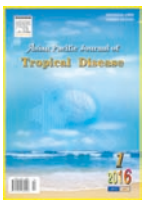
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Original article doi: 10.1016/S2222-1808(15)60981-1

Comparative pharmacoeconomics and efficacy analysis of a new antibiotic adjuvant entity and piperacillin-tazobactam for the management of intra-abdominal infections: A retrospective study

Sandip Jadhav*, Nitin Sawant

Shri Siddhivinayak Hospital and Criti Care, Lonad, Satara, Maharashtra 415521, India

ARTICLE INFO

Article history:
Received 15 Oct 2015
Received in revised form 30 Nov 2015
Accepted 10 Dec 2015
Available online 18 Dec 2015

Keywords:
Gram-negative bacteria
Intra-abdominal infections
Antibiotic adjuvant entity
Pharmacoeconomic analysis

ABSTRACT

Objective: To analyze the comparative efficacy of piperacillin-tazobactam (PIP-TAZ) and ceftriaxone-sulbactam with adjuvant (CSA) in the treatment of intra-abdominal infections (IAIs) and to assess the costs associated with respective therapies.
Methods: The present study analyzed the data collected from 94 IAI patients treated at a tertiary-care hospital. Patient characteristics, infection types, surgical procedures, antibiotic therapies, treatment durations were recorded and overall cost involved in the infections management was estimated in Indian rupee.
Results: In total, 46 patients received PIP-TAZ and 48 patients received CSA. The clinical cure was seen in 39.13% patients of PIP-TAZ group and 62.50% patients of CSA group. The patients diagnosed with mixed culture (Gram-positive and negative) infections, needed additional cover of clindamycin to achieve clinical success. The failure patients from PIP-TAZ group were shifted to meropenem therapy. For the patients where meropenem and CSA therapy failed, colistin was given as an additional cover. Comparative cost expenditure analysis of the two drug treatment groups revealed that, the overall treatment cost for patients cured with empirical PIP-TAZ group was 51.79% more than that of CSA therapy. The strongest predictor of the increase in treatment costs was clinical failure. Similar trends were maintained for the patients cured with clindamycin additional therapy and change of therapy, with PIP-TAZ group accounting 36.11% and 39.99% more expenditure than CSA group.
Conclusions: This study demonstrates that CSA has comparatively higher efficacy as compared to PIP-TAZ when used along with metronidazole in patients with different types of IAIs. Pharmacoeconomic analysis clearly shows that starting appropriate empirical antibiotic therapy has a large impact on the cost of treatment in management of IAIs and selection of CSA, can significantly reduce the cost involved in the treatment.

1. Introduction

Intra-abdominal infections (IAIs), encompassing a wide spectrum of pathological conditions from uncomplicated appendicitis to fecal peritonitis, are a common cause of morbidity worldwide[1]. Uncomplicated IAIs involve a single organ and do not spread to the peritoneum[2], where as, complicated IAIs can be referred to those infections, which results from perforation of the gastrointestinal tract that extend into the peritoneal space and are associated with either abscess formation or peritonitis[3,4]. Complicated IAIs are those that require a combination of appropriate and timely surgical source control and broad spectrum antimicrobial therapy for satisfactory clinical outcomes. Most of the complicated IAIs are polymicrobial in nature and often involve aerobic, facultative and obligate anaerobic microbes a plethora of Gram-positive anaerobes, with members of Enterobacteriaceae and *Bacteroides* sp. isolated most frequently[5-8].

The choice of prelusive empirical antimicrobial therapy for the treatment of IAIs is pivotal and needs careful consideration, as improper antimicrobial therapy may delay clinical outcome and increase the duration of hospital stay and risk of mortality[9,10]. The choice of antimicrobial therapy for IAIs depends on numerous factors including severity of the illness, whether the infection was community or hospital-acquired, and the history of bacterial resistance in the hospital and community[5]. Based on the patient characteristics, current guidelines recommend a wide range of first-line single or multiple antimicrobial regimens like carbapenem and combination therapies [piperacillin tazobactam (PIP-TAZ), third- or fourth-generation cephalosporins, or fluoroquinolones plus metronidazole] is recommended in high risk patients with severe IAIs[5].

Over the years, resistance to β-lactams among many Gram-

*Corresponding author: Dr. Sandip Jadhav, Shri Siddhivinayak Hospital and Criti Care, Lonad, Satara, Maharashtra 415521, India.
Tel: +91-9318001430
E-mail: sandipjadhav100@rediffmail.com

negative pathogens has been observed due to development of various resistance mechanisms including β-lactamase production, AmpC over expression, decreased outer membrane protein expression, and efflux pump up-regulation[11,12]. Recent reports pointed out the increase in the prevalence of PIP-TAZ resistant strains isolated from clinical specimens in intensive care unit[13,14]. The emergence of highly resistant strains, capable of producing novel carbapenem hydrolyzing β-lactamase has worsen the situation mainly because of the frequency with which they cause infections[15]. Therefore, new therapeutic options are needed for patients at high risk of infections caused by multi drug-resistant pathogens.

Ceftriaxone-sulbactam with adjuvant (CSA), a newly introduced antibiotic adjuvant entity (AAE) of ceftriaxone + sulbactam along with adjuvant disodium edetate is increasingly being used in Indian hospitals. Various reports of *in-vitro* susceptibility studies hint the possibility of this AAE to overcome the hurdles of both extended spectrum β-lactamases and metallo-β-lactamases producers clinically and it can be a potent alternative to treat infections caused by the multi-drug resistant bacteria[16-18].

