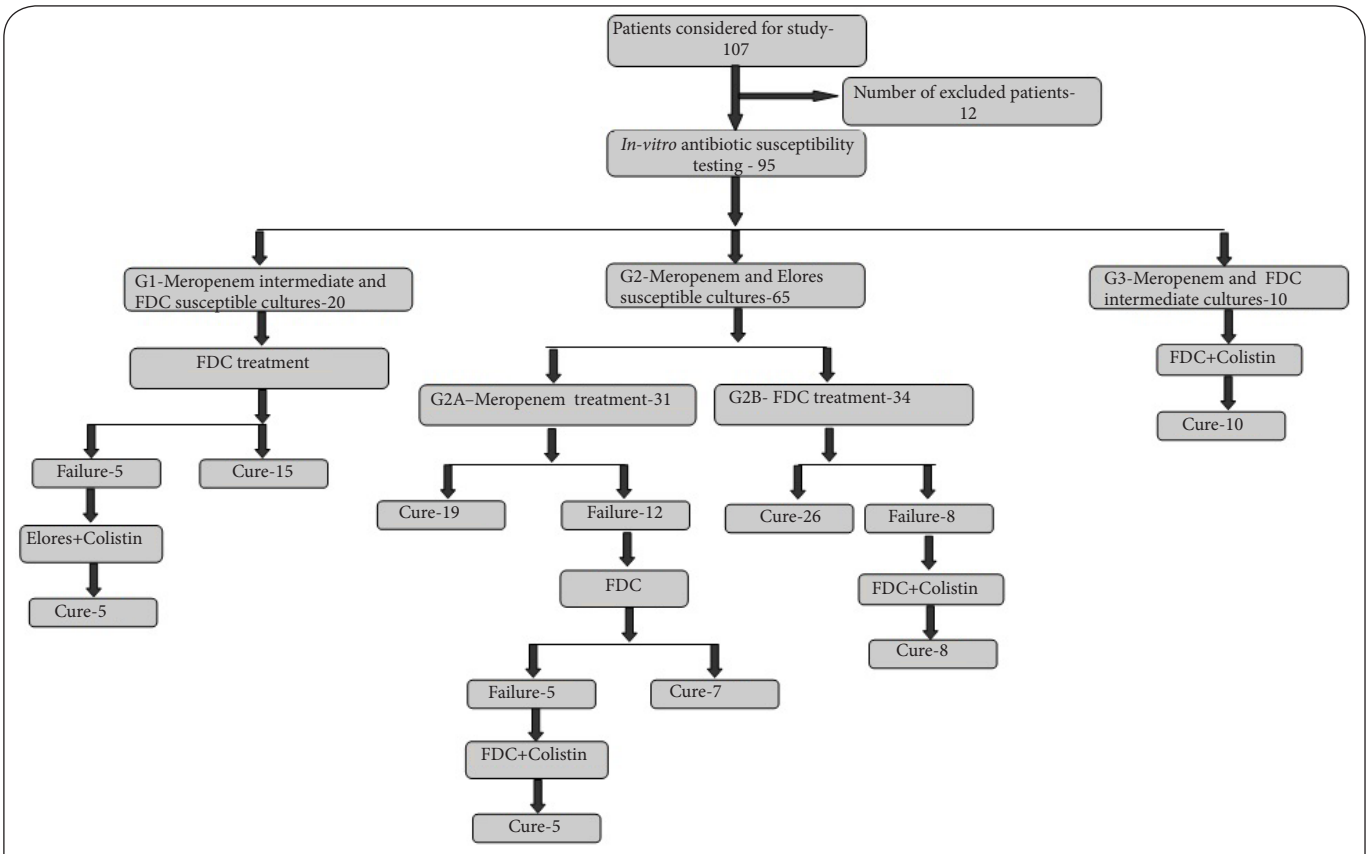

Figure 1. Overview of the study design.

moderate to severe infections treated with this new FDC or meropenem were retrospectively analyzed. The general distribution pattern of nosocomial infections that emerged in our study showed LRTIs (45.26%) to be the most common, followed by UTIs (33.68%) and IAIs (21.05%). This is in agreement with the study performed by earlier researcher [14]. The most frequently isolated pathogen was *E. coli* (38.94%), followed by *Klebsiella spp*. (26.31%), *Pseudomonas spp*. (18.94%) and *Acinetobacter spp*. (15.78%). This data is in line with many previous studies where *E. coli*, *Klebsiella spp*., *Pseudomonas spp*., and *Acinetobacter spp*. were reported to be causative agents of LRTIs. UTIs and IAIs [19,29].

