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MAJOR ARTICLE

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

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Background. Carbapenem-resistant *Enterobacteriaceae* has increased dramatically in the last decade, resulting in infections that are difficult to treat and associated with high mortality rates. To prevent further antibacterial resistance, it is necessary to use carbapenem selectively. A combination of metronidazole with an antimicrobial agent active against aerobes is an alternative effective treatment for patients with complicated intra-abdominal infections (cIAIs). This study aimed to compare efficacy and safety of metronidazole combination therapies and carbapenem and to provide clinical evidence regarding the optimal treatment of cIAI.

Methods. A systematic review and a meta-analysis of randomized clinical trials in the treatment of cIAI were conducted. The systematic review with PubMed, Embase, and the Cochrane Database of Systematic Reviews followed the Cochrane Handbook's recommended methodology, and the meta-analysis used a Mantel-Haenszel random-effects model with RevMan, version 5.3. Primary endpoints were clinical success and bacteriological eradication, and secondary endpoints were all-cause mortality and drug-related adverse events.

Results. Eight studies comparing metronidazole combination therapies and carbapenem were included in the meta-analysis. No difference was found between combined therapy with metronidazole and carbapenem regarding clinical success (odds ratio [OR] = 1.31; 95% confidence interval [CI], .75–2.31), bacteriological eradication (OR = 1.27; 95% CI, .84–1.91), all-cause mortality (OR = 0.61; 95% CI, .37–1.00), or drug-related adverse events (OR = 0.58; 95% CI, .18–1.88). Sensitivity analyses found similar results.

Conclusions. Combined therapy with metronidazole is as effective and safe as carbapenem in treatment of cIAI. Therefore, combined therapy with metronidazole offers an effective alternative to carbapenem with low risk of drug resistance.

Keywords. carbapenem-resistant *Enterobacteriaceae*; complicated intra-abdominal infection; CRE; meta-analysis; metronidazole.

Recent years have seen widespread antibacterial-resistance due to the increased use of antibiotics with a broad spectrum of antibacterial activity. Carbapenem-resistant *Enterobacteriaceae* (CRE) including *Klebsiella* species and *Escherichia coli*, in particular, has increased dramatically in the last decade [1]. There are limited therapeutic options available for infections caused by CRE; therefore, they are difficult to treat and associated with high mortality rates [1]. A positive correlation between carbapenem usage and the prevalence of imipenem and meropenem-resistant bacteria such as Pseudomonas *aeruginosa* has been reported in the literature, suggesting the importance of selective use of carbapenem for infections that can be only treated by this class of antibiotic [2]. With limited development of novel antibacterial agents, it is vital to use existing agents carefully to prevent the emergence of drug-resistant bacteria.

Complicated intra-abdominal infections (cIAIs) are common in clinical practice and often caused by a mixture of aerobic and anaerobic bacteria. The incidence of anaerobic bacteria isolated from cIAIs is high. A pooled analysis from 3 randomized prospective trials with cIAIs found that in 1237 patients with microbiologically confirmed infections, *Bacteroides fragilis* and other *Bacteroides* species were isolated from 35% and 71% of these patients, respectively [3, 4]. The antimicrobial therapies recommended for cIAIs in the guidelines by the Expert Panel of the Surgical Infection Society and the Infectious Diseases Society of America [3] include a single-agent therapy with carbapenem and a combination therapy with metronidazole and cephalosporin or fluoroquinolone. Although metronidazole has been used as a standard therapy for trichomoniasis, anaerobic, and

Received 7 June 2016; accepted 1 July 2016.

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 DOI: 10.1093/ofid/ofw143

amebic infections worldwide since the 1970s, resistance to metronidazole remains low [5]. Combination therapies with metronidazole are still reported to be effective in the treatment of cIAIs [6].

In 2014, the intravenous formulation of metronidazole was approved in Japan, long after the oral formulation was first approved in 1961. The recent approval allowed metronidazole to be one of the therapeutic options, when used in combination with an antiaerobic agent, for patients with mixed infections caused by aerobic and anaerobic bacteria and for patients unsuitable for oral administration, such as those with cIAIs [7].

Although there are several randomized clinical trials (RCTs) comparing the efficacy and safety of a combined therapy with metronidazole and carbapenem regimen [8–10], systematic reviews and meta-analyses of these antibiotic therapies are limited. The current study aimed to provide clinical evidence regarding the optimal treatment of cIAI by conducting a systematic literature review and a meta-analysis of clinical efficacy and safety between combined therapy with metronidazole and carbapenem in patients with cIAI.

