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Association of oral vancomycin prophylaxis with *Clostridium difficile* infection in hematopoietic stem cell transplant recipients

A systematic review and meta-analysis

Maaz Amir, MBBS[a], Khkula Kamal, MBBS[b], Muhammad Asad Jahangir, MBBS[a], Muneeb Faiz, MBBS[a], Zonaira Mushahid, MBBS[c], Mohammad Mujtaba Khokhar, MBBS[d], Ayesha Wasim, MBBS[a], Muhammad Sarmad, MBBS[a], Asad Ullah Mehboob, MBBS[d], Muhammad Moneeb Anwar, MBBS[a], Muhammad Maaz, MBBS[d], Muhammad Huzefa Amjad, MBBS[a], Hafiz Muhammad Haris, MBBS[a], Muhammad Numan Awais, MBBS[e,*], Ahmad Hassan, MBBS[a]

Abstract

Background: *Clostridium difficile* infection (CDI) occurs in up to 30% of hematopoietic stem cell transplant (HSCT) recipients and remains a significant cause of infectious diarrhea. This meta-analysis evaluated the association of oral vancomycin prophylaxis (OVP) with CDI prevention after HSCT.

Methods: We conducted a literature search of PubMed, Cochrane, and Google Scholar for articles from inception to July 2025 that compared the safety and efficacy of OVP for CDI in post-HSCT patients. Statistical analysis of the extracted data was conducted using Review Manager 5.4. The odds ratio for dichotomous variables and the mean difference for continuous variables were analyzed along with the corresponding 95% confidence intervals. A random-effects model was applied when heterogeneity was high ($I^2 \geq 50\%$), and a fixed-effect model was applied when heterogeneity was low ($I^2 \leq 50\%$).

Results: This meta-analysis included 5 studies comprising 957 patients, with 490 (51.2%) receiving OVP and 467 (48.8%) not receiving OVP (no OVP). OVP was significantly associated with a reduced incidence of CDI during hospitalization ($P < .00001$). Although a lower overall incidence of CDI (hospitalization plus 180-day follow-up) was observed in the OVP group, the result was not statistically significant ($P = .06$). A leave-one-out analysis was performed to establish a significant association ($P = .04$). In the OVP group, higher rates of grade 2 to 4 acute graft-versus-host disease ($P = .13$) and lower rates of bloodstream infections ($P = .74$), 1-year event-free survival ($P = .44$), and longer hospital stays ($P = .36$) were observed, although none reached statistical significance.

Conclusion: We conclude that oral vancomycin might be associated with a lower incidence of CDI during hospitalization in post-HSCT recipients and can be considered for CDI prophylaxis. No statistically significant adverse outcomes were observed in the OVP group compared with placebo. However, given the observational nature of these studies, these findings should be considered preliminary. Large-scale randomized controlled trials are needed to confirm the true efficacy and safety profile of OVP in post-HSCT recipients.

Abbreviations: aGVHD = acute graft-versus-host disease, CDI = *Clostridium difficile* infection, CI = confidence interval, EFS = event-free survival, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSCT = hematopoietic stem cell transplant, I^2 = Higgins heterogeneity statistic, NOS = Newcastle–Ottawa Scale, OR = odds ratio, OVP = oral vancomycin prophylaxis, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO = International Prospective Register of Systematic Reviews, VRE = vancomycin-resistant enterococci.

Keywords: *Clostridium difficile* infection, hematopoietic stem cell transplant, oral vancomycin

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[a] Department of Medicine, Mayo Hospital Lahore, King Edward Medical University, Lahore, Punjab, Pakistan, [b] Department of Medicine, Khyber Medical College, Peshawar, Khyber Pakhtunkhwa, Pakistan, [c] Department of Medicine, Dow University of Health Sciences, Karachi, Sindh, Pakistan, [d] Department of Medicine, Shalamar Medical and Dental College, Lahore, Punjab, Pakistan, [e] Department of Medicine, Shaheed Ziaur Rahman Medical College & Hospital, Bogura, Bangladesh.

** Correspondence: Muhammad Numan Awais, Department of Medicine, Shaheed Ziaur Rahman Medical College & Hospital, Silimpur, Bogura, Rajshahi Division 5800, Bangladesh (e-mail: muhammadnumanawais433@gmail.com).*

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1. Introduction

Clostridium difficile infection (CDI) poses a notable risk for people who have received hematopoietic stem cell transplants (HSCTs), with an incidence rate of approximately 9.2% within the first year posttransplantation.[1] These patients are at heightened risk due to factors such as frequent hospitalizations and impaired humoral response.[2] Moreover, extensive antibiotic use disrupts the gut microbiome and increases susceptibility to CDI.[3] HSCT patients are at increased risk of developing graft-versus-host disease (GVHD),[4] since both GVHD and CDI cause mucosal injury and inflammation of the intestinal epithelium, which lead to severe diarrhea and increased morbidity and mortality rates.[5]

Oral vancomycin plays a vital role in treating CDI due to its ability to reach high concentrations in the intestines while being absorbed minimally, thereby increasing its efficacy against *C difficile*, along with minimal systemic side effects.[6] Vancomycin, which is a glycopeptide antibiotic, disrupts bacterial cell wall synthesis by firmly attaching to the D-alanyl-D-alanine end of the precursors of peptidoglycan. This binding inhibits the transglycosylation and transpeptidation processes that are important for the cross-linking of the cell wall, thereby exerting a bacteriostatic effect.[7] Although the prophylactic use of vancomycin has demonstrated efficacy in preventing recurrent CDI, it also increases the risk of vancomycin-resistant enterococci (VRE) colonization.[8] This can make treating subsequent infections more difficult.

