Systematic Review and Meta-Analysis

Medicine

OPEN

Efficacy of fidaxomicin versus vancomycin in the treatment of *Clostridium difficile* infection

A systematic meta-analysis

Zihan Zhao, MD[a], Yarui Wu, MD[a], Xuhua Geng, MD[a], Congrui Yuan, MD[a], Yi Fu, MD[a], Guibin Yang, MD, PhD[a,*]

Abstract

Purpose: To compare the efficacy, recurrence rate, adverse event rate and mortality of fidaxomicin compared with vancomycin in treating different types of *Clostridium difficile* infection (CDI).

Methods: A systematic search was conducted on PubMed, Embase, Web of Science, Cochrane Library and clinical trial registration databases for research on fidaxomicin versus vancomycin in the treatment of CDI and the retrieval period extended from the establishment of the database to July 22, 2022. A total of 15 studies were included, including 8 RCTs and 7 retrospective cohort studies.

Results: Results showed that there was no significant difference in the overall efficacy of the treatment between fidaxomicin and vancomycin, and results in the subgroups of CDI hypervirulent strains and recurrent CDI were obtained, but vancomycin was more effective than fidaxomicin in the treatment of severe CDI (RR = 0.94, 95% CI: 0.90–0.98, $P < .01$). Results showed that fidaxomicin is superior to vancomycin in terms of 40-day recurrence rate (RR = 0.52, 95% CI: 0.38–0.70, $P < .01$), 60-day recurrence rate (RR = 0.38, 95% CI: 0.21–0.69, $P < .01$) and 90-day recurrence rate (RR = 0.62, 95% CI: 0.50–0.77, $P < .01$). For the recurrence rate of the treatment in CDI hypervirulent strains, severe CDI and recurrent CDI, there was no significant difference between the 2 groups. In addition, there was no significant difference in the incidence of clinical adverse reactions, and same outcomes appeared in all-cause mortality at 40-day, severe CDI and recurrent CDI, but fidaxomicin was superior to vancomycin in all-cause mortality over 60-day (RR = 0.57, 95% CI: 0.34–0.96, $P = .03$).

Conclusion: There were no significant differences between fidaxomicin and vancomycin in the treatment of CDI in therapeutic effectiveness and adverse reactions, while fidaxomicin was superior to vancomycin in terms of recurrence rate and long-term mortality, and vancomycin is more effective in treating severe CDI.

Abbreviations: CDI = *Clostridium difficile* infection, CI = confidence interval, ECCMID = European Congress of Clinical Microbiology and Infectious Diseases, RR = risk ratio.

Keywords: *Clostridium difficile* infection, fidaxomicin, meta-analysis, vancomycin

1. Introduction

Antibiotics are secondary metabolites produced by microorganisms, higher animals and plants during metabolic process. These compounds possess the ability to antagonize pathogens or exhibit other active properties. With the progress of biotechnology, manufacturing antibiotics involves not only direct extraction but also methods such as artificial semi-synthesis or chemical synthesis based on the structure of natural product. Antibiotics are vital medications utilized in the treatment of bacterial infections. However, excessive reliance on antibiotics not only escalates the economic burden of medical care, but also leads to the emergence of drug-resistant bacteria. In recent years, Methicillin-Resistant Staphylococcus aureus[1] is isolated from various departments in the hospital, especially the intensive care unit, which can resist almost all antibiotics, including cephalosporins.[2] As a consequence of inappropriate antibiotic usage and irregular supply, resistance has proliferated even in developing nations, where the overall quantity of antibiotics administered is less than that in developed countries.[3] At present, some medical institutions have found vancomycin-resistant enterococci,[4] the evidences indicate that the standard use of antibiotics and the development of new antibiotics are significant issues. Minimizing the use of vancomycin and seeking alternative antibacterial drugs[5] is one of the current research hotspots in the treatment of *Clostridium*

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

[a] Department of Gastroenterology, Aerospace Center Hospital, Peking University, Beijing, China.

[*] Correspondence: Guibin Yang, Department of Gastroenterology, Aerospace Center Hospital, Peking University, Beijing 100049, China (e-mails: yanggb2013@126.com/yanggb@pku.org.cn).

How to cite this article: Zhao Z, Wu Y, Geng X, Yuan C, Fu Y, Yang G. Efficacy of fidaxomicin versus vancomycin in the treatment of Clostridium difficile infection: A systematic meta-analysis. Medicine 2024;103:32(e39213).

Received: 13 February 2024 / Received in final form: 12 April 2024 / Accepted: 17 July 2024

http://dx.doi.org/10.1097/MD.0000000000039213

difficile infection (CDI). In addition, with the continuous production of drug-resistant bacteria, the treatment course and dosage of antibiotics are also increasing, the adverse effects were brought by a variety of antibiotics.[6] Reducing the treatment course and dosage of antibiotics and reducing the recurrence rate of patients with CDI are urgent problems to be solved in clinical practice.

According to the updated guidelines for the treatment of CDI issued by the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in 2014,[7] patients with mild CDI are recommended to be treated with metronidazole, patients with severe CDI are recommended to be treated with vancomycin. And fidaxomicin, a newly marketed antibacterial drug, was proposed for the first time as an alternative drug for patients with mild and severe CDI. In addition, fidaxomicin is also recommended as a treatment drug for patients with CDI that recurs after treatment. According to the guidelines issued by the Infectious Diseases Society of America in 2018,[8] vancomycin and fidaxomicin can be the first choice for the treatment of patients with CDI for the first episode, and fidaxomicin is placed at the same recommendation level as vancomycin. According to the guidelines recently released by ECCMID in 2021,[9] fidaxomicin has been recommended as the first choice for the treatment of patients with initial and high-risk recurrent CDI. And when fidaxomicin is not available, vancomycin will be given priority. Some clinical trials have shown that the effect of fidaxomicin in the treatment of CDI is not weaker than vancomycin, and it is better than vancomycin in prognosis or incidence of adverse reactions, but each trial has individual differences and randomness, previous RCT studies have compared the effects in terms of overall treatment effectiveness and recurrence rate. In recent years, RCTs and cohort studies have been conducted on the types of disease, drug regimens, prognosis, and incidence of adverse reactions. In this paper, the efficacy, recurrence rate, adverse reaction, and prognosis of fidaxomicin in the treatment of various types CDI were statistically analyzed, and the comparison of the advantages and disadvantages of fidaxomicin and vancomycin was verified.

2. Materials and method

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (CRD 42022359255) and this study was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis (Material S1, Supplemental Digital Content, http://links.lww.com/MD/N307).