METHODOLOGY

Systematic Literature Review

A systematic literature review based on the predefined protocol was conducted in September 2015 following the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* [11]. The literature search was conducted using PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The scope of the systematic literature review, defined in terms of criteria including the patient population, the interventions, the comparators, the outcome measures, and the study design, is shown Figure 1. The search terms used for PubMed, Embase, and CENTRAL searches include intra-abdominal infections, metronidazole, carbapenem, and phase II and III clinical trials, for all available years, fully utilizing the databases' headings systems, such as the Medical Subject Headings, wherever possible. The exact search equations used in this study are shown in Supplementary Tables 1–3. In addition, a gray literature search was conducted using Google in English with the search keywords included in the PubMed, Embase, and CENTRAL searches. Studies referenced in more than 2 identified articles were also reviewed.

Studies retrieved by the search strategies were first reviewed based on their title and abstract. Relevance of the study was evaluated based upon the inclusion criteria (Table 1) by the lead reviewer and cross-checked by another. Those studies selected after title and abstract review were reviewed in full text and evaluated in a similar manner. An Excel-based selection tracking spreadsheet was used for the process. The selected studies were then exported and organized into an EndNote database.

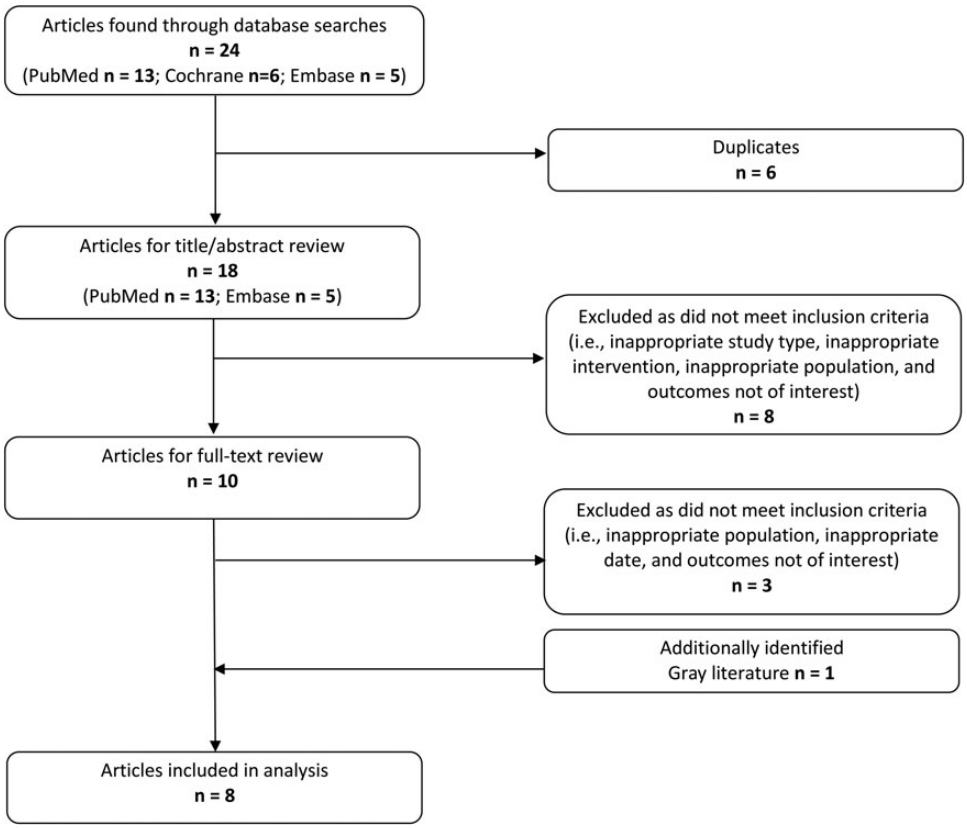

Figure 1. PRISMA flow diagram of study inclusion.

Table 1. Scope of the Systematic Literature Review

Topic	Scope
Patient population	Adult patients with complicated intra-abdominal infection
Intervention	Combination therapy with metronidazole and penicillins or cephalosporins or combination therapy with metronidazole and fluoroquinolones (both intravenous administration)
Comparator	Monotherapy with carbapenems (intravenous administration)
Outcome measures	Clinical treatment success rates (ie, clinical cure rates, test-of-cure, macrobiotic cure etc) and incidence of adverse events (ie, all-cause mortality, drug-related mortality etc)
Study design	Phase II and III randomized clinical trials (Note: Only phase II studies investigating the approved dosages in Japan will be included)
Publication year	No limit
Language	English or Japanese

Quality Assessment and Data Extraction

A quality assessment of each study identified in the systematic literature review was performed to evaluate the internal and external validity using the Cochrane Collaboration "Risk of Bias" tool [11]. All studies were classified as low risk, high risk, or unclear risk.

