International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

The Effect of Ceftazidime/Avibactam Plus Metronidazole Over Meropenem for the Treatment of Complicated Intra-Abdominal Infection in Adult Patients – A Systematic Review and Meta-Analysis

*Jyothi Krishna P, Prithika S I, Pooja Sudarsan, Aswathy V S, K. Rohith Chandra[1], Arun KP**

[1]*Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, 643001, The Nilgiris, Tamil Nadu, India.*

Abstract

Complicated Intra-abdominal infections (cIAIs) are the most common infectious diseases in clinical settings. Antibiotic resistance among microorganisms, particularly Gram-negative bacteria, has become a major concern for doctors treating cIAIs. still have extremely high mortality rates. This study examined the effect of ceftazidime/avibactam (CAZ-AVI) plus metronidazole over meropenem in adult patients using a systematic review and meta-analysis. Three randomized controlled trials were obtained after searching Cochrane CENTRAL, PubMed, and Scopus. The 95 % Confidence Intervals (CI) and Risk difference (RD) were determined using a fixed effect model. CAZ-AVI with metronidazole showed a lower clinical cure rate in CE, TOC, EOT and LFU patients (RD: -0.01; 95% CI: -0.02%, 0.01%; I^2=0%) and the clinical cure rate at TOC in nMITT population was higher (RD: -0.04; 95%CI: -0.08 to -0.00). No significance difference observed with Adverse events (AE) and serious adverse events (SAE) (RD: 0.02; 95% CI: -0.01%, 0.04%; I^2=0%). Based on these findings, the study indicated that CAZ-AVI plus metronidazole is not a superior substitute to meropenem for the management of cIAI.

Keywords: Complicated Intra-Abdominal Infection, meropenem, ceftazidime/avibactam, metronidazole, antimicrobial resistance, randomized controlled trials

Full length article **Corresponding author's* e-mail: kparun@jssuni.edu.in

1. Introduction

Complicated intra-abdominal infections (cIAIs) are life-threatening microbial infections that spread beyond the gut wall into the peritoneal cavity, producing serious health consequences including significant morbidity and mortality [1]. cIAIs are caused by perforation or necrosis of the gastrointestinal tract viscera, as well as bacterial invasion into the peritoneal and retroperitoneal regions [2, 3, 4]. cIAIs have been related to Gram-negative bacteria such as E. coli, Klebsiella pneumoniae, and Enterobacter species, as well as other resistant infections. And they are regarded to be the cause of the biggest number of incidents worldwide [5]. Antibiotics termed β-lactams are commonly used to treat Gram-negative infections like cIAI and carbapenems becoming a more prominent treatment option. Meropenem, a broad-spectrum beta-lactam antibiotic, is more effective against gram-negative pathogens than imipenem and has been linked to a shorter hospital stay and treatment duration in patients with complicated intra-abdominal infections.

However, the rising occurrence of infections caused by β-lactam-resistant microorganisms has greatly diminished their utility for empiric therapy [6]. Furthermore, the emergence of carbapenem-resistant *Enterobacteriaceae* is becoming a major concern. As a result, successful treatment of cIAIs requires both effective source management and empirical antimicrobial therapy, carbapenem-sparing medicines are in high demand [7, 8]. According to the Centers for Disease Control and Prevention in the United States (CDC), some of the most common Gram-negative bacteria that cause cIAIs and other infections have evolved resistance to currently available antibiotics [9]. *Enterobacteriaceae* isolates are major causes of community-acquired and healthcare-associated infections (HAI), with the latter being more prevalent among ICU patients [10]. This combination of therapy has been approved in United states.

Lucasti C et.al., and Mazuski JE et.al., described that, CAZ-AVI seems to be a fixed-dose combination medication comprising ceftazidime, an established, extended

spectrum cephalosporin antibiotic works by binding to penicillin-binding proteins (PBPs) and preventing peptidoglycan crosslinking during cell wall synthesis, resulting in bacterial cell death and rupture) and avibactam, a unique, non-β-lactam, β-lactamase inhibitor that has potent inhibitory activity against most Ambler classes A, C, and some class D serine β-lactamases [11-13]. The aim of this work is to determine if CAZ-AVI with metronidazole is preferable over meropenem for the management of cIAIs based on RCT studies.

2. Methodology

2.1. Search methods

Studies were found through a systematic analysis of the literature in electronic databases such as PubMed, Embase, and Cochrane CENTRAL, using relevant MeSH (Medical Subject Heading) terms such as "ceftazidime/avibactam" AND “metronidazole” AND “Complicated intra-abdominal infection” AND “meropenem” AND “adult” OR “ceftazidime/avibactam drug combination” AND “randomized controlled trials” OR “carbapenems” OR “Adolescents” OR “cephalosporin combination therapy” from 10th April 2020 to 11th May 2020, studies published since 2010 were considered for inclusion. Clinicaltrials.gov and ICTRP (International Clinical Trial Registry Platform) were used to locate ongoing trials.

2.2. Study selection criteria

RCT, placebo-controlled trials, and quasi-randomized studies were all taken into consideration for inclusion. RCT studies evaluating the effectiveness of CAZ-AVI plus metronidazole vs meropenem for the treatment of cIAI, were included. The review excluded trials on pharmacokinetic variables, articles without full text, review articles, editorials, letters, case reports, articles written in a foreign language, and conference abstracts.

2.3. Type of participants

Studies that recruited adult participants with cIAI were confirmed based on clinical assessment, specimen culture, intra-operatively or postoperatively upon visual confirmation, laparoscopic findings, and confirmed during surgical intervention or percutaneous draining of an abscess.

2.4. Study selection

The authors proposed a study hypothesis based on current trends on anti-microbial resistance in cIAIs and formulated and finalised the research question. Five impartial reviewers conducted a literature search to obtain all relevant citations pertaining on the topic of interest. The retrieved literature was exported to Rayyan using Zotero, and the study abstracts were evaluated against the eligibility criteria. To reduce bias, the researchers were blinded during the screening phase. Finally, the results were discussed and any discrepancies were resolved by the sixth and seventh reviewer.