Even though there is an increasing amount of research on how to prevent and treat CDI in individuals with compromised immune systems, a noticeable gap in knowledge remains regarding the potential benefit of oral vancomycin prophylaxis (OVP) in patients undergoing HSCT. While there have been meta-analyses examining the effectiveness of oral vancomycin for other high-risk populations, such as individuals with hematologic cancers or those receiving solid organ transplants,[9] the particular situation of HSCT has been largely overlooked by comprehensive review.

The importance of vancomycin prophylaxis in the prevention of CDI has gained increasing importance, particularly in high-risk groups such as recipients of allogeneic hematopoietic cell transplants (HCTs). Given the increased vulnerability of HSCT patients to CDI, this study aims to assess the association between vancomycin prophylaxis and CDI occurrence in this high-risk population.

2. Materials and methods

2.1. Search strategy

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] It was registered in the International Prospective Register of Systematic Reviews with registration number CRD420251127776. A formal protocol was developed prior to the study and is available upon request. A systematic search of the literature was undertaken in July 2025 using the following databases: PubMed/Medical Literature Analysis and Retrieval System Online, Cochrane, and Google Scholar. The complete search strategy, including key terms such as "oral vancomycin," "*Clostridium difficile* infection," and "hematopoietic stem cell transplant," is reported in the Supplementary File 1, Supplemental Digital Content 1. To ensure comprehensive coverage, additional studies were identified through manual screening of the reference lists of pertinent meta-analyses and by reviewing the bibliographies of articles retrieved in the initial search.

2.2. Eligibility criteria

The included study population comprised patients who had undergone HSCT. The included original research studies divided HSCT patients into OVP and no OVP groups to evaluate and compare the efficacy and safety of OVP in preventing CDI. Excluded studies included abstracts, letters to the editor, reviews, case reports, and studies comparing OVP with interventions other than placebo.

2.3. Data extraction and quality assessment

Two reviewers independently screened titles and abstracts, followed by full-text assessment using predefined eligibility criteria; discrepancies were resolved with a third reviewer. The extracted data included study identifiers, study characteristics, demographic data, patient characteristics, and relevant clinical outcomes. Primary outcomes included the incidence of CDI during hospitalization and the overall incidence of CDI, while secondary outcomes included the incidence of acute graft-versus-host disease (aGVHD; grades 2–4), the incidence of bloodstream infections, event-free survival (EFS) at 1 year, and the length of hospital stay. Among these, the length of stay was analyzed as a continuous variable, while the remaining outcomes were treated as dichotomous variables. Baseline study characteristics, including age, sex distribution, diagnosis, donor type, and conditioning intensity, were extracted and are summarized in Table 1.

The quality of the studies was evaluated using the Newcastle–Ottawa Scale (NOS), which was independently applied by 2 authors. The NOS assesses key aspects of cohort studies, specifically focusing on selection, comparability, and outcome assessment. Further details are provided in the Supplementary File 1, Supplemental Digital Content 1.

2.4. Statistical analysis

Statistical analysis of the extracted data was conducted using Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, London, United Kingdom) of the data was performed using Review Manager 5.4. The odds ratio (OR) or mean difference, along with the respective 95% confidence intervals (CI), were computed. Heterogeneity among studies was assessed using the chi-square (I^2) statistic and was used as a guide to choose either a fixed-effect or random-effect model. Heterogeneity was classified as low ($I^2 \leq 50\%$) or high ($I^2 \geq 50\%$). A random-effects model was applied when substantial heterogeneity ($I^2 > 50\%$ or P value $< .05$) was detected; otherwise, a fixed-effect model was used. A sensitivity analysis was performed when significant heterogeneity ($I^2 > 50\%$) was observed. All tests were two-tailed, with statistical significance set at $P < .05$.

2.5. Antibiotic prophylaxis

All included trials employed consistent OVP protocols, with each study reporting the conventional dose of 125 mg administered twice daily. Prophylaxis was initiated on the day of inpatient admission for transplantation and continued until hospital discharge following hematologic recovery. Beyond this, the studies varied in their approaches to concurrent bacterial prophylaxis. In Fusco et al,[13] OVP significantly reduced infection risk in the unadjusted analysis, but the effect became nonsignificant after adjusting for baseline factors (age, sex, underlying malignancy, conditioning regimen intensity, donor match, and levofloxacin exposure). Stepwise regression showed that no covariates significantly influenced outcomes, and ORs for secondary outcomes also remained nonsignificant.