Along with increasing mortality and morbidity rates, multi-drug-resistant Gram-negative bacterial infections also increase the duration of the hospital stay and higher health costs compared to those that result from infections with their antibiotic susceptible counter parts[19]. It is universally accepted that drug resistance results in prolonged hospitalization and higher economic costs compared to similar infections caused by antibiotic-susceptible Gram-negative bacteria[20-22]. In addition to significant morbidity and mortality for patients, IAIs consume substantial hospital resources. This is compounded by the potential misuse of antimicrobial agents that may result in suboptimal treatment as well as encourage the selection and spread of antibiotic-resistant microorganisms in the health care setting. In view of all these aspects, we have conducted a retrospective study aimed to assess the efficacy and pharmacoeconomic difference associated with treatment of different types of IAIs using CSA and commonly used drug PIP-TAZ.

2. Materials and methods

2.1. Study design

A retrospective study was conducted to evaluate the efficacy and pharmacoeconomic difference of *i.v.* PIP-TAZ and CSA (AAE) in patients with IAIs requiring parenteral antibiotic therapy. The patients were evaluated prior to the treatment, during treatment and at the end of the therapy. The present study was conducted at 115 bedded tertiary care hospital at Lonad, Maharashtra, India. The data of patients suffering from different IAIs who were treated between January 2013 and May 2015 were collected and analyzed for the antibiotic regimes used, microbiological and clinical outcome along with the cost involved in the therapy.

2.2. Treatment regimens

Patients received intravenous PIP-TAZ (3.375 g every 6 h) along with intravenous metronidazole (1 g every 6 h as standard of care) or intravenous CSA (1.5 g every 12 h) with metronidazole (1 g every 6 h as standard of care) empirically. PIP-TAZ or AAE were used randomly based on the clinical presentation and was at the discretion of doctor. The patient group that received PIP-TAZ with metronidazole empirically is referred to herein as the PIP-TAZ group and the group which received AAE plus metronidazole is referred to as CSA group. The empirical regimens were continued/given an additional cover/shifted to other antibiotics based on the microbiological susceptibility towards the respective antibiotics used and/or the clinical outcome after 2/3 days. Clindamycin, used as an additional cover in those patients diagnosed with Gram-positive bacterial infections was given at a dose of 600 mg every 8 h in either group. Colistin was used as an additional cover in failure cases of both groups at a loading dose of 6 mIU followed by TID doses of 3 mIU were used. Meropenem was used in cases which failed to respond to PIP-TAZ.

2.3. Inclusion and exclusion criteria for the analysis

Adult (age > 18) hospitalized male and female patients with confirmed IAIs requiring *i.v.* antibiotic therapy with a diagnosis of one of the following; ruptured appendix, hepatobiliary infections, colon perforation, infected diverticulitis, post-traumatic peritonitis, anal abscess, peritonitis, abdominal abscess were considered for the analysis. Along with these, the patients with suspected IAIs with abdominal cavity symptoms (fever, localized or diffuse abdominal wall rigidity or involuntary guarding, abdominal tenderness of pain, nausea, vomiting pain, absent or diminished bowel sounds) and systemic inflammatory response syndrome criteria [increased body temperature, increased heart rate (> 90 beats/min), increased respiratory rate (> 20 breaths/min) and white blood cell count > 12 000 cells/mm^3 or < 4000 cells/mm^3] were also considered. Demographic data, the type of initial surgery, and the origin, primary cause and type of infection were recorded at baseline. Disease severity was assessed using the acute physiology and chronic health evaluation (APACHE) score. Data of those patients in whom, systemic antibiotics had been used for 24 h in the 48-h period prior to the first dose of empirical therapy along with severely ill patients (APACHE II score of > 30) who had any life-threatening disease (including acute hepatic failure and hepatic disease) or immunocompromising illness leading to death were not considered for the analysis.

2.4. Microbiological evaluations and definitions

Pre-therapy samples obtained from the primary intra-abdominal site of infection were cultured for aerobic and anaerobic organisms and 2 sets of blood samples for culture were obtained within 24 h of the first dose of the empirical therapy. Minimum inhibitory concentrations of test antibiotics were determined for aerobic organisms according to Clinical and Laboratory Standards Institute broth micro dilution methodology. Anaerobes were tested by agar dilution according to Clinical and Laboratory Standards Institute guidelines[23]. The assessment of microbiological response at patient and isolate level was based on the results of the 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 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. Clinical assessments and definitions

Clinical signs and symptoms associated with IAIs were re-evaluated initially after 2/3 days of empirical antibiotic therapy, at serial visits during treatment and also at the end of therapy by the presence or absence of the signs and symptoms defined earlier. The clinical response was categorized as cure or failure. The clinical cure was defined as complete resolution or significant improvement in all signs and symptoms of the infection, so that no additional antibiotic therapy was essential. The therapy was considered as clinical failure in patients who had shown no improvement or persisted infection, or who required additional antibiotic cover for their infection.

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 of per day doses. 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 per unit of antibiotics. Hospitalization charges, laboratory tests, instrumental tests and overhead charges were directly recorded and their costs were individually assessed accordingly. Costs related to initial surgical procedures were not included in analysis, as we assume that they were independent of the adopted antibiotic therapy. Costs were expressed in Indian rupees.