2.1. Search strategies

To compare the efficacy, recurrence rate, adverse reaction, and prognosis between fidaxomicin and vancomycin, a systematic search was conducted on PubMed, Embase, Web of Science, Cochrane Library and clinical trial registration databases. The retrieval time was from the time of database establishment to July 22, 2022. Searching was conducted by each engine using the key words: ("Fidaxomicin," "lipiarmycin*," "tiacumicin*," "par 101," "Dificid") and ("Clostridioides difficile," "Clostridium difficile," "c.diff," "Clostridium Infections," "pseudomembranous," "diar*") (Material S2, Supplemental Digital Content, http://links.lww.com/MD/N308).

2.2. Study selection

The inclusion criteria are as follows: The research type of the literature is RCT or cohort study with no language constraints. The research subjects have clear diagnostic criteria, the first diagnosis is CDI, and there are no restrictions on age, gender, and nationality. Observation to evaluate the literature on outcome indicators such as cure rate, recurrence rate, and adverse reaction. The intervention measures are the fidaxomicin and vancomycin. The exclusion criteria are as follows: The study population or trial size was not clear. Duplicate published data or literature. Case reports, editorials, comments, and reviews, or just abstract alone were ruled out.

2.3. Outcomes

Our primary outcome is the rate of clinical cure, defined as the resolution of diarrhea and other symptoms of CDI without the need of additional anti-clostridial medication. The secondary outcomes are the following: the clinical recurrence rate, the incidence of clinical adverse reactions and all-cause mortality after clinical treatment.

2.4. Data analysis

Two authors independently reviewed papers and extract relevant data including first author, year of publication, study type, country, mean age, numbers of participants, gender, drug dose and outcomes. The divergences in the data extraction process were resolved by discussion. The Cochrane risk of bias tool was used to assess the risk of bias of RCTs, and Newcastle-Ottawa Scale was used to assess the risk of bias of cohort studies.

Data were analyzed by using Review Manager (Version5.4), and results for subgroups based on time, severity and recurrence were performed. Risk ratio (RR) with 95% confidence interval (CI) was used to evaluate the outcome. The χ^2 test was used to analyze the heterogeneity of the results of each group, and the size of the heterogeneity was quantitatively judged by combining with I^2. When $P \geq .1$ and $I^2 \leq 50\%$, a fixed-effect model was used for meta-analysis. On the contrary, when $P < .1$ and $I^2 > 50\%$, it indicated that the heterogeneity among the trials was large, and the random effects model was used for data merging. Statistical significance was defined as a P value $< .05$.

3. Results

3.1. Selection of studies

We identified a total of 2898 citations from electronic database searches. In strict accordance with the inclusion criteria, exclusion criteria and the literature screening process, screening was conducted, and a total of 15 related studies were finally included. A flowchart was showed in Figure 1, and general information of the studies were performed in Tables 1 and 2 divided by RCTs and cohort studies. Among the included studies, 8 RCTs involving a total of 2298 participants compared the efficacy of fidaxomicin and vancomycin, whereas 7 cohort studies involving a total of 3349 participants conducted similar comparisons.

3.2. Risk of bias

Quality of RCT studies were assessed using the Cochrane risk of bias tool, and random sequence generation and blinding of participants and personnel were found in 6 studies. In addition, blinding of outcomes assessment was found in 5 studies, and one of studies was assessed to high risk of bias in incomplete outcome data because of the high loss ratio of follow-up. The results of RCTs study quality assessment in the meta-analysis were performed in Figure 2. Quality of cohort studies was assessed using the Newcastle–Ottawa Scale. The scale assessed the cohort studies from selection, comparability and outcome. A greater number of stars suggested a higher quality study. The results for the cohort studies quality of assessment are presented in Table 3. For the potential publication bias, the funnel plot about efficacy of fidaxomicin versus vancomycin in

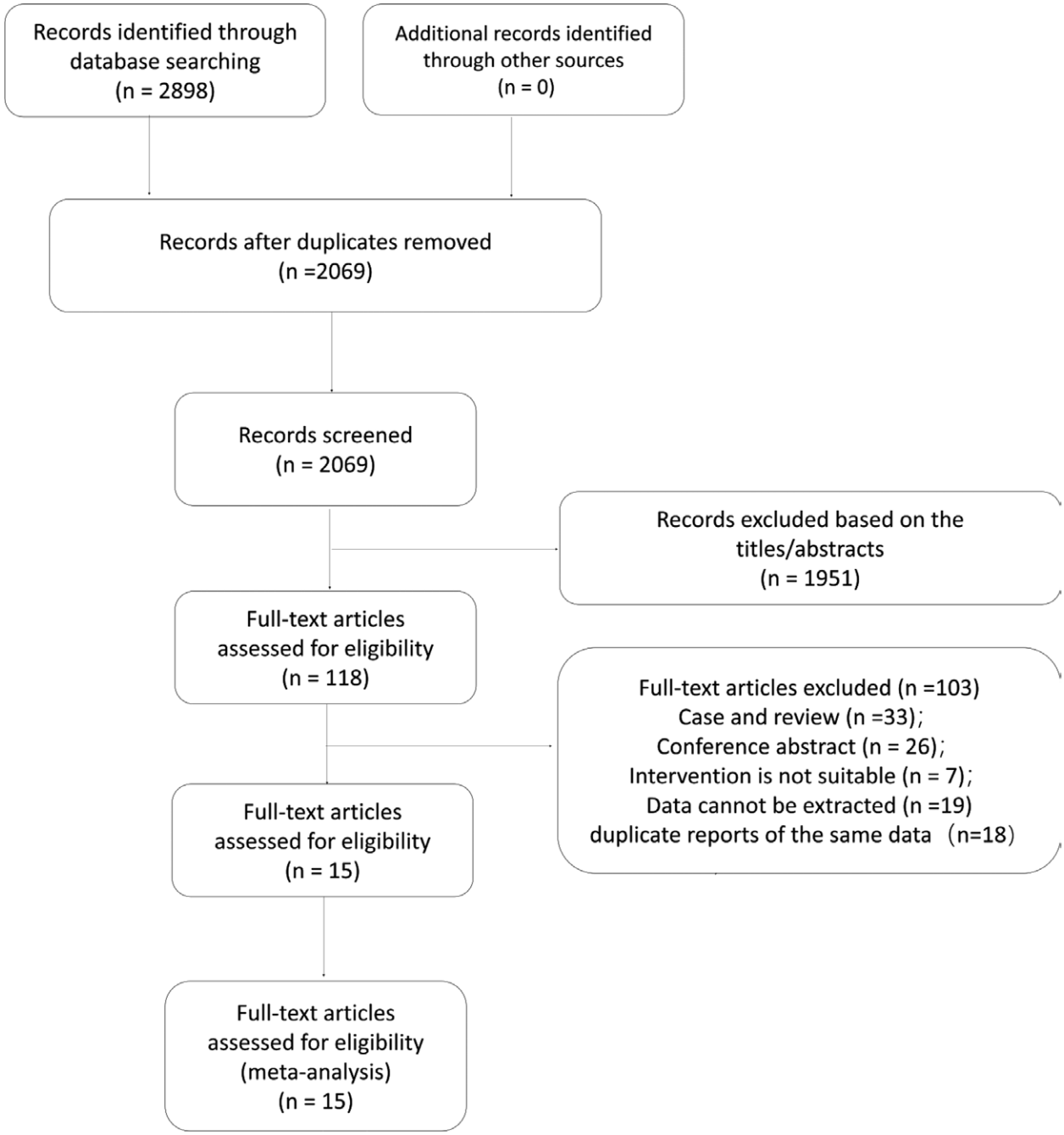

Figure 1. Flowchart of the study selection process.

the treatment of CDI was performed, and there was no publication bias in the included studies.

