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Review Article

The overlooked triad: interrelationship between diabetes mellitus, diabetic foot, and acute diarrhoea. A systematic review of clinical and pathophysiological correlates.

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Abstract

Background:

Diabetes mellitus (DM) and its complications, particularly diabetic foot disease (DFD), substantially increase morbidity through vascular, immune, and microbiome dysfunction. Acute diarrhoeal illnesses, including *Clostridioides difficile* infection (CDI), antibiotic-associated diarrhoea (AAD), and cholera, can further destabilize metabolic and infectious trajectories in diabetic patients. Despite this overlap, integrated evidence on their interrelationship remains limited.

Objective:

To systematically evaluate current evidence on (1) the role of diabetes as a risk factor for CDI and other diarrhoeal diseases; (2) the impact of antibiotic exposure and metabolic instability on outcomes; (3) the potential protective effect of metformin therapy; and (4) the broader clinical implications for diabetic foot and inpatient management.

Methods:

Following PRISMA-2020 guidelines, open-access observational studies were identified in PubMed, DOAJ, PMC, Google Scholar, and OpenAIRE up to July 2025. Eligible studies included adults (≥18 years) with DM experiencing diarrhoeal illness. Outcomes analyzed were CDI incidence or recurrence, AAD occurrence, in-hospital mortality, and length of stay (LOS). Quality was assessed using the Newcastle–Ottawa Scale (NOS).

Results:

Six studies (2011–2024) met the inclusion criteria. Diabetes independently increased CDI risk and recurrence (OR ≈ 2.0–2.5), with antibiotic and PPI exposure as key cofactors. "4C" antibiotic use in diabetic foot ulcer patients quintupled CDI risk. Metabolic decompensation, such as diabetic ketoacidosis (DKA), significantly elevated mortality (5.8 % vs 2.7 %) and LOS. Conversely, metformin therapy reduced CDI odds by ~42 %, likely through gut-microbiota modulation. Diabetic patients with cholera showed prolonged hospitalization (IRR ≈ 2.0) without excess mortality. NOS scores (6–8/9) indicated moderate–high methodological quality.

Conclusion:

Diabetes amplifies susceptibility and worsens outcomes of CDI and related enteric infections, while metformin may offer partial protection. Incorporating glycaemic optimization, antibiotic stewardship, and microbiome-preserving strategies into diabetic care could mitigate infection-related morbidity and healthcare burden.

Keywords: *Diabetes mellitus; Diabetic foot; Clostridioides difficile infection; Antibiotic-associated diarrhoea; Cholera; Metformin; Gut microbiota; Antimicrobial stewardship.*

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Introduction

Diabetes mellitus (DM) and its complications, particularly diabetic foot disease (DFD), represent significant global health challenges contributing substantially to morbidity, hospitalisation, and mortality. DFD—encompassing diabetic foot ulcers, infections, and ischaemic changes—is one of the most debilitating chronic complications of diabetes, with an estimated lifetime risk ranging from 19% to 34% among individuals with DM1.DFD remains a major contributor to lower extremity amputations (LEA), recurrent hospital admissions, and significant impairment in health-related quality of life. Current evidence-based guidelines, including those from the American Diabetes Association (ADA, 2025) and the International Working Group on the Diabetic Foot (IWGDF), advocate for a multidimensional approach to diabetic foot infection (DFI) management. This includes structured risk stratification, quantitative assessment of limb perfusion, and judicious use of targeted antimicrobial regimens, all of which are pivotal in reducing complications and improving clinical outcomes 2,3. However, these guidelines rarely consider the influence of intercurrent illnesses, such as acute diarrhoea, on the clinical course and progression of diabetic foot disease (DFD).

From a clinical standpoint, acute diarrhoea is characterized by the occurrence of three or more loose or watery stools within 24 hours, with the illness generally resolving within 14 days. Despite advances in preventive and therapeutic strategies, it remains a significant cause of morbidity and healthcare utilization worldwide, especially in low- and middle-income countries 4.

Among patients with diabetes mellitus, episodes of acute diarrhoea may be attributed to diverse causes, including infectious agents (such as *Vibrio cholerae*), antibiotic-associated diarrhoea (AAD)—notably Clostridioides difficile infection (CDI)—and drug-induced gastrointestinal intolerance from medications like metformin and α-glucosidase inhibitors. These events frequently lead to fluid depletion, electrolyte derangements, and acute kidney injury (AKI), and may further disrupt the pharmacokinetic profiles of concurrently administered antidiabetic and antimicrobial therapies, warranting timely dose reassessment or modification. In the setting of diabetic foot disease (DFD), such systemic metabolic and circulatory imbalances may diminish tissue oxygenation, impair immune defence, and delay reparative processes, ultimately predisposing patients to therapeutic failure, increased amputation risk, and unfavourable outcomes 5,6.

The association between diabetes mellitus (DM) and diarrheal disorders is multifaceted, reflecting both disease-related susceptibility and treatment-induced risk. Antibiotic therapy, which is integral to the management of diabetic foot infections (DFIs), often necessitates the use of broad-spectrum agents due to polymicrobial involvement. However, agents such as clindamycin, cephalosporins, amoxicillin–clavulanate, and fluoroquinolones (e.g., ciprofloxacin) are well established to predispose patients to Clostridioides difficile infection (CDI) and other forms of antibiotic-associated diarrhoea (AAD). These dual risks underscore the importance of judicious antibiotic selection, antimicrobial stewardship, and vigilant monitoring to optimize therapeutic outcomes in this vulnerable population 5,6.