3. Results

3.1. Patients and demographic characteristics

Initially, data for 138 IAIs patients treated at tertiary hospital were considered for the retrospective analysis. Among these, 44 patients were excluded from the analysis as they did not meet the study inclusion criteria (Figure 1). The demographic and baseline characteristics of the remaining 94 patients whose data were analyzed in this study are given in Table 1. The demographic and baseline characteristics of PIP-TAZ (n = 46) and CSA (n = 48) groups were generally compared. Both the treatment groups were dominated by male populations with the male: female ratio of 28:18 and 28:20 for PIP-TAZ and CSA group respectively. The average

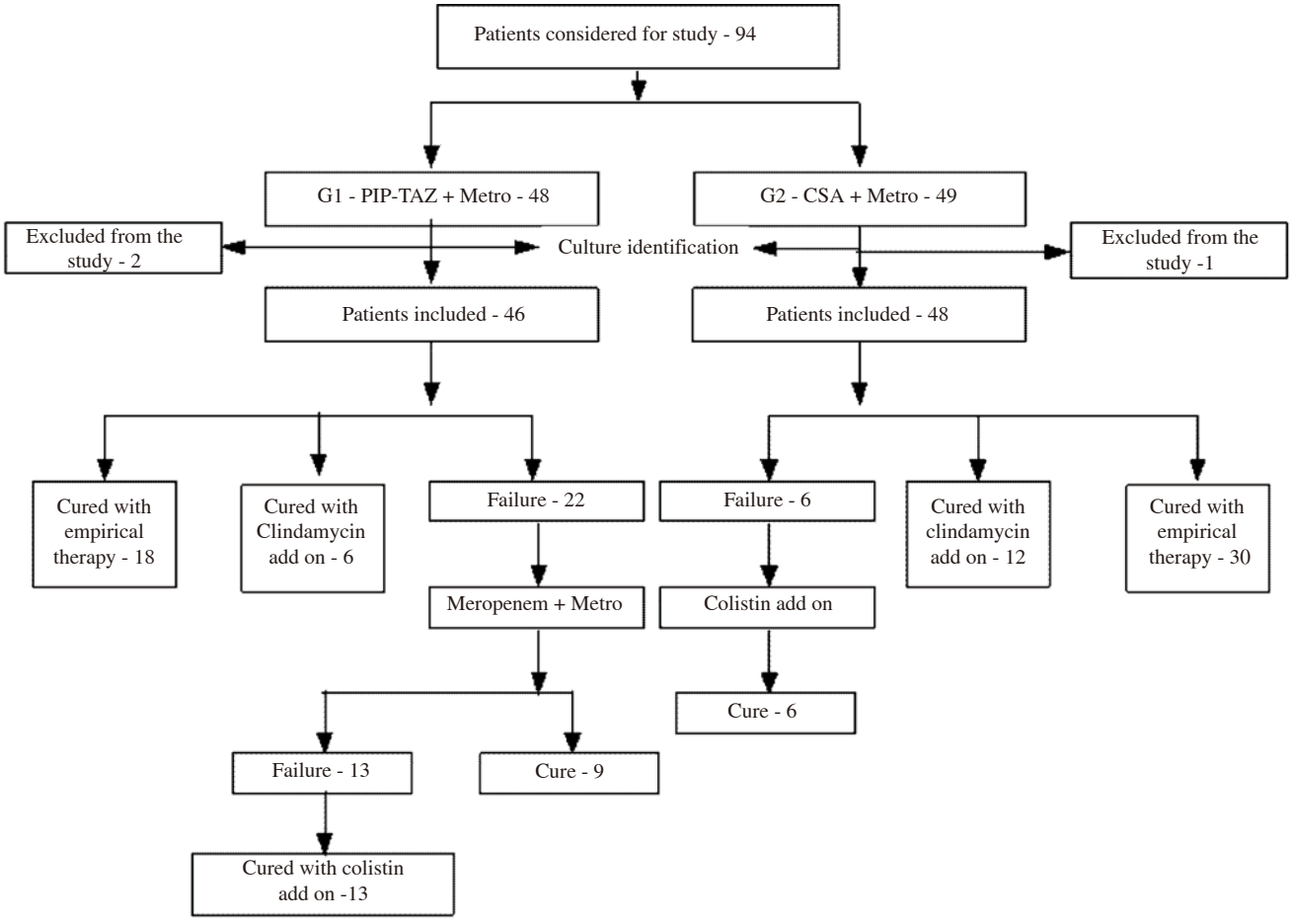


Figure 1. Overview of the study.

age of the patients treated in the PIP-TAZ group was (58.58 ± 14.39) years and the same for CSA was (59.12 ± 13.01) years. Majority of the patients in both groups had baseline APACHE II score of < 15 (PIP-TAZ 71.73%; CSA 62.50%). More number of patients in CSA group (37.50%) had APACHE II score of 15 than PIP-TAZ group which had 28.27% of patients with 15 APACHE II score. Laparotomy (n = 32) was the most common initial surgical intervention followed by incision and drainage (n = 19), hepatobiliary surgeries (n = 18), appendectomy (n = 13) and laparotomy with repair of the injured organs (n = 12) (Table 1).

Table 1
Baseline and demographic characteristics. n (%).

Characteristics	PIP-TAZ + Metro	CSA + Metro
Evaluable patients	46	48
Sex ratio - male: female	28:18 (60.86%:39.14%)	28:20 (58.33%:41.67%)
Age (mean ± SD)	58.58 ± 14.39	59.12 ± 13.01
APACHE II score		
< 15	33 (71.73)	30 (62.50)
15	13 (28.27)	18 (37.50)
Initial intervention type		
Appendectomy (13)	7 (15.21)	6 (12.50)
Laparotomy (32)	19 (41.30)	13 (27.08)
Laparotomy + repair of the injured organs (12)	5 (10.86)	7 (14.58)
Incision and drainage (14)	7 (15.21)	7 (14.58)
Hepatobiliary surgeries (18)	8 (17.39)	10 (20.83)

The most common diagnosed causes for IAIs were peritonitis (19.14%), hepatobiliary infections (19.14%), ruptured appendix (13.82%), post-traumatic peritonitis (12.76%), anal abscess (10.63%), abdominal abscess (9.57%), colon perforation (7.44%), infected diverticulitis (7.44%). The predominant site of origin of infection was found to be hepatobiliary systems (30.85%) followed by intestine (25.53%) colon (21.27%), appendix (18.08%), anal canal (10.63%) and the least number of cases had diverticulum (7.44%) and stomach (5.31%) as their site of origin of infection (Tables 2 and 3).