3.3. The efficacy of fidaxomicin versus vancomycin in the treatment of CDI

Seven studies included the evaluation of the clinical efficacy of fidaxomicin and vancomycin in the treatment of CDI, and the forest plot showed that there was no significant difference for the overall effective rate in fidaxomicin compared with vancomycin in the treatment of CDI (RR = 1.01, 95% CI: [0.97–1.05], I^2 = 7%, P = .55, Fig. 3A). Owing to the bias from Hartford Hospital was higher than other studies, results of sensitivity analysis showed that there was no significant change in the statistical outcome after removing this study, but the heterogeneity was reduced to 1% (RR = 1.01, 95% CI: [0.97–1.05], I^2 = 1%, P = .66). Two studies included the evaluation of the clinical efficacy of fidaxomicin and vancomycin in the treatment of CDI hypervirulent strains (NAP1/BI/027) and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.98, 95% CI [0.88–1.10], I^2 = 0%, P = .79, Fig. 3B). Five studies included the evaluation of the clinical efficacy of fidaxomicin and vancomycin in the treatment of severe CDI and the forest plot showed that the effective rate of vancomycin was better than that of fidaxomicin in the treatment of severe CDI (RR = 0.94, 95% CI: [0.90–0.98], I^2 = 5%, P < .01, Fig. 3C). Four studies included the evaluation of the efficacy of fidaxomicin and vancomycin in the treatment of recurrent CDI and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.97, 95% CI: [0.91–1.03], I^2 = 15%, P = .34, Fig. 3D).

Table 1

Characteristics of the included RCT studies.

Authors	Year	Country	Mean age (years) E:C	No. of patients E:C	Female E:C	Outcomes measures	Interventions E:C	
Thomas J. Louie[9]	2011	Canada	60.3/62.9	287/309	164/169	Overall efficacy Efficacy of severe CDI Overall recurrence rate Recurrence rate of severe CDI Adverse reaction incidence	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days
Oliver A Cornely[10]	2012	USA, Canada, Europe	64.3/62.5	252/257	148/162	Overall efficacy Efficacy of severe CDI Overall recurrence rate Recurrence rate of severe CDI Adverse reaction incidence	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days
Hartford Hospital	2017	USA	69.0/66.0	18/16	11/9	Overall efficacy	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4t imes/day × 10 days
Benoit Guery[11]	2018	Europe	75.0/75.0	177/179	107/100	Overall efficacy Overall recurrence rate Adverse reaction incidence	200 mg Fidaxomicin 2 times/day × 5 days +200 mg Fidaxomicin 2 day/times × 16 days	125 mg Vancomycin 4 times/day × 10 days
Hiroshige Mikamo[12]	2018	Japan	74.0/75.0	104/108	56/54	Overall efficacy Overall recurrence rate Adverse reaction incidence Overall mortality	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days
Christian Lodberg Hvas[13]	2019	Denmark	64.0/72.0	24/16	13/11	Efficacy of recurrent CDI Recurrence rate of recurrent CDI	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days
Joshua Wolf[14]	2019	USA, Canada, Europe	5.0/4.0	98/44	41/19	Overall efficacy Overall recurrence rate Adverse reaction incidence	<6 yr:16 mg/kg/d with a maximum dose of 200 mg/d 2 times/d × 10 days 6–18 yr: 200 mg Fidaxomicin 2 times/day × 10 days	<6 years:10 mg/kg/d with a maximum dose of 125 mg/d 4 times/day × 10 days 6–18 yrs: 125 mg Vancomycin 4 times/day × 10 days
Erik R Dubberke[15]	2020	Worldwide	61.3/64.9	26/373	NA	Overall efficacy Overall recurrence rate Overall mortality	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days

C = treatment group with vancomycin, CDI = *Clostridium difficile* infection, E = treatment group with fidaxomicin.

3.4. The clinical recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI

There were many outcome indicators associated with the overall recurrence rate, so the outcomes were divided into 3 different time subgroups for 40, 60, and 90 days, and the difference of the total recurrence rate was studied. Results showed that fidaxomicin was superior to vancomycin in terms of 40-day recurrence rate (RR = 0.52, 95% CI: 0.38–0.70, $P < .01$, Fig. 4A), 60-day recurrence rate (RR = 0.38, 95% CI: 0.21–0.69, $P < .01$, Fig. 4B), and 90-day recurrence rate (RR = 0.62, 95% CI: 0.50–0.77, $P < .01$, Fig. 4C). The line graph performed to compare the recurrence rate of fidaxomicin and vancomycin was showed in Figure 4D.

Two studies included the evaluation of recurrence rate for fidaxomicin versus vancomycin in the treatment of hypervirulent strains of CDI and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.87, 95% CI: [0.40–1.90], $I^2 = 69\%$, $P = .72$, Fig. 5A). Five studies included the evaluation of the clinical recurrence rate of severe CDI treated with fidaxomicin and vancomycin and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.67, 95% CI: [0.36–1.27], $I^2 = 70\%$, $P = .22$, Fig. 5B). Five cohort studies included the evaluation of the recurrence rate of recurrent CDI treated with fidaxomicin and vancomycin and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.81, 95% CI: [0.46–1.43], $I^2 = 66\%$, $P = .46$, Fig. 5C).

3.5. The incidence of clinical adverse reactions of fidaxomicin versus vancomycin in the treatment of CDI

Five studies assessed the incidence of adverse events in the treatment of CDI with fidaxomicin and vancomycin and the forest

Table 2

Characteristics of the included cohort studies.

Authors	Year	Country	Mean age (years) E:C	No. of patients E:C	Female E:C	Interventions E:C	Authors
Jason C Gallagher[16]	2015	USA	73.2/72.1	49/46	NA	200 mg Fidaxomicin 2 times/day	125 mg or 25 0mg Vancomycin 4 times/day
Jennifer D. Tieu[17]	2018	USA	67.4/66.4	65/195	7/15	Fidaxomicin	Vancomycin
C.A.Gentry[18]	2019	USA	69.7/71.0	213/639	11/31	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10–14 days
Nimish Patel[19]	2021	USA	74.2/74.9	38/54	1/1	200 mg Fidaxomicin 2 times/day × 10 days	125/250/500 mg Vancomycin 4 times/day × 10 day
Sylvia Polivkova[20]	2021	Czech Republic	75.2	57/80	NA	200 mg Fidaxomicin 2 times/day × 10 days	125 mg Vancomycin 4 times/day × 10 days
Alyssa Rinaldi[21]	2021	USA	58/61.5	35/100	23/57	200 mg Fidaxomicin 2 times/day × 10 days	125/250/500 mg Vancomycin 4 times/day × 14 days
Ronald G Hall 2nd[22]	2022	USA	64.17/65.04	889/889	547/558	Fidaxomicin	Vancomycin

C = treatment group with vancomycin, E = treatment group with fidaxomicin.

