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SYSTEMATIC REVIEW ARTICLE

Cadazolid *vs* Vancomycin for the Treatment of *Clostridioides difficile* Infection: Systematic Review with Meta-analysis

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Abstract: ***Background***: Current guidelines recommend the use of vancomycin for the initial treatment of *Clostridioides difficile* Infection (CDI). Cadazolid, an experimental drug, has been utilized and compared in several studies with varying results.

Methods: A systematic literature search was performed using electronic databases [Medline, Google Scholar and Cochrane] for eligible studies. Randomized Controlled Trials (RCTs) comparing cadazolid with vancomycin for CDI treatment were included. Demographic variables and outcomes (CDI resolution, CDI recurrence, and adverse events) were collected. The primary outcome was clinical cure rate defined as the resolution of CDI at the end of a 10-day course.

Results: Two studies with three RCTs met the inclusion criteria with a total of 1283 patients with CDI who received either cadazolid 250 mg twice daily (624 patients) or vancomycin 125 mg four times daily (659 patients). Clinical cure rate at the end of the treatment was not statistically significant (pooled OR= 0.82; 95% CI = 0.61 to 1.11; p=0.20; I^2= 0%). Sustained clinical response at clinical follow-up was also not significantly different (pooled OR = 1.14; 95% CI = 0.91 to 1.43; p=0.27; I^2 = 0 %). Cadazolid had a lower recurrence rate than vancomycin (pooled OR = 0.71; 95% CI = 0.52 to 0.98; p=0.04; I^2 = 13 %).

Conclusion: Cadazolid is non-inferior to vancomycin and offers a promising alternative for the treatment of CDI. More studies including RCTs and longitudinal studies with large and diverse patient population are needed to further confirm this. Furthermore, cadazolid should also be compared with fidaxomicin in a head-to-head trial to evaluate their efficacy for CDI.

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1. INTRODUCTION

Clostridioides difficile-an anaerobic, spore-forming, gram-positive rod-is notorious for its role as the leading cause of nosocomial diarrhea worldwide. Notably, the incidence of *Clostridioides difficile* Infection (CDI) has increased substantially over the last several years [1, 2]. In addition, it accounts for nearly all the reported cases of pseudomembranous colitis [3]. According to the currently postulated pathophysiology, the infectious process occurs following a disturbance to the gut's normal microbiota, leading to an overgrowth of *Clostridioides difficile*. While symptoms can range from mild to severe, its complications of toxic mega-colon and shock contribute to high morbidity and mortality rates [4].

The increase in CDI incidence is attributed to the growing number of patients in long-term care facilities and the excessive usage of antibiotics [2]. As the cost of hospitalization for CDI is over 4 billion dollars per annum, the healthcare burden has become staggering. In addition, the approved medications for this condition - namely vancomycin, metronidazole, and fidaxomicin - are associated with a Clinical Cure Rate (CCR) of approximately 81.1 - 86.2%, 72.7 - 76.7%, and 87.9%, respectively. Recurrence rates are 16.5 - 26%, 18.5 - 23.0%, and 14.1%, respectively [5-7]. Furthermore, with the emergence of resistant strains, as well as strains associated with severe diseases, such as the NAP1/BI/027 strain, the need to recognize and develop new effective medicines is of paramount importance [8, 9].

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Cadazolid is a highly acidic novel fluoroquinolone-oxazolidinone antibiotic with strong lipophilic properties[2, 4]. This organic heterocyclic compound's quinolone characteristics allow it to act as a potent inhibitor of both DNA and protein synthesis. Due to its poor water solubility, orally administered cadazolid has negligible systemic bioavailability with a reported concentration of <3ng/ml after a single oral dose of 3000mg [2]. Hence, due to low intestinal absorption, its safety profile is markedly increased.

Randomized Controlled Trials (RCTs) comparing cadazolid and vancomycin in treating CDI have shown varying results [4, 10]. Individually, there was no statistically significant difference in their primary endpoints. In order to improve statistical power, we conducted a systematic review and meta-analysis of RCTs comparing cadazolid and vancomycin to assess the efficacy (including CCR and sustained CCR Sustained Clinical Response Rate (SCRR)), ability to prevent recurrence, and safety profile in the management of CDI.

