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A New Fixed Dose Combination of Ceftriaxone + Sulbactam + Disodium Edetate for Definitive Treatment of Infections Due to Piperacillin/ Tazobactam Resistant Bacteria: A Retrospective Efficacy and Pharmacoeconomic Study

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Authors' contributions

This work was carried out in collaboration between both authors. Author PB designed, analyzed and conducted the study. Author MAM prepared the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: Present retrospective study was aimed to analyze comparative efficacy of fixed dose combination (FDC) (ceftriaxone + sulbactam + disodium edetate) and meropenem used alone or in combinations with other antibiotics for management of intensive care unit (ICU) patients suffering with infections from piperacillin-tazobactam (pip-taz) resistant bacteria and to assess the costs associated with respective therapies.
Methodology: Patients records were collected and their demographic characteristics, infection types, co-morbidities, antibiotic therapy, dosage, treatment duration microbial and clinical success rates were evaluated. Effectiveness and costs analysis between antibiotic regimens were estimated in Indian rupees (INR). A total of 136 patients data treated at a tertiary-care hospital was

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analyzed. These 136 patients included 28, 18, 19, 17, 31 and 23 patients of urinary tract infection (UTI), blood stream infection (BSI), community acquired infection (CAI), skin structure infection (SSI), intra-abdominal infection (IAI) and ventilator associated pneumonia (VAP), respectively. Out of 136 patients, 56 patients received FDC and another 80 patients were administered with meropenem empirically.

Results: Clinical cure observed was 71.42% and 67.50% in FDC and meropenem groups, respectively. The patients in whom meropenem and FDC treatment regime failed to show improvement, colistin was given as an additional cover, which resulted in clinical cure of 86.95% and 85.71% patients respectively. Comparative cost expenditure analysis of these two drug treatment regimens revealed that, the overall treatment cost for patients cured with antibiotic regimen containing meropenem was 107.39% more than that of FDC. The strongest contributors of the increase in treatment costs were cost of antibiotic, number of dosages, average treatment duration and clinical failure rates.

Conclusion: Infections with pip-taz resistant bacteria are frequent in ICU patients and the present study demonstrates that FDC has comparatively similar efficacy as that of meropenem which is considered as an appropriate option to treat pip-taz resistant cases. Pharmacoeconomic analysis clearly advocates in favor of FDC as a cheaper and safer alternative to meropenem to treat ICU patients with infections caused due to pip-taz resistant bacteria.

Keywords: Piperacillin/tazobactam; fixed dose combination; intensive care units; pharmacoeconomic; multi-drug resistant bacteria.

1. INTRODUCTION

Severe infections in critically ill patients and increasing antibiotic resistance are major health care problems affecting morbidity and mortality in the intensive care unit [1]. Development of resistance to antimicrobial agents has been an ongoing and evolving process since antibiotics were introduced. Antimicrobial-resistant pathogens are becoming a common cause of hospital acquired infections, particularly in intensive care units (ICU) [2,3]. Antibacterial drug discovery and development have slowed considerably in recent years. The number of new antibacterial medicines entering the clinic has been declining and, in view of this fact, new compounds for multi-drug resistant Gram-negative bacilli will unlikely be available for more than 10 years [1,4,5]. The problems associated with escalating resistance and decreased development of antibiotics with novel mechanisms of action require more research into existing antibiotics.

β-lactam/β-lactamase inhibitor combination drugs are currently a major class of antibiotics used to manage bacterial infections. Although most traditional penicillins are ineffective against many pathogens, certain new-generation penicillins combined with β-lactamase inhibitors do have potential anti-bacterial activities. Piperacillin-tazobactam (pip-taz) in particular remains a drug combination in very widespread use as a broad-spectrum agent with relatively high effectiveness. By many analyses, pip-taz is the most effective non-polymyxin anti-bacterial drug in current use, [6,7] with activity both against Gram-negative and Gram-positive bacteria (including β-lactamase producers). Pip-taz, was considered as an appropriate choice in the ICU because of its broad spectrum of action and is notably proposed for the treatment of intra-abdominal infections, febrile neutropenic patients at high risk, late-onset ventilator-associated pneumonia and others [8-11]. However, over the years there has been considerable increase in the pip-taz resistance cases [2,12]. On this account of the increased resistance towards beta lactam antibiotics, carbapenems have become the drug of choice to treat such severe infections, however, increase in carbapenem usage has lead to the emergence of a new class of β-lactamases with direct carbapenem-hydrolyzing activity, which ultimately lead to carbapenem resistant bacteria [13,14]. Therefore, new therapeutic options are needed for patients at high risk of infections caused by multidrug-resistant (MDR) pathogens. Along with efficacy, knowledge of antibiotic drugs cost is suggested as additional criteria supporting clinical decision-making [15-17] In fact, in some US and European studies, a significant influence of empiric antibiotic therapy choice on economic outcome of infections has emerged [18-21]. In view of all these aspects, we have conducted a retrospective study aimed to assess the comparative efficacy and pharmacoeconomics associated with

management of ICU patients suffering with different pip-taz resistant bacterial infections using antibiotics like FDC (ceftriaxone + sulbactam + disodium edetate) and meropenem empirically.