Table 2
Primary diagnosis for different IAIs. n (%).

Diagnosis	Total No.	PIP-TAZ + Metro[a]	CSA + Metro[a]
Ruptured appendix	13 (13.82)	7 (15.21)	6 (12.50)
Hepatobiliary infections	18 (19.14)	8 (17.39)	10 (20.83)
Colon perforation	7 (7.44)	4 (8.69)	3 (6.25)
Infected diverticulitis	7 (7.44)	4 (8.69)	3 (6.25)
Post-traumatic peritonitis	12 (12.76)	5 (10.86)	7 (14.58)
Anal abscess	10 (10.63)	4 (8.69)	6 (12.50)
Peritonitis	18 (19.14)	11 (23.91)	7 (14.58)
Abdominal abscess	9 (9.57)	3 (6.52)	6 (12.50)

[a]: Patients may have had more than one infection site.

Table 3
Site of origin of infection for different IAIs. n (%).

Site of origin of infection	Total No.	PIP-TAZ + Metro[a]	CSA + Metro[a]
Appendix	17 (18.08)	8 (17.39)	9 (18.75)
Colon	20 (21.27)	9 (19.56)	11 (22.91)
Diverticulum	7 (7.44)	4 (8.69)	3 (6.25)
Intestine	24 (25.53)	10 (21.73)	14 (29.16)
Stomach	5 (5.31)	3 (6.52)	2 (4.16)
Hepatobiliary system	29 (30.85)	12 (26.08)	17 (35.41)
Anal canal	10 (10.63)	4 (8.69)	6 (12.50)

[a]: Patients may have had more than one infection site.

3.2. Baseline microbial pathogens

A total of 173 bacterial pathogens were isolated from 94 patients suffering from IAIs. Among these 94 patients, only 27 (28.72%) patients were diagnosed with mono-microbial infections and the remaining patients [67 (71.28%)] had polymicrobial infections. Among the isolated pathogens, Gram-negative bacteria had a significantly higher share with *Escherichia coli* (*E. coli*) being the most predominant pathogen (25.43%) closely followed by *Pseudomonas* sp. (21.38%), *Klebsiella* sp. (19.07%) and *Klebsiella oxytoca* (*K. oxytoca*) (14.45%). Totally 16 patients (9.24%) were identified with anaerobic bacterial (*Bacteroides* sp.) infection, while 18 suffered with mixed Gram-negative and Gram-positive bacterial infections [with *Staphylococcus aureus* (*S. aureus*) 13 (7.51%) and *Streptococcus faecalis* (*S. faecalis*) 5 (2.89%)] (Table 4).

3.3. Microbial success assessment for per patient

All the 27 IAIs patients diagnosed with Gram-negative mono culture infections, were treated randomly with either CSA or PIP-TAZ along with metronidazole and achieved 100% microbiological success rates. On the other hand, the patients with poly culture infections were diagnosed with the combination of two or more cultures of the following; *E coli*, *Pseudomonas* spp., *Klebsiella* spp., *K. oxytoca*, *S. aureus*, *S. faecalis* and *Bacteroides* sp. In these patients, CSA group achieved significantly higher microbial success rates (54.83%) as compared to PIP-TAZ group in which only 8 (22.22%) achieved microbial success. However, in poly culture diagnosed patients with Gram-positive bacteria, both groups achieved microbial success after additional cover of clindamycin was given. The detailed break up for per patient microbial success in different poly cultural infection cases is depicted in Table 4, and it strongly suggested the considerable higher microbial success rates in CSA group than PIP-TAZ group.

3.4. Clinical success assessment

Result of clinical outcomes of the antibiotic therapies in different IAIs was in accordance with the microbiological success, except in a few cases where false susceptibility and clinical failures were observed. Clinical success rates in empirical therapy were the highest in CSA group [30/48 (62.50%)] as compared to PIP-TAZ group [18/46 (39.13%)]. The success rates of PIP-TAZ: CSA group in different IAIs was as follows; ruptured appendix [3/7 (42.85%):4/6 (66.66%)], hepatobiliary infections [4/8 (50.00%):6/10 (60.00%)], colon perforation [1/4 (25.00%):2/3 (66.66%)], infected diverticulitis [2/4 (50.00%):2/3 (66.66%)], post-traumatic peritonitis [1/5 (20.00%):4/7 (57.14%)], anal abscess [2/4 (50.00%):3/6 (50.00%)], peritonitis [3/11 (27.27%):5/7 (71.42%)] and abdominal abscess [2/3 (66.66%):4/6 (66.66%)] (Table 5). The mean duration for the patients treated empirically in PIP-TAZ group was (11.16 ± 1.42) days and the same in CSA group was (7.93 ± 0.90) days. Six patients in PIP-TAZ group and 8 patients in CSA group, who were given an additional antibiotic cover of clindamycin after the identification of Gram-positive bacteria, achieved 100% clinical success with

Table 4

Per patient microbial success rates treated with different antibiotic regimes.