Data extraction was conducted using an Excel-based data extraction form developed before extracting data. All extracted data for the analysis were checked by a researcher not involved in the analysis.

Outcomes of Interest

This study compared the efficacy and safety endpoints reported in the identified studies (clinical success and bacteriological eradication, all-cause mortality, and drug-related adverse events). In the identified studies, clinical success was defined as "favorable, satisfactory clinical response resulting in complete resolution (cure) or significant improvement in all signs and symptoms of the infection". The identified studies used a combined number of cases for cure and/or improvement; therefore, our study extracted data for a combined number of cases for cure and improvement whenever possible. In the studies that did not provide information for improvement, clinical success was defined as complete resolution of all signs and symptoms. In the identified studies, bacteriological eradication was defined as eradication or presumed eradication of the baseline pathogen. All-cause mortality was number of deaths reported, and drug-related adverse events were defined as treatment-emergent adverse events occurring or worsening after the first dose of the study medication, which were considered by the investigator to be drug related. The definitions of outcomes for the 4 endpoints (as described above) reported in each identified study are summarized in Supplementary Table 4.

Meta-Analysis

A meta-analysis was conducted to synthesize data extracted to obtain a single-summary estimate of effect from the studies identified in the systematic literature review. A standard meta-analysis was conducted using Review Manager (RevMan, version 5.3.5). The Cochrane χ^2 (ie, Q-statistic) and I^2 were used for model fit and assessment of heterogeneity. Given the likely heterogeneity of the studies identified, this meta-analysis used a random effect model in the primary analysis and a fixed effect model in the sensitivity analyses as supporting data. A DerSimonian-Laird random-effects method [12] was used to calculate odds ratio (OR) with 95% confidence interval (CI).

Several sensitivity analyses were conducted according to the protocol. First, an analysis excluding any studies investigating metronidazole in combination with a drug other than cephalosporin or penicillin was conducted. Second, analyses excluding studies determined to be at high risk of bias (defined as 2 or more attributes on the risk of bias assessment) were conducted. Finally, an analysis, which excluded all studies investigating combination therapies other than metronidazole and cephalosporin or penicillin as well as studies determined to be at high risk of bias, was conducted.

RESULTS

Studies Identified

The study selection process is illustrated in Figure 1. A total of 24 studies were identified, 6 of which were duplicates; therefore, the remaining 18 studies were assessed for inclusion against the eligibility criteria. After screening the 18 abstracts, 8 studies were excluded, resulting in 10 studies for full-text review. Excluded studies focused on a population not of interest (ie, children), intervention not of interest (ie, ertapenem alone or triple therapy with cefotaxime combined with metronidazole and cloxacillin), or inappropriate study design (ie, literature review). After full-text review of these 10 studies, 3 studies were further excluded (2 studies with a population not of interest such as patients with uncomplicated intra-abdominal infections and 1 pharmacoeconomic study using the same trial data as another included study). In addition, 1 study was identified through the gray literature review. As a result, 8 studies were selected to be extracted and included in the primary analysis [13–20]. An overall summary of characteristics of the studies is shown in Table 2. In addition, the detailed definitions of endpoints in each identified study are detailed in Supplementary Table 4.

Study Quality

Our study quality assessment using the Cochrane risk of bias assessment tool found 3 studies to be at high risk of bias across 2 or 3 assessment domains. A summary of risk of bias is shown in Figure 2. There were 2 studies, Angeras et al [13] and Kempf et al [17], that were found to be potentially biased across 2 assessment domains (did not use blinding of participants or outcome assessment). Because open trials were not expected to have an impact on the primary endpoints given the nature of endpoints (bacterial eradication), they were retained for the