Emerging observational data suggest that diabetes mellitus (DM) constitutes an independent risk factor for the recurrence of Clostridioides difficile infection (CDI), irrespective of prior antibiotic exposure, possibly reflecting the combined effects of immune dysregulation, altered gut microbiota, and impaired mucosal defenses inherent to the diabetic state 5. In addition to Clostridioides difficile infection (CDI), acute diarrheal illnesses—notably cholera—have been demonstrated to exacerbate disease severity and extend hospital stay among patients with diabetes mellitus (DM). These adverse outcomes are largely attributable to blunted thirst perception, reduced renal concentrating ability, autonomic neuropathy, and underlying metabolic derangements, which collectively impair compensatory responses to dehydration and infection 4.

The intersection between diabetic foot infections (DFIs) and acute diarrheal disorders represents an underrecognized yet clinically significant phenomenon. Volume depletion secondary to diarrhoea can precipitate peripheral vasoconstriction and ischemia in microvascularly compromised diabetic limbs, thereby delaying wound granulation and epithelialization and increasing susceptibility to recurrent infection. In parallel, the prolonged or empirical use of broad-spectrum antimicrobial agents for DFI management disrupts gut microbial homeostasis, fostering antibiotic-associated diarrhoea (AAD) and markedly elevating the risk of Clostridioides difficile infection (CDI)—a complication that may be fatal if not promptly identified and managed 7,8. When diabetic foot pathology and acute diarrheal disorders occur concurrently, patients exhibit a markedly increased propensity for systemic inflammatory activation, metabolic acidosis, and electrolyte derangements, which may precipitate hyperglycaemic emergencies such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS). This overlap not only complicates metabolic control but also adversely affects hemodynamic stability and wound recovery outcomes.

Although the pathophysiological and clinical overlap between diabetes mellitus (DM), diabetic foot disease (DFD), and acute diarrheal illnesses is increasingly evident, the literature rarely conceptualizes diarrhoea as a time-dependent determinant of outcomes in DFD. Furthermore, no major international guideline currently delineates an integrated approach to the simultaneous management of diabetic foot infections (DFIs) and diarrheal conditions. Accordingly, there is a compelling need for a unified

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evidence synthesis that examines this neglected interface—spanning infectious gastroenteritis, antibiotic-associated diarrhoea (AAD), Clostridioides difficile infection (CDI), and drug-related gastrointestinal adverse effects. Through this systematic review, we aim to generate an evidence-based conceptual framework to guide comprehensive care models incorporating antimicrobial stewardship, sick-day management, and fluid-electrolyte support within standard diabetic foot care protocols.

This systematic review is designed to comprehensively evaluate and integrate current evidence addressing the clinical and mechanistic interplay between diabetes mellitus (DM), diabetic foot disease (DFD), and acute diarrheal disorders. Specifically, it seeks to:

(1) assess the contribution of DM as a predisposing factor for both the development and recurrence of Clostridioides difficile infection (CDI);

(2) examine the influence of antimicrobial stewardship within the context of diabetic foot infection (DFI) management;

(3) explore the effects of enteric infections such as cholera on hydration status, metabolic control, and clinical outcomes in diabetic patients; and

(4) identify potential protective factors, particularly the metformin-associated modulation of gut microbiota and immune responses.

Materials and Methods

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review focused exclusively on open-access literature to ensure transparency, reproducibility, and global accessibility of findings. It aimed to explore the clinical and epidemiological overlap between diabetes mellitus (DM), diabetic foot (DF), and diabetic foot ulcer (DFU), and acute diarrheal illnesses, including both infectious diarrhoea (e.g., cholera) and antibiotic-associated diarrhoea (AAD), with particular emphasis on Clostridioides difficile infection (CDI).

Information sources

A comprehensive literature search was conducted across multiple open-access databases and repositories, including PubMed, PubMed Central (PMC), Directory of Open Access Journals (DOAJ), Google Scholar, OpenAIRE, and official websites of relevant infectious-disease journals and guideline bodies. The final search was completed on 18 July 2025 (Asia/Kolkata time zone).

Search strategies

Search strategies were iteratively refined and adapted for each platform using Boolean operators, Medical Subject Headings (MeSH), and free-text keywords. The core search terms were:

- ("diabetes mellitus" OR "diabetic foot" OR "DFU")
- AND ("diarrhea" OR "acute gastroenteritis" OR "cholera" OR "antibiotic-associated diarrhea")
- AND ("Clostridioides difficile" OR "C. difficile" OR "CDI").

Eligibility Criteria

Studies were screened according to predefined inclusion and exclusion criteria.

Inclusion Criteria

- **Population:** Adults (≥18 years) with type 1 or type 2 diabetes, with or without documented DF or DFU.
- **Exposure:** Acute diarrheal episodes, including CDI, cholera, or antibiotic exposure leading to AAD.
- **Study Design:** Observational studies (cohort, case–control, cross-sectional) and open-access systematic reviews or meta-analyses.
- **Outcomes:** At least one of the following: CDI incidence or recurrence, AAD incidence, in-hospital mortality, **length of hospital stay (LOS)**, healthcare costs, or cholera-related outcomes.