2. MATERIALS AND METHODS

2.1 Study Design

This retrospective, observational study has been conducted at tertiary care hospital in north India. The primary objective of this study was to evaluate the efficacy and costs involved in management of ICU patients suffering from different infections caused due to pip-taz resistant pathogens and treated with FDC or meropenem (used alone or along with different antibiotic combinations). The data for patients suffering from different infections caused due to pip-taz resistant pathogens who were treated between September 2013 to February 2015 were collected and analyzed for the antibiotic regimens used, microbiological and clinical outcome along with the costs involved in the therapy.

2.2 Patient Selection

The ICU patients who had infections caused by pip-taz resistant Gram negative bacteria were included in this retrospective study. Furthermore, hospital records like case sheets and other relevant documents of patients were evaluated. The selected patients were managed with antibiotic regimen containing either of intravenous FDC or meropenem in combination with antibiotics like amikacin, metronidazole, ciprofloxacin, clindamycin and colistin etc. The following were the exclusion criteria for individuals into the study: patients cured with pip-taz therapy, whose medical records were not available.

2.3 Treatment Regimens

The selected patients have received either empirical FDC (ceftriaxone 2.0 g + sulbactam 1.0 g+ disodium edetate 74 mg) (3 g every 12 hrs) or meropenem (1 g every 8 hrs) intravenously along with other antibacterial drugs for management of different infections caused by pip-taz resistant pathogens. Intravenous amikacin (250 mg every 12 hrs) was used empirically in combination with either FDC or meropenem for the management of complicated *urinary tract infections* (cUTIs), *blood stream infections* (BSIs), and community-acquired infections (CAIs) and intravenous metronidazole (1 g every 6 hrs) was used to manage skin structure infections (SSIs) and intra-abdominal infections (IAIs) uniformally in both groups. For management of ventilator-associated pneumonia (VAPs) ciprofloxacin (400 mg every 8 hrs) was used intravenously along with empirical FDC or meropenem therapies. For the management of CAIs, SSIs and IAIs, clindamycin was also given as an empirical therapy at a dose of 600 mg every 8 hrs. The selection of empiric antibiotic regimens; FDC or meropenem were random based on the clinical presentation and at the discretion of doctor. Irrespective of the antibiotic combinations used, the patient group that received FDC empirically is referred to herein as the FDC group and the group which received meropenem is referred to as meropenem group. The empirical regimens were continued/ deescalated and/or other antibiotics added based on the microbiological susceptibility towards the respective antibiotics used and/or the clinical outcome after 2/3 days. Colistin, was added in those patients which did not show improvement with either empirical therapy. Colistin was used with a loading dose of 9 million international units (MIU) followed by BID (*bis in die*) doses of 4.5 MIU.

2.4 Microbial Evaluations and Definitions

Culture reports of the patients with different infections were assessed at the baseline and at the end of therapy. Repeat cultures were performed for all patients at 48-72 hours after treatment initiation and at end of the treatment. Minimum inhibitory concentrations (MICs) and antimicrobial susceptibility of test antibiotics were determined for aerobic organisms according to Clinical and Laboratory Standards Institute (CLSI) [22]. The assessment of microbiological response at patient level was based on the results of pre-therapy isolation and identification of isolates, susceptibilities of the isolated pathogens and clinical outcome of the patients. The microbiological response was considered satisfactory/ success when the original causative pathogen was completely eradicated or presumed to be eradicated (i.e. when further sampling for culture was not considered significant because of clinical cure/ improvement). The response was considered unsuccessful/failure if the diagnosed pathogen persisted or presumed to be persisted or a new pathogen was isolated from the original site of infection during the study (super-infection).

2.5 Diagnosis Criteria and Definitions

On evaluations of case sheets of individual patient utmost care has been taken to classify the the population into different groups based on clinical diagnosis. The diagnosis of each patient has been verified and rechecked inline with clinical protocol or standard references. Basic criteria for VAP included, a new or persistent (>48 h) or progressive radiographic infiltrate [23]. In addition, patients must have had fever of ≥38℃ with no other recognized cause or an abnormal white blood cell (WBC) count (leukopenia [4,000 WBC/mm3] or leukocytosis [12,000 WBC/mm3]) and at least two of the following: new onset of purulent sputum or change in character of sputum, increased respiratory secretions or increased suctioning requirements, new onset or worsening of cough or dyspnea or tachypnea, rales or bronchial breath sounds, or worsening gas exchange.[24] The patient with blood stream infections (BSIs) required either growth of a recognized pathogen from one or more blood specimen cultures or at least one of the following signs or symptoms: (≥ 38℃), chills, hypotension and (i) a common skin contaminant (e.g., diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative staphylococci, or micrococci) grown from two or more blood cultures drawn on separate occasions and/or (ii) a common skin contaminant grown from at least one blood culture from a patient with an intravascular line and physician-instituted antimicrobial therapy [24,25].