Table 2. Summary of Study Characteristics

		Patient Characteristics							
Study	Study Design	Setting	Infection Site	Treatment	Duration (Days)	Age (Mean ± SD) (Years)	Gender (Male%)	APACHE II Score	Outcomes Considered for Analysis
Lucasti et al [18]	Double-blind RCT	Hospitalized cIAI patients requiring surgical intervention in US, Argentina, Russia, Georgia, and Serbia	Appendix	Ceftolozane-tazobactam + metronidazole	Mean: 5.7	48.5 ± 18.8	54.9	Median: 7	At Test-of-Cure Visit: Cure; Microbiological eradication; All-cause mortality; Adverse events
				Meropenem	Mean: 6	46.4 ± 18.5	61.5	Median: 6	
Lucasti et al [19]	Double-blind, RCT	cIAI patients requiring surgical intervention and antibiotics in 8 countries	Appendix, stomach/ duodenum	Ceftazidime/ avibactam + metronidazole	Median: 6	43.0 ± 15.9	69.3	≤10; 83.2%	At End of Therapy: Favorable clinical response; Microbiological eradication; All-cause mortality; Adverse events
				Meropenem + saline solution	Median: 6.5	42.6 ± 18.1	79.4	≤10; 83.3%	
Garbino et al [15]	Double-blind RCT	Patients with intra-abdominal infections	Peritonitis	Cefepime + metronidazole	Mean: 8	63 ± 18	45	Mean ± SD: 6.15 ± 4.13	At Test-of-Cure Visit: Cure; Bacteriological eradication; All-cause mortality; Adverse events
				Imipenem-cilastatin	Mean: 9	57 ± 16	45	Mean ± SD: 5.48 ± 2.90	
Barie et al [14]	Double-blind RCT	Hospitalized cIAI patients requiring operative procedure or percutaneous drainage in US and Canada	Appendicitis, other abscess	Cefepime + metronidazole	Mean: 8.8	49.3	72	Mean: 7.8	At End of Therapy: Cure; Bacterial eradication; All-cause mortality; Side effects
				Imipenem-cilastatin sodium	Mean: 9.4	51.5	67	Mean: 9.3	
Kempf et al [17]	Open RTC	Hospitalized patients with intra-abdominal infection requiring surgical treatment	Appendix, colon	Cefotaxime + metronidazole	Mean: 6.9	56.6	24	≤10; 70%	At End of Therapy: Satisfactory clinical response; Satisfactory bacteriological response; All-cause mortality; Adverse events
				Meropenem	Mean: 7.3	61.5	22	≤10; 60%	
Solomkin et al [20]	Double-blind RTC	Patients age with intra-abdominal infections requiring operative/ percutaneous drainage in US and Canada	Colon peritonitis, colon abscess	Ciprofloxacin + metronidazole	Mean: 9.67	49.7 ± 19.7	41	Mean ± SD: 9.2 ± 5.3	At Follow-Up: Clinical success; Bacteriological eradication
				Imipenem-cilastatin + placebo	Mean: 9.67	56.1 ± 20.2	47	Mean ± SD: 10.5 ± 6.3	
Angeras et al [13]	Open RCT	Hospitalized patients with intra-abdominal infection or systemic infection originating from the intra-abdominal region	Appendicitis, perforated colon	Cefuroxime + metronidazole	Median: 6	54	59	≤10; 82%	Time point not reported Clinical cure; Bacteriological eradication; All-cause mortality; Adverse events
				Imipenem-cilastatin	Median: 6	56	55	≤10; 84%	
Huizinga et al [16]	Open RCT	Hospitalized patients with intra-abdominal infections requiring surgery in South Africa, England, Holland, France	Peritonitis	Cefotaxime + metronidazole	Mean: 6.0	35.5 ± 14.9	76	≤5; 58%	At End of Therapy: Satisfactory clinical response: cured or improved; Bacteriological success; All-cause mortality; Adverse events
				Meropenem	Mean: 6.5	38.0 ± 16.6	71	≤5; 53%	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; cIAI, complicated intra-abdominal infection; RCT, randomized clinical trial; SD, standard deviation; US, United States.