2.5. Data extraction and Management

The modified Cochrane data extraction forms specifically designed for RCTs was used to extract data. The form was filled out with author information, publication date, study design, location, participant demographics, type of outcome measurements, intervention, control, and various outcome measurement tools. Data was extracted from the included studies by three reviewers, which were then cross-checked by other reviewers. An excel spreadsheet was created based on the designed form, and any questions about missing data were directed to the appropriate study investigators for clarification.

2.6. Risk of bias (quality) assessment

The risk of bias was assessed using a modified Cochrane collaboration tool (RevMan 5.4). The risk of bias of the included studies was assessed by three review authors, and the variances were cross-checked by the remaining authors. The bias was assessed under domains such as Random sequence generation, selection bias, attrition, performance bias, detection bias, and reporting bias. The judgement was divided into three types: 'low risk,' 'high risk,' and 'unclear risk.

2.7. Type of outcome analyzed

The primary outcome included, clinical cure rate at test of cure (TOC), end-of-treatment (EOT) and late Follow up (LFU) in clinically evaluable population and the secondary objective were to analyse the clinical cure rate at TOC in microbiological modified intent-to-treat (mMITT) population, comparison with ceftazidime cure rate, microbiological cure rate, and adverse events(AE) and serious adverse events (SAE)

2.8. Statistical analysis

Review Manager 5.4 was used to perform the statistical analysis. Cochran's Q is a traditional measure of heterogeneity, Q statistics derived from the x^2 test were used to measure the degree of statistical heterogeneity. Risk difference (RD) was used to assess treatment effects with a 95% confidence interval (CI). The Cochrane I^2 statistic was used to determine heterogeneity, When $P < .10$ or $I^2 > 50\%$, heterogeneity was considered significant [14].

3. Results

A total of 74 references were found using electronic search, after the deletion of duplicate, there were 61 citations from which 53 records evaluated following the initial screening. Finally, four articles were included for review and analysis. One text article was removed due to lack of findings. Finally, three RCT publications that satisfied the inclusion criteria were selected to perform the meta-analysis. Figure 1 shows a flow diagram representing the whole screening and selection procedure for the trials included in our analysis.

The three studies were identical in every way. The trials were multicentric, randomised, and blinded in every manner. Lucasti et al., studied at 33 sites in eight countries (Bulgaria, France, India, Lebanon, Poland, Romania, Russia and the USA), Mazuski et al., looked a3t 136 sites in thirty countries, and Qin et al., studied at three countries, China, the Republic of Korea and Vietnam. Two of the studies were in Phase III, while the third was still in the Phase I. Participants in all of the studies were between the ages of 18 and 90 and had been diagnosed with cIAI. The study population was

divided into four different categories: i) Clinically Evaluable (CE) population ii) Modified intention-to-treat (MITT) population iii) Microbiologically modified intention-to-treat (mMITT) population and iv) Microbiologically evaluable (ME) population. CAZ-AVI 2000/500 mg iv infusion followed by metronidazole 500 mg iv infusion every 8 hours versus meropenem 1000 mg iv infusion every 8 hours were provided in three trials. The Cochrane risk of bias analysis technique was used to assess the quality of our study (Fig.2). Attrition bias, allocation concealment bias, sequence generation bias, performance bias, unclear detection bias and reporting bias were all low risks in all studies.

3.1. Clinical outcome

a) Clinical cure rate in CE population

The pooled analysis of 3 studies consisting of 1710 subjects reported Clinical cure rate in Clinically Evaluable population. In the CE population, the clinical cure rate was lower in CAZ-AVI plus metronidazole treated patients than in meropenem treated patients at TOC, EOT, and LFU (RD: -0.01; 95% CI: -0.02%, 0.01%; I^2=0%). The clinical cure rate was low in all evaluated populations (Fig.3).

b) Clinical cure rate at TOC

The clinical cure rate at TOC in mMITT patients was higher in ceftazidime/avibactam plus metronidazole treated patients than in meropenem treated patients (RD: -0.04; 95%CI: -0.08 to -0.00) according to a pooled analysis of three studies involving 1710 subjects. Test for overall effect of the clinical cure rate at TOC in CE and mMITT population were statistically insignificant (RD: -0.03; 95% CI: -0.05%, -0.00%; I^2=0%) (Fig. 4).

c) Clinical cure rate based on ceftazidime Susceptibility

The clinical cure rate in the total population based on ceftazidime susceptibility was greater in ceftazidime/avibactam plus metronidazole treated patients than in the meropenem treated arm, according to the findings of a pooled analysis of three trials including 1710 participants (RD: -0.04; 95% CI: -0.08%, -0.00%; I^2=0) are shown in Fig. 5.

d) Clinical cure rate based on organism detected

Escherichia coli was the most identified organism in all the studies. The clinical cure rate in the entire population based on the organism identified was greater in ceftazidime/avibactam plus metronidazole treated patients than in meropenem treated patients, according to a pooled analysis of three trials (n=1710) (RD: -0.04; 95% CI: -0.07%, -0.01%; I^2=0), Fig. 6 illustrated the details.

e) Adverse events and Serious adverse events

There was no significant difference in the overall incidence of AE and SAE between CAZ-AVI plus metronidazole treated patients and meropenem treated patients (RD: 0.02; 95% CI: -0.01%, 0.04%; I^2=0%), the details are shown in Fig.7. The adverse events and serious adverse events are summarised in Table 2.

4. Discussion

cIAIs are a primary cause of morbidity and mortality worldwide, and they are hard to treat [18]. Early clinical identification, adequate source control to prevent continuing contamination, suitable antimicrobial medicine, infection risk factors, and timely resuscitation in critically ill patients are the cornerstones of cIAI management [19]. Resistance rates rise as a result of the overuse of broad-spectrum drugs in situations when they aren't needed to combat prospective diseases [20, 21]. cIAI often need a comprehensive treatment plan, which includes source management and appropriate antibiotic coverage. For many years, carbapenems have been progressively used in cIAI as the first line of defense against infection [22]. We systematically reviewed three published RCTs comparing CAZ-AVI plus metronidazole over meropenem for the treatment of patients with cIAIs. The clinical cure rate at TOC, EOT, and LFU in the CE population was lesser in CAZ-AVI plus metronidazole treated patients than in meropenem treated patients, according to the primary outcomes. While the clinical cure rate in mMITT populations and ceftazidime susceptibility were both higher at TOC. In terms of AE and SAE, there were no significant variations between both groups.