Patients of intra-abdominal infections (IAIs) (diagnosed with either ruptured appendix, hepatobiliary infections, colon perforation, infected diverticulitis, post traumatic peritonitis, anal abscess, peritonitis, abdominal abscess), were having following signs and symptoms; fever (≥38℃), nausea, vomiting, abdominal pain, or jaundice with no other recognized cause and (i) organisms cultured from drainage from a surgically placed drain, (ii) organisms seen on a Gram stain of drainage or tissue obtained during surgical operation or needle aspiration, and/or (iii) organisms cultured from blood and radiographic evidence of infection, e.g., abnormal findings on ultrasound, CT scan, magnetic resonance imaging, radio-label scans (gallium, technetium, etc.), or abdominal X ray [24,25]. Patients with SSI were having foci of infection in skin/ subcutaneous tissue, soft tissue of incision or any part of the anatomy which was opened or manipulated during an operation and at least one of the following; 1. purulent drainage from the incision or part of the organ, 2. organism isolated from an asceptically obtained culture if fluid or tissue in the incision or organ, 3. Superficial or deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain, or tenderness, unless site is culture-negative, an abscess or other evidence of infection involving the organ/space that is found on direct examination, during re-operation, or by histopathologic or radiologic examination or 4. when diagnosis of a incisional or organ/space SSI by a surgeon or attending physician [25,26]. Infections at other body sites or fluids, such as urinary tract infections and central venous catheter-related infections, were defined based on guidelines from the Centers for Disease Control and Prevention [24,25].

2.5.1 Clinical success

The patient's response was considered as clinical success when, the patient recovered with either first line empiric antibiotic therapy or a step down from the initial therapy [27].

2.5.2 Clinical failure

An individual case was defined as clinical failure when either the treatment was switched to the second line antibiotics or when the death of patients occurs.

2.6 Antibiotic Therapy Cost Analysis

An assessment of the direct cost of antibiotics was performed by multiplying the number of days of antibiotic therapy by the unit price of respective individual antibiotic and by the number doses per day. The overall cost of antibiotic treatment for each patient was the sum of costs calculated for all parenteral antibiotics received by the patient during the hospitalization period. The unit price of antibiotics was based on maximum retail price (MRP) per unit of antibiotics. Hospitalization charges, laboratory tests, instrumental charges and overhead charges were directly recorded and their costs were individually assessed accordingly. Therapy costs incurred towards prior treatment procedures carried out before admitting patients to ICU and prior antibiotic therapies (pip-taz / other) used before FDC and meropenem treatment were not included in analysis, as we assume they were independent of the adopted

antibiotic therapy. Costs are expressed in Indian rupees.

3. RESULTS

3.1 Study Populations

During study period considered for analysis, 310 patients received intravenous pip-taz empirically for the management different infections. The data from the medical records reveals that, 151 patients out of 310 (43.87%) patients were cured with the pip-taz therapy and were excluded from the present study. However 136 patients identified with pip-taz resistant pathogens and who subsequently received either FDC or meropenem were included in the study and their data was analyzed (Fig. 1). Medical records for the remaining 23 (7.42%) patients were not available and hence were excluded in the study. The demographic and baseline characteristics of 136 patients whose data were analyzed in this study are given in Table 1. The demographic and baseline characteristics of FDC (n = 56) and meropenem (n = 80) groups were generally comparable. Both the treatment groups were dominated by male populations with the male: female ratio of 33:23 and 49:31 for FDC and meropenem group, respectively. The average age of the patients treated in the FDC group was 59.87±13.81 and the same for meropenem was 62.24±13.20. Average APACHE II score in both groups were almost similar with FDC group having a score of 16.67±3.85 and meropenem having 16.27±3.51.

Among the ICU patients studied from both the groups, IAIs was the most predominant infection (22.79%) followed by UTIs (20.58%), VAP (16.91%), CAIs (13.97%), BSIs (13.23%) and the least cases were of SSIs (12.50%). Among the patients using catheters, maximum patients were with urinary tract catheters (53.27%) followed by cerebrospinal drainage (29.54%) and abdominal drainage (18.18%). Among the ICU patients, 21 (37.50%) patients from FDC group and 18 (22.50%) from meropenem group were on mechanical ventilators during course of treatment. Cardiac diseases (45.58%) were the most common co-morbidity observed in patients from both the groups followed by lung disorders (38.97%), diabetes mellitus (36.76%), neurological disorders (28.67%), urogenital disorders (25%) and least common co-morbidity observed was hepatic disorders (5.14%) (Table 1).

3.2 Baseline Microbial Pathogens

A total of 314 pathogens were isolated from 136 patients suffering from different types of infections. Out of these136 patients, only 2 (1.47%) patients were diagnosed with mono-bacterial infections and the remaining all the patients [134 (98.52%)] had poly-bacterial infections. Among the isolated pathogens Gram negative bacteria had a significantly higher share (85.03% to 14.97% Gram positive isolates) with, *E coli* being the most predominant pathogen (19.10%) closely followed by *A. baumannii* (17.19%), *K. pneumoniae* (16.87%), *P. aeruginosa* (12.73%), *K. oxytoca* (7.96%), *Proteus spp.* (5.41%), *Enterobacter spp*. (3.50%) and *E. faecalis* (2.22%). 47 (34.55%) out of 136 patients suffered with mixed Gram negative and Gram positive mixed bacterial infections, whereas the remaining were diagnosed with only Gram negative pathogens (Table 2).