2. MATERIALS AND METHODS

2.1. Search Strategy

We performed a comprehensive search using the following electronic databases, MEDLINE, Cochrane and Google Scholar on March 15, 2019, to identify all pertinent articles. MeSH terms, "Cadazolid", "Vancomycin", "ACT-179811", "*Clostridioides difficile*" and "*Clostridium difficile,"* were used in different combinations to create an up-to-date list. The search strategy was limited to clinical trials and randomized controlled studies. Two individual reviewers (MA and RF) performed the search independently and short listed the articles for final review. Citations were initially screened by title alone, followed by abstract screening. Full-text articles were extracted for final studies. We adhered to PRISMA guidelines while preparing this manuscript. Study flow diagram of literature review, screening, and selection is shown in Fig. (**1**).

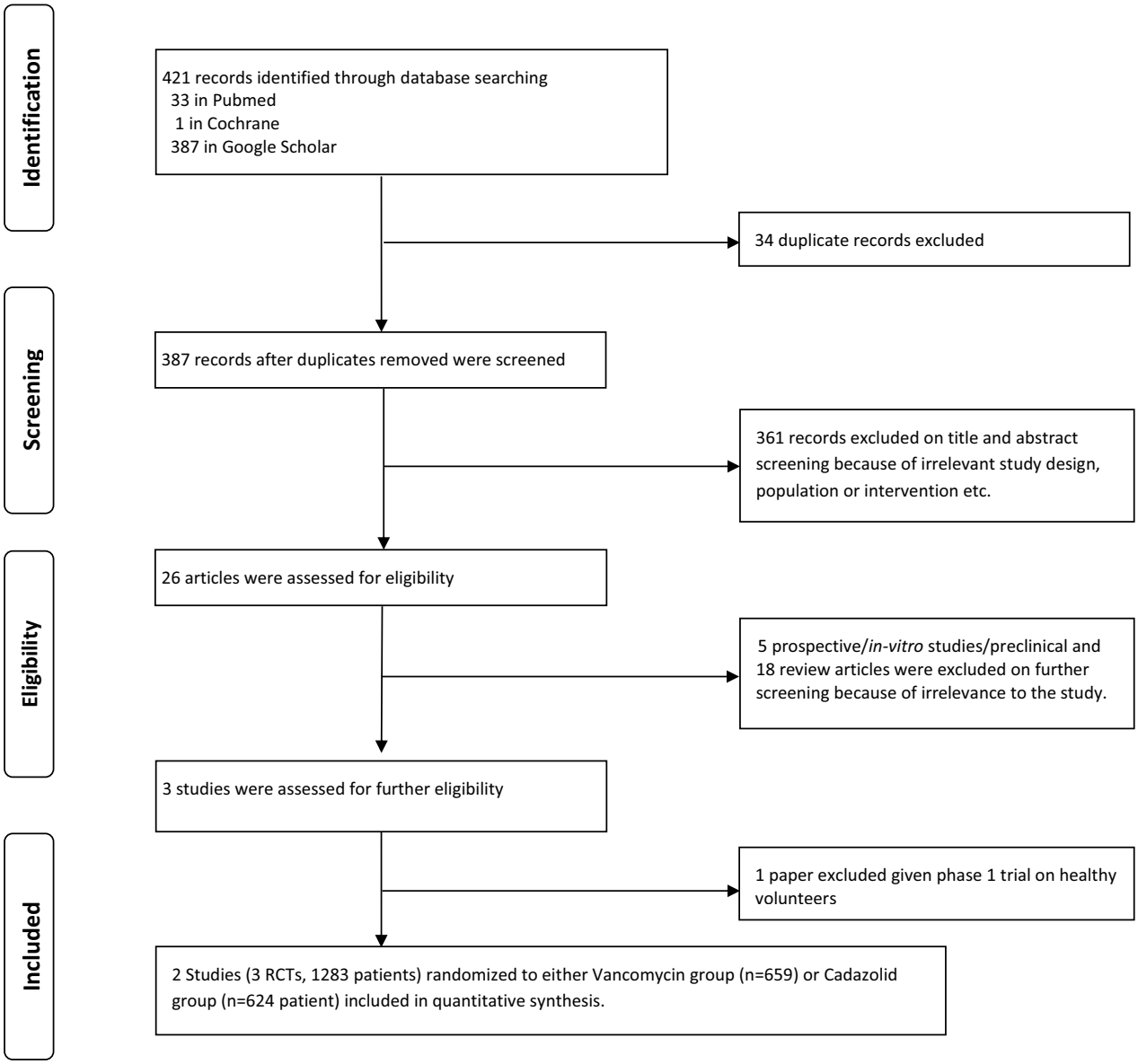

Fig. (1). PRISMA flow diagram for selection of studies.