Ganetsky et al[11] reported significantly higher pre-HCT metronidazole use in the control group, also noting the use of other antibiotics, including Gram-negative agents and IV vancomycin, and stated that supportive treatments were also continued post-HCT. In Reitmeyer et al,[14] patients received

Table 1

Study characteristics.

Study author	Year	Country	Study design	Population OVP (n)	Population no OVP (n)	CDI during hospitalization in OVP (n)	CDI during hospitalization in no OVP (n)	Overall incidence of CDI in OVP (n)	Overall incidence of CDI in no OVP (n)
Ganetsky et al[11]	2018	USA	Retrospective cohort	90	55	0	11	NA	NA
Altemeier and Konrardy[12]	2021	USA	Retrospective cohort	100	100	2	11	8	15
Fusco et al[13]	2025	USA	Retrospective cohort	71	131	NA	NA	1	31
Reitmeyer et al[14]	2024	USA	Retrospective cohort	81	75	1	8	NA	NA
Williams et al[15]	2024	USA	Retrospective cohort	146	106	6	12	12	14

CDI = *Clostridium difficile* infection, NA = not available, OVP = oral vancomycin prophylaxis, USA = United States of America.

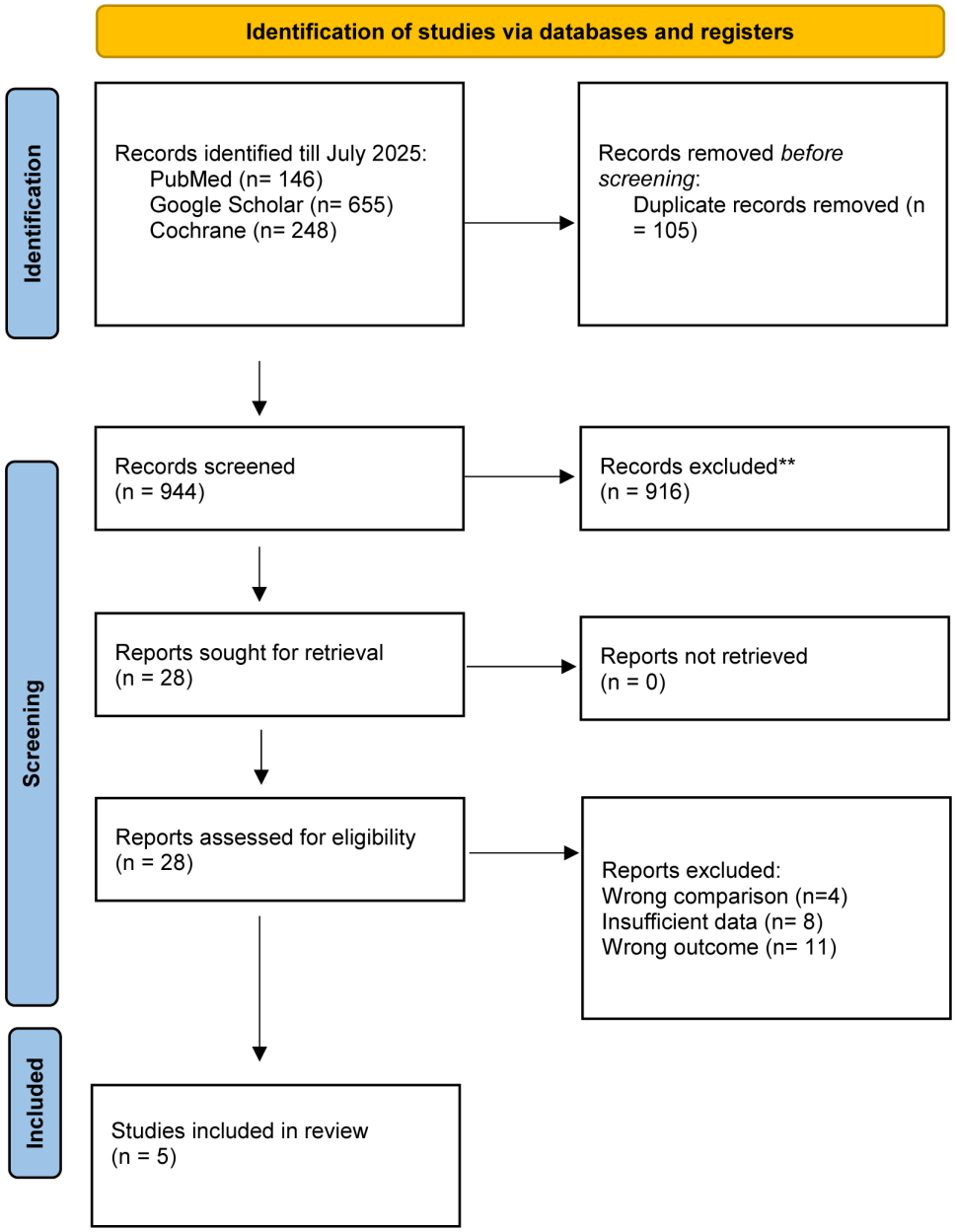

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

multiple antibiotics with oral vancomycin, including cefazolin, cefepime, levofloxacin, meropenem, piperacillin-tazobactam, IV vancomycin, clindamycin, metronidazole, daptomycin, linezolid, and sulfamethoxazole-trimethoprim; only levofloxacin use was significantly higher in the experimental group. In the study by Williams et al,[15] *Pneumocystis*