Few meta-analyses comparing the effectiveness and safety of CAZ-AVI plus metronidazole with meropenem in the treatment of cIAI indicated that CAZ–AVI had equivalent efficacy to meropenem for the management of cIAI. Haoyue Che et al., reported that, for Enterobacteriaceae infections, CAZ-AVI is comparable to carbapenems, and the meta-analysis found no significant differences in therapeutic efficacy between CAZ-AVI and carbapenems [RD = 0.00, 95% CI -0.06 to 0.06; P = 0.99], microbiological success (RD = 0.07, 95% CI -0.04 to 0.18; P = 0.21) or AEs (RD = 0.00, 95% CI -0.02 to 0.03; P = 0.81) (23). This conclusion was supported by Neta Sternbach et al., (clinical response., Relative risk (RR)= 0.98, 95% CI 0.96–1.01, P=0.21, I^2=0)) (24). According to Zhong H et al., CAZ-AVI was found to be as effective as carbapenems in the treatment of serious Gram-negative bacterial infections (clinical response: (RR = 0.99, 95% CI 0.96–1.02; I^2 = 0%) and non-inferior bacterial eradication (RR = 1.04, 95% CI 0.93–1.17; I^2 = 79.1%) (25). Hiroshige Mikamo et al., confirmed that metronidazole in combination with carbapenem is as effective and safe over carbapenem monotherapy with a low risk of drug resistance, (clinical success: (odds ratio [OR] = 1.31; 95% CI 75–2.31), bacteriological eradication: (OR = 1.27; 95% CI, .84–1.91) (26). In this research we evaluated the clinical cure rate of CAZ-AVI among individual gram negative bacterias (*Enterobacteriaceae* (RD: -0.05; 95%CI: -0.10 to -0.00), *E.coli* (RD: -0.05; 95%CI: -0.10 to -0.00), *Klbsiella pneumoniae* (RD: 0.02; 95%CI: -0.10 to 0.14), *Pseudomonas aeruginosa* (RD: 0.01; 95%CI: -0.10 to 0.12)*and Non-Enterobactericeae* (RD: -0.05; 95%CI: -0.12 to 0.03)). The study limitations of this systematic review are, the research was based on three RCTs, and the test of cure rate varies amongst them, despite the fact that more clinical data are needed to draw a valid conclusion and the three studies included a small number of patients, limiting their robustness when evaluating the clinical efficacy of the two treatment arms. More study data should be needed for efficacy evaluation.