2.2. Inclusion and Exclusion Criteria

All the RCTs comparing cadazolid to vancomycin for the treatment of CDI were included. We only used full-length articles for this meta-analysis. All other publications including retrospective or single-arm studies, phase 1 studies, preclinical studies (or non-human studies), case reports, case series, review articles, and letters to the editor were excluded. Our search was not restricted by dates or language.

2.3. Data Collection

Baseline demographic data (age, sex, and ethnicity), number of study participants, study drug completion rate, CDI confirmation tool, CCR, SCRR, Recurrence Rate (ReR), number of deaths, and Adverse Events (AEs) were extracted for each study. Study quality was assessed by Cochrane risk of bias tool for RCTs. Any discrepancy in data collection was resolved with mutual discussion.

2.4. Primary and Secondary Outcomes

The primary outcome of our analysis was CCR, defined as the resolution of diarrhea in the treatment group requiring no further intervention at the End of Treatment (EOT). Resolution of diarrhea was defined as less than 3 bowel movements per day for two consecutive days [4, 10]. EOT for all studies was 10 days after the start of therapy. Secondary endpoints assessed included SCRR (defined as a sustained clinical cure without recurrence for CDI on clinical follow-up), ReR of CDI (defined as CDI after achieving clinical cure at EOT before or at clinical follow-up), and AEs. The actual length of the clinical follow-up was obtained from the studies.

2.5. Data Synthesis and Statistical Analysis

Data were collected in Microsoft Excel (Microsoft, Redmond, Washington, United States). Pooled rates for the aforementioned outcomes were calculated and compared using the Odds Ratio (OR) with 95% Confidence Interval (CI). A p-value of <0.05 was considered statistically significant. The I^2 statistic was used to evaluate the heterogeneity between studies as defined by the Cochrane handbook for systematic reviews [11, 12]. Fixed effect analysis model using the Mantel-Haenszel method was employed as the pooling method and the random effect model was used alternatively as a sensitivity test. Review Manager V5.3 (The Cochrane Collaboration, Oxford, Oxfordshire, United Kingdom) was used for the analysis. Forest plots for each primary and secondary outcome were generated.

We reported outcomes based on a modified Intention-To-Treat (mITT) approach where patients were included in the final analysis if they had been randomized, had a positive CDI confirmatory test and had received at least one dose of the drug to which they had been randomized.

2.6. Bias Assessment

Risk of bias was evaluated using the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions [13]. Publication bias was not assessed due to the low number of studies.

3. RESULTS

A total of 421 records were retrieved based on our search strategy (Fig. **1**). Three RCTs published as two manuscripts were selected after the screening and exclusion of studies [4, 10]. Risk of bias assessment is given in Table **1**. The included studies were high-quality RCTs and had a minimal bias. Study details are summarized in Table **2**. The total number of patients randomized was 1283 (659 to vancomycin and 624 to cadazolid).

3.1. Diagnosis of CDI

Patients had diarrhea with at least three unformed bowel movements in the 24-hour period prior to randomization. CDI diagnosis was made using *C. difficile* toxin A/B Enzyme Immunosorbent Assay (EIA) [4, 10]. Approximately 80.5% and 80.0% of patients randomized to vancomycin and cadazolid, respectively, had the first occurrence of CDI, while the remainder had the first recurrence of CDI. Only one study reported a diagnosis based on hospitalization. Inpatient diagnosis of CDI was made in 2.7% and 17.6% of patients randomized to vancomycin and cadazolid, respectively [10]. Patients were also stratified based on severity; severe CDI was defined as having either white blood cell count $>15{,}000/mm^3$, fever with temperature >38.5 C, or a rise in serum creatinine of 50% compared to baseline. Severe CDI was reported in 17.3% and 18.7% of patients assigned to vancomycin and cadazolid, respectively [4, 10]. Two

Table 1. Risk of bias assessment in included RCTs.