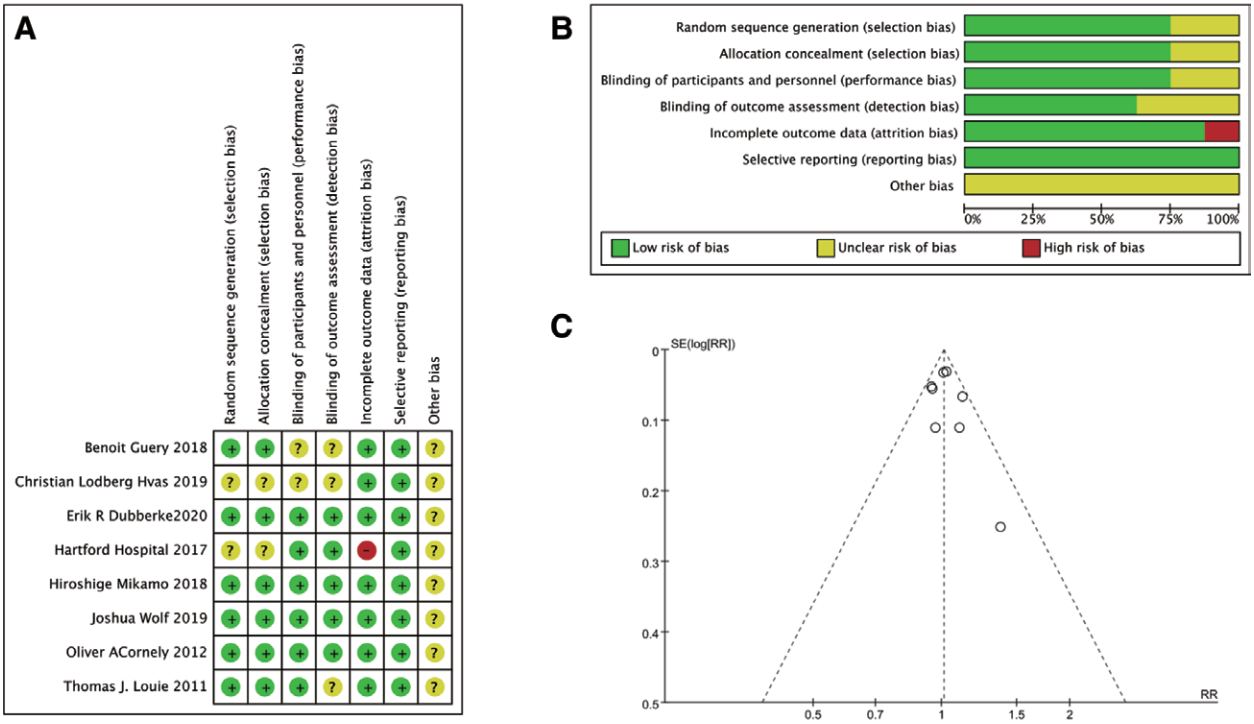

Figure 2. RCT study quality was assessed by using the Cochrane risk of bias tool. (A) Risks of bias graph: +, low risk of bias: -, high risk of bias:?, unclear risk of bias. (B) Risks of bias summary. (C) The potential publication bias of the study.

plot showed that there was no significant difference between the 2 groups (RR = 1.01, 95% CI: [0.91–1.08], I^2 = 0%, P = .72, Fig. 6).

3.6. All-cause mortality after clinical treatment of fidaxomicin versus vancomycin in the treatment of CDI

Four studies included the assessment of clinical all-cause mortality less than 40 days in the treatment of CDI with fidaxomicin versus vancomycin and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.70, 95% CI: [0.37–1.29], I^2 = 0%, P = .25, Fig. 7A). Three studies included the assessment of clinical all-cause mortality over 60 days in the treatment of CDI with fidaxomicin and vancomycin, and the forest plot showed that the fidaxomicin group had a lower mortality rate over 60 days after CDI treatment than that in the vancomycin group (RR = 0.57, 95% CI: [0.34–0.96], I^2 = 0%, P = .03, Fig. 7B). The line graph performed to compare all-cause mortality of fidaxomicin and vancomycin was showed in Figure 7C.

Three studies included the assessment of clinical mortality in severe CDI treated with fidaxomicin and vancomycin, and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.88, 95% CI: [0.59–1.32], I^2 = 0%, P = .53, Fig. 8A). Three studies included the assessment of mortality in recurrent CDI treated with fidaxomicin and vancomycin and the forest plot showed that there was no significant difference between the 2 groups (RR = 0.48, 95% CI: [0.17–1.35], I^2 = 14%, P = .16, Fig. 8B).

Table 3

Cohort studies quality was assessed by using the Newcastle–Ottawa Scale.

	Selection					Outcome			
Study	Representative-ness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Score
Jason C Gallagher 2019	—	—	☆	—	☆☆	—	☆	☆	6
Jennifer D. Tieu 2018	☆	☆	☆	—	☆☆	—	☆	☆	7
Christian Lodberg Hvas 2019	—	☆	☆	—	☆	—	☆	☆	6
C.A.Gentry 2019[18]	☆	☆	☆	—	☆☆	☆	☆	☆	8
Nimish Patel 2021[23]	☆	☆	☆	—	☆☆	—	☆	☆	7
Sylvia Polivkova 2021[16]	☆	☆	☆	—	☆☆	—	☆	☆	7
Alyssa Rinaldi 2021	☆	☆	☆	—	☆☆	☆	☆	☆	8
Ronald 2022	☆	☆	☆	—	☆☆	☆	☆	☆	8