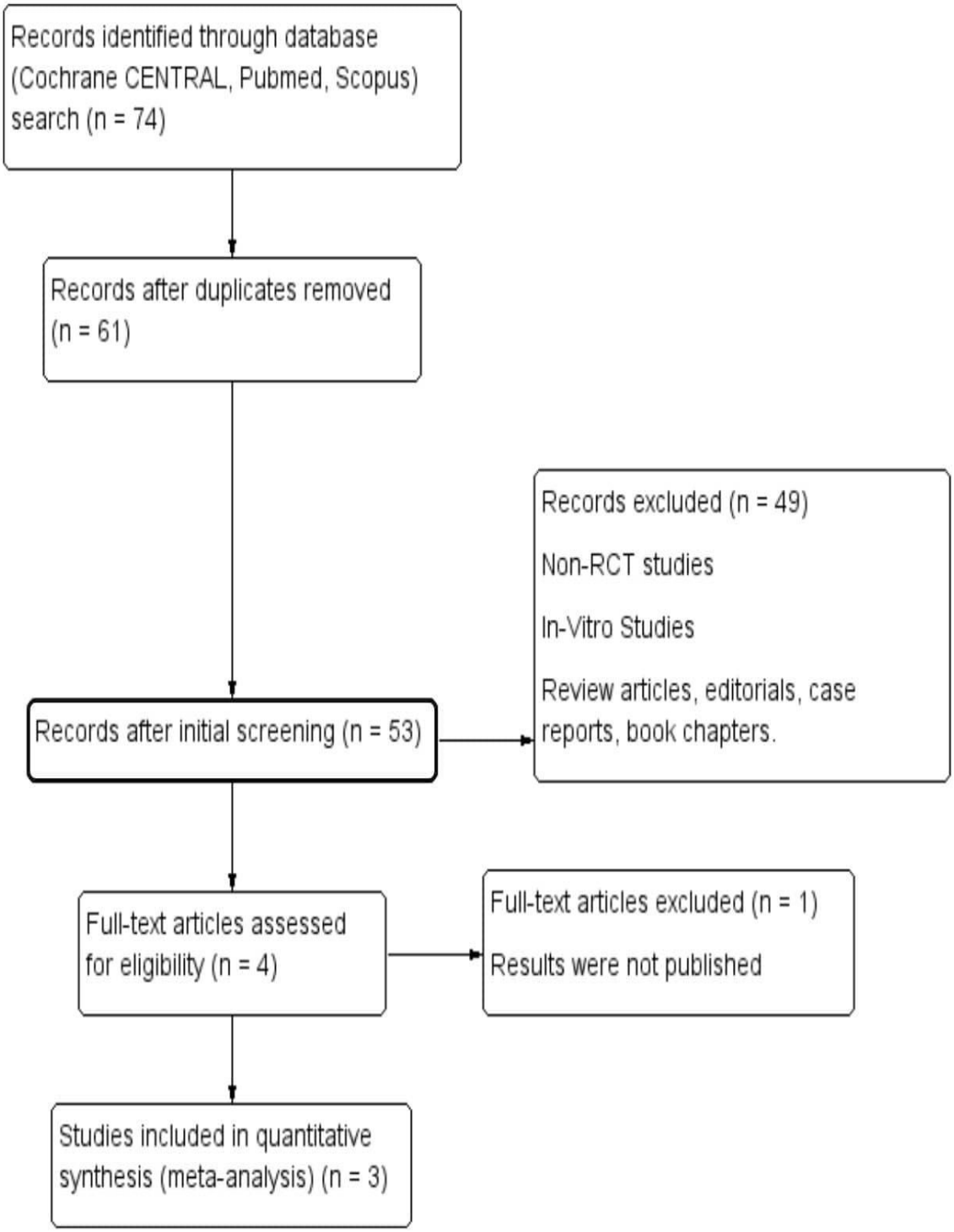

Figure 1. PRISMA Diagram

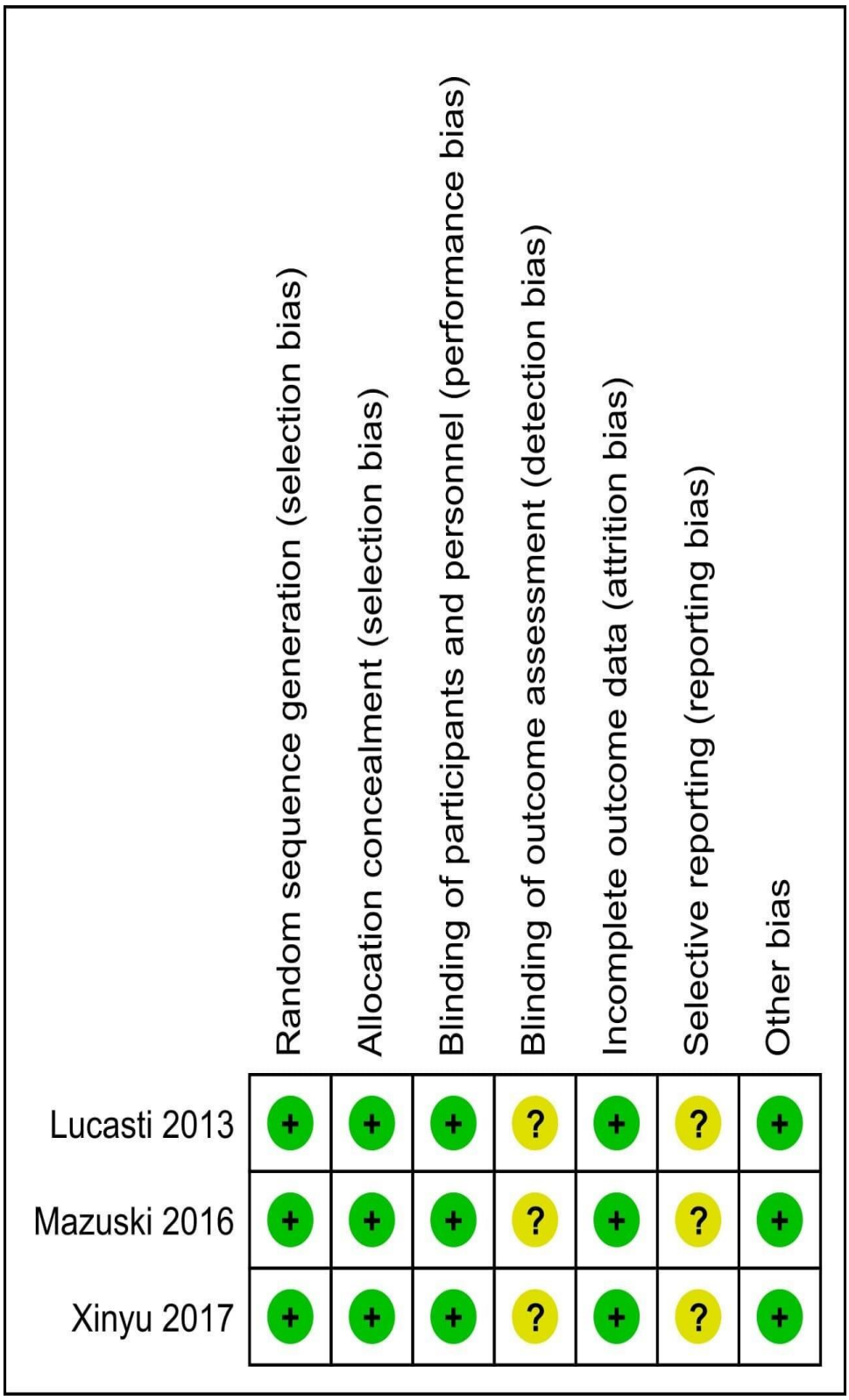

Figure 2. Risk of bias assessment for included study

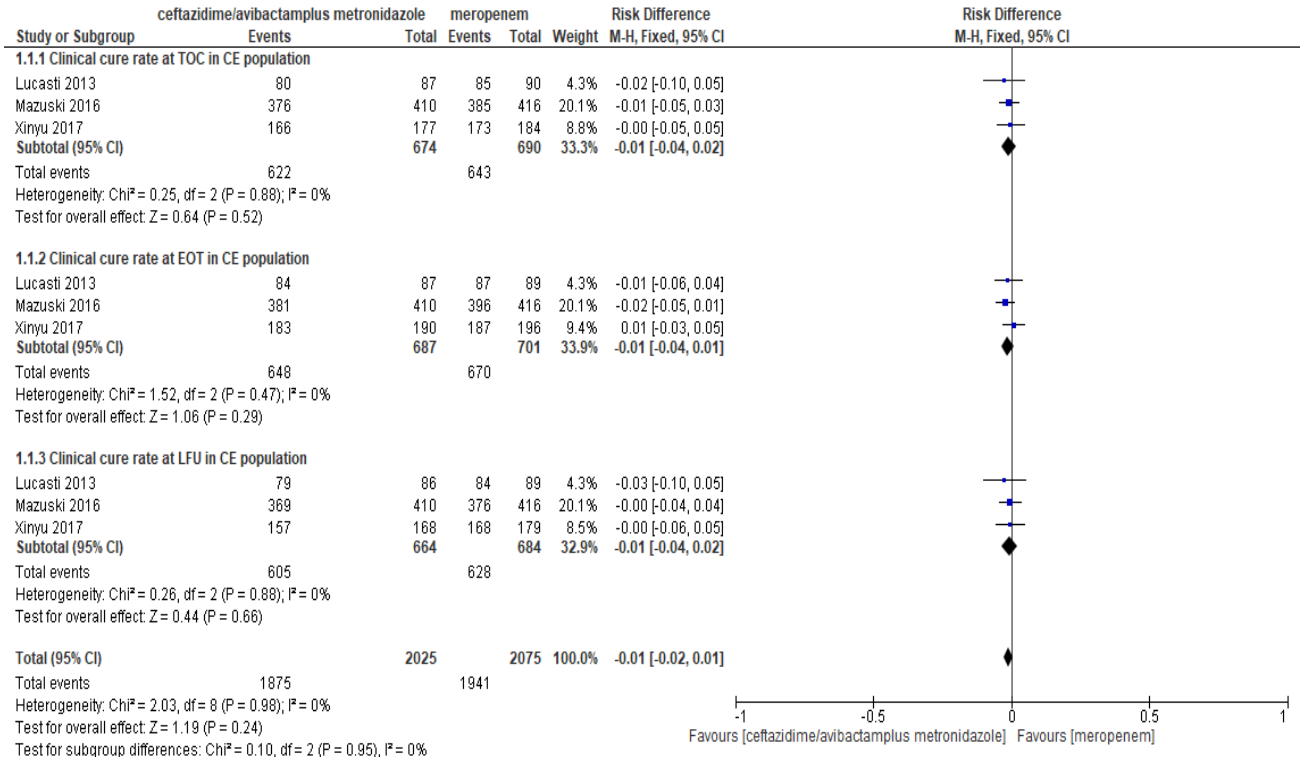

Figure 3. Clinical cure rate in CE population

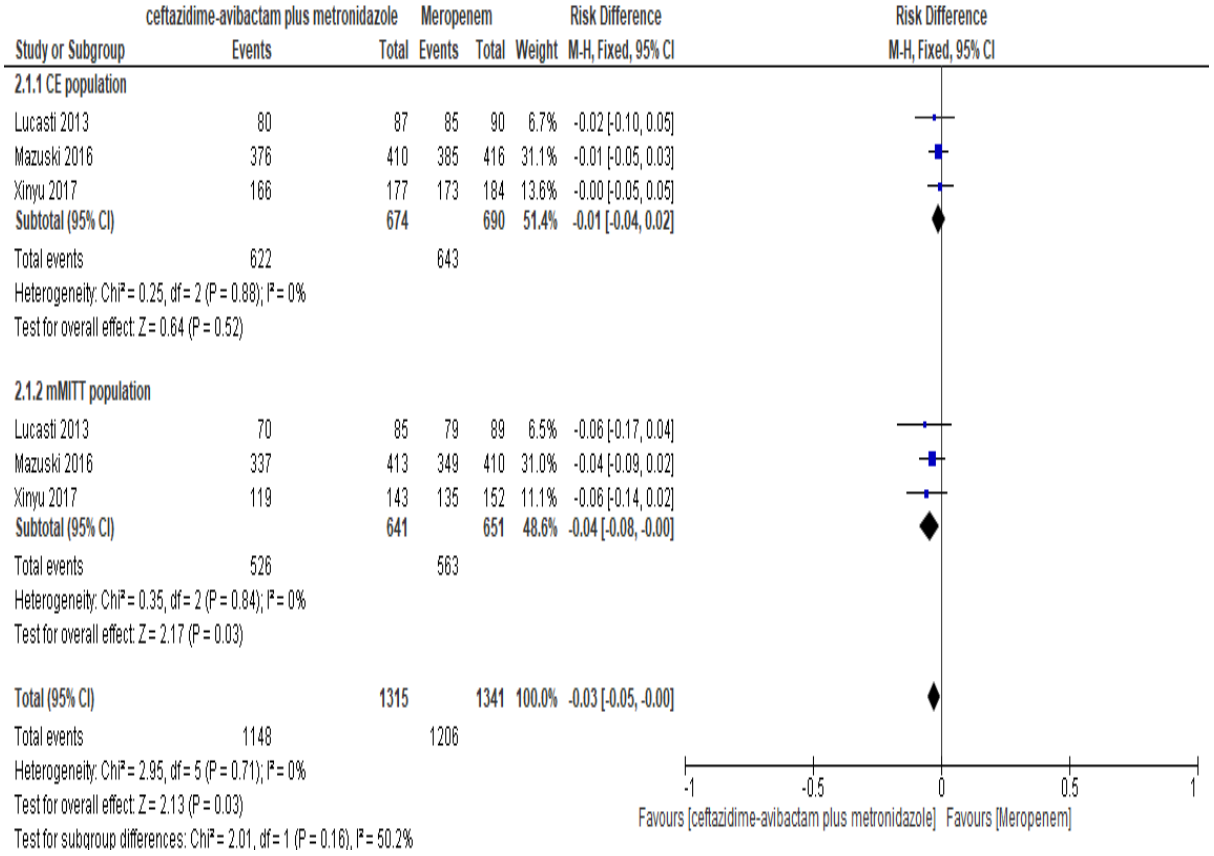

Figure 4. Clinical cure rate at TOC

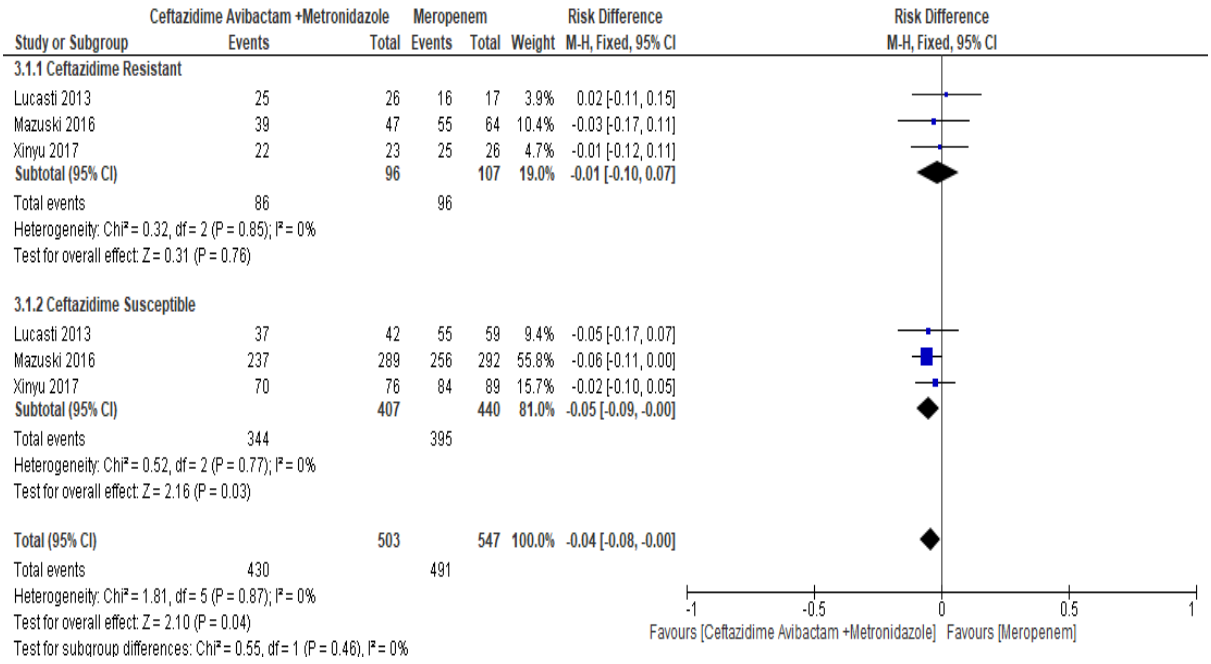

Figure 5. Clinical cure rate based on Ceftazidime Susceptibility

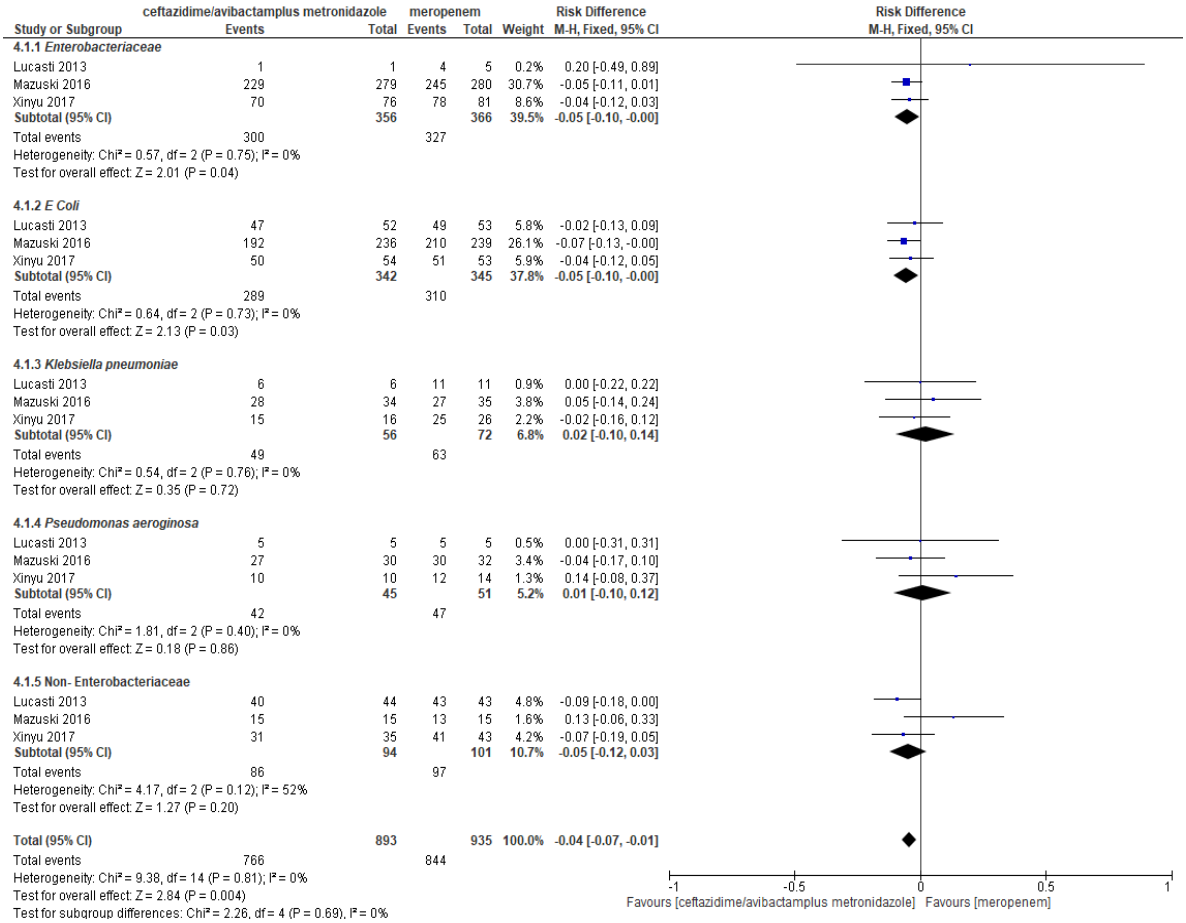

Figure 6. Clinical cure rate based on organism detected

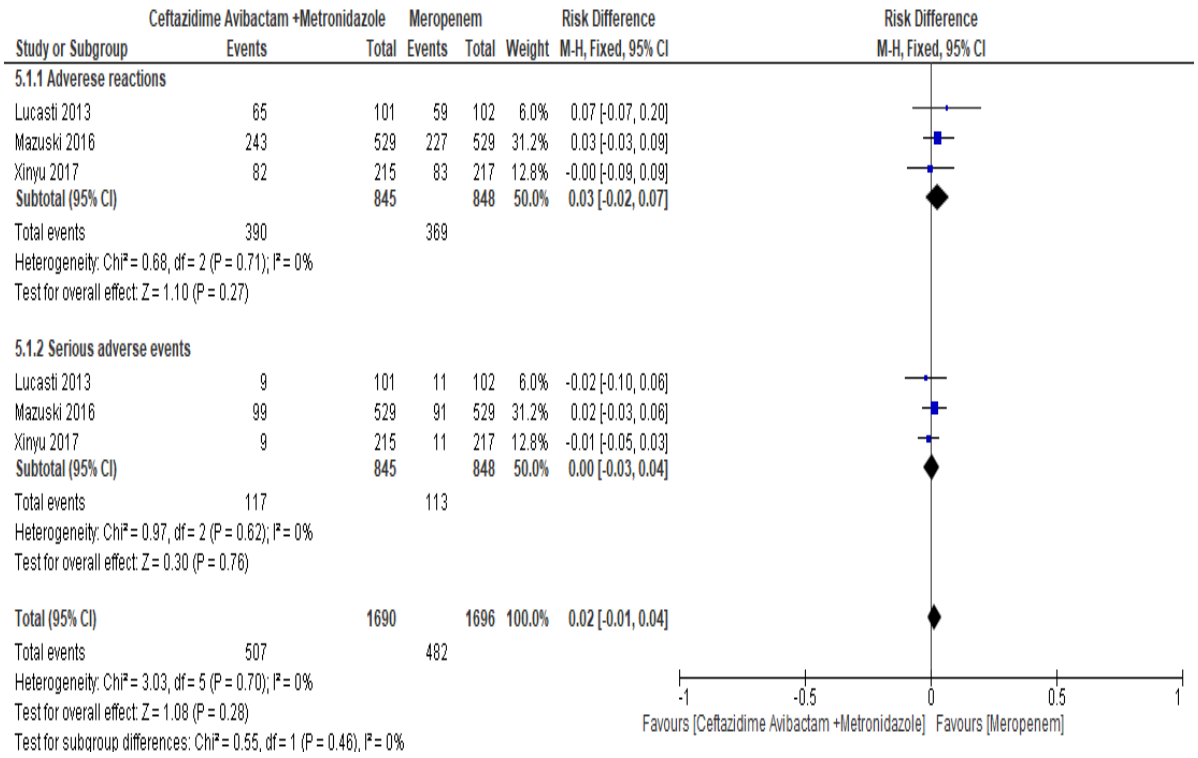

Figure 7. Comparison on adverse events and serious adverse events

Table 1: Characteristics of the included studies

Study	Study design	Participants	n	Duration of study	Intervention and control	Outcome