-	Louie *et al.* 2015	Gerding *et al.* 2019 (IMPACT I)	Gerding *et al.* 2019 (IMPACT II)
Random sequence generation (selection bias)	Low	Low	Low
Allocation concealment (selection bias)	Unclear	Low	Low
Blinding of participants and personnel (performance bias)	Low	Low	Low
Blinding of outcome assessment (detection bias)	Unclear	Low	Low
Incomplete outcome data (attrition bias)	Low	Low	Low
Selective reporting (reporting bias)	Low	Low	Low
Other bias	Risk of funding bias	Risk of funding bias	Risk of funding bias

Table 2. Baseline demographic characteristics of the participants across the three RCTs. (RCT: Randomized controlled trial, BID: Twice daily dosing, QID: Four times daily dosing, NA: Not applicable).

Study	Louie *et al.* 2015	Gerding *et al.* 2019 (IMPACT I)	Gerding *et al.* 2019 (IMPACT II)
Type of study	RCT (phase 2)	RCT (phase 3)	RCT (phase 3)
Study Group Control Experimental	 Vancomycin 125 mg QID + *placebo* Cadazolid 250 mg BID + *placebo*	 Vancomycin 125 mg QID + *placebo* Cadazolid 250 mg BID + *placebo*	 Vancomycin 125 mg QID + *placebo* Cadazolid 250 mg BID + *placebo*
Total Study Population Vancomycin Cadazolid	42 22 20	632 326 306	609 311 298
Place of trial	Canada, Germany, UK, US	Australia, Brazil, Canada, France, Germany, Italy, Netherlands, Peru, Poland, Romania, Spain, USA	Argentina, Belgium, Brazil, Canada, Chile, Croatia, Czech Republic, Greece, Hungary, Israel, Romania, Slovakia, South Korea, UK, USA
CDI confirmation	Positive stool toxin A or B	Positive stool toxin A or B	Positive stool toxin A or B
Inclusion Criteria	Age >17 years, with a first occurrence or recurrence	Age >17 years, with a first occurrence or recurrence	Age >17 years, with a first occurrence or recurrence
Study Drug completion rate Vancomycin % n Cadazolid n (%)	 21/22 (95.5%) 20/20 (100%)	 297/326 (91.1%) 276/306 (90.2%)	 262/311 (84.2%) 263/298 (88.3%)
Females Vancomycin n (%) Cadazolid n (%)	 15/22 (68.2%) 12/17 (70.6%)	 195/318 (61.3%) 183/302 (60.6%)	 183/301 (60.7%) 187/290 (64.5%)
Caucasians Vancomycin n (%) Cadazolid n (%)	 21/22 (95.5%) 15/17 (88.2%)	 299/318 (94.0%) 288/302 (95.4%)	 271/301 (90.0%) 266/290 (91.7%)
Mean Age (years) Vancomycin n (SD) Cadazolid n (SD)	 53.2 (19.0) 53.6 (20.8)	 55.5 (18.0) 57.6 (17.1)	 62.1 (17.9) 61.7 (18.7)
Inpatient Hospitalization Vancomycin n (%) Cadazolid n (%)	 5/22 (22.7%) 3/17 (17.6%)	 NA NA	 NA NA
Severe CDI Vancomycin n (%) Cadazolid n (%)	 3/22 (13.6%) 1/17 (5.9%)	 51/318 (16.0%) 59/302 (19.5%)	 57/301 (18.9%) 54/290 (18.6%)
Hypervirulent strain Vancomycin n (%) Cadazolid n (%)	 NA NA	 82/318 (25.8%) 58/302 (19.2%)	 88/301 (29.3%) 75/290 (25.9%)

RCTs also listed patients with CDI caused by a hypervirulent strain. 27.5% and 22.5% of cases were treated with vancomycin and cadazolid, respectively [4].

3.2. Clinical Efficacy

Overall CCR at EOT for cadazolid and vancomycin was 82.3% and 84.9%, respectively (Table **3**). This was not significantly different (pooled OR 0.82; 95% CI 0.61 to 1.11; p=0.20; I^2= 0%) (Fig. **2A**). Although SCRR was numerically higher with cadazolid, this was not statistically significant compared to vancomycin (64.4% *vs* 61.3%, respectively) with a pooled OR of 1.14 (95% CI 0.91 to 1.43; p=0.27; I^2 = 0%) (Fig. **2B**). The overall recurrence of CDI was lower with cadazolid than with vancomycin (15.4% *vs* 20.4%, respectively). This was statistically significant with a pooled OR of 0.71 (95% CI 0.52 to 0.98; p=0.04; I^2 = 13%) (Fig. **2C**).