In the present study, *in vitro* antimicrobial susceptibility results revealed that 84% to 91% of members of *Enterobacteriaceae* family and 86 to 94% of non-*Enterobacteriaceae* family members were sensitive to new FDC. Consistent with these results, earlier reports also demonstrated enhanced activity of this new FDC against members of *Enterobacteriaceae* and non-*Enterobacteriaceae* [4,34]. On other hands, 64% to 86% isolates of *Enterobacteriaceae* family whereas and 66% to 78% members of non-*Enterobacteriaceae* were susceptible to Meropenem, which is in accordance with previous observations [4,34].

Further, in FDC treated patients an overall success rate was >75% against ~61% in meropenem treated. In G1 15/20 patients and in G2B 26/34 (75.9%) who were susceptible to FDC and were administered with FDC achieved clinical and microbiological success suggesting the consistency in *in vitro* and *in vivo* results. On the other hand, 5/20 in G1 and 8/34 in G2B (24%) pathogens who did not respond to FDC in first 3 days were successfully treated when colistin was given with FDC, exploring the new therapeutic options in these failure cases.

In G2A to whom meropenem was given empirically, only 19/31 patients (61.29%) achieved clinical cure whereas 12 patients failed to respond to meropenem indicating false susceptibility of carbapenem *in vitro* which is in agreement with previous reports where false susceptibility of carbapenems has been observed in MBL producing strains [5,25]. Another possibility of the decreased susceptibility of meropenem to members to these isolates implied the presence of outer membrane protein mutation [2,28]. Further when these patients were shifted to Meropenem+Colistin, 5/12 patients (41.67%) showed no improvement and were cured when shifted to FDC+Colistin thus indicating presence of MBL strains to which FDC is reported to be active [4,34]. This data advocates use of this new FDC as a better alternative to meropenem. Overall, our results indicate the approximately 17% superiority of new FDC alone over meropenem therapy. It

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Table 4. Summary of antibiotic therapy for the group G2A (Empirical-Meropenem) patients with cultures showing susceptibility to both FDC and meropenem.

S. No	Age	Organism	Meropenem dose	Duration (days)	Clinical response	Colistin add on	Duration (days)	Clinical response	FDC+colistin	Duration (days)	Clinical response
1	57	*Acinetobacter sp.*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
2	48	*E. coli*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured	NA	NA	NA
3	68	*Pseudomonas sp.*	1 g TID	7	Cured	NA	NA	NA	NA	NA	NA
4	61	*Klebsiella sp.*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	2	Deteriorated	FDC+Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
5	53	*Klebsiella sp.*	1 g TID	9	Cured	NA	NA	NA	NA	NA	NA
6	74	*E. coli*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
7	55	*E. coli*	1 g TID	7	Cured	NA	NA	NA	NA	NA	NA
8	62	*Acinetobacter sp.*	1 g TID	3	Deteriorated	3.0 g BID	7	Cured	NA	NA	NA
9	83	*E. coli*	1 g TID	3	Deteriorated	3.0 g BID	7	Cured	NA	NA	NA
10	40	*Pseudomonas sp.*	1 g TID	10	Cured	NA	NA	NA	NA	NA	NA
11	76	*Klebsiella sp.*	1 g TID	10	Cured	NA	NA	NA	NA	NA	NA
12	54	*Acinetobacter sp.*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
13	68	*Klebsiella sp.*	1 g TID	2	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	2	Deteriorated	FDC+Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
14	39	*E. coli*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
15	70	*Pseudomonas sp.*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	2	Deteriorated	FDC+Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
16	42	*Pseudomonas sp.*	1 g TID	9	Cured	NA	NA	NA	NA	NA	NA
17	64	*Acinetobacter sp.*	1 g TID	9	Cured	NA	NA	NA	NA	NA	NA
18	37	*Acinetobacter sp.*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured	NA	NA	NA
19	78	*E. coli*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
20	66	*Klebsiella sp.*	1 g TID	9	Cured	NA	NA	NA	NA	NA	NA
21	59	*Klebsiella sp.*	1 g TID	2	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured	NA	NA	NA
22	40	*E. coli*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	2	Deteriorated	FDC+Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
23	59	*Acinetobacter sp.*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
24	60	*Klebsiella sp.*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
25	47	*E. coli*	1 g TID	2	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured	NA	NA	NA
26	70	*Pseudomonas sp.*	1 g TID	10	Cured	NA	NA	NA	NA	NA	NA
27	46	*E. coli*	1 g TID	8	Cured	NA	NA	NA	NA	NA	NA
28	51	*Klebsiella sp.*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	9	Cured	NA	NA	NA
29	60	*E. coli*	1 g TID	9	Cured	NA	NA	NA	NA	NA	NA
30	72	*Pseudomonas sp.*	1 g TID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	2	Deteriorated	FDC+Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
31	48	*E. coli*	1 g TID	10	Cured	NA	NA	NA	NA	NA	NA

Note: NA: Not applicable

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Table 5. Summary of antibiotic therapy for the group G2B (Empirical–FDC) patients with cultures showing susceptibility to both FDC and meropenem.