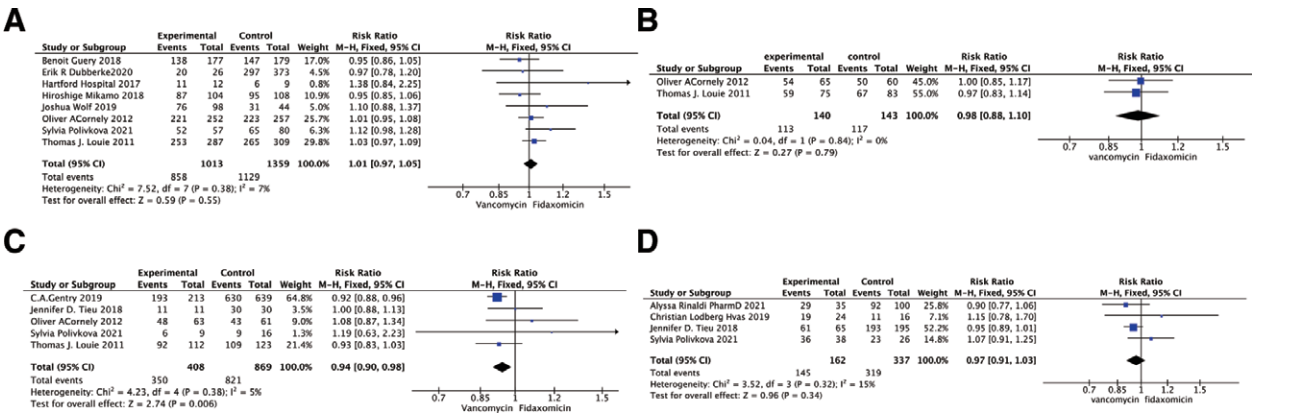

Figure 3. The efficacy of fidaxomicin versus vancomycin in the treatment of CDI. (A) The overall effective rate of fidaxomicin compared with vancomycin in the treatment of CDI. (B) The effective rate of fidaxomicin compared with vancomycin in the treatment of CDI hypervirulent strains. (C) The effective rate of fidaxomicin compared with vancomycin in the treatment of severe CDI. (D) The effective rate of fidaxomicin compared with vancomycin in the treatment of recurrent CDI. CDI = *Clostridium difficile* infection.

4. Discussion

CD is a gram-positive, anaerobic, spore-borne bacterium that was originally extracted from the feces of healthy infants. Although it is very common in the digestive tract of infants, CD does not exhibit significant toxic effects and the corresponding Clinical symptoms.[10,11] Although the microecological environment of the digestive tract gradually changes, the number of CD gradually decreases, and asymptomatic colonization of the bacteria in the digestive tract of healthy adults is rare.[12] With the widespread use of antibiotics, the incidence of CDI has gradually increased.[13] Although the resistance of CD to vancomycin is still low, in recent years, the emergence of drug-resistant enterococci and other drug-resistant bacteria[4] suggests that we cannot rely too much on vancomycin therapy, and it is imminent to seek new treatments for CD.

As a new type of macrolide antibiotic, Fidaxomicin has been upgraded again in the latest guidelines.[9] It was first recommended as an alternative drug for fidaxomicin treatment in 2014,[7] and its status in the treatment of *Clostridium difficile* has gradually surpassed that of vancomycin, but the current guidelines on the efficacy and safety of fidaxomicin in the treatment of *Clostridium difficile* are still in the market stage. We included randomized controlled trials and cohort studies on multiple databases from the establishment of the database to June 2022, aiming to compare the effectiveness and security of fidaxomicin compared with vancomycin in the treatment of CDI.

4.1. The efficacy of fidaxomicin versus vancomycin in the treatment of CDI

According to the latest guidelines published by the ECCMID in 2021,[9] for elderly patients with initial onset of CDI, fidaxomicin 200 mg bid × 10 days may be recommended for treatment, and when fidaxomicin is unavailable, it is recommended to use vancomycin 125 mg qid × 10 days for treatment. It believes that there is no significant difference in the overall cure rate between the 2 groups, and both are better than metronidazole. In the

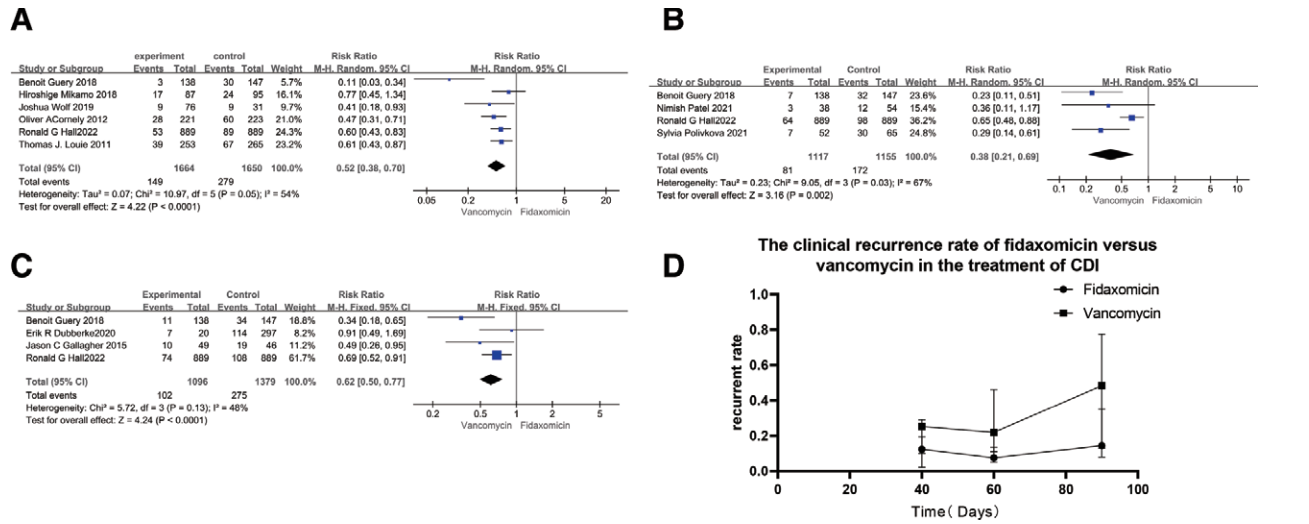

Figure 4. The clinical recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. (A) 40-day recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. (B) 60-day recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. (C) 90-day recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. (D) The line graph to perform the clinical recurrence. CDI = *Clostridium difficile* infection.