Exclusion Criteria

- Studies evaluating **chronic diarrhea** only
- Editorials, commentaries, or reviews without original data
- Non-diabetic populations without subgroup analysis

Outcomes of Interest

The primary outcomes were:

- Incidence and recurrence of Clostridioides difficile infection (CDI)
- Antibiotic-associated diarrhea (AAD) incidence among DF or DFU patients
- In-hospital mortality
- Length of hospital stay (LOS)
- Cholera-related outcomes, including LOS and complications

Secondary outcomes (when available) included healthcare costs, incidence of diabetic ketoacidosis (DKA), and the potential protective influence of metformin therapy.

Data Extraction and Risk of Bias Assessment

The study selection and data extraction process were carried out methodically to ensure scientific rigor, reproducibility, and minimization of bias. Two independent

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Review Article

reviewers initially screened the titles and abstracts of all retrieved records to identify studies that met the predefined eligibility criteria. Full-text articles of potentially relevant studies were subsequently obtained and assessed for inclusion. Data extraction was then performed independently by both reviewers using a standardized data extraction form that had been pre-tested for consistency. Any disagreements during the study selection or data extraction stages were resolved through discussion and mutual consensus, and when consensus could not be reached, a third reviewer adjudicated to provide the final decision.

For each study that satisfied the inclusion criteria, key methodological and outcome information was systematically extracted. Extracted variables included the names of the authors, year of publication, country or region of study, study design, and study setting—such as tertiary care hospitals, national databases, or specific diabetic foot cohorts. Additional details captured comprised the total sample size, baseline characteristics of the patient population, and the presence or absence of diabetic foot ulcers. Information was also collected regarding the type of diarrheal illness investigated, which included *Clostridioides difficile* infection (CDI), antibiotic-associated diarrhea (AAD), or cholera, as well as the nature and duration of antibiotic exposure, the use of metformin therapy, and other relevant clinical covariates.

Particular attention was given to the primary and secondary outcomes reported in each study. These included CDI incidence and recurrence, AAD incidence among diabetic or DFU patients, in-hospital mortality, and length of hospital stay (LOS). Where available, additional endpoints such as cholera-related complications, diabetic ketoacidosis (DKA) incidence, and healthcare costs were extracted. Quantitative measures of association, such as odds ratios (ORs), incidence rate ratios (IRRs), or hazard ratios (HRs), along with their 95% confidence intervals and p-values, were recorded whenever provided. Each study was also reviewed to identify predictors significantly associated with favourable or unfavourable outcomes. The direction of these associations was documented to clarify whether a particular factor conferred a risk or protective effect. Definitions of key endpoints such as CDI recurrence, hospital mortality, or prolonged LOS were preserved verbatim from the original publications to maintain contextual precision.

All extracted data were tabulated to allow comparison across studies in terms of design, outcome measures, and key findings. Given the heterogeneity in outcome definitions, patient populations, and study designs, data synthesis was descriptive and narrative rather than quantitative.

The methodological quality and risk of bias of the included observational studies were evaluated using the Newcastle–Ottawa Scale (NOS), a validated instrument for assessing non-randomized studies. The NOS evaluates three principal domains: (i) selection of study groups, with a maximum of four points; (ii) comparability of cohorts or cases, with a maximum of two points; and (iii) ascertainment of exposure and outcome, with a maximum of three points. The maximum attainable score is nine, with studies scoring seven to nine considered high quality, those scoring five to six considered moderate quality, and those below five considered low quality. Two reviewers independently assessed each included study, and any discrepancies in scoring were resolved through discussion and re-evaluation of the full-text articles to ensure scoring consistency.

In addition to the formal NOS scoring, qualitative considerations were integrated into the overall assessment. These included the representativeness of study populations, the clarity and robustness of outcome definitions, and the use of multivariable statistical models to adjust for potential confounders. Retrospective database-based studies, such as those utilizing the U.S. National Inpatient Sample (NIS), generally achieved higher scores in the selection domain due to their large sample size and national representativeness, though some degree of exposure misclassification contributed to moderate ratings in outcome assessment. Conversely, hospital-based case–control or cohort studies provided more detailed clinical information and better-defined exposure ascertainment but were limited by smaller sample sizes and narrower external generalizability.

Overall, NOS scores among the included studies ranged from six to eight, indicating predominantly moderate to high methodological quality. *Eliakim-Raz et al.* (2015) achieved the highest rating (8/9) owing to clear case definitions and robust multivariable adjustment. Studies by *Shakov* (2011), *Lin* (2015), *Collier* (2014), and *Antoun* (2024) scored between six and seven, reflecting moderate quality with limitations primarily in comparability and potential residual confounding. The large database study by *Polpichai* (2024) was rated 7/9 due to its comprehensive sampling but moderate ascertainment reliability. None of the studies were randomized controlled trials, and the overall evidence base was judged to have a moderate risk of bias, typical for observational epidemiologic research exploring multifactorial disease intersections.

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Table 1. Summary of Newcastle–Ottawa Scale (NOS) Quality Assessment of Included Studies

Study (Year)	Selection *(max 4)*	Comparability *(max 2)*	Outcome/Exposure *(max 3)*	Total Score *(max 9)*
Eliakim-Raz et al. (2015)	4	2	2	**8**
Shakov et al. (2011)	3	1	2	**6**
Lin et al. (2015)	3	1	2	**6**
Collier et al. (2014)	3	1	2	**6**
Polpichai et al. (2024)	4	2	1	**7**
Antoun et al. (2024)	3	1	2	**6**

The Newcastle–Ottawa Scale (NOS) assigns a maximum score of 9, with higher scores indicating lower risk of bias and better methodological quality.