Lucasti et al.,	Multicentric, Prospective, randomized, double-blind, Phase II study	18–90 years with evidence of cIAI requiring surgical intervention	203	5-14 days, depending upon clinical response.	Intervention group: Ceftazidime/avibactam plus metronidazole Control group: Meropenem	Clinical cure rate
Mazuski et al.,	Multicentric, Prospective, randomized, double-blind, Phase III study	18–90 years with cIAI diagnosis requiring surgical intervention	1066	5-14 days	Intervention group: Ceftazidime/avibactam plus metronidazole Control group: Meropenem	Clinical cure rate
Qin et al.,	Multicentric, randomized, double-blind, Phase III study	18–90 years with evidence of cIAI requiring surgical intervention	441	5-14 days	Intervention group: Ceftazidime/avibactam plus metronidazole Control group: Meropenem	Clinical cure rate

'n' indicates that number of study participants.

Table 2: Adverse events and serious adverse events

Adverse events	Lucasti 2013		Xinyu 2017		Mazuski 2016	
	CAZ/AVI + Metronidazole (n = 101)	Meropenem (n = 102)	CAZ/AVI + Metronidazole (n = 215)	Meropenem (n = 217)	CAZ/AVI + Metronidazole (n = 529)	Meropenem (n = 529)
Nausea	10(9.9%)	6(5.9%)	18(8.4%)	4(1.8%)	36(6.8%)	24(4.5%)
Vomiting	14(13.9%)	5(4.9%)	5(2.3%)	4(1.8%)	24(4.5%)	10(1.9%)
Pyrexia	9(8.9%)	11(10.8%)	9(4.2%)	13(6.0%)	24(4.5%)	24(4.5%)
Cough	6(5.9%)	4(3.9%)	3(1.4%)	8(3.7%)	11(2.1%)	13(2.5%)
Headache	-	-	3(1.4%)	5(2.3%)	15(2.8%)	9(1.7%)
Diarrhoea	-	-	13(6.0%)	16(7.4%)	40(7.6%)	17(3.2%)
Constipation	-	-	5(2.3%)	3(1.4%)	8(1.5%)	20(3.8%)
Liver disorder	-	-	6(2.8%)	10(4.6%)	11(2.1%)	8(1.5%)
Hypersenitivity/ Anaphylaxis	-	-	7(3.3%)	8(3.7%)	23(4.3%)	16(3.0%)
Haemotological disorder	-	-	2(0.9%)	1(0.5%)	16(3.0%)	15(2.8%)
Renal disorder	-	-	1(0.5%)	1(0.5%)	12(2.3%)	3(0.6%)

5. Conclusion

The current systematic review and meta-analysis based on three randomized controlled trials found that CAZ-AVI plus Metronidazole is not a superior alternative for treating complicated intra-abdominal infectious disease over meropenem. This study found a decreased clinical cure rate in various study populations (TOC, EOT, and LFU in CE population) treated with CAZ-AVI plus metronidazole and a greater clinical cure rate in the mMITT study population as compared to meropenem. To forecast the outcome, more clinical data must be analyzed, and this data solely focused on meropenem, it cannot be justified in terms of other carbapenems.

Conflict of interest

None

Acknowledgment

The authors acknowledge the support of the department of pharmacy practise at JSS College of Pharmacy-Ooty.