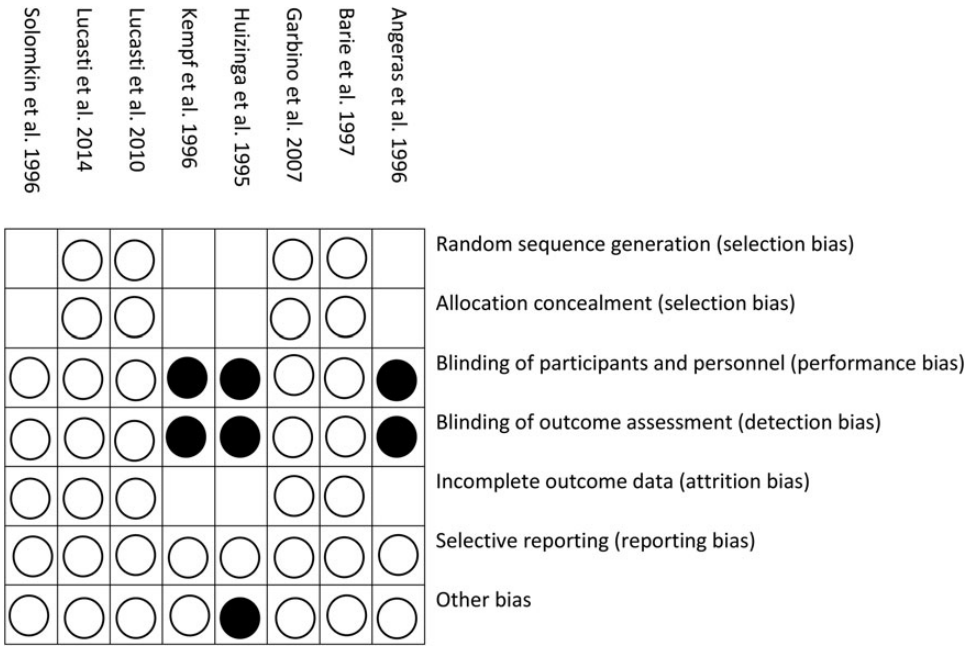

Figure 2. Risk of bias summary. Black circles indicate high risk, white circles indicate low risk, and blank cells indicate unclear risk.

primary analysis. Furthermore, one study, Huizinga et al [16], was found to be potentially biased across 3 assessment domains. The study had the same blinding risks as Angeras et al [13] and Kempf et al [17], in addition to other biases such as providing insufficient details for patient dropouts and slight imbalance of health condition between the treatment and comparator groups. In particular, as shown Table 2, the meropenem group in Huizinga et al [16] was reported to have a higher Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score (19% of patients having a score of 11–20, compared with 12% in the metronidazole group). The same group also had a higher proportion of patients with indwelling catheters (68% vs 55%) and nasogastric tubes (74% vs 59%) at the baseline [16]. These factors are considered to be associated with a higher risk of subsequent infection; therefore, it is possible that this study may have a bias in favor of the metronidazole group. However, the study was retained for the primary analysis because of uncertainty of the significance of these differences between the 2 groups (statistical test of significant difference was not performed).

Meta-Analysis Results

The primary analysis included all studies. All studies reported clinical success. The pooled OR for clinical success between patients treated with combined therapy with metronidazole (n = 609) and carbapenem (n = 583) was 1.31 (95% CI, .75–2.31; $P = .35$; $I^2 = 55\%$) (Figure 3). No difference between combined therapy with metronidazole and carbapenem was found in terms of clinical success.

All studies reported bacteriological eradication. The pooled OR for bacteriological eradication between patients treated

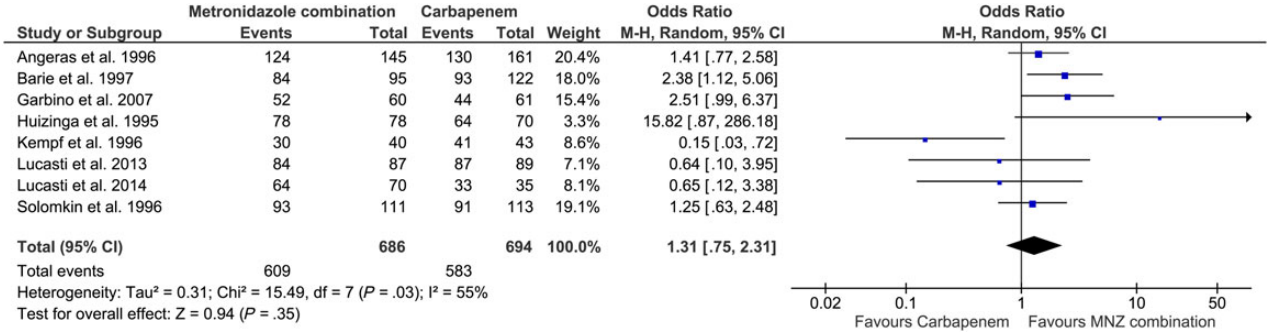

Figure 3. Forest plot of clinical success. Abbreviations: CI, confidence; MNX, Metronidazole.