jirovecii pneumonia prophylaxis was administered using oral sulfamethoxazole-trimethoprim or intravenous pentamidine, starting on the day of cell infusion and continuing until neutrophil recovery. In contrast, Altemeier and Konrardy[12] utilized levofloxacin prophylaxis when the absolute neutrophil count dropped below 500 cells/μL, with cefuroxime provided as an alternative for patients with a levofloxacin allergy.

However, the independent impact of these antibiotics on CDI or other outcomes was not analyzed, as the studies primarily focused on the effect of OVP.

2.6. Ethical approval and patient consent

Ethical approval and informed patient consent were not required for this study because it was a systematic review and meta-analysis based exclusively on data from previously published studies. No individual patient data were collected, accessed, or analyzed.

3. Results

3.1. Selected studies and study characteristics

Out of 1049 studies initially identified from various databases, 5 retrospective cohort studies involving a total of 957 participants were ultimately included. Study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines, as depicted in Figure 1. Key study characteristics are outlined in Table 1, while baseline characteristics are highlighted in Table 2. Across all included studies, participants were divided into 2 groups: those who received OVP (n = 490, 51.21%) and those who did not (n = 467, 48.79%). All studies were conducted in the United States.

3.2. Outcome

3.2.1. Primary outcome. Two predefined primary outcomes were used to directly explore the efficacy of OVP for CDI in patients undergoing HSCT: the incidence of CDI during hospitalization and the overall incidence of CDI, which included cases occurring during the hospital stay and throughout the 180-day follow-up period.

Our statistical analysis showed that OVP was significantly associated with a reduced incidence of CDI during hospitalization compared with patients who did not receive OVP (OR = 0.16, CI = 0.08–0.32, $P < .00001$). While a reduction in the overall incidence of CDI was also noted among patients receiving OVP, this association did not reach statistical significance (OR = 0.33, CI = 0.10–1.04, $P = .06$). These findings are summarized in Table 3 and illustrated in Figures 2 and 3.

3.2.2. Secondary outcome. The secondary outcomes assessed included the incidence of aGVHD (grades 2–4), the incidence of bloodstream infections, length of hospital stay, and EFS at 1 year, defined as the time from transplant until relapse, progression, or death from any cause.

Incidence of aGVHD was noted to be higher in the OVP group (OR = 1.40, CI = 0.90–2.19, $P = .13$), while bloodstream infections were reported less frequently in the OVP group (OR = 0.92, CI = 0.56–1.52, $P = .74$). Patients receiving OVP also had a lower EFS at 1 year (OR = 0.85, CI = 0.56–1.28, $P = .44$) and a longer hospital stay (mean difference = 0.71, CI = −0.81 to 2.23, $P = .36$). However, none of these differences reached statistical significance ($P < .05$). These findings are detailed in Table 4 and shown in Figures 4 to 7.

Table 2

Baseline characteristics.

Study authors	Altemeier and Konrardy[12]		Fusco et al[13]		Ganetsky et al[11]		Reitmeyer et al[14]		Williams et al[15]	
	Oral vancomycin	No prophylaxis	Oral vancomycin	No prophylaxis	Oral vancomycin	No prophylaxis	Oral vancomycin	No prophylaxis	Oral vancomycin	No prophylaxis
Age, mean ± SD (yr)	50 ± 16	53 ± 14	55.94 ± 12.08	52.32 ± 13.77	52.75 ± 10.76	51.25 ± 11.62	55.33 ± 10.57	58 ± 7.56	53.50 ± 43.42	56.67 ± 45.85
Sex										
Male (n)	67	64	43	79	NA	NA	55	53	69	63
Female (n)	33	36	28	52	NA	NA	26	22	79	43
Diagnosis										
ALL (n)	7	16	5	24	15	6	2	4	NA	NA
AML (n)	46	33	40	70	47	35	17	6	NA	NA
CML (n)	5	5	3	3	4	1	2	0	NA	NA
Myelofibrosis (n)	NA	NA	3	7	2	2	4	3	NA	NA
MDS/MPN (n)	21	28	13	9	13	7	4	0	NA	NA
Other (n)	20	16	7	18	NA	NA	15	19	NA	NA
Donor										
Related (n)	47	42	17	40	27	14	14	12	NA	NA
Unrelated (n)	53	58	17	29	49	35	15	4	NA	NA
Conditioning intensity										
Myeloablative (n)	45	38	52	74	48	25	70	65	NA	NA
Reduced intensity (n)	54	60	19	57	42	30	11	10	NA	NA

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CML = chronic myelogenous leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, SD = standard deviation.