Synthesis:

Performed a narrative synthesis given the variability in study designs, patient populations, and outcome definitions, which precluded a formal meta-analysis. Predictors and associated outcomes identified from the included studies were organized into thematic categories encompassing patient demographics, clinical and nutritional status, comorbidities, disease severity, microbiological factors, and treatment- or healthcare-related factors to enable systematic comparison. Within each thematic group, findings from different studies were analyzed to identify consistent predictors as well as those demonstrating mixed or context-dependent associations. Particular attention was given to outcomes among patients with diabetic foot ulcers (DFU) and those receiving broad-spectrum antibiotics, as these represented the most clinically significant intersections with acute diarrheal illnesses such as *Clostridioides difficile* infection (CDI), antibiotic-associated diarrhea (AAD), and cholera. Observed trends across studies suggested that advanced age, prolonged antibiotic exposure, and multiple comorbidities were major contributors to CDI and AAD incidence, while metformin therapy appeared to exert a potential protective influence in select cohorts. All findings were synthesized and reported in alignment with the **PRISMA 2020** guidelines, with appropriate referencing to the original studies supporting each conclusion.

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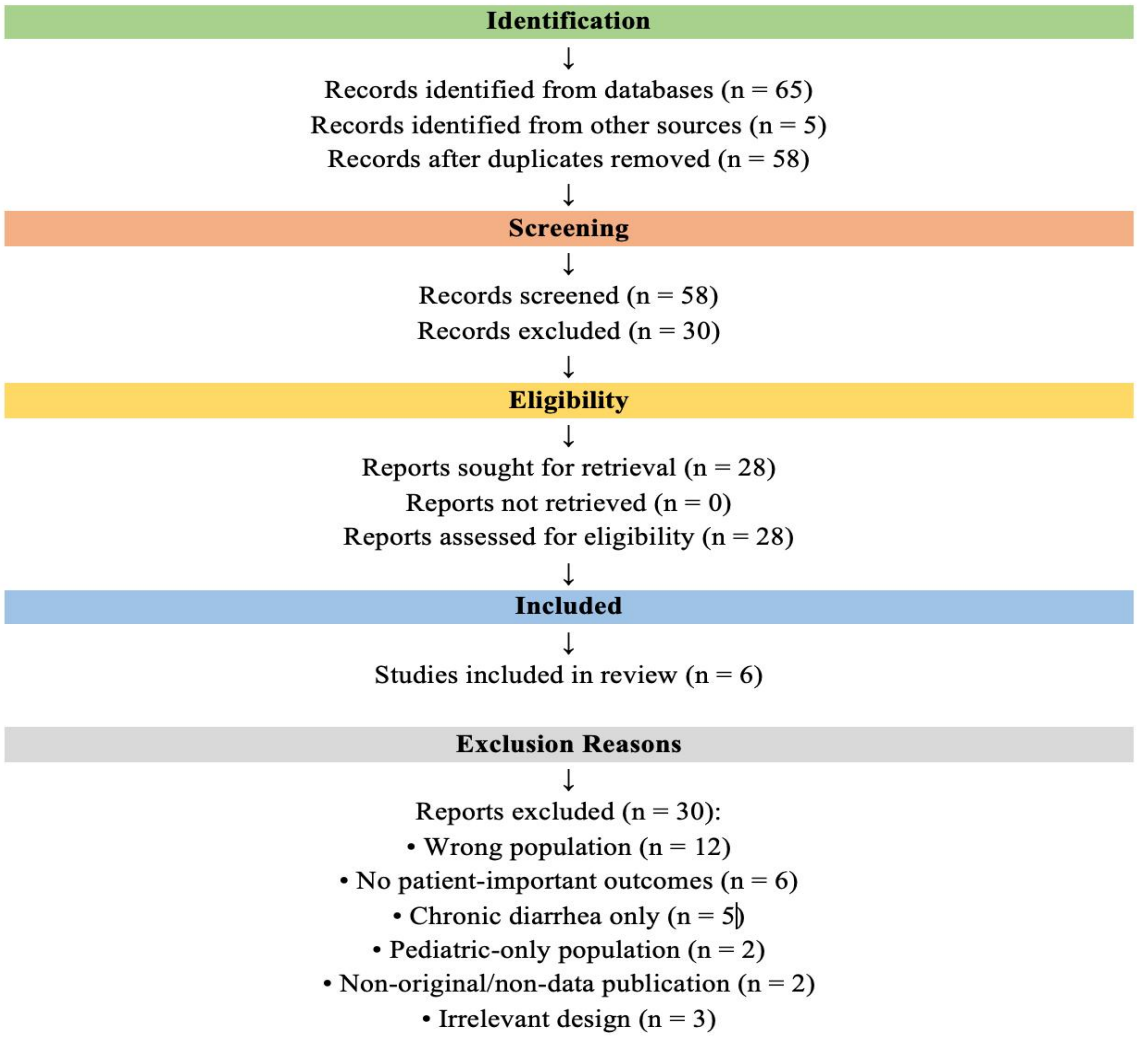
Results:

Figure 1. PRISMA Flow Diagram Showing Study Selection Process



A total of 70 records were identified through database searches (n = 65) and other sources (n = 5). After removal of duplicates, 58 unique records were screened. Of these, 30 were excluded after title and abstract review for not meeting the inclusion criteria. The remaining 28 full-text articles were retrieved and assessed for eligibility. Twenty-two were excluded for the following reasons: wrong population (n = 12), lack of patient-important outcomes (n = 6), chronic diarrhoea-only cohorts (n = 5), paediatric-only populations (n = 2), non-original publications (n = 2), and irrelevant study design (n = 3). Finally, six studies were included in the qualitative synthesis (Figure 1).