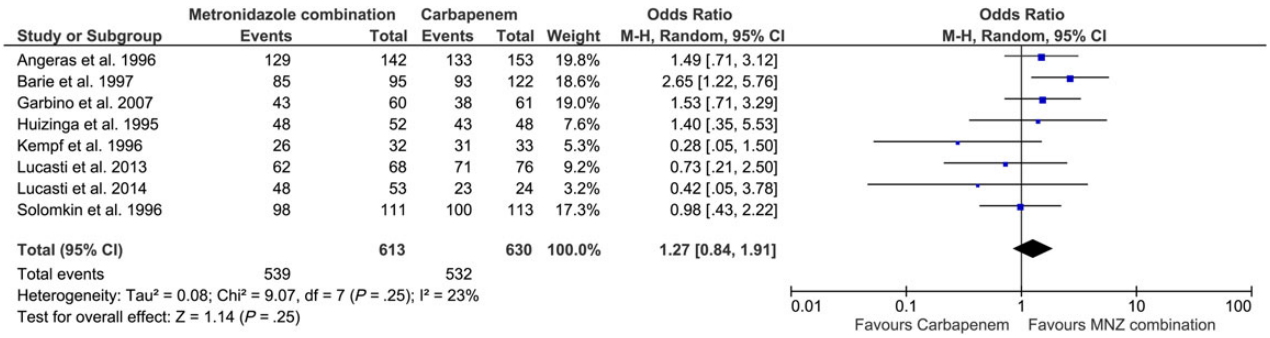

Figure 4. Forest plot of bacteriological eradication. Abbreviations: CI, confidence; MNX, Metronidazole.

with combined therapy with metronidazole (n = 613) and carbapenem (n = 630) was 1.27 (95% CI, .84–1.91; $P = .25$; $I^2 = 23\%$) (Figure 4). No difference between combined therapy with metronidazole and carbapenem was found in terms of bacteriological eradication.

All studies reported all-cause mortality. Seven studies reported data on the safety population, and the remaining study reported data on the intention-to-treat population. All studies reported mortality at the end of therapy. The pooled OR for mortality between patients treated with combined therapy with metronidazole (n = 904) and carbapenem (n = 854) was 0.61 (95% CI, .37–1.00; $P = .05$; $I^2 = 0\%$) (Figure 5). Although there was a trend towards a higher risk of mortality with carbapenem compared with combined therapy with metronidazole, no difference between combined therapy with metronidazole and carbapenem was found in terms of all-cause mortality.

Six studies reported drug-related adverse events, with 2 studies reporting zero events for both treatment groups, which were labeled as not estimable and removed from the analysis. Hence, 4 studies were evaluated for drug-related adverse events. These studies reported data on the safety population and did not specify their measurement time point. The pooled OR for drug-related adverse events between patients treated with combined therapy with metronidazole (n = 629) and carbapenem (n = 585) was 0.67 (95% CI, .36–1.25; $P = .21$; $I^2 = 0\%$) (Figure 6). No difference between combined therapy with metronidazole and carbapenem was found in terms of drug-related adverse events.

Sensitivity Analyses

The first sensitivity analysis included all studies except Solomkin et al [20], which investigated metronidazole in combination with a fluoroquinolone drug (ciprofloxacin). No difference between combined therapy with metronidazole and carbapenem was found for all endpoints. The second sensitivity analysis included all studies except Huizinga et al [16], which had a high risk of bias across 3 assessment domains including the imbalance of APACHE II scores between the treatment groups. No difference was found between combined therapy with metronidazole and carbapenem for all endpoints. The third sensitivity analysis further excluded Angeras et al [13] and Kempf et al [17] in addition to Huizinga et al [16], removing all studies with a high risk of bias across at least 2 assessment domains. Combined therapy with metronidazole was associated with a significantly higher number of clinical success cases than carbapenem (OR = 1.63; 95% CI, 1.08–2.45; $P = .02$; $I^2 = 13\%$) (Supplementary Figure 1). No other difference was found between the