3.3. Risk of bias in individual studies

Using the NOS, the assessment showed that the majority of studies were of high quality, with 3 out of 5 earning 9 stars. The other 2 studies received 8 stars, indicating high quality despite minor limitations. Individual study scores related to risk of bias are provided in the Supplementary File 1, Supplemental Digital Content 1.

3.4. Sensitivity analysis

A sensitivity analysis identified substantial heterogeneity in only 1 outcome measure: the overall incidence of CDI, which exceeded 50%, as indicated by the chi-square (I^2) statistic. This outcome was further evaluated using a leave-one-out analysis, systematically excluding the 3 individual studies initially included, to assess their impact on the overall incidence. Notably, after excluding the Fusco et al study,[13] the association of oral vancomycin with the overall incidence of CDI, which was initially insignificant, became statistically significant with a P value of <.05 (Table 5; Fig. 8).

3.5. Publication bias

In accordance with recommended methodological guidelines, formal evaluation of publication bias using Egger's test was not performed, as such statistical approaches are considered unreliable in meta-analyses with fewer than 10 included studies.[16]

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that addresses the clinical question of the potential association of OVP with CDI prevention specifically in HSCT recipients. HSCT recipients are susceptible to CDI due to iatrogenic immunosuppression, exposure to antimicrobials, and extended hospital stays that increase the risk of exposure.[17] This risk is especially high during the initial hospitalization for transplant.[18] Our meta-analysis demonstrated a statistically significant reduction in the incidence of CDI during hospitalization in patients receiving oral vancomycin compared with those who received no prophylaxis. Consistent with our results, a systematic review by Maraolo et al[19] found that OVP had a protective effect against CDI in patients undergoing systemic antibiotic therapy. In contrast, a systematic review by Tariq et al[20] evaluated OVP for primary CDI prevention and found no statistically significant reduction in CDI risk in patients on systemic antimicrobial therapy. However, this study reported significant heterogeneity among the included studies, which limits the strength of the conclusions.

The rationale for OVP is primarily pharmacological and microbiological. Unlike systemic antibiotics, oral vancomycin acts locally within the gastrointestinal tract and produces high fecal concentrations with minimal systemic toxicity.[20] This may be advantageous in HSCT recipients during periods of intensive antibiotic exposure and microbiome disruption. However, the potential benefit must be balanced against concerns regarding microbiome effects, antimicrobial stewardship, cost, and the theoretical risk of selecting VRE.[19] Fidaxomicin is another microbiome-sparing agent that has been evaluated for CDI

Table 3

Primary outcomes evaluated in the meta-analysis effect sizes, *P* values, and heterogeneity across risk factors.

Outcome	No. of studies	Effect model	MD/OR	I^2 (%)	Ph	Effect size (95% CI)	*P* value
CDI during hospitalization, n	4	FE	OR	26	0.25	0.16 (0.08–0.32)	**<.00001**
Incidence of CDI, n	3	RE	OR	68	0.04	0.33 (0.10–1.04)	**.06**

P values < .05 are highlighted in bold.

CDI = *Clostridium difficile* infection, CI = confidence interval, FE = fixed-effect, MD = mean difference, OR = odds ratio, Ph = *P* value of heterogeneity, RE = random-effect.

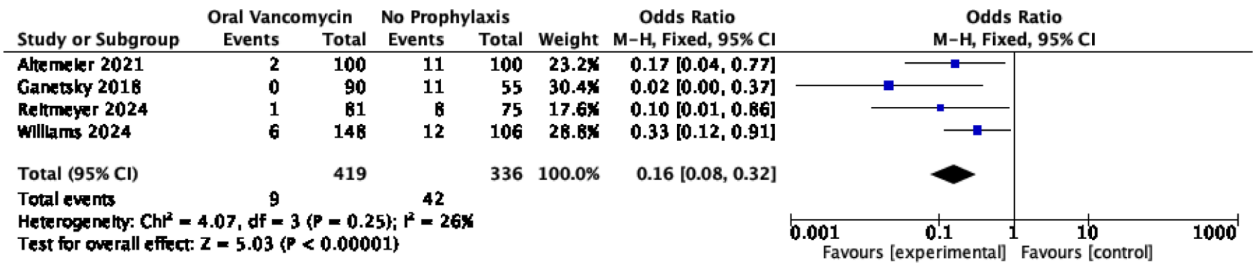

Figure 2. Forest plot for CDI during hospitalization in OVP versus no OVP groups. CDI = *Clostridium difficile* infection, CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