Pathogens	Success rate [No. of successes/Total No. (%)]						
	PIP-TAZ+ Metro group				CSA + Metro group		
	Empirical therapy	Clindamycin add on therapy	Shifted therapy (CSA + Metro)	Colistin add on therapy	Empirical therapy	Clindamycin add on therapy	Colistin add on therapy
Mono culture							
E. coli	2/2 (100)	0/0	0/0	0/0	7/7 (100)	0/0	0/0
K. oxytoca	3/3 (100)	0/0	0/0	0/0	3/3 (100)	0/0	0/0
Klebsiella sp.	4/4 (100)	0/0	0/0	0/0	4/4 (100)	0/0	0/0
Pseudomonas sp.	1/1 (100)	0/0	0/0	0/0	3/3 (100)	0/0	0/0
Mixed cultures combinations							
E. coli + *K. oxytoca*	2/4 (50)	0/0	1/2 (50)	1/1 (100)	2/2 (100)	0/0	0/0
E. coli + *Pseudomonas* sp.	2/6 (33.33)	0/0	0/4 (0)	4/4 (100)	4/4 (100)	0/0	0/0
K. oxytoca + *Pseudomonas* sp.	2/4 (50)	0/0	1/2 (50)	1/1 (100)	3/4 (75)	0/0	1/1 (100)
Klebsiella sp. + *E. coli*	2/4 (50)	0/0	0/2 (0)	2/2 (100)	2/2 (100)	0/0	0/0
E. coli + *S. aureus*	0/1 (0)	1/1 (100)	0/0	0/0	0/0	0/0	0/0
E. coli + *Klebsiella* sp. + *S. aureus*	0/2 (0)	2/2 (100)	0/0	0/0	0/3 (0)	3/3 (100)	0/0
Klebsiella sp. + *Pseudomonas* sp. + *S. aureus*	0/1 (0)	1/1 (100)	0/0	0/0	0/1 (0)	1/1 (100)	0/0
Klebsiella sp. + *S. aureus*	0/1 (0)	1/1 (100)	0/0	0/0	0/0	0/0	0/0
Klebsiella sp. + *Pseudomonas* sp. + *S. faecalis*	0/1 (0)	1/1 (100)	0/0	0/0	0/1 (0)	1/1 (100)	0/0
E. coli + *Bacteroides* sp.	0/3 (0)	0/0	2/3 (66.66)	1/1 (100)	0/1 (0)	0/0	1/1 (100)
K. oxytoca + *Bacteroides* sp.	0/2 (0)	0/0	1/2 (50)	1/1 (100)	0/2 (0)	0/0	2/2 (100)
Klebsiella sp. + *Bacteroides* sp.	0/3 (0)	0/0	1/3 (33.33)	2/2 (100)	0/1 (0)	0/0	1/1 (100)
Pseudomonas sp. + *Bacteroides* sp.	0/4 (0)	0/0	3/4 (75)	1/1 (100)	0/0	0/0	0/0
Klebsiella sp. + *Pseudomonas* sp.	0/0	0/0	0/0	0/0	2/3 (66.66)	0/0	1/1 (100)
E. coli + *Pseudomonas* sp. + *S. aureus*	0/0	0/0	0/0	0/0	2/2 (100)	0/0	0/0
E. coli + *Pseudomonas* sp. + *S. faecalis*	0/0	0/0	0/0	0/0	1/1 (100)	0/0	0/0
K. oxytoca + *S. aureus*	0/0	0/0	0/0	0/0	1/1 (100)	0/0	0/0
Klebsiella sp. + *S. faecalis*	0/0	0/0	0/0	0/0	0/2 (0)	2/2 (100)	0/0
Pseudomonas sp. + *S. aureus*	0/0	0/0	0/0	0/0	0/1 (0)	1/1 (100)	0/0

Table 5

Clinical success rates among different IAIs treated with different antibiotic regimes.

Indication	Total No. of cases	Clinical Success rate [No. of successes/Total No. (%)]						
		PIP-TAZ + Metro group				CSA + Metro group		
		Empirical therapy	Clindamycin add on	Shifted therapy (CSA + metro)	Colistin add on therapy	Empirical therapy	Clindamycin add on	Colistin add on therapy
Ruptured Appendix	13	3/7 (42.85)	2/2 (100)	1/2 (50.0)	1/1 (100)	4/6 (66.66)	2/2 (100)	0/0
Hepatobiliary infections	18	4/8 (50.00)	2/2 (100)	1/2 (50.0)	1/1 (100)	6/10 (60.00)	3/3 (100)	1/1 (100)
Colon Perforation	7	1/4 (25.00)	1/1 (100)	2/2 (100.0)	0/0	2/3 (66.66)	1/1 (100)	0/0
Infected Diverticulitis	7	2/4 (50.00)	1/1 (100)	0/1 (0)	1/1 (100)	2/3 (66.66)	1/1 (100)	0/0
Post traumatic peritonitis	12	1/5 (20.00)	0/0	1/4 (25.0)	3/3 (100)	4/7 (57.14)	1/1 (100)	2/2 (100)
Anal abscess	10	2/4 (50.00)	0/0	1/2 (50.0)	1/1 (100)	3/6 (50.00)	2/2 (100)	1/1 (100)
Peritonitis	18	3/11 (27.27)	0/0	3/8 (37.5)	5/5 (100)	5/7 (71.42)	1/1 (100)	1/1 (100)
Abdominal Abscess	9	2/3 (66.66)	0/0	0/1 (0)	1/1 (100)	4/6 (66.66)	1/1 (100)	1/1 (100)

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.

mean treatment duration of (12.83 ± 0.75) and (10.16 ± 1.26) days respectively. On the other hand, an outcome of clinical failure was observed for 22 patients in PIP-TAZ group and 6 patients in CSA group. The patients in whom therapy failed ranged in age from 19 to 84 years and were suffering from different IAIs. Reasons for clinical failure were the persistent or recurrent infection requiring treatment with additional antibiotics. The clinical and microbiological success were consistent with the respective bacterial susceptibilities.