3.3 Per Patient Microbial Success Assessment

Two patients diagnosed with Gram negative mono-bacterial infections, were treated in FDC group, achieved 100% microbiological success rate. The patients with poly-bacterial infections were diagnosed with the combination of two or more cultures of following; *E coli, P. aeruginosa, A. baumannii, K. pneumoniae, K. oxytoca, Enterobacter spp., Proteus spp., E faecalis and S. aureus.* In the patients with only mixed Gram negative bacterial infections, FDC group achieved a success of 68.88% (31/45) as compared to the meropenem group 64.58% (31/48). On the other hand, FDC and meropenem groups had a microbial success rate of 66.66% (10/15) and 75% (24/32) in Gram positive and negative mixed bacterial infections respectively. However, microbiological success in patients which did not show improvement with empirical therapy was achieved with addition of colistin to ongoing antibiotic regimen in both the groups. The detailed break up for per patient microbial success in different poly-bacterial infection cases is depicted in Table 2 and it strongly suggest the comparable microbial success rates in FDC and meropenem group.

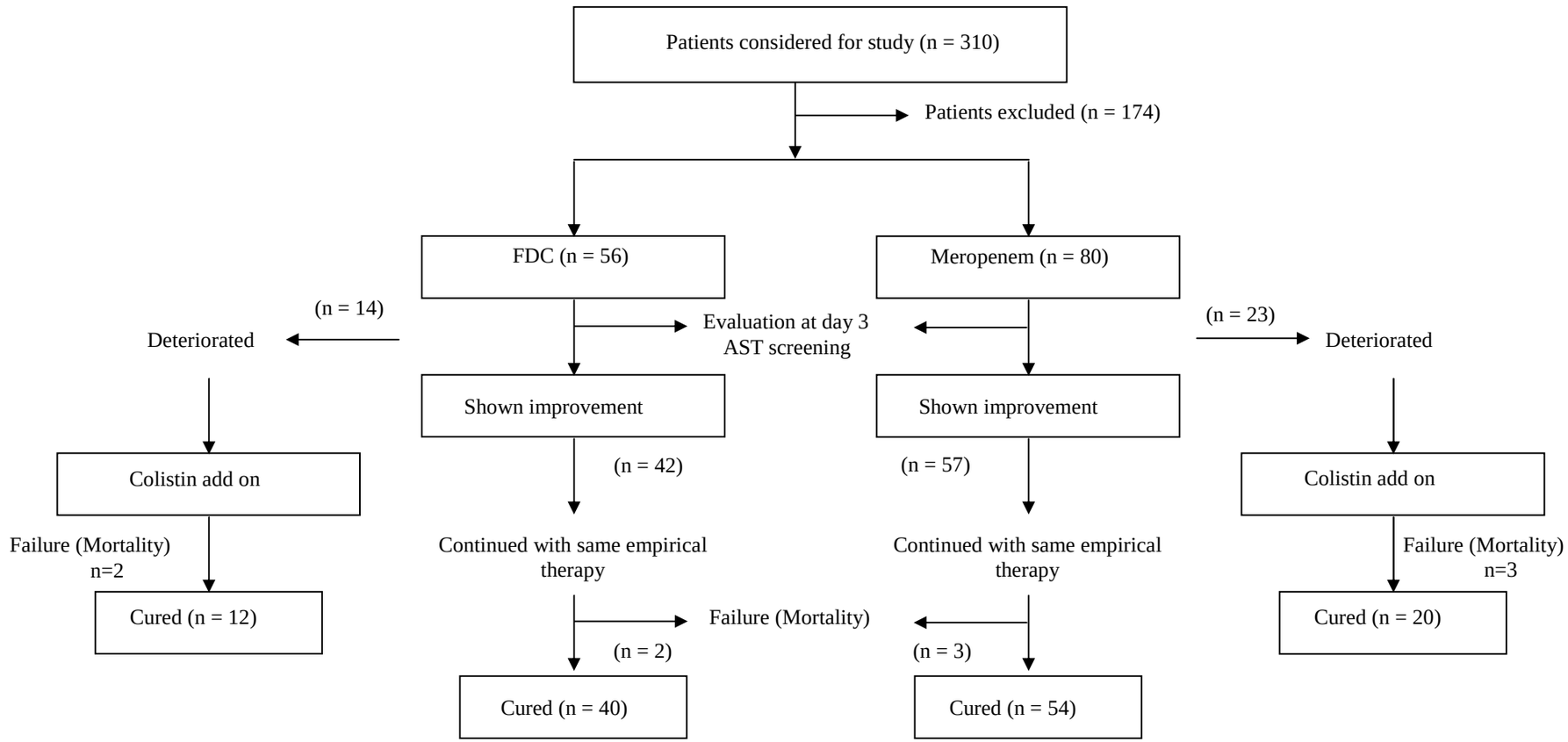

Fig. 1. Flow diagram for the analysis of ICU patient managed for different infections