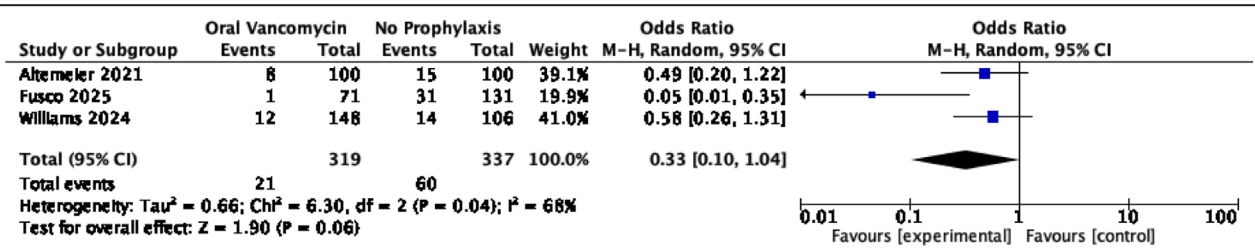

Figure 3. Forest plot for overall incidence of CDI in OVP versus no OVP groups. CDI = *Clostridium difficile* infection, CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

Table 4

Secondary outcomes evaluated in the meta-analysis effect sizes, *P* values, and heterogeneity across risk factors.

Outcome	No. of studies	Effect model	MD/OR	I^2 (%)	Ph	Effect size (95% CI)	*P* value
Incidence of aGVHD grades 2–4, n	3	FE	OR	34	0.22	1.40 (0.90–2.19)	**.13**
Incidence of bloodstream infections, n	3	FE	OR	38	0.20	0.92 (0.56–1.52)	**.74**
Event-free survival at 1 yr, n	3	FE	OR	34	0.22	0.85 (0.56–1.28)	**.44**
Length of stay, mean ± SD (d)	4	FE	MD	0	0.90	0.71 (−0.81 to 2.23)	**.36**

Bold values indicate statistically significant.

aGVHD = acute graft-versus-host disease, CI = confidence interval, FE = fixed-effect, MD = mean difference, OR = odds ratio, Ph = *P* value of heterogeneity, SD = standard deviation.

prevention in HSCT recipients, but its availability and cost may limit widespread prophylactic use.[21] Metronidazole is not preferred for prophylaxis because of systemic toxicity concerns,[22] lower efficacy for CDI treatment compared with vancomycin,[23] and limited evidence supporting prophylactic use in this setting.

Vancomycin inhibits *C difficile* by adhering to the D-alanine-D-alanine terminus of the lipid II bacterial cell wall precursor, inhibiting cell wall synthesis and ultimately leading to bacterial death.[24] The concentration of vancomycin remains suitably high for 3 to 5 days after completion of treatment to suppress the in vitro growth of *C difficile*. Due to its limited systemic absorption, oral vancomycin can reach high concentrations in the gastrointestinal tract, specifically targeting *C difficile* in the gut lumen.[25] Given that the risk of CDI persists even for 90 days following systemic therapy when using vancomycin prophylaxis,[20] our investigation studied the incidence of CDI during hospitalization and after follow-up separately. Although the overall incidence of CDI, defined as CDI occurring during hospitalization and within 180 days of follow-up, tended to be lower in the OVP group, this difference did not achieve statistical significance. Sensitivity analysis revealed substantial heterogeneity, and a leave-one-out analysis showed a significant benefit of OVP after excluding 1 study.

The primary concern is whether oral vancomycin increases the risk of acute GVHD, and this remains an active area of research. In our study, there was a trend toward a higher incidence of acute GVHD; however, this did not reach statistical significance, suggesting a possible but not confirmed increased risk of GVHD with oral vancomycin. Studies have shown that the loss of beneficial bacteria through bacterial growth suppression may lead to an increased acute GVHD risk.[26,27] Another study linked vancomycin to an increased risk of cytomegalovirus reactivation after allogeneic HCTs, which subsequently is associated with GVHD and worse transplant outcomes.[28] These findings raise questions about the safety profile of oral vancomycin regarding GVHD risk, but future studies are needed to reach firm conclusions.

Evidence consistently supports that oral vancomycin is also associated with an increased risk of VRE colonization.[29,30] Only 1 of our included studies reported data on the incidence of VRE; therefore, it was not possible to conduct statistical pooling for VRE incidence or include it in our meta-analysis.

Other parameters of the safety profile that we assessed are EFS at 1 year and length of hospital stay. Although the OVP group exhibited a trend toward lower EFS at 1 year and prolonged hospital stay, these differences did not reach statistical significance. Existing literature has shown that extended hospital stays may be linked to hospital-acquired infections as a result of repeated invasive procedures and extended exposure to microorganisms. This, in turn, may increase healthcare costs and mortality rates.[31,32]

The heterogeneity in CDI incidence was primarily driven by the Fusco et al[13] study. Unlike other included cohorts, which were conducted in pre-COVID-19 settings with stable infection-control practices and without concurrent major changes in antimicrobial prophylaxis, Fusco et al[13] reflects a more contemporary cohort with multiple co-interventions. These include widespread levofloxacin prophylaxis, enhanced COVID-era infection-control measures, and modified CDI testing thresholds that increased case detection. These differences likely affected both baseline CDI risk and outcome ascertainment, making its effect estimate less comparable with earlier studies. The removal of this study eliminated heterogeneity ($I^2 = 0\%$), indicating greater homogeneity among the remaining cohorts.