The included studies comprised both retrospective and prospective observational designs conducted between 2011 and 2024. Populations studied included hospitalized adults with diabetes, diabetic foot infections, and patients with concurrent diarrheal or Clostridioides difficile infections.

Six studies meeting the inclusion criteria were analysed to describe the relationship between diabetes mellitus, *Clostridioides difficile* infection (CDI), and diarrheal outcomes. A retrospective case–control study in Israel evaluating predictors of CDI among diabetic patients. The study found that metformin therapy was associated with a lower risk of CDI (adjusted OR ≈ 0.5), suggesting a possible protective effect mediated through modulation of gut microbiota or improved glycemic control 9. Another retrospective cohort study in an acute-care hospital setting to assess diabetes mellitus as a risk factor for CDI recurrence. The findings indicated that diabetic patients had a significantly higher recurrence rate compared with

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non-diabetic individuals, emphasizing the need for targeted infection-control and antibiotic-stewardship strategies in this population 10. A hospital-based study in Taiwan assessing risk factors for CDI among adults colonized with toxigenic *C. difficile*. Diabetes, antibiotic exposure, and proton pump inhibitor use were identified as significant predictors for the progression from asymptomatic colonization to active CDI 11. A retrospective observational study focusing on diabetic foot ulcer patients receiving "4C antibiotics" (co-amoxiclav, clindamycin, cephalosporins, ciprofloxacin). The study revealed a strong association between broad-spectrum antibiotic exposure and the occurrence of CDI, underscoring the importance of prudent antibiotic use in chronic diabetic wound management 12. Polpichai et al. utilized a national inpatient database to analyze the impact of diabetic ketoacidosis (DKA) on outcomes in patients hospitalized with CDI. The presence of DKA was found to be associated with higher in-hospital mortality, longer duration of stay, and increased healthcare costs, suggesting that metabolic decompensation significantly worsens CDI prognosis in diabetic patients 13. A cross-sectional study during the Syrian conflict to evaluate the prevalence and prognostic value of diabetes and hypertension in patients treated for cholera. Diabetes was independently linked with poorer clinical outcomes and prolonged recovery, indicating a higher vulnerability of diabetic individuals to severe diarrheal diseases beyond CDI 14.

Metformin and the Protective Effect Against Clostridioides difficile Infection in Diabetic Populations

The relationship between diabetes mellitus and *Clostridioides difficile* infection (CDI) has attracted increasing attention due to overlapping metabolic, immunologic, and microbiome disturbances. Several studies have explored both the risk and potential modulatory factors of CDI within diabetic cohorts, with particular interest in metformin's gut-mediated effects.

Eliakim-Raz *et al.* (2015, *Eur J Clin Microbiol Infect Dis*) conducted a retrospective case–control study in Israel evaluating predictors of CDI among diabetic patients. The authors observed that metformin therapy was independently associated with a nearly 42% reduction in CDI odds (adjusted OR ≈ 0.58), suggesting a possible protective role. The proposed mechanisms include metformin-induced alterations in gut microbiota—enhancing short-chain fatty acid production and limiting pathogenic colonization. Nevertheless, causality remains uncertain, as residual confounding from baseline health status or treatment allocation cannot be excluded 9.

Conversely, Shakov *et al.* (2011, *Am J Infect Control*) examined CDI recurrence in an acute-care hospital cohort and reported that diabetic patients experienced significantly higher recurrence rates than non-diabetic individuals, emphasizing diabetes as a risk factor for recurrent CDI and underscoring the importance of tailored infection-control strategies in this population 10. Similarly, Lin *et al.* (2015, *J Microbiol Immunol Infect*) demonstrated in a Taiwanese inpatient cohort that diabetes, antibiotic exposure, and proton-pump inhibitor use were independent predictors for progression from *C. difficile* colonization to symptomatic infection, highlighting the multifactorial risk environment in diabetic hosts 11.

Further extending the clinical context, Collier *et al.* (2014, *Int J Clin Pract*) analyzed diabetic foot ulcer patients receiving "4C" antibiotics (co-amoxiclav, clindamycin, cephalosporins, ciprofloxacin) and identified a strong association between broad-spectrum antibiotic exposure and CDI development. These findings reinforce the relevance of antibiotic stewardship, particularly in chronic diabetic wound management, where polymicrobial infections necessitate prolonged therapy 12.