The 22 failure patients from PIP-TAZ group were shifted to meropenem + metronidazole and 9 out of these 22 achieved clinical success and the remaining 13 were given additional antibiotic cover of colistin. The mean treatment duration for these 22 patients was (14.59 ± 3.09) days. On the other hand, 6 patients from CSA group were also given colistin as an additional therapy to achieve clinical success with mean treatment duration of (11.16 ± 1.16) days (Table 6).

3.5. Antibiotic therapy cost analysis

The cost expenditure for the patients considered in the study is depicted in Table 7. The average cost of the empirical drugs used to treat the patients in PIP-TAZ group (35 923.16 ± 4 582.85) was significantly higher (approx 180.20%) as compared to the cost of CSA group empirical drugs (12 820.26 ± 1 441.37). Significant difference (40.75%) of cost towards hospitalization and overhead charges (diagnosis and instrumentations) was also observed. The average overall treatment charges for PIP-TAZ group (245 856.50

Table 6

Treatment duration for different patient groups.

Patient groups	Mean treatment duration (days)		Difference of treatment duration (%)
	PIP-TAZ Group	CSA group	
Patients cured with empirical therapy	11.16 ± 1.42	7.93 ± 0.90	40.73
Patients cured with clindamycin add on therapy	12.83 ± 0.75	10.16 ± 1.26	26.27
Patients cured with change of therapy	14.59 ± 3.09	11.16 ± 1.16	30.73

The data were presented as mean ± SD.

Table 7

Cost expenditure analysis.

Cost expenditure	PIP-TAZ + Metro group (A)	CSA + Metro group (B)	Difference among two drugs (% more cost involved in A compared to B)
Cost expenditure summary of patients responded to empirical therapy			
Number of patients cured with empirical therapy	18/46 (39.13%)	30/48 (62.50%)	
Average cost of drugs	35 923.16 ± 4 582.85	12 820.26 ± 1 441.37	180.20
Average hospital and overhead charges	209 933.33 ± 26 781.99	149 146.66 ± 16 768.45	40.75
Average overall treatment charges (dugs + hospital and overhead charges)	245 856.50 ± 31 364.85	161 966.93 ± 18 521.13	51.79
Cost expenditure summary of patients cured with clindamycin add on therapy			
Average cost of drugs	48 909.83 ± 2 876.50	22 054.33 ± 2 760.68	121.76
Average hospital and overhead charges	241 266.66 ± 14 152.12	191 133 ± 23 825.32	26.22
Average overall treatment charges (dugs + hospital and overhead charges)	290 176.50 ± 17 009.42	213 187.66 ± 26 574.07	36.11
Cost expenditure summary of patients cured with change of therapy			
Average cost of drugs	75 189.40 ± 27 547.25	39 720.33 ± 3 941.84	89.29
Average hospital and overhead charges	274 309.09 ± 58 208.94	209 933.33 ± 21 978.04	30.66
Average overall treatment charges (dugs + hospital and overhead charges)	349 498.50 ± 85 337.23	249 653.66 ± 25 843.87	39.99

The data were presented as mean ± SD.

± 31 364.85) was 51.79% higher than that of CSA group charges (161 966.93 ± 18 521.13). Similar pattern of costs were observed for the patients cured with clindamycin additional cover antibiotic therapy. There was a considerable difference (approx 121.76%) between the average cost of drugs in PIP-TAZ group and CSA group [(48 909.83 ± 2 876.50) and (22 054.33 ± 2 760.68)] respectively. The average overall treatment charges in the PIP-TAZ group (290 176.50 ± 17 009.42) was 36.11% higher than that of CSA group charges (213 187.66 ± 26 574.07). Similarly, there was no change in the cost expenditure pattern among both groups cured with change of therapy and/or colistin additional cover. The overall treatment cost in such patients treated in PIP-TAZ group (349 498.50 ± 85 337.23) was 39.99% higher than that of CSA group charges (249 653.66 ± 25 843.87) (Table 7).

4. Discussion

IAIs are the second most common in the health-care settings causing severe sepsis and septic shocks, in fact various data bases show that one in four cases of severe sepsis and septic shocks are caused due to IAIs[24-27]. The delayed diagnosis and improper antibiotic usage are thought to be the prime causes of clinical failures and increased morbidity and mortality[28]. Carbapenems, combinations of penicillins with β-lactamase inhibitors, extended spectrum of cephalosporins and fluoroquinolones usually in combination with metronidazole are currently recommended for the management of IAIs[4,29]. The present study retrospectively analyzed data collected for 94 patients suffering from mild (APACHE II < 15) to severe (APACHE II 15) IAIs and treated empirically with PIP-TAZ or CSA in combination with metronidazole.

Soon after the confirmed or highly suspected diagnosis of IAIs, antibiotic therapy was initiated along with the appropriate and adequate surgical source control measures. Without adequate drainage or debridement and restoration of anatomic structures, antibiotic therapy will be ineffective or will be administered for a prolonged duration and may unnecessarily lead to increased antimicrobial resistance[30]. The most common site of infections for different types of the IAIs were hepatobiliary system, intestine, colon, appendix anal canal and stomach. The timing and adequacy of source control are the most important issues in the management of IAIs and the early control of the source can be achieved either by non-surgical or surgical means[31]. The non-surgical procedures like drainages of the abscess were carried out for the management of abdominal and anal abscess. Surgical procedures like laparotomy with or without repair of the injured organ, appendectomy and hepatobiliary surgeries are used for the management of IAIs subtypes like colon perforation, infected diverticulitis, peritonitis, post-traumatic peritonitis, ruptured appendix and hepatobiliary infections respectively.