Beyond the outcomes synthesized in this meta-analysis, 2 clinically important domains were consistently absent from the included studies: overall survival and health-related quality of life. None of the studies reported mean or median overall survival in a format suitable for pooling; the closest available proxy was EFS at 1 year, which did not differ significantly

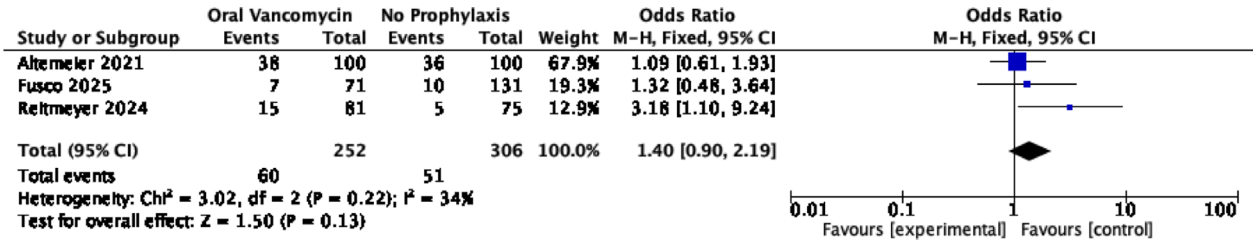

Figure 4. Forest plot for incidence of aGVHD (grades 2–4) in OVP versus no OVP groups. aGVHD = acute graft-versus-host disease, CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

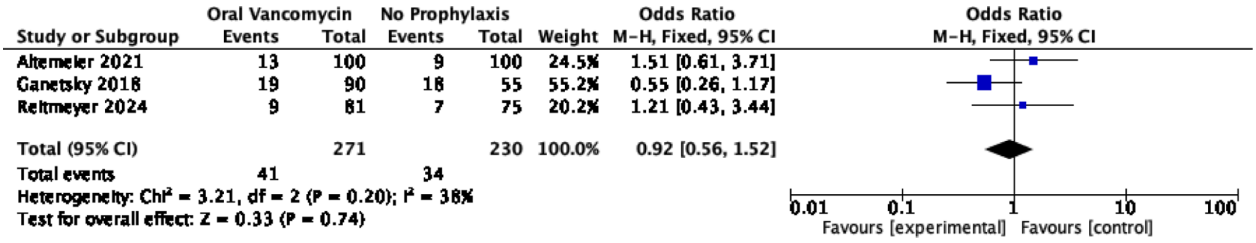

Figure 5. Forest plot for incidence of bloodstream infections in OVP versus no OVP groups. CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

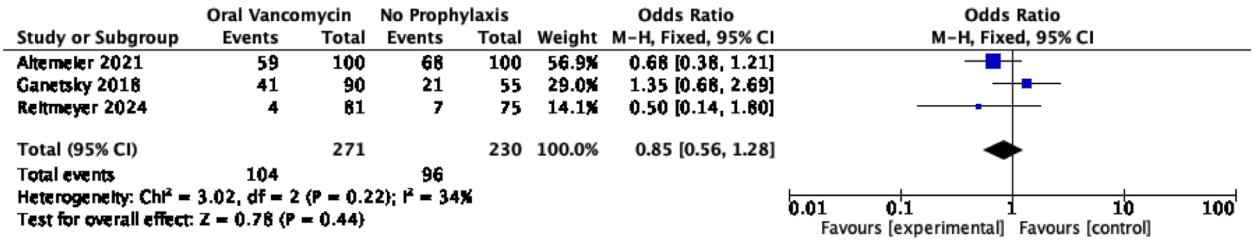

Figure 6. Forest plot for EFS at 1 year in OVP versus no OVP groups. CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

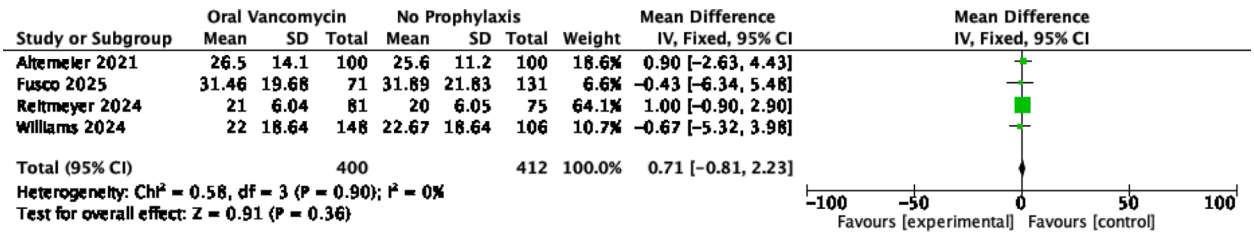

Figure 7. Forest plot for length of stay in OVP versus no OVP groups. CI = confidence interval, OVP = oral vancomycin prophylaxis, SD = standard deviation.

between groups. Future prospective trials of OVP in HSCT recipients should prespecify both overall survival and standardized quality-of-life endpoints, as their routine inclusion would substantially strengthen the evidence base and inform more patient-centered clinical decision-making.