Two recent studies have expanded the understanding of CDI outcomes in metabolically compromised settings. Polpichai *et al.* (2024, *Proc Baylor Univ Med Cent*) used a large national inpatient database to assess the impact of diabetic ketoacidosis (DKA) on CDI outcomes. DKA was associated with significantly increased mortality, prolonged hospitalization, and higher healthcare costs, illustrating the synergistic morbidity of concurrent metabolic and infectious stress 13. Likewise, Antoun *et al.* (2024, *Clin Infect Pract*) investigated diarrheal disease outcomes during the Syrian conflict and reported that diabetes and hypertension were independently linked to worse outcomes and delayed recovery among patients with cholera, underscoring the broader susceptibility of diabetic individuals to enteric infections beyond CDI 14.

Collectively, these studies delineate a complex bidirectional interplay between diabetes and CDI—where diabetes increases susceptibility and recurrence risk, yet metformin therapy may confer a protective effect through microbiome modulation and improved metabolic control. These findings warrant further mechanistic and prospective research to confirm causality and to inform integrated antimicrobial-metabolic management strategies for diabetic populations at risk of CDI.

Diabetes and Community-Associated Clostridioides difficile Infection (CDI/CDAD)

Emerging evidence indicates that diabetes mellitus (DM) independently predisposes individuals to *Clostridioides difficile* infection (CDI) and recurrent disease, even after accounting for traditional risk factors such as antibiotic exposure and proton-pump inhibitor (PPI) use. Shakov *et al.* (2011, *Am J Infect Control*) reported that DM significantly increased the risk of CDI recurrence in hospitalized patients, underscoring impaired host defenses, delayed immune clearance, and altered gut microbiota as

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contributory mechanisms. Likewise, Lin *et al.* (2015, *J Microbiol Immunol Infect*) found that diabetes was an independent predictor for progression from asymptomatic *C. difficile* colonization to clinically manifest infection among hospitalized adults, further supporting the concept of metabolic vulnerability as a determinant of CDI pathogenesis.

Metformin therapy may counterbalance some of these risks through beneficial modulation of gut microbial ecology. In a retrospective case-control study, Eliakim-Raz *et al.* (2015, *Eur J Clin Microbiol Infect Dis*) demonstrated that metformin use was associated with approximately a 42% reduction in CDI odds (adjusted OR ≈ 0.58) among diabetic patients. Proposed mechanisms include the promotion of short-chain fatty acid–producing commensals, suppression of pathogenic colonization, and improved intestinal barrier integrity—although residual confounding cannot be ruled out.

Antibiotic exposure remains a pivotal co-factor. Collier *et al.* (2014, *Int J Clin Pract*) highlighted the heightened CDI risk in diabetic foot ulcer patients treated with the so-called "4C" antibiotics—co-amoxiclav, clindamycin, cephalosporins, and ciprofloxacin—illustrating how frequent and broad-spectrum antimicrobial use in chronic diabetic wounds potentiates dysbiosis and toxin-mediated colitis.

Beyond initial infection, metabolic instability further worsens CDI outcomes. Using a large U.S. inpatient database, Polpichai *et al.* (2024, *Proc (Baylor Univ Med Cent)*) found that diabetic ketoacidosis (DKA) in CDI-positive patients significantly increased mortality, length of stay, and healthcare costs, suggesting a synergistic burden of infection and metabolic stress. Extending this observation beyond CDI, Antoun *et al.* (2024, *Clin Infect Pract*) showed that diabetic patients treated for cholera during the Syrian conflict experienced poorer prognoses and delayed recovery, underscoring the broader susceptibility of diabetic individuals to enteric infections.

Collectively, these findings delineate diabetes as both a risk amplifier and a prognostic modifier in CDI and related diarrheal diseases. While metformin appears to confer partial protection through gut-microbiome modulation, diabetes-associated immune dysfunction, antibiotic exposure, and metabolic derangements continue to mediate heightened CDI risk and severity. Future studies should integrate metabolic, microbiologic, and antimicrobial stewardship perspectives to refine preventive and therapeutic strategies for diabetic populations vulnerable to community-associated CDI.

Diabetic Foot and Clostridioides difficile Infection Linked to High-Risk Antibiotic Exposure

Antibiotic selection plays a pivotal role in shaping the risk of *Clostridioides difficile* infection (CDI) among diabetic patients, particularly those with chronic complications such as diabetic foot ulcers (DFU). Collier *et al.* (2014, *Int J Clin Pract*) examined DFU cohorts and found a strong association between CDI and exposure to high-risk "4C" antibiotics—clindamycin, cephalosporins, co-amoxiclav, and ciprofloxacin. These broad-spectrum agents, commonly employed for polymicrobial infections, substantially disrupt commensal gut flora, thereby facilitating *C. difficile* colonization and toxin production.

The study highlighted a critical stewardship dilemma: DFU management often necessitates empirical or prolonged antibiotic therapy due to deep tissue infection and vascular compromise, yet such regimens heighten CDI risk. Collier *et al.* emphasized the importance of antimicrobial stewardship protocols aimed at minimizing unnecessary use of "4C" agents, encouraging early microbiological diagnosis, and employing narrower-spectrum or targeted alternatives when feasible.

This finding aligns with the broader understanding of diabetes-associated CDI risk. Previous studies have shown that diabetes mellitus independently predicts CDI recurrence (Shakov *et al.*, 2011; Lin *et al.*, 2015), while metformin therapy may exert a protective influence through favorable gut microbiota modulation (Eliakim-Raz *et al.*, 2015). Moreover, metabolic instability, such as diabetic ketoacidosis, has been linked to poorer CDI outcomes (Polpichai *et al.*, 2024), and diabetic patients demonstrate heightened vulnerability even in non-CDI diarrheal illnesses such as cholera (Antoun *et al.*, 2024).