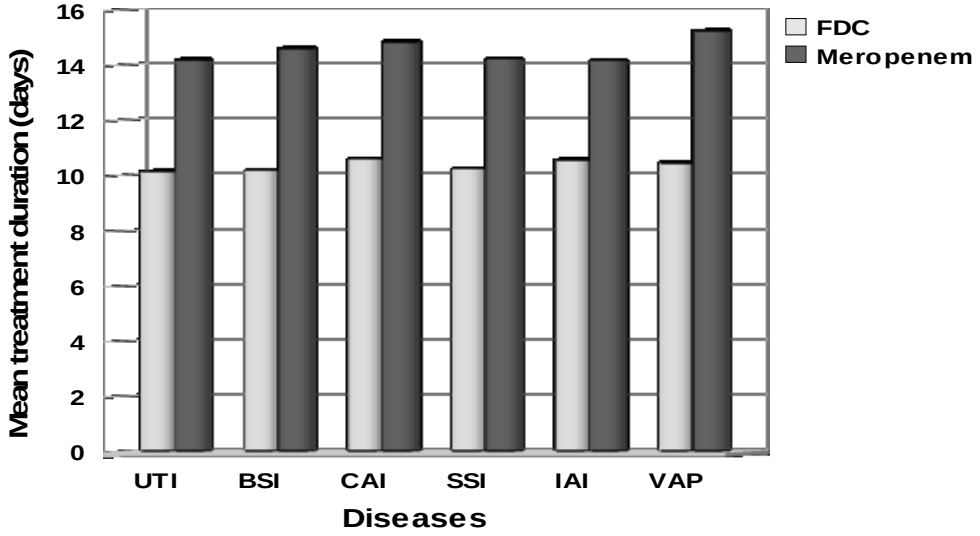

Fig. 2. Average treatment duration for different types of infections treated with different antibiotic regimes in FDC and Meropenem groups

UTI, Urinary tract infections; BSI, Blood stream infections; CAI, Catheter associated infections; SSI, skin structure infections; IAI, Intra-abdominal infections; VAP, Ventilator associated pneumonia

Table 1. Demographic and clinical features of ICU patients managed with intravenous FDC or meropenem with/without colistin for different infections (n 136)

Characteristic	Data for patients who received	
	FDC	**Meropenem**
Evaluable patients	**56**	**80**
Sex ratio – male:female [*n* (%)]	33:23 (58.92% : 41.08%)	49:31 (61.25%: 38.75%)
Age, mean year SD	59.87±13.81	62.24±13.20
APACHE II score mean SD	16.67±3.85	16.27±3.51
Prior antibiotic use	54 (96.42%)	79 (98.75%)
Types of infections		
UTI	13 (23.21%)	15 (18.75%)
BSI	05 (08.92%)	13 (16.25%)
CAI	05 (08.92%)	14 (17.50%)
SSI	04 (07.14%)	13 (16.25%)
IAI	14 (25.00%)	17 (21.25%)
VAP	15 (26.78%)	08 (10.00%)
Co-morbidities		
Diabetes mellitus	19 (33.92%)	31 (38.75%)
Cardiac diseases	26 (46.42%)	36 (45%)
Urogenital disorders	13 (23.21%)	21 (26.25%)
Lung disorders	24 (42.85%)	29 (36.25%)
Hepatic disorders	2 (3.57%)	5 (6.25%)
Neurological disease	14 (25%)	25 (31.25%)
Types of catheters		
Urinary tract catheters	9 (16.07%)	14 (17.5%)
Cerebrospinal fluid drainage	6 (10.71%)	7 (8.75%)
Abdominal drainage	2 (3.57%)	6 (7.5%)
Mechanical ventilator	21 (37.5%)	18 (22.5%)

Note: *UTI, Urinary tract infections; BSI, Blood stream infections; CAI, Catheter associated infections; SSI, skin structure infections; IAI, Intra-abdominal infections; VAP, Ventilator associated pneumonia; SD, Standard deviation;*

Table 2. Per patient microbial success rates treated with different antibiotic regimes