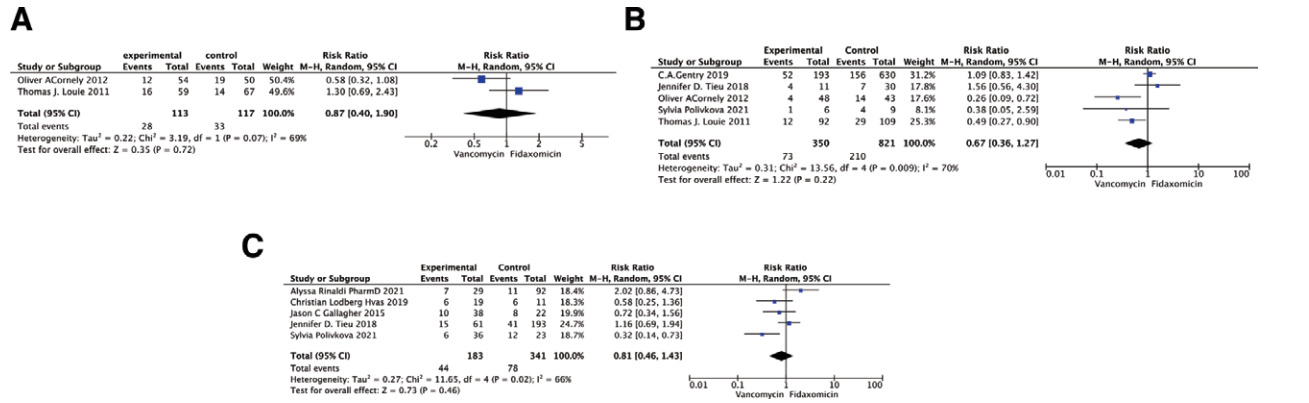

Figure 5. Subgroups of the clinical recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. (A) The clinical recurrence rate of fidaxomicin compared with vancomycin in the treatment of CDI hypervirulent strains. (B) The clinical recurrence rate of fidaxomicin compared with vancomycin in the treatment of severe CDI. (C) The clinical recurrence rate of fidaxomicin compared with vancomycin in the treatment of recurrent CDI. CDI = *Clostridium difficile* infection.

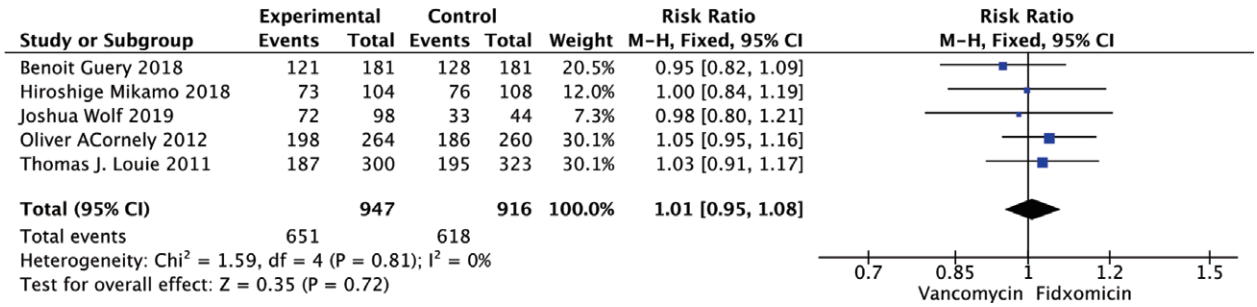

Figure 6. The incidence of clinical adverse reactions of fidaxomicin versus vancomycin in the treatment of CDI. CDI = *Clostridium difficile* infection.

study, a number of studies were included to evaluate the overall efficacy of fidaxomicin and vancomycin in the treatment of CDI, showing that there was no significant difference between the 2 groups, and their heterogeneity was small, so the results of the study were highly reliable. It was consistent with the evidence recommended by current guidelines. But the evaluation of the overall effectiveness showed that there were some limitations in the difference for the 2 treatments. Overall efficacy was not stratified according to patient age, medication regimen, disease severity, etc. At present, fidaxomicin is mainly used for the treatment of CDI in adults. A RCT study conducted by Joshua Wolf in 2019[14] proved that for juveniles with CDI, there was no significant difference in the efficacy of fidaxomicin and vancomycin. But there were still few studies on the testification of fidaxomicin in the treatment of CDI in children, and more studies are needed to further confirm. Regarding the fidaxomicin dosage regimen, most of studies still use 200 mg bid × 10 days for treatment, but a RCT study with pulsed dosing regimen

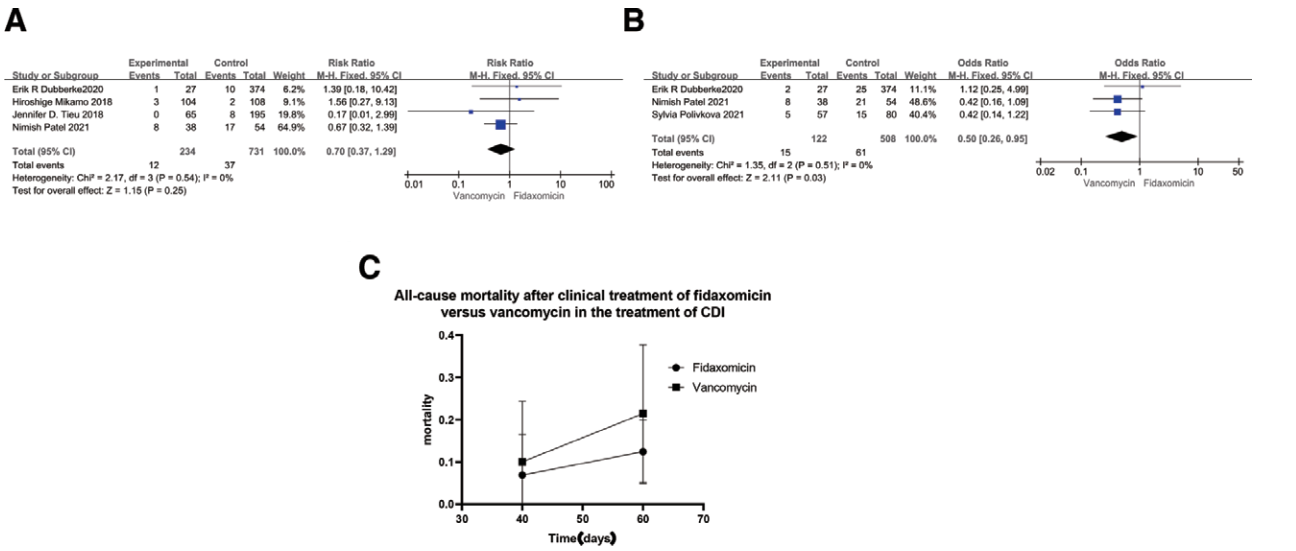

Figure 7. All-cause mortality after clinical treatment of fidaxomicin versus vancomycin in the treatment of CDI. (A) Less than 40-days all-cause mortality after clinical treatment of fidaxomicin versus vancomycin in the treatment of CDI. (B) Over 60-days all-cause mortality after clinical treatment of fidaxomicin versus vancomycin in the treatment of CDI. (C) The line graph to perform the mortality. CDI = *Clostridium difficile* infection.