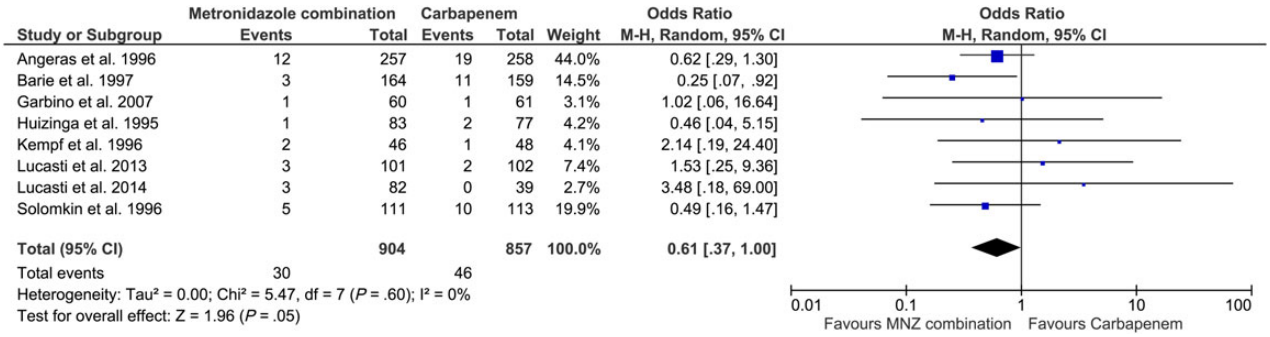

Figure 5. Forest plot of all-cause mortality. Abbreviations: CI, confidence; MNX, Metronidazole.

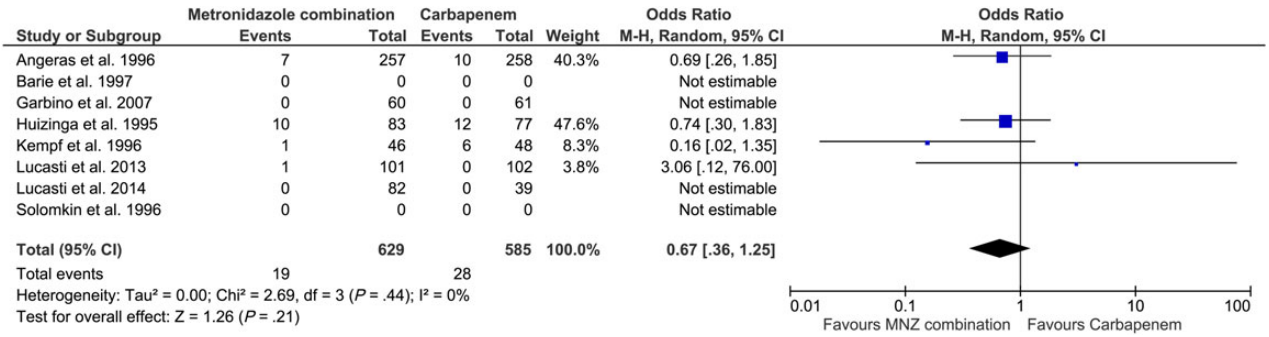

Figure 6. Forest plot of drug-related adverse events. Abbreviations: CI, confidence; MNX, Metronidazole.

2 groups for other endpoints. Finally, the fourth sensitivity analysis, excluding all the studies above [13, 16, 17, 20], found no difference between combined therapy with metronidazole and carbapenem for all endpoints.

DISCUSSION

A systematic literature review identified 8 RCTs comparing combined therapy with metronidazole and carbapenem for the treatment of cIAIs. The results of the primary meta-analysis showed no significant differences between combined therapy with metronidazole and carbapenem in efficacy endpoints (clinical success and bacteriological eradication) or safety endpoints (all-cause mortality and drug-related adverse events).

Few meta-analysis studies compared efficacy and safety of combined therapy with metronidazole to those of carbapenem as single-agent therapy in treatment of cIAIs in recent years. A similar meta-analysis conducted in 2006 investigated the efficacy of ciprofloxacin in combination with metronidazole and several β-lactam-based regimens and suggested that the combined therapy with metronidazole was superior to β-lactam-based regimens with regard to cure, but the comparators included a variety of β-lactam-based regimens [10]. The study did not include analyses of safety endpoints, resulting in an unclear picture regarding the optimal treatment of cIAI; therefore, it is not directly comparable to our analysis, despite similar findings in a carbapenem group.

Several RCTs and meta-analyses investigating relevant antimicrobial therapies for cIAIs have been reported over the last several decades. When carbapenem first became available for treating microbial infections in the 1980s, clindamycin had long been the golden standard for the treatment of anaerobic infections [21]. Several RCTs, each comparing carbapenem and a conventional combination therapy with clindamycin and aminoglycoside, consistently reported that carbapenem was an effective antimicrobial drug for monotherapy of IAIs with efficacy similar to or better than the combination of clindamycin and aminoglycoside [22–25]. A meta-analysis of 28 clinical trials also concluded that broad-spectrum β-lactams were more effective than the clindamycin combination therapy in treating IAIs [26]. These findings can be used to infer the important prospect of metronidazole (in combination with an antiaerobic agent) in fulfilling the role of carbapenem as well as the classic clindamycin regimen in the treatment of IAIs when possible.