3.3. Mortality and Adverse Events

Six patients on each treatment died. The study investigators attributed these deaths to be due to underlying chronic medical conditions and not directly related to the treatment [4, 10]. A total of 299 (48.4%) patients on cadazolid and 345 (53.0%) on vancomycin had at least one reported AE related

Table 3. Results of three RCTs based on overall Clinical Cure Rate (CCR), overall sustained clinical response rate (SCRR), recurrence rate (RR), and at least 1 adverse event per patient (AE).

Study	Louie *et al.* 2015	Gerding *et al.* 2019 (IMPACT I)	Gerding *et al.* 2019 (IMPACT II)
CCR			
Vancomycin % (n)	68.2% (15/22)	85.2% (271/318)	85.7% (258/301)
Cadazolid % (n)	76.5% (13/17)	83.8% (253/302)	81.0% (235/290)
SCRR			
Vancomycin % (n)	33.3% (8/21)	62.3% (198/318)	61.8% (186/301)
Cadazolid % (n)	60.0% (9/15)	65.6% (198/302)	63.4% (184/290)
RR			
Vancomycin % (n)	50.0% (7/14)	21.4% (58/271)	17.8 (46/258)
Cadazolid % (n)	18.2% (2/11)	15.0% (38/253)	15.7 (37/235)
AE			
Vancomycin % (n)	45.5% (10/22)	51.2% (165/322)	55.4% (170/307)
Cadazolid % (n)	30.0% (6/20)	43.1% (131/304)	55.1% (162/294)