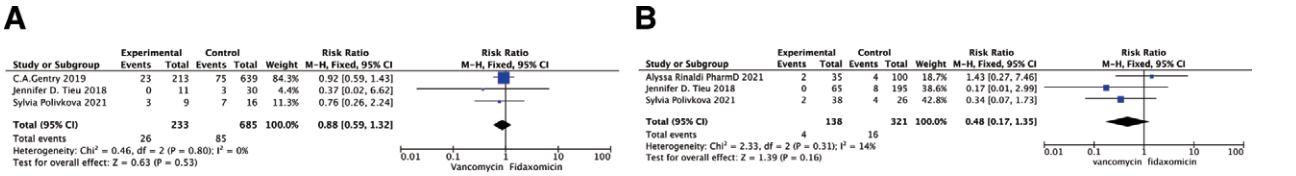

Figure 8. Subgroups of the incidence of clinical adverse reactions of fidaxomicin versus vancomycin in the treatment of CDI. (A) All-cause mortality in severe CDI with fidaxomicin and vancomycin. (B) All-cause mortality in recurrent CDI with fidaxomicin and vancomycin. CDI = *Clostridium difficile* infection.

for CDI conducted by Benoit Guery in 2018[15] also obtained impressive results. Therefore, the efficacy of different regimens of fidaxomicin in the treatment of CDI still need to be corroborated by a large amount of data in the future.

For the treatment of CDI hypervirulent strains (NAP1/BI/027), the current guidelines have not recommended this type. Our study showed that there was no significant statistical difference between the 2 treatments. But the sizes of sample were small, and more data were needed to corroborate the differences of the effectiveness in highly virulent strains.

For the treatment of severe CDI, most of the current guidelines believed that there was no significant difference in the efficacy of fidaxomicin and vancomycin, but our study showed that vancomycin may have more advantages than fidaxomicin, which was inconsistent with the current guideline recommendations. There were also studies considering that in non-severe CDI, fidaxomicin had more advantages than vancomycin in the treatment of CDI, but in severe infection, there was no significant difference between the 2 groups.[16] In the future, it will be necessary to classify the severity of CDI to further explore the difference in efficacy between the 2 groups.

For the treatment of recurrent CDI, there was no statistically significant difference between fidaxomicin and vancomycin, and the current guidelines recommend fecal microbiota transplantation for the treatment of recurrent CDI, which is far more effective than oral antibiotics treatment.[9]

4.2. The clinical recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI

CDI is a disease that is prone to recurrence, and the recurrence rate is one of the indicators of clinical efficacy evaluation. Although the current guidelines and reviews believe that fidaxomicin is superior to vancomycin in terms of recurrence rate, there is no significant difference between the 2 groups in terms of cure rate. Therefore, ECCMID recommended the use of fidaxomicin to treat CDI in order to reduce the clinical burden and improve the patient's condition. However, in recent years, new RCTs and cohort studies[17–19] have shown that there was no statistically significant difference in the recurrence rate between the 2 under certain conditions. Considering that the current guidelines was not discussed in terms of the duration time, the medication regimen and the severity of the disease. Our study discussed the recurrence rate of the two by subgroup analysis.

In this study, a number of studies were included to evaluate the overall recurrence rate of fidaxomicin versus vancomycin in the treatment of CDI. Fidaxomicin has certain advantages over vancomycin in terms of recurrence rates in 40-day, 60-day, and 90-day, which was consistent with the current guideline recommendations. But most of the previous guidelines did not discuss the recurrence rate based on time, more data are needed in the future to verify the difference between the short-term and long-term recurrence rates. From the data included in this article, the statistics of recurrence rate had a large heterogeneity, which might be caused by different fidaxomicin treatment used in some studies. Benoit Guery[15] thought that fidaxomicin of pulsed dosing regimen had a lower recurrence rate than vancomycin at each time period, but due to the lack of data on this treatment regimen, further improvement of clinical research is needed to expand the sample size, and more reliable conclusions can be drawn.

Regarding the recurrence rate of CDI hypervirulent strains, this study showed that there was no significant difference

between the 2 groups, which contradicts findings from a previous study.[20] This inconsistency may be attributed to the small sample size and high heterogeneity in our study. Consequently, further research is warranted to validate these results.

In the treatment of severe CDI, there was no significant difference between fidaxomicin and vancomycin in terms of the recurrence rate. There were certain deviations in the guidelines recommended treatment regimens. However, this study showed greater bias, a sensitivity analysis was implemented to value the dependability. This analysis revealed that the study conducted by C.A. Gentry had a notable impact. Even if the study was removed, the result was still negative. Nevertheless, to ensure the accuracy of our findings, further data collection is warranted in future studies.

The recurrence rate of CDI post-treatment displayed no statistically significant difference between the 2 groups, alongside a noticeable bias detected in the study. We supplied the sensitivity analysis for it, and found that the results of the meta-analysis did not change after excluding each article. Some studies had demonstrated that fecal transplantation had obvious advantages over the two in the treatment of recurrent *Clostridium difficile*.[21,22,24]

4.3. The security of fidaxomicin versus vancomycin in the treatment of CDI

For the safety of drug, the occurrence of adverse reactions and the mortality rate during treatment are the evaluation indicators. At present, most of the guidelines and studies have found that there is no significant difference in the incidence of adverse reactions between the 2 groups through the statistics of multiple RCT studies. However, in recent years, new cohort studies have also conducted statistics on the all-cause mortality of the two to further verify their far-reaching effects. Some studies[16,23] showed that the mortality rate of vancomycin in the treatment of CDI was higher than that of fidaxomicin, but most studies believed that there was no significant difference between the 2 groups. Adverse reactions and all-cause mortality were counted in our study. The results of this study found that there was no significant difference in the overall incidence of adverse events (including abdominal distention, diarrhea, nausea, abdominal pain, etc.) between the 2 groups. There was also no statistically significant difference between the 2 groups in terms of the rate of 40-day death, and there was no significant difference in the mortality rate of severe and recurrent CDI. However, in terms of all-cause mortality over 60 days, fidaxomicin has a lower mortality rate than vancomycin. In general, there was no significant difference between the two in short-term mortality, fidaxomicin performed better than vancomycin for long-term mortality.

4.4. The cost-effectiveness of fidaxomicin versus vancomycin in the treatment of CDI

Although our study did not use cost-effectiveness as a research indicator, the effective rate and recurrence rate can indicate the cost-effectiveness to a certain extent. Several previous studies have shown that there was no significant difference in efficacy between vancomycin and fidaxomicin, and the unit price of fidaxomicin was higher than that of vancomycin, so the treatment cost of fidaxomicin was higher. In recent years, studies had compared the recurrence rate and average hospital stay of CDI patients treated with 2 antibiotics, which showed that the cost-effectiveness of fidaxomicin in the treatment of CDI was more advantageous than that of vancomycin.[25–27] However, drug prices and hospitalization costs vary greatly in different regions, and the cost-effectiveness of drugs should be determined according to local conditions.

5. Strengths and limitations

This meta-analysis identified a total of 2898 citations from electronic database searches and a total of 15 related studies were finally included. Our study further summarized previous data, and discuss the effectiveness, recurrence rate and security by means of subgroup analysis, and provided more evidence for clinical practice. However, clinical studies are more to verify the efficacy, recurrence rate and safety of the two in general, and there are few studies about the severity and recurrence of the disease. At present, more researches compared the overall therapeutic effect of CDI for vancomycin and fidaxomicin, there are few studies comparing the therapeutic effect between different strain types. For the specific treatment options of fidaxomicin for the treatment of CDI, currently more choices are 200 mg 2/day, but in recent years, the choice of pulsed dosing regimen for fidaxomicin has become a research hotspot, and there are still few evaluations of its therapeutic effect compared with traditional doses. At last, there are few studies on the treatment of CDI in children, and most of the evidence comes from studies on adult CDI patients, more data are needed to support the comparison of efficacy and safety in children.