Furthermore, the efficacy and safety of combined therapy with metronidazole have also been compared with those of tigecycline in the literature. The results in the RCTs demonstrated that tigecycline monotherapy was similar to a combined therapy with metronidazole with respect to treating patients with cIAI; however, more safety events of nausea and/or vomiting were reported when treated with tigecycline [27–29]. These findings, coupled with the cIAI guidelines' concerns for the use of tigecycline in mild-to-moderate complicated intra-abdominal infection due to its very broad spectrum of tigecycline and for the use of carbapenem due to CRE [3], further suggest combined therapy with metronidazole as one of the few valuable options left for the treatment of cIAIs.

There are some limitations in this study. First, this study used the endpoint of clinical success to reduce the likelihood of misclassification bias, but the identified studies used different definitions of "clinical success". There were 5 studies that combined the number of cured and improved cases when reporting clinical success; there were 2 studies that reported only cure; and the 1 remaining study reported those who were "not considered failure" as their success cases (Supplementary Table 1). This slight inconsistency in endpoint definition may have underestimated the efficacy of both treatment arms because a larger number of events would have been expected if all studies reported both cure and improvement.

Second, there were potential confounders among the included studies. For example, for the primary analysis of clinical success, 5 of the studies reported data on the clinically evaluable population, and the remaining studies reported data on the protocol valid population (2 studies) or did not specify their population in detail (1 study). Three of the studies evaluated clinical success at the end of therapy, 1 study evaluated clinical success

at the test of cure, and the 4 remaining studies did not specify their measurement time point. For the primary analysis of bacteriological eradication, 5 of the studies reported data on the microbiologically evaluable population, and the remaining studies reported data on the protocol valid population (2 studies) or did not specify their population in detail (1 study). Three of the studies evaluated bacteriological eradication at the end of therapy, and the 4 remaining studies did not specify their measurement time point. This limitation due to differences across the identified studies and lack of detailed information from some studies is inherent to a meta-analysis study; however, given that these studies had relatively smaller sample sizes compared with the studies with detailed findings and clear definition of endpoints, only little impact, if any, is expected.

Third, our assessment of validity and quality of the identified studies revealed that some of the included studies were at high risk of bias. Three of the studies lacked blinding of participants and outcome assessments [13, 16, 17], and 1 study reported notable differences in patient characteristics between treatment groups within this particular study [16]. To assess the robustness of the findings from the primary analysis and to better understand the impact of heterogeneity and potential confounders across the identified studies, several sensitivity analyses were conducted. The findings from the primary and sensitivity analyses were consistent with no difference between combined therapy with metronidazole and carbapenem when removing Huizinga et al [16]. Hence, the imbalance of APACHE II scores between the treatment groups did not seem to impact the results in our study. Combined therapy with metronidazole had more clinical success cases when removing those studies with a high risk of bias [13, 16, 17] all together ($P = .04$); therefore, it is possible that a nonblinding design may have underestimated the efficacy of combined therapy with metronidazole. However, because no other endpoints were affected by any of the sensitivity analyses, a careful interpretation is required.

Overall, our findings were robust and mostly consistent across different inclusion and exclusion criteria, supporting the guideline recommendation of treating cIAIs with metronidazole and ceftazidime or cefepime [3]. Because of the continued effectiveness of metronidazole for cIAIs and the importance of selectively using carbapenem to prevent the spread of CRE, it is optimal to consider combined therapy with metronidazole whenever possible in treating patients with cIAI.

CONCLUSIONS

In conclusion, the current meta-analysis revealed that combined therapy with metronidazole can be an effective and safe treatment option for cIAI, similar to carbapenem. The results were consistent when differences in therapy drug type and potential cofounders of the identified studies were considered. We believe that combined therapy with metronidazole can be considered as one of the alternatives in the treatment of cIAIs in the era of drug resistance.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

Acknowledgments

Financial support. This work was supported by Pfizer Japan Inc.

Potential conflicts of interest. H. M. has been an advisor to Toyama Chemical Co., Ltd., has received research funding from Bayer Yakuhin, Ltd., Kyorin Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Taisho Pharmaceutical Co., Ltd., has received scholarship donations from Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., FUJIFILM Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., MSD K.K., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, and Toyama Chemical Co., Ltd., and has been on the speakers' bureau for Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Miyarisan Pharmaceutical Co., Ltd. MSD K.K., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co., Ltd., and Toyama Chemical Co., Ltd. K. W. and B. C. are consultants to Pfizer Japan Inc. N. S. and A. Y. are employees of Pfizer Japan Inc. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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