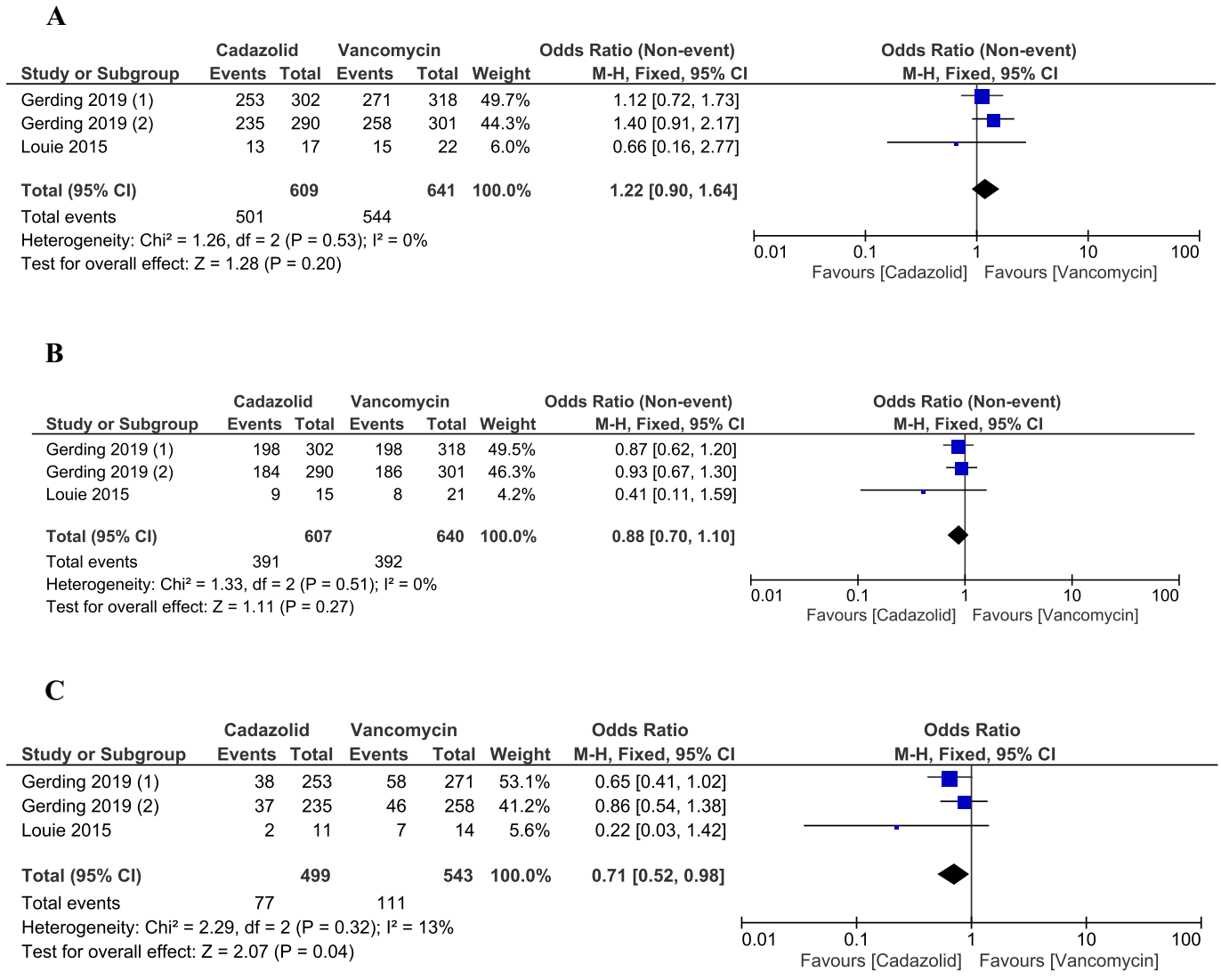

Fig. (2). Forrest plot demonstrating comparison of Vancomycin and Cadazolid in terms of (**A**) CCR for CDI (**B**) SCRR for CDI and (**C**) CDI recurrence. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

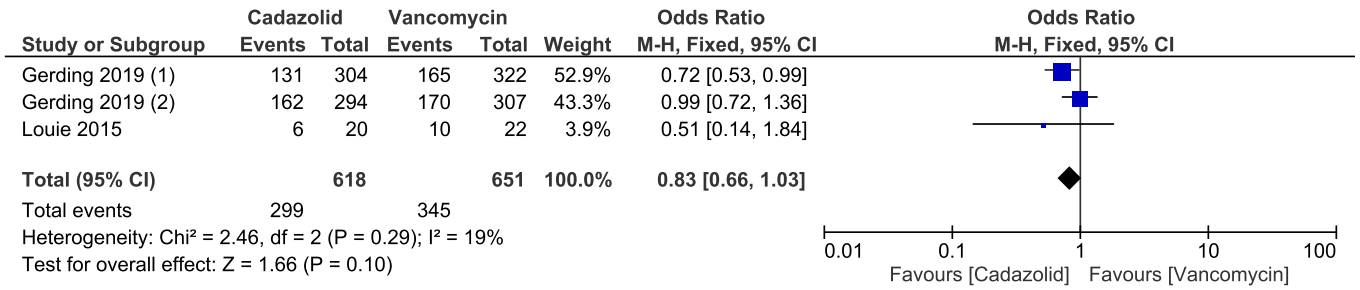

Fig. (3). Forrest plot demonstrating comparison of Vancomycin and Cadazolid in terms of at least 1 adverse event per patient.

to the intervention. Although there were fewer AEs on cadazolid, the difference was not statistically significant with a pooled OR of 0.83 (95% CI 0.66 to 1.03; p=0.10; I^2 = 19%) (Fig. **3**) (Table **3**). The most frequent AEs reported were headache, dizziness, altered mental status, dyspepsia, and pruritus.

4. DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis comparing the efficacy, recurrence rates, and safety profile of cadazolid and vancomycin, for the treatment of CDI. Our results indicate that cadazolid did not differ significantly from vancomycin in terms of achieving a higher CCR, SCRR, or fewer AEs. However, cadazolid was associated with a lower rate of recurrences than vancomycin.

Clostridioides difficile is a challenging pathogen to treat from a clinical perspective. Its high rate of recurrence, ability to produce other toxins in addition to Toxins A and B, of which there is little data, as well as its several hypervirulent ribotypes, which contribute to the difficulty [9]. Risk factors that have been associated with the recurrent disease include age ≥ 65 (RR: 1.63, p <0.01), use of proton pump inhibitors (RR: 1.58, p <0.01), renal insufficiency (RR: 1.59, p <0.01), and additional antibiotics during follow-up (RR: 1.76, p <0.01) [14]. Morbidity and mortality due to CDI also increase with age, ranging from 5% for individuals under the age of 70 to >10% for individuals over the age of 80 [15, 16]. In fact, in 2010, over 90% of deaths due to CDI occurred in individuals more than 65 years of age, making it the 18th leading cause of death for this age group [16]. With an increasing elderly population with prolonged nursing home stays, the risk of acquisition of CDI is increasing.