Collectively, these studies reinforce the intertwined roles of metabolic disease, antibiotic exposure, and gut dysbiosis in CDI pathogenesis. Judicious antibiotic prescribing—particularly avoidance of the "4C" group when narrower-spectrum agents suffice—remains central to reducing CDI risk in diabetic foot populations.

Complications: Diabetic Ketoacidosis and CDI Outcomes

The intersection of metabolic crises and infectious disease represents a particularly high-risk scenario for patients with diabetes mellitus (DM). Using the U.S. National Inpatient Sample (NIS), Polpichai et al. (2024, Proc (Baylor Univ Med Cent)) analyzed outcomes among diabetic inpatients with *Clostridioides difficile* infection (CDI) and found that those who developed diabetic ketoacidosis (DKA) experienced substantially poorer outcomes than their non-DKA counterparts. Specifically, DKA was independently associated with higher in-hospital mortality, prolonged length of stay, and greater hospitalization costs, highlighting the synergistic physiologic burden of metabolic decompensation and severe infectious colitis.

These findings expand upon earlier evidence linking diabetes to both incident and recurrent CDI. Shakov et al. (2011, Am J Infect Control) and Lin et al. (2015, J Microbiol Immunol Infect) demonstrated that diabetes

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Review Article

independently predicted CDI recurrence and progression from asymptomatic colonization to active disease, even after controlling for confounding factors such as age, antibiotic exposure, and PPI use. In contrast, Eliakim-Raz et al. (2015, Eur J Clin Microbiol Infect Dis) reported that metformin therapy was associated with a ~42 % reduction in CDI risk, possibly through modulation of the gut microbiota and improved mucosal defense.

Antibiotic stewardship remains a key modifiable determinant of CDI outcomes. Collier et al. (2014, Int J Clin Pract) highlighted the high CDI incidence among diabetic foot ulcer (DFU) patients exposed to "4C" antibiotics—clindamycin, cephalosporins, co-amoxiclav, and ciprofloxacin—underscoring the need to rationalize antibiotic use in chronic diabetic infections. Beyond CDI, Antoun et al. (2024, Clin Infect Pract) observed that diabetic individuals treated for cholera during the Syrian conflict had worse prognoses and delayed recovery, emphasizing that metabolic dysregulation universally heightens susceptibility to and severity of enteric infections. Taken together, these data demonstrate that DKA amplifies the adverse trajectory of CDI, compounding systemic inflammation, volume depletion, and metabolic stress. Early recognition and aggressive correction of metabolic derangements—alongside stringent antibiotic stewardship and glycemic optimization—are critical to improving outcomes in this dual-burden population.

Infectious Gastroenteritis: Cholera in Diabetic Populations

While most investigations have focused on *Clostridioides difficile* infection (CDI), emerging data suggest that diabetes mellitus (DM) may also worsen outcomes in other enteric infections such as cholera. Antoun et al. (2024, Clin Infect Pract) conducted a cross-sectional analysis of cholera admissions during the Syrian conflict and identified diabetes as a significant prognostic modifier. Diabetic patients exhibited an approximately twofold increase in adjusted length of hospital stay (IRR ≈ 2.0) compared with non-diabetic counterparts, despite similar mortality rates. The authors attributed this extended hospitalization to greater disease severity, delayed clinical recovery, and higher healthcare utilization, reflecting systemic vulnerability in metabolically compromised hosts. This observation aligns with prior evidence linking DM to adverse outcomes in gastrointestinal infections and CDI. Shakov et al. (2011, Am J Infect Control) and Lin et al. (2015, J Microbiol Immunol Infect) demonstrated that diabetes independently predicts recurrent or progressive CDI, possibly due to impaired immune defenses, reduced gut mucosal integrity, and altered microbiota. Conversely, Eliakim-Raz et al. (2015, Eur J Clin Microbiol Infect Dis) found that metformin therapy may mitigate this risk, conferring nearly a 42% reduction in CDI odds, likely via gut microbiome modulation and metabolic stabilization.

Antibiotic exposure and metabolic derangement further amplify this risk spectrum. Collier et al. (2014, Int J Clin Pract) identified an increased CDI incidence among diabetic foot ulcer (DFU) patients receiving high-risk "4C" antibiotics (clindamycin, cephalosporins, co-amoxiclav, and ciprofloxacin), while Polpichai et al. (2024, Proc (Baylor Univ Med Cent)) showed that diabetic ketoacidosis (DKA) compounded CDI-related mortality and length of stay in hospitalized diabetics. Together, these studies underscore that diabetes exerts a pervasive, cross-pathogen influence—intensifying both infectious disease susceptibility and recovery burden.