Combination of pathogens isolated from patients	Number of patients	Success rate [no. of successes/total no. (%)] for:			
		FDC group		Meropenem group	
		Empirical therapy	Colistin add on therapy	Empirical therapy	Colistin add on therapy
A. baumannii + S. aureus	2	2/2 (100)	-	-	-
P. aeruginosa + K. pneumoniae + S. aureus	1	1/1 (100)	-	-	-
P. aeruginosa + A. baumannii + S. aureus	7	1/2 (50)	1/1 (100)	3/5 (60)	0/2 (0)
P. aeruginosa + E. coli + S. aureus	6	1/2 (50)	1/1 (100)	4/4 (100)	-
A. baumannii + K. oxytoca	5	2/4 (50)	2/2 (100)	1/1 (100)	-
A. baumannii + P. aeruginosa	7	4/5 ()	1/1 (100)	0/2 (0)	2/2 (100)
A. baumannii + Enterobacter spp. + S. aureus	1	1/1 (80)	-	-	-
E. coli + K. oxytoca	3	3/3 (100)	-	-	-
E. coli	2	2/2 (100)	-	-	-
E. coli + K. pneumoniae	11	3/4 (75)	1/1 (100)	4/7 (57.14)	3/3 (100)
E. coli + A. baumannii	11	4/4 (100)	-	5/7 (71.42)	2/2 (100)
E. coli + A. baumannii + S. aureus	1	0/1 (0)	-	-	-
E. coli + K. pneumoniae + S. aureus	5	2/3 (66.66)	0/1 (0)	2/2 (100)	-
K. pneumoniae + K. oxytoca	5	1/2 (50)	1/1 (100)	2/3 (66.66)	1/1 (100)
K. pneumoniae + P. aeruginosa	5	2/3 (66.66)	1/1 (100)	1/2 (50)	1/1 (100)
K. pneumoniae + Proteus spp.	5	2/3 (66.66)	1/1 (100)	1/2 (50)	0/1 (100)
P. aeruginosa + E. faecalis	1	1/1 (100)	-	-	-
P. aeruginosa + Proteus spp.	2	1/1 (100)	-	0/1 (0)	1/1 (100)
P. aeruginosa + Proteus spp. + S. aureus	1	1/1 (100)	-	-	-
P. aeruginosa + S. aureus	1	1/1 (100)	-	-	-
E. coli + P. aeruginosa	7	3/3 (100)	-	3/4 (75)	1/1 (100)
K. pneumoniae + A. baumannii	12	3/5 (60)	1/2 (50)	6/7 (85.71)	0/1 (0)
Enterobacter spp. + K. pneumoniae	3	0/3 (0)	1/1 (100)	1/2 (50)	1/1 (100)
Proteus spp. + K. oxytoca + S. aureus	3	0/3 (0)	1/1 (100)	1/2 (50)	0/1 (0)
A. baumannii + K. oxytoca + S. aureus	2	-	-	2/2 (100)	-
A. baumannii + K. pneumoniae + S. aureus	4	-	-	3/4 (75)	1/1 (100)
A. baumannii + Proteus spp. + S. aureus	1	-	-	1/1 (100)	-
E. coli + Enterobacter + S. aureus	1	-	-	1/1 (100)	-
E. coli + K. oxytoca + S. aureus	4	-	-	2/4 (50)	2/2 (100)
E. coli + Proteus spp. + S. aureus	4	-	-	3/4 (75)	0/1 (0)
E. coli + E. faecalis	3	-	-	3/3 (100)	-
E. coli + Enterobacter spp.	1	-	-	1/1 (100)	-
Enterobacter spp. + A. baumannii	1	-	-	1/1 (100)	-
Enterobacter spp. + E. faecalis	2	-	-	1/2 (50)	1/1 (100)
Enterobacter spp. + K. oxytoca + S. aureus	1	-	-	1/1 (100)	-
Enterobacter spp. + K. pneumoniae + S. aureus	1	-	-	1/1 (100)	-
K. pneumoniae + E. faecalis	1	-	-	1/1 (100)	-
E. coli + Proteus spp.	1	-	-	0/1 (0)	1/1 (100)
P. aeruginosa + K. oxytoca + S. aureus	1	-	-	0/1 (0)	1/1 (100)
P. aeruginosa. + K. oxytoca	1	-	-	0/1 (0)	1/1 (100)

Table 3. Clinical success rates among different types of infections treated with different antibiotic regimes

Type of infection	Total number of cases	Clinical Success rate [no. of successes/total no. (%)]* for:			
		FDC group		Meropenem group	
		Empirical therapy	Colistin add on therapy	Empirical therapy	Colistin add on therapy
UTI[a]	28	10/13 (76.92)	3/3 (100)	10/15 (66.66)	4/5 (80)
BSI[a]	18	3/5 (60)	2/2 (100)	10/13 (76.92)	3/3 (100)
CAI[a,d]	19	3/5 (60)	1/1 (100)	9/14 (64.28)	3/4 (75)
SSI[b,d]	17	3/4 (75)	1/1 (100)	10/13 (76.92)	3/3 (100)
IAI[b,d]	31	11/14 (78.57)	2/3 (66.66)	10/17 (58.82)	5/6 (83.33)
VAP[c]	23	10/15 (66.66)	4/4 (100)	5/8 (62.50)	2/2 (100)

Note: *UTI, Urinary tract infections; BSI, Blood stream infections; CAI, Catheter associated infections; SSI, skin structure infections; IAI, Intra-abdominal infections; VAP, Ventilator associated pneumonia*

**Clinical success: complete resolution or significant improvement in all signs and symptoms of the infection, so that no additional antibiotic therapy was essential. Clinical failure: No signs of improvement or persisted infection, or required additional antibiotic cover for the infection*

[a], [b], [c], [d] refers to Amikacin, Metronidazole, Ciprofloxacin and Clindamycin respectively used in combination for empirical therapies.

The number of patients deescalated for clindamycin were 7, 3 and 11 for CAI, SSI and IAI respectively

3.4 Clinical Success Assessment

Result of clinical outcomes of the antibiotic therapies in patients suffering from different infections was in accordance with the microbiological success. The clinical success rates in empirical therapy were the highest in FDC group [40/56 (71.42%)] as compared to meropenem group [54/80 (67.50%)]. The success rates of FDC: meropenem group in ICU patients with different infections were as follows; UTIs [10/13 (76.92%): 10/15 (66.66%)], BSIs [3/5 (60.00%): 10/13 (76.92%)], CAIs [3/5 (60.00%): 9/14 (64.28%)], SSIs [3/4 (75.00%): 10/13 (76.92%)], IAIs [11/14 (78.57%): 10/17 (58.82%)] and VAPs [10/15 (66.66%): 5/8 (62.50%)] (Table 3 above). Fourteen failure patients from FDC group were given an additional antibiotic cover and 12 out of these 14 achieved clinical success. On the other hand, 23 patients from meropenem group were also given colistin as an additional therapy out of which 20 patients achieved clinical success (Table 3 above). The mean treatment duration of FDC: meropenem group in ICU patients with different infections were as follows; UTIs [10.15±0.80 (SD) : 14.2±1.14 (SD)], BSIs [10.2±1.64 (SD) : 14.61±0.960 (SD)], CAIs [10.6±2.07 (SD): 14.85±1.29 (SD)], SSIs [10.25±0.95 (SD) : 14.23±1.87 (SD)], IAIs [10.57±1.08 (SD) : 14.17±1.23 (SD)] and treatment duration is VAP patients was [10.46±1.30 (SD) : 15.25±1.48 (SD)] (Fig. 2). The patients in whom therapy failed (n=10; 7.35%) ranged in age from 37 to 81 years and were suffering from different infections. The reason for the clinical failure was the persistence or recurrent infection requiring treatment with additional antibiotics.