6. Conclusion

There were no significant differences between fidaxomicin and vancomycin in the treatment of CDI in therapeutic effectiveness and adverse reactions, while fidaxomicin was superior to vancomycin in terms of recurrence rate and long-term mortality, and vancomycin is more effective in treating severe CDI.

Author contributions

Conceptualization: Zihan Zhao, Yarui Wu, Xuhua Geng, Guibin Yang.
Data curation: Zihan Zhao, Yarui Wu, Congrui Yuan.
Formal analysis: Zihan Zhao, Yarui Wu.
Investigation: Yarui Wu, Congrui Yuan.
Methodology: Zihan Zhao, Yarui Wu, Guibin Yang.
Project administration: Xuhua Geng, Yi Fu, Guibin Yang.
Software: Yarui Wu, Xuhua Geng, Congrui Yuan.
Supervision: Xuhua Geng, Congrui Yuan, Yi Fu, Guibin Yang.
Validation: Yi Fu, Guibin Yang.
Visualization: Yi Fu, Guibin Yang.
Writing – original draft: Zihan Zhao, Yarui Wu.
Writing – review & editing: Yi Fu, Guibin Yang.

References

[1] Lakhundi S, Zhang K. Methicillin-resistant staphylococcus aureus: molecular characterization, evolution, and epidemiology. Clin Microbiol Rev. 2018;31:e00020–18.
[2] Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS. Antibiotic resistance and persistence-implications for human health and treatment perspectives. EMBO Rep. 2020;21:e51034.
[3] Viderman D, Brotfain E, Khamzina Y, Kapanova G, Zhumadilov A, Poddighe D. Bacterial resistance in the intensive care unit of developing countries: report from a tertiary hospital in Kazakhstan. J Glob Antimicrob Resist. 2019;17:35–8.
[4] Reyes K, Bardossy AC, Zervos M. Vancomycin-resistant enterococci: epidemiology, infection prevention, and control. Infect Dis Clin North Am. 2016;30:953–65.
[5] Tse Sum Bui B, Auroy T, Haupt K. Fighting antibiotic-resistant bacteria: promising strategies orchestrated by molecularly imprinted polymers. Angew Chem Int Ed Engl. 2022;61:e202106493.
[6] Alós JI. [Antibiotic resistance: a global crisis]. Enferm Infecc Microbiol Clin. 2015;33:692–9.
[7] Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20:1–26.

[8] McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1–e48.
[9] van Prehn J, Reigadas E, Vogelzang EH, et al.; Guideline Committee of the European Study Group on Clostridioides difficile. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect. 2021;27:S1–S21.
[10] Rousseau C, Poilane I, De Pontual L, Maherault AC, Le Monnier A, Collignon A. Clostridium difficile carriage in healthy infants in the community: a potential reservoir for pathogenic strains. Clin Infect Dis. 2012;55:1209–15.
[11] Thompson CM Jr., Gilligan PH, Fisher MC, Long SS. Clostridium difficile cytotoxin in a pediatric population. Am J Dis Child. 1983;137:271–4.
[12] Rea MC, O'Sullivan O, Shanahan F, et al. Clostridium difficile carriage in elderly subjects and associated changes in the intestinal microbiota. J Clin Microbiol. 2012;50:867–75.
[13] Pépin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171:466–72.
[14] Wolf J, Kalocsai K, Fortuny C, et al. Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with clostridioides (Clostridium) difficile infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). Clin Infect Dis. 2020;71:2581–8.
[15] Guery B, Menichetti F, Anttila V-J, et al.; EXTEND Clinical Study Group. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis. 2018;18:296–307.
[16] Polivkova S, Krutova M, Capek V, Sykorova B, Benes J. Fidaxomicin versus metronidazole, vancomycin and their combination for initial episode, first recurrence and severe Clostridioides difficile infection - An observational cohort study. Int J Infect Dis. 2021;103:226–33.
[17] Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in a randomized, double-blind, comparative Phase III study in Japan. J Infect Chemother. 2018;24:744–52.
[18] Gentry CA, Nguyen PK, Thind S, Kurdgelashvili G, Skrepnek GH, Williams RJ II. Fidaxomicin versus oral vancomycin for severe Clostridium difficile infection: a retrospective cohort study. Clin Microbiol Infect. 2019;25:987–93.
[19] Dubberke ER, Gerding DN, Kelly CP, et al. Efficacy of bezlotoxumab in participants receiving metronidazole, vancomycin, or fidaxomicin for treatment of clostridioides (Clostridium) difficile Infection. Open Forum Infect Dis. 2020;7:ofaa157.
[20] Louie TJ, Miller MA, Mullane KM, et al.; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for clostridium difficile infection. N Engl J Med. 2011;364:422–31.
[21] Hvas CL, Dahl Jørgensen SM, Jørgensen SP, et al. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent clostridium difficile infection. Gastroenterology. 2019;156:1324–32.e1323.
[22] Abdallah M, Abdalla A, Wiedel N, Baloun B, Gilbert J. Fecal microbiota transplantation for recurrent clostridioides difficile infection: efficacy and predictors of success. Am J Gastroenterol. 2019;114:S78–S78.
[23] Patel N, Lowry C, Morgenson D, Shah V, Stornelli N, Lodise TP. Comparative effectiveness of early-targeted use of fidaxomicin versus oral vancomycin among hospitalized veterans' affairs patients with infections due to Clostridioides difficile. Pharmacotherapy. 2021;41:212–9.
[24] Coffman K, Chen XJ, Okamura C, Louie E. IVIG - A cure to severe refractory NAP-1 Clostridium difficile colitis? A case of successful treatment of severe infection, which failed standard therapy including fecal microbiota transplants and fidaxomicin. IDCases. 2017;8:27–8.
[25] Cobo Reinoso J, Grau Cerrato S, Mensa Pueyo J, et al. Economic evaluation of fidaxomicin for the treatment of Clostridium Difficile Infections (CDI) also known as Clostridium Difficile-Associated Diarrhoea (CDAD) in Spain. Value Health. 2014;17:A674.
[26] Abdali ZI, Roberts TE, Barton P, Hawkey PM. Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent Clostridioides difficile infection. EClinicalMedicine. 2020;24:100420.
[27] Wagner M, Lavoie L, Goetghebeur M. Clinical and economic consequences of vancomycin and fidaxomicin for the treatment of Clostridium difficile infection in Canada. Can J Infect Dis Med Microbiol. 2014;25:87–94.