S. No	Age	Organism	FDC dose	Duration (days)	Clinical response	Colistin add on	Duration (days)	Clinical response
1	7	*Acinetobacter sp.*	1.5 g BID	7	Cured	NA	NA	NA
2	81	*E. coli*	1.5 g BID	6	Cured	NA	NA	NA
3	65	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
4	80	*Pseudomonas sp.*	3.0 g BID	9	Cured	NA	NA	NA
5	72	*Klebsiella sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIUBID)	7	Cured
6	65	*E. coli*	1.5 g BID	5	Cured	NA	NA	NA
7	40	*Acinetobacter sp.*	3.0 g BID	6	Cured	NA	NA	NA
8	62	*Klebsiella sp.*	1.5 g BID	8	Cured	NA	NA	NA
9	51	*E. coli*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
10	39	*E. coli*	1.5 g BID	8	Cured	NA	NA	NA
11	35	*Pseudomonas sp.*	3.0 g BID	8	Cured	NA	NA	NA
12	47	*Pseudomonas sp.*	1.5 g BID	9	Cured	NA	NA	NA
13	55	*Klebsiella sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
14	70	*Pseudomonas sp.*	3.0 g BID	9	Cured	NA	NA	NA
15	61	*E. coli*	3.0 g BID	8	Cured	NA	NA	NA
16	45	*E. coli*	1.5 g BID	6	Cured	NA	NA	NA
17	66	*Klebsiella sp.*	1.5 g BID	2	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
18	76	*E. coli*	1.5 g BID	6	Cured	NA	NA	NA
19	49	*Acinetobacter sp.*	3.0 g BID	9	Cured	NA	NA	NA
20	71	*E. coli*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
21	62	*Pseudomonas sp.*	3.0 g BID	10	Cured	NA	NA	NA
22	68	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
23	50	*Acinetobacter sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
24	53	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
25	40	*E. coli*	3.0 g BID	7	Cured	NA	NA	NA
26	38	*Klebsiella sp.*	3.0 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	6	Cured
27	72	*Klebsiella sp.*	3.0 g BID	8	Cured	NA	NA	NA
28	44	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
29	46	*Pseudomonas sp.*	1.5 g BID	3	Deteriorated	Colistin (9 MIU loading and 4.5 MIU BID)	7	Cured
30	57	*E. coli*	1.5 g BID	7	Cured	NA	NA	NA
31	68	*Klebsiella sp.*	3.0 g BID	9	Cured	NA	NA	NA
32	75	*E. coli*	1.5 g BID	6	Cured	NA	NA	NA
33	60	*Acinetobacter sp.*	1.5 g BID	8	Cured	NA	NA	NA
34	44	*Klebsiella sp.*	3.0 g BID	7	Cured	NA	NA	NA

Note: NA: Not applicable

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Table 6. Summary of antibiotic therapy for the group G3 patients with cultures showing intermediate resistance to FDC and Meropenem.

S. No	Age	Organism	FDC+Colistin dose	Duration (days)	Clinical response
1	79	*E. coli*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
2	41	*Klebsiella sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
3	65	*E. coli*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	9	Cured
4	82	*E. coli*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	9	Cured
5	66	*Klebsiella sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	10	Cured
6	74	*Klebsiella sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	9	Cured
7	50	*Pseudomonas sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
8	43	*Klebsiella sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured
9	71	*Acinetobacter sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	9	Cured
10	36	*Acinetobacter sp.*	3.0 g FDC+Colistin (9 MIU loading and 4.5 MIU BID)	8	Cured

has been noticed that 15 to 20% mortality rates in patients of nosocomial infections has been associated [**14**]. However, this percentage was very low in our case. There was no significant difference in treatment regimen of two therapies however, dosing frequency and cost of drug was lower in FDC treated group as compared to meropenem treated.

Conclusion

Our data showed that FDC can be a good option as carbapenem sparing drug and combination of FDC and colistin can successfully treat complicated multi drug resistant cases of LRTIs, UTIs, and IAIs without mortality within 8-11 days.

Competing interests

The author declares that he has no competing interests.

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