Funding

Indian council of medical research, New Delhi (Award No: 5/3/8/41/ITR-F/2018-ITR dated 14/05/2018 to Jyothikrishna P.)

References

[1] M. Sartelli, A. Chichom-Mefire, F.M. Labricciosa, T. Hardcastle, F.M. Abu-Zidan, A.K. Adesunkanmi, L. Ansaloni, M. Bala, Z.J. Balogh, M.A. Beltran, and O. Ben-Ishay. (2017). The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World Journal of Emergency Surgery. 12(1): 1-34.

[2] J. Hafner, F. Tuma, G.J. Hoilat, O. Marar. (2021). Intestinal Perforation. In: StatPearls [Internet https://www.ncbi.nlm.nih.gov/books/NBK538191/

[3] C. Payá-Llorente, E. Martínez-López, J.C. Sebastián-Tomás, S. Santarrufina-Martínez, N. de'Angelis, A. Martínez-Pérez. (2020). The impact of age and comorbidity on the postoperative outcomes after emergency surgical management of complicated intra-abdominal infections. Scientific Reports. 10(1): 1-8.

[4] L. Clara, V.M. Rodriguez, P. Saul, C. Dominguez, M. Esteban. (2018). Intra-abdominal infections. Update and recommendations. Medicina. 78(6): 417-26.

[5] Y.R. Lee, D. McMahan, C. McCall, G.K. Perry. (2015). Complicated intra-abdominal infections: the old antimicrobials and the new players. Drugs. 75(18): 2097-117.

[6] K. Bush, P.A. Bradford. (2016). β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harb Perspectives in Medicine. 6(8): a025247.

[7] C.C. Sheu, Y.T. Chang, S.Y. Lin, Y.H. Chen, P.R. Hsueh. (2019). Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. Frontiers in Microbiology. 10: 80.

[8] G. Meletis. (2016). Carbapenem resistance: overview of the problem and future perspectives. Therapeutics Advances in Infectious Diseases. 3(1): 15-21.

[9] S.S. Kadri. (2020). Key Takeaways From the US CDC's 2019 Antibiotic Resistance Threats Report for Frontline Providers. Critical Care Medicine. 48(7): 939-945.

[10] B. Ramu, K. Kaushal, P. Chandrul, P. Shanmuga. (2021). Using 24 Factorial Designs optimization of Repaglinide Gastroretentive Drug Delivery System. Research Journal of Pharmacy and Technology. 14(2): 725-729.

[11] C. Lucasti, E. Hershberger, B. Miller, S. Yankelev, J. Steenbergen, I. Friedland, J. Solomkin. (2014). Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrobial Agents and Chemotherapy. 58(9): 5350.

[12] J.E. Mazuski, L.B. Gasink, J. Armstrong, H. Broadhurst, G.G. Stone, and D. Rank, L. Llorens, P. Newell, and J. Pachl. (2016). Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clinical Infectious Diseases. 62(11): 1380-9.

[13] J.F. Mosley, L.L. Smith, C.K. Parke, Brown JA, Wilson AL, Gibbs LV. 2016. Ceftazidime-avibactam (Avycaz): for the treatment of complicated intra-abdominal and urinary tract infections. Pharmacy and Therapeutics. 41(8): 479.

[14] B. Nagaraju, B. Ramu, S.V. Saibaba, B. Rajkamal. (2016). Formulation and evaluation of floating bioadhesive Doxofylline tablets. International Journal of Drug Delivery. 8: 134–141.

[15] X. Qin, B.G. Tran, M.J. Kim, L. Wang, D.A. Nguyen, Q. Chen, J. Song, P.J. Laud, G.G. Stone, and J.W. Chow. (2017). A randomized, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. International Journal of Antimicrobial Agents 49(5): 579-88.

[16] J.E. Mazuski, L.B. Gasink, J. Armstrong, H. Broadhurst, G.G. Stone, D. Rank, L. Llorens, P. Newell, and J. Pachl. (2016). Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clinical Infectious Diseases. 62(11): 1380-9.

[17] C. Lucasti, I. Popescu, M.K. Ramesh, J. Lipka, C. Sable. (2013). 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. Journal of Antimicrobial Chemotherapy. 68(5): 1183-92.

[18] T. Herzog, A.M. Chromik, W. Uhl. (2010). Treatment of complicated intra-abdominal infections in the era of multi-drug resistant bacteria. European Journal of Medical Research. 15(12): 525-32.

[19] B. Tellor, L.P. Skrupky, W. Symons, S.T. High E, Micek, J.E. Mazuski. (2015). Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. Surgical Infections. 16(6): 785-93.

[20] C.L. Ventola. (2015). The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and Therapeutics. 40(4): 277.

[21] R.J. Fair, Y. Tor. (2014). Antibiotics and bacterial resistance in the 21st century. Perspectives in Medicinal Chemistry. 6: 25-64.

[22] G. Meletis. (2016). Carbapenem resistance: overview of the problem and future perspectives. Therapeutic Advances in Infectious Diseases. 3(1): 15-21.

[23] H. Che, R. Wang, J. Wang, Y. Cai. (2019).Ceftazidime/avibactam versus carbapenems for the treatment of infections caused by Enterobacteriaceae: A meta-analysis of randomised controlled trials. International Journal of Antimicrobial Agents. 54(6): 809-13.

[24] N. Sternbach, Y.L. Weissman, T. Avni, D. Yahav. (2018). Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 73(8): 2021-9.

[25] H. Zhong, X.Y. Zhao, Z.L. Zhang, Z.C. Gu, C. Zhang, Y. Gao, and M. Cui. (2018). Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis. International Journal of Antimicrobial Agents. 52(4): 443-50.

[26] H. Mikamo, A. Yuasa, K. Wada, B. Crawford, N. Sugimoto. (2016). Optimal Treatment for Complicated Intra-abdominal Infections in the Era of Antibiotic Resistance: A Systematic Review and Meta-Analysis of the Efficacy and Safety of Combined Therapy With Metronidazole. Open Forum Infectious Diseases. 3(3): 143. doi: 10.1093/ofid/ofw143.