This meta-analysis has several limitations. First, all included studies were retrospective cohort designs, which are inherently subject to selection bias, recall bias, and unmeasured confounding variables. Therefore, we can report only associations, not causal relationships. Second, the total sample size across the 5 studies was relatively small (n = 957), which may limit the statistical power and generalizability of the findings. Third, due to the small number of included studies, we did not formally assess publication bias using funnel plots or statistical tests (e.g., Egger's or Begg's test). This limits our ability to determine whether the published studies may overestimate treatment effects. Fourth, we carried out a sensitivity analysis, a risk of bias assessment, and also employed an effect model in statistical analysis, but there might still be residual heterogeneity in results. Fifth, the absence of randomized controlled trials limits the strength of our evidence. Finally, none of the included studies reported mean or median overall survival time or assessed health-related quality of life using validated instruments such as the EuroQol Five-Dimension Questionnaire or Functional Assessment of Cancer Therapy–Bone Marrow Transplant. As a result, the impact of OVP on these 2 clinically meaningful endpoints could not be evaluated, and the findings of this review should be interpreted with this important gap in mind. Additionally, Embase and Web of Science were not searched; although this was partially mitigated by the use of Google Scholar and comprehensive manual reference screening, it remains a potential limitation of the search strategy.

5. Conclusion

Our meta-analysis suggests that OVP might be associated with a reduction in the incidence of CDI among HSCT recipients, particularly during hospitalization. The findings indicate a

Table 5

Leave-one-out analysis.

Outcome	No. of studies	Initial I^2 (%)	Initial Ph	Initial *P* value	Study removed	Final I^2 (%)	Final Ph	Final *P* value
Incidence of CDI	3	68	0.04	.06	Fusco et al[13]	0	0.79	.04

CDI = *Clostridium difficile* infection, Ph = *P* value of heterogeneity.

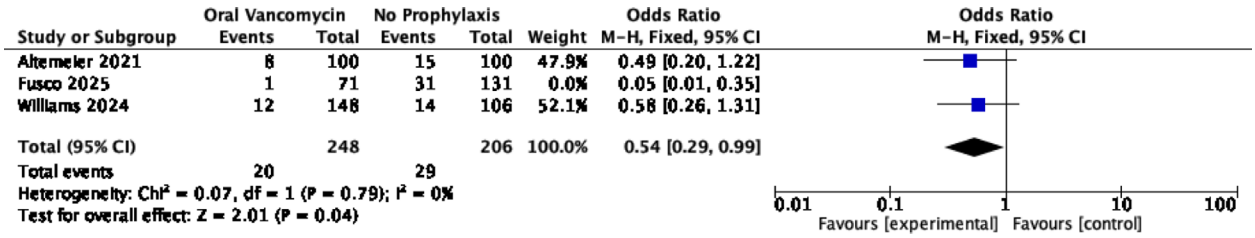

Figure 8. Forest plot for overall incidence of CDI in OVP versus no OVP groups, leave-one-out analysis performed excluding Fusco et al.[13] CDI = *Clostridium difficile* infection, CI = confidence interval, M–H = Mantel–Haenszel, OVP = oral vancomycin prophylaxis.

potential protective effect; however, the overall safety profile remains less clearly defined, with no consistent evidence of adverse outcomes. Importantly, since all included studies were retrospective cohort analyses, we can only suggest an association rather than establish definitive causal effects. Therefore, the results should be interpreted with caution, given the heterogeneity and observational design of the available data. Future large-scale, prospective randomized controlled trials are warranted to evaluate both the efficacy and safety of OVP in this high-risk population.

Author contributions

Conceptualization: Maaz Amir, Muhammad Huzefa Amjad.
Methodology: Maaz Amir, Khkula Kamal, Muhammad Asad Jahangir, Muneeb Faiz, Muhammad Sarmad, Muhammad Moneeb Anwar, Muhammad Numan Awais.
Project administration: Khkula Kamal, Muneeb Faiz.
Formal analysis: Muhammad Asad Jahangir, Hafiz Muhammad Haris.
Software: Zonaira Mushahid, Muhammad Sarmad, Muhammad Moneeb Anwar, Muhammad Huzefa Amjad, Muhammad Asad Jahangir.
Validation: Zonaira Mushahid, Mohammad Mujtaba Khokhar, Asad Ullah Mehboob.
Supervision: Muhammad Maaz.
Visualization: Muhammad Maaz, Ahmad Hassan.
Data curation: Ayesha Wasim, Hafiz Muhammad Haris, Muhammad Numan Awais.
Writing – original draft: Mohammad Mujtaba Khokhar, Ayesha Wasim, Muhammad Sarmad, Muhammad Huzefa Amjad, Ahmad Hassan.
Writing – review & editing: Muhammad Sarmad, Asad Ullah Mehboob, Muhammad Asad Jahangir.

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