3.5 Antibiotic Therapy Cost analysis

The cost (calculated in Indian rupees) of FDC used in UTIs, BSIs, CAIs, SSIs, IAIs and VAPs was 21305±2123 (standard deviation; SD), 25540±1986 (SD), 29472±2142 (SD), 28226±2361 (SD), 26522±2657 (SD) and 23952±2443 (SD), respectively which was less compared to meropenem where its cost incurred 117722±13543 (SD), 117533±16543 (SD), 128076±13428 (SD), 124464±14321 (SD), 125423±12548 (SD), 125723±11294 (SD) for UTIs, BSIs, CAIs, SSIs, IAIs and VAPs patients, respectively. Overall, the average cost (calculated in Indian rupees) of the empirical drugs used to treat the patients with different infections in meropenem group [123157±4445 (standard deviation; SD)] was significantly higher (approx 376.68%) as compared to the cost of FDC group drugs [25836.66±2953 (SD)]. The average treatment charges (including hospitalization charges) of FDC for UTIs, BSIs, CAIs, SSIs, IAIs and VAPs was 122844±13652 (SD), 127540±13142 (SD), 135422±12854 (SD), 130726±13658 (SD), 132237±14210 (SD), 128619±11985 (SD), respectively. The average treatment charges of meropenem was 259722±23431 (SD), 263686±24983 (SD), 276648±2653 (SD), 266772±24985 (SD), 267187±27653 (SD), 278223±27638 (SD) in patients of UTI, BSI, CAI, SSI, IAI and VAP, respectively. Overall, the average treatment charges for meropenem group [268706.83±2288.31 (SD)] was 107.39% higher than that of FDC group charges [129565.01±4311.62 (SD)]. The average overall treatment costs also included the cost of colistin used for cases where ongoing regimen failed to

cure. Highest difference of average overall treatment costs between the groups was observed in ICU patients with VAPs (approx 116.31%) followed by UTIs (approx 111.42%), BSIs (approx 106.7), CAIs (approx 104.2%), SSIs (approx 104.06) and least difference was observed in patients with IAIs (approx 102.05%).

4. DISCUSSION

Multi drug resistant bacteria are the most feared pathogens, especially in high risk departments such as ICUs, neonatal and burn units [28]. Present retrospective study analyzed the clinical data sheets of 310 patients with different bacterial infections. All the selected patients have received pip-taz as presumptive therapy. Out of these, 151 (48.70%) patients were identified with pip-taz susceptible strains and were subsequently cured with the same therapy. Similar cure rates were reported by Malangoni et al. [29], reporting 55% cure rates with pip-taz in the hospital acquired infections. The management of the remaining 136 patients (identified with either pip-taz resistant/ intermediate resistant pathogens), whose clinical data has been evaluated and discussed in this retro-respective study. The pip-taz resistant cases observed in our study were significantly more than the rates observed and reported in previous studies [2,12]. The increased prevalence of pip-taz resistant pathogens is an alarming indication for the need of an effective alternative. The main mechanism of this resistance is the emergence of broad spectrum β-lactamases, in particular ESBLs [2] that inhibit the effect of most cephalosporin and penicillin antibiotics. It is common fact that isolates producing these enzymes are also resistant to other group of antibiotics such as fluoroquinolones, aminoglycosides, tetracyclins and co-trimoxazoles [30,31]. This retrospective study analyses the efficacy and cost effectiveness of FDC or meropenem given along with other antibiotics as combination therapy for the management of these 136 pip-taz resistant ICU patients.

Bacterial pathogens isolated from the patients at baseline were almost similar among FDC and meropenem group. The common Gram negative pathogens isolated from the patients were *E. coli, A. baumannii, K. pneumoniae, P. aeruginosa, K. oxytoca, Proteus spp., Enterobacter spp. and E. faecalis* with members of the *Enterobacteriaceae* family dominating the population. This might be one of the major contributing factors to the high resistance rates towards pip-taz, as members of the *Enterobacteriaceae* family are predominant ESBL and AmpC producers with high prevalence in ICU patients [32,33]. Even tough, our study did not characterize the mechanism of pip-taz resistance as carried out by Meybeck et al. [2], we can presume the emergence and high production of ESBL and AmpC lactamases as the main contributor for the resistance, as higher resistance rates in ICUs is believed to be due to the increased use of antimicrobial agents with the selection pressure in turn resulting in higher resistant strains [28]. However, the only type of Gram positive pathogen detected in ICU patients was *S. aureus*, which is an indicative of the high prevalence of *S. aureus* in the region. Silvana et al. [34], also reported high prevalence of *S. aureus* in ICU settings. Per patient microbial success data analysis for both the drug groups yielded expected results with slightly higher microbial success rates in Gram negative culture infections as compared to Gram positive and negative mixed infections. Our respective study also highlights the similar/ slightly higher microbial success rates among FDC group as compared to meropenem. The microbial success rates were almost similar in patients whom colistin was used as an additional cover.