In the last two decades, there has been a dramatic increase in both the incidence and severity of CDI. This was directly linked to an epidemic *Clostridioides difficile* strain, characterized as toxinotype III, restricting endonuclease group BI, North American pulsed-field gel electrophoresis type 1, ribotype 027, namely-the BI/NAP1/027 strain [9, 15]. Factors that increase the virulence of this strain include Toxin A, Toxin B, CDTa toxin, CDTb toxin, hypersporulation, and TcdC gene (which increases toxin production) [9]. The resistance rate of *Clostridioides difficile* to metronidazole, as noted in the literature, is around 13.3-18%, and to vancomycin it is around 8-17.9% [17]. Of the currently approved drugs for CDI *i.e.* metronidazole, vancomycin and fidaxomicin, the ReR are approximately 19 to 23%, 18 to 21%, and 14 to 15%, respectively [5, 18, 19]. The pooled recurrence rate for cadazolid in our meta-analysis was lower compared to vancomycin (15.5% and 20.4%, respectively; p <0.05). This further validates the need to conduct more studies to elucidate the efficacy profile of cadazolid.

After two conflicting phase 3 RCTs (IMPACT 1 and IMPACT 2), further development of cadazolid was discouraged. In the mITT population, CCRs were 81-84% and 85 - 86%, respectively for cadazolid and vancomycin [4]. This was consistent with our meta-analysis with pooled CCRs of 82.3% and 84.9% for cadazolid and vancomycin, respectively. Furthermore, although we also found a numerically higher SCRR for cadazolid compared to vancomycin (64.4% *vs* 61.3%, respectively), this was not a statistically significant difference. However, given the apparent superiority of cadazolid in preventing recurrence, further studies should be performed to confirm this, particularly for the treatment of virulent strains of *Clostridioides difficile*.

The overall safety profile of cadazolid also favors its further development. No treatment-related deaths were observed in the two RCTs that reported mortality in patients on cadazolid [4]. Baldoni *et al* also reported cadazolid to be safe when using daily doses of up to 3000 mg in healthy individuals, in whom headache (4 patients, 11.4%) and diarrhea (3 patients, 8.6%) were the most frequent AEs. The low plasma concentrations and high fecal excretion (81.0-93.5%) of cadazolid also make it a potentially attractive agent for the treatment of CDI [20]. The phase 2 RCT by Louie *et al* did not demonstrate a dose-dependent response when doses of 500 mg and 1000 mg were used twice daily [10]. Our meta-analysis also showed a similar safety profile for cadazolid and vancomycin.

The biggest limitation of our meta-analysis is that there were only three RCTs that could be included. Furthermore, one of the three trials was a relatively small phase 2 study. Another limitation was the inconsistency in the clinical follow-up between the different studies; two RCTs followed patients at 28-32 days [4] and one at 26-30 days [10]. A longer clinical follow-up tend to decrease SCRR and increase recurrence rates compared to shorter follow-up. Lastly, more epidemic strains were reported for vancomycin which could have affected the study results [4]. Despite the aforementioned limitations, all the three studies were high-quality RCTs with strict inclusion and exclusion criteria. Another strength was the particularly high overall completion rate. In addition, all the RCTs used the same doses of cadazolid and vancomycin, which enabled a collective analysis. Furthermore, our meta-analysis had a robust num-

ber of pooled subjects in intervention and control arms. Although the patients randomized to vancomycin had more epidemic strains, the severity of CDI was higher in those on cadazolid (18.7% *vs* 17.3%, respectively).

CONCLUSION

In conclusion, cadazolid appears non-inferior to vancomycin for CCR and SCCR. Cadazolid and vancomycin were generally safe and well-tolerated. Cadazolid had a lower CDI recurrence rate than vancomycin requiring its further evaluation.

LIST OF ABBREVIATIONS

AE	=	Adverse Events
CCR	=	Clinical Cure Rate
CDI	=	Clostridium / Clostridioides Difficile Infection
CI	=	Confidence Interval
EOT	=	End of Treatment
mITT	=	Modified Intention-to-treat
OR	=	Odds Ratio
RCT	=	Randomized Controlled Trial
ReR	=	Recurrence Rate
RR	=	Risk Ratios
SCRR	=	Sustained Clinical Response Rate

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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