Bacterial pathogens isolated from the patients at baseline were almost similar among PIP-TAZ and CSA groups. Similar results for the baseline pathogens have been reported by Lucasti *et al.*[3]. The most common pathogens isolated from the patients were *E. coli*, *Pseudomonas* sp., *Klebsiella* sp., *K. oxytoca*, *S. aureus*, *S. faecalis* and *Bacteroides* sp., with members of the Enterobacteriaceae family dominating the population. Per patient microbial success data analysis for both the drug group yielded expected results with higher microbial success rates in mono culture infections as compared to mixed culture infections. However, the analysis also highlights significantly higher microbial success rates among CSA group as compared to PIP-TAZ group. On the other hand, in the patients with identified Gram-positive infection, microbial success was observed

with clindamycin additional cover, advocating the essentialness of the Gram-positive antibacterial cover in mixed culture infections.

The results of the clinical success assessment for the analyzed antibiotics were in accordance with the results of the microbial success rates. The results revealed that, the clinical cure rate for empirical therapy among PIP-TAZ group patients was low (39.13%) with only 18 out of 46 achieving clinical success. Higher failure rate may be attributed to the identified PIP-TAZ intermediate resistant isolates, false susceptible results obtained in *in-vitro* susceptibility testing or to the inconsistent efficacy of drug in *in-vitro* and *in-vivo* conditions. Similar rates were reported by Sartelli *et al*.[2], reporting 55% cure rates with PIP-TAZ in the hospital acquired IAIs. Out of 22 failure patients from PIP-TAZ group who were shifted to meropenem therapy, 9 patients (40.90%) achieved clinical success and the remaining 13 (59.10%) patients required an additional cover of colistin to get cured. However, 6 failure cases of CSA group treated with colistin combination therapy achieved complete clinical cure. Clinical success in failure patients of both the groups was achieved with colistin additional cover. However, the empirical CSA therapy has better efficacy than PIP-TAZ with 62.50 % clinical cure rates. These higher cure rates strongly advocate the CSA usage appropriateness in PIP-TAZ intermediate resistant and false susceptible cases.

The clinical assessment data analyzed reveal that the clinical efficacy of PIP-TAZ and CSA differs among different types of IAIs, with CSA being more efficacious in majority of the infections. The highest difference among the two groups were observed in the patients suffering from peritonitis (27.27%–71.42%) followed by colon perforation (25.00%–66.66%), post-traumatic peritonitis (20.00%–57.14%), ruptured appendix (42.85%–66.66%), infected diverticulitis (50.00%–66.66%), hepatobiliary infections (50.00%–60.00%). There was no difference observed among the groups in clinical efficacies while treating the patients suffering with anal abscess and abdominal abscess. Interestingly, no consistent demographic or baseline characteristics between patients for whom treatment failed were noted, suggesting that there was no relationship between the risk factors for poor response and those for poor clinical outcome for the treatment groups.

Clinical failure is believed to be the strongest independent predictor of increased hospital costs. Compared to the ones treated successfully, patients who failed to receive appropriate antibiotic therapy resulted in the increased antibiotic cost by failures. Cost expenditure analysis for PIP-TAZ and CSA empirical therapy revealed that, 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[32,33]. The present study shows the substantial increase in the hospitalization costs in clinical failure cases in comparison with the patients who achieved clinical success. However, the average antibiotic costs for patients who achieved clinical success with empirical PIP-TAZ therapy was 180.20% more than that of CSA cured patients. Similar expenditure trends were observed for patients failed to respond to empirical therapies (cured with clindamycin or change of therapy) with PIP-TAZ group spending 121.76% or 89.29% more amount for drugs than that of CSA treated group. Antibiotic therapy was the leading contributor to inpatient charges, and multiple drug regimens was an independent predictor of increases in costs. The overall treatment cost for successful patients treated with PIP-TAZ group was 51.79% more than that of CSA treated group. Similarly, the patients cured with clindamycin additional cover also resulted in 36.11% higher expenditure in PIP-TAZ group as compared to CSA group. The same trends were maintained for empirical therapy failure cases with a cost difference of 39.99% in favor of the CSA group. Our results are in accordance with previous studies which have shown that antibiotics contribute up to 70% of extra costs associated with IAIs[33]. This large proportion of clinical failure costs deriving from antibiotic therapy most probably arises from the overlap existing between the failure of antibiotic therapy and clinical failure. Although clinical failure, a widely employed measure of drug effectiveness[10,32-35], is a composite of three different outcomes (antibiotic therapy switch, re-operation or death), in most instances, it is driven by failure of first-line antibiotic therapy[1].

In conclusion, the present retrospective study revealed the comparative efficacy and superiority of the CSA over PIP-TAZ in different IAIs. The rise in the rates of clinical failures in PIP-TAZ group, in many types of IAIs, sets the stage for CSA potential role in the empirical treatment of these conditions. This study sheds light on an alternative option to use CSA along with colistin to successfully treat the patients which failed to respond to CSA mono therapy. Pharmacoeconomic analysis clearly shows that starting empirical antibiotic therapy has a large impact on the cost of treatment in IAIs, with CSA therapy showing higher efficacy with lesser antibiotic and lesser hospitalization charges. Thus the selection of CSA empirically with the necessary source control procedures is preferable for the effective and economical treatment option for the management of different types of IAIs.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Dalfino L, Bruno F, Colizza S, Concia E, Novelli A, Rebecchi F, et al. Cost of care and antibiotic prescribing attitudes for community-acquired complicated intra-abdominal infections in Italy: a retrospective study. *World J Emerg Surg* 2014; **9**: 39.

[2] Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M, et al. 2013 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg* 2013; **8**: 3.

[3] Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. *J Antimicrob Chemother* 2013; **68**: 1183-92.

[4] Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-

abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50**: 133-64.

[5] Solomkin JS, Mazuski JE, Baron EJ, Sawyer RG, Nathens AB, DiPiro JT, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. *Clin Infect Dis* 2003; **37**: 997-1005.