The data analyzed for clinical success assessment for the particular antibiotic regimen i.e. FDC or meropenem regimen were in accordance with the microbial success rates. The results revealed that, clinical cure rates for empirical therapy among both the groups is largely comparable, with cure rates for FDC and meropenem being 71.42% and 67.50% respectively. The results of the present study, are in accordance with the previous study by Chytra et al. [1], who reported similar clinical cure rates (74.3%) of critically ill patients by meropenem. The detailed clinical efficacy analysis also reveals similar cure rates for FDC and meropenem group among different types of infections in ICU populations. The effectiveness of FDC in pip-taz resistant cases may be attributed to the different ways through which FDC target various resistance mechanism in bacteria. The various mechanisms including, inhibition of conjugal spreading of resistant gene from one bacteria to another. FDC does this by chelating Mg^{2+} ions required for the activity of relaxases and thereby inhibiting conjugation process [35]. It has also been reported that the FDC down-regulates the expression of *MexAB-OprM* and *AcrAB-tolC* efflux pumps [36].

Sulbactam prevents inactivation of beta-lactam antibiotics by binding to the beta-lactamases. It not only increased volume of distribution compared to other beta-lactamase inhibitor but ir-reversibly binds to enzyme and remains for 9 hrs. The adjuvant present in FDC chelates the divalent ions (Zn^{2+}) required for the activity of MBLs and thus deactivate the MBLs activity which in turn increase activity of β-lactam towards microorganisms [37]. Further, FDC 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 in biofilm cases [38]. FDC having similar efficacy as that of meropenem is a significant fact to consider and advocate FDC as an efficient alternative for meropenem as the later being the only choice of drug to treat severe infections with MDR strains [13]. There is an urgent need to find an alternative for meropenem as emergence of novel β-lactamases with direct carbapenem-hydrolyzing activity has contributed to an increased prevalence of carbapenem resistant bacteria, especially *Enterobacteriaceae* (CRE). As demonstrated in our study, CRE are particularly problematic given the frequency with which *Enterobacteriaceae* cause infections [39], the high mortality associated with infections caused by CRE [40-42], and the potential for widespread transmission of carbapenem resistance via mobile genetic elements [43,44]. Along with carbapenemase production, probability of carbapenem resistance towards the meropenem is compounded with various other resistance mechanisms harbored by isolates. Such resistance mechanism are over-expression of efflux pumps like MexAB-OprM efflux system in *Pseudomonas sp.* (specific to meropenem resistance) [45], AcrB efflux pumps in *E coli* [46], AcrAB efflux pumps in *Klebsiella sp.* [47] and AdeABC type efflux pumps identified in *Acinetobacter sp.* [48].

Hospital stay, antibiotic therapy cost and / or duration and clinical failures are believed to be the strongest independent predictor of increased hospital costs. Compared to the successful patients (who received appropriate antibiotic therapy with lesser ICU stay), patients who failed to receive appropriate antibiotic therapy resulted in the increased costs [27]. In agreement to this, cost expenditure analysis for FDC and meropenem group empirical therapy revealed that, antibiotic selection, dosage and clinical failure resulted in significant increase in antibiotic expenditures. Previous reports have shown that hospitalization costs are 1.2 – 1.5 times higher in patients who have failed treatment compared with patients who were treated successfully [19,49]. The present study shows the substantial increase in the hospitalization costs in meropenem group patients as compared to the FDC group patients. Increased cost is the cumulative effect of the dosage (FDC *b.i.d* and meropenem *t.i.d*), cost of the antibiotic and average treatment duration (which ranged from 10.15±0.80 (SD) to 10.6±2.07 (SD) in FDC group and from 14.17±1.23 (SD) to 15.25±1.48 (SD) in meropenem group). The overall treatment cost for meropenem group patients was 107.39% (approx) more than that of FDC treated groups. These significant cost differences further add points in favor of FDC to consider it as an meropenem sparing drug.

5. CONCLUSION

In conclusion, the present retrospective study revealed the comparable efficacy of FDC and meropenem for the management of pip-taz resistant ICU infections with different pathogens. Rise in the rates of meropenem resistance through out the world is the biggest threat to human health. To avoid further spread of carbapenem resistance, the need of hour is to spare carbapenems and restrict its use. Findings of present study clearly set the stage for FDC potential role in empirical treatment of pip-taz resistant cases and help the medical community in sparing and restricting the carbapenem use. This study also sheds light on an alternative option to use FDC along with colistin to successfully treat the patients which failed to respond to FDC/meropenem therapy. Pharmacoeconomic analysis also clearly shows that appropriate antibiotic therapy has a large impact on the treatment cost of ICU patients, with FDC therapy showing similar efficacy with lesser antibiotic and lesser hospitalization than meropenem. Thus the use of FDC (with the necessary combinations where needed) is preferable for the effective and economical treatment option than meropenem for the management of different types of infections in ICU populations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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