[6] Swenson BR, Metzer R, Hedrick TL, McElearney St, Evans HL, Smith RL. Choosing antibiotics for intra-abdominal infections: what do we mean by "high risk"? *Surg Infect (Larchmt)* 2009; **10**(1): 29-39.

[7] Chow AW, Evans GA, Nathens AB, Ball CG, Hansen G, Harding GK, et al. Canadian practice guidelines for surgical intra-abdominal infections. *Can J Infect Dis Med Microbiol* 2010; **21**(1): 11-37.

[8] Nichols RL, Muzik AC. Enterococcal infections in surgical patients: the mystery continues. *Clin Infect Dis* 1992; **15**: 72-6.

[9] Arabi YM, Dara SI, Memish Z, Abdulkareem AA Tamin HM, Al-Shirawi N, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. *Hepatology* 2012; **56**(6): 2305-15.

[10] Krobot K, Yin D, Zhang Q, Sen S, Altendorf-Hofmann A, Scheele J, et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community acquired intra-abdominal infections requiring surgery. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 682-7.

[11] Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev* 2009; **22**: 582- 610.

[12] Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 2001; **14**: 933-51.

[13] Lee J, Oh CE, Choi EH, Lee HJ. The impact of the increased use of piperacillin/tazobactam on the selection of antibiotic resistance among invasive *Escherichia coli* and *Klebsiella pneumoniae* isolates. *Int J Infect Dis* 2013; **17**: 638-43.

[14] Mohammedi I, Ploin D, Duperret S, Chapuis F, Petit P. Risk factors for piperacillin/tazobactam-resistant *Escherichia coli* in ICU patients: a clinical study. *Intensive Care Med* 2003; **29**: 1164-8.

[15] Patel G, Bonomo RA. "Stormy waters ahead": global emergence of carbapenemases. *Front Microbiol* 2013; **4**: 48.

[16] Sahu M, Sanjith S, Bhalekar P, Keny D. Waging war against extended spectrum Beta lactamase and metallo betalactamase producing pathogens- novel adjuvant antimicrobial agent cse1034- an extended hope. *J Clin Diagn Res* 2014; **8**: DC20-3.

[17] Chaudhary M, Kumar S, Payasi A. *In vitro* susceptibilities of clinical isolates of *Escherichia coli* and *Klebsiella* species to CSE1034 and other β-lactams. *J Antibiot (Tokyo)* 2013; **66**: 495-7.

[18] Chaudhary M, Payasi A. Molecular characterization and *in vitro* susceptibilities of β-lactamase producing *Escherichia coli*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* to CSE1034 and other β-lactams. *Asian Pac J Trop Med* 2014; **7**: S217-23.

[19] Holmberg SD, Solomon SL, Blake PA. Health and economic impacts of antimicrobial resistance. *Rev Infect Dis* 1987; **9**: 1065-78.

[20] Ng E, Earnest A, Lye DC, Ling ML, Ding Y, Hsu Y. The excess financial burden of multidrug resistance in severe Gram-negative infections in Singaporean hospitals. *Ann Acad Med Singapore* 2012; **41**: 189-93.

[21] Nathwani D, Raman G, Sulham K, Gavaghan M, Menon V. Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 2014; **3**: 32.

[22] Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant Gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.

[23] Clinical Laboratory Standard Institute. Performance standards for antimicrobial susceptibility testing; Twenty-second informational supplement. Vol 32. Wayne: Clinical Laboratory Standard Institute; 2012. [Online] Available from: http://antimicrobianos.com.ar/ATB/wp-content/uploads/2012/11/M100S22E.pdf [Accessed on 15th December, 2015]

[24] Mazuski JE, Solomkin JS. Intra-abdominal infections. *Surg Clin North Am* 2009; **89**: 421-37.

[25] Dupont H, Friggeri A, Touzeau J, Airapetian N, Tinturier F, Lobjoie E, et al. Enterococci increase the morbidity and mortality associated with severe intra-abdominal infections in elderly patients hospitalized in the intensive care unit. *J Antimicrob Chemother* 2011; **66**(10): 2379-85.

[26] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; **136**: 1237-48.

[27] Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med* 2008; **33**: 606-18.

[28] Falagas ME, Barefoot L, Griffith J, Ruthazar R, Snydman DR. Risk factors leading to clinical failure in the treatment of intra- abdominal or skin/soft tissue infections. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 913-21.

[29] Guirao X, Arias J, Badía JM, Garcia-Rodriguez JA, Mensa J, Alvarez-Lerma F, et al. [Recommendations in the empiric anti-infective agents of intra-abdominal infection]. *Rev Esp Quimioter* 2009; **22**: 151-72. Spanish.

[30] Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. *Drugs* 2005; **65**: 1611-20.

[31] Sartelli M. A focus on intra-abdominal infections. *World J Emerg Surg* 2010; **5**: 9.

[32] Cattan P, Yin DD, Sarfati E, Lyu R, De Zelicourt M, Fagnani F. Cost of care for inpatients with community-acquired intra- abdominal infections. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 787-93.

[33] Sturkenboom MC, Goettsch WG, Picelli G, int't Veld B, Yin DD, de Jong RB, et al. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. *Br J Clin Pharmacol* 2005; **60**: 438-43.

[34] Reygaert WC. Antibiotic optimization in the difficult-to-treat patient with complicated intra-abdominal or complicated skin and skin structure infections: focus on tigecycline. *Ther Clin Risk Manag* 2010; **6**: 419-30.

[35] Edelsberg J, Berger A, Schell S, Mallick R, Kuznik A, Oster G. Economic consequences of failure of initial antibiotic therapy in hospitalized adults with complicated intra-abdominal infections. *Surg Infect (Larchmt)* 2008; **9**: 335-47.