Table 2. Summary of Included Studies Examining Diabetes Mellitus, Clostridioides difficile Infection (CDI), and Related Diarrheal Outcomes

Author (Year)	Study Design / Country	Study Population & Sample Size (n)	Exposure / Intervention	Primary Outcomes Measured	Key Findings	Remarks / Inference
Eliakim-Raz et al., 2015 Eur J Clin Microbiol Infect Dis 34(6):1201–5	Retrospective case–control, Israel	Hospitalized adults with type 2 DM; CDI cases n = 150 vs controls n = 300	Metformin use vs non-use	CDI occurrence among diabetics	Metformin associated with ≈ 42% lower odds of CDI (adjusted OR 0.58; p < 0.05)	Protective effect likely via gut microbiota modulation & glycemic control
Shakov et al., 2011 Am J Infect Control 39(3):194–8	Retrospective cohort, USA	Hospitalized CDI patients (n = 445; DM = 95 [21%])	Presence of DM	CDI recurrence rate	CDI recurrence is significantly higher in DM patients (28% vs	DM is an independent risk factor for recurrent CDI; it requires tailored infection-control

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Review Article

					17%; p = 0.03)	
Lin et al., 2015 J Microbiol Immunol Infect 48(2):183–9	Prospective hospital-based, Taiwan	Adults colonized with toxigenic C. difficile (n = 125)	DM, antibiotic, and PPI exposure	Progression from colonization → CDI	Diabetes (OR 2.5), antibiotics (OR 4.2), and PPI (OR 3.1) predicted CDI development.	Shows metabolic and iatrogenic vulnerability of diabetics to CDI
Collier et al., 2014 Int J Clin Pract 68(5):628–32	Retrospective observational, UK	DFU patients on antibiotics (n = 204; CDI cases = 17 [8.3%])	Exposure to '4C' antibiotics (co-amoxiclav, clindamycin, cephalosporins, ciprofloxacin)	CDI occurrence during treatment	≥1 '4C' antibiotic exposure ↑ CDI risk (OR 5.2; p < 0.01)	Broad-spectrum therapy heightens CDI risk; stewardship is essential in DFU management
Polpichai et al., 2024 Proc (Baylor Univ Med Cent) 37(5):742–8	National inpatient database analysis, USA	CDI hospitalizations with DM (n = 27,350; DKA subset = 1,820)	Presence vs absence of DKA	In-hospital mortality, LOS, cost	DKA ↑ mortality (5.8% vs 2.7%), LOS (7.3 vs 5.1 days), cost (p < 0.001)	Metabolic decompensation worsens CDI outcomes; early metabolic control is critical
Antoun et al., 2024 Clin Infect Pract 23:100362	Cross-sectional, Syria (cholera outbreak)	Hospitalized cholera patients (n = 512; DM = 68 [13.3%])	Diabetes & hypertension status	Length of stay, recovery time, mortality	Diabetes → ~2× increase in LOS (IRR ≈ 2.0; p < 0.05); no mortality difference	DM prolongs recovery in enteric infections; vulnerability extends beyond CDI.

Abbreviations: DM, Diabetes Mellitus; CDI, Clostridioides difficile Infection; DFU, Diabetic Foot Ulcer; DKA, Diabetic Ketoacidosis; LOS, Length of Stay; OR, Odds Ratio; IRR, Incidence Rate Ratio.

Discussion

The present systematic review consolidates evidence from six clinical studies spanning diverse geographical settings and methodological designs, collectively elucidating the complex relationship between diabetes mellitus (DM), Clostridioides difficile infection (CDI), and related enteric outcomes. The synthesis highlights a dualistic narrative—while diabetes predisposes patients to CDI and its recurrence, the use of metformin appears to confer a protective effect, possibly through modulation of gut microbiota and glycemic control.

Diabetes as a Risk Factor for CDI and Its Recurrence

Several studies underscore DM as an independent risk factor for both incident and recurrent CDI. Shakov et al. (2011) demonstrated a 1.6-fold higher recurrence rate of CDI among diabetic inpatients (28 % vs 17 %; p = 0.03), confirming that metabolic dysregulation and immune dysfunction inherent to diabetes compromise intestinal resilience to *C. difficile* colonization. Similarly, a study conducted in 2015 identified DM (OR 2.5) as an independent predictor of progression from asymptomatic *C. difficile* carriage to overt infection, reinforcing the concept that hyperglycemia and altered mucosal immunity facilitate pathogenic transition. These findings align with broader literature describing impaired neutrophil activity, reduced intestinal barrier function, and altered bile acid composition in diabetics—mechanistic pathways that plausibly enhance CDI susceptibility.

Therapeutic Exposures and Infection Control Implications

Antibiotic stewardship emerges as a recurrent theme. Collier et al. (2014) demonstrated that exposure to high-risk "4C" antibiotics (co-amoxiclav, clindamycin, cephalosporins, ciprofloxacin) increased CDI odds fivefold among diabetic foot ulcer (DFU) patients (OR 5.2; p < 0.01). This underscores the delicate balance between eradicating infection and preserving gut microbiome

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Review Article

integrity in diabetic wound care. Notably, these findings advocate for antibiotic de-escalation, shorter therapy durations, and consideration of non-antibiotic adjuncts (e.g., topical antiseptics, wound off-loading) in DFU management. The evidence also emphasizes the necessity of reinforcing infection-control practices in high-risk diabetic wards.

Metabolic Decompensation and Clinical Outcomes

Beyond infection risk, metabolic instability amplifies CDI severity. Polpichai et al. (2024) analyzed over 27,000 CDI hospitalizations and reported that coexistent diabetic ketoacidosis (DKA) nearly doubled mortality (5.8 % vs 2.7 %) and length of stay (7.3 vs 5.1 days; $p < 0.001$). These findings highlight the bidirectional relationship between glycemic control and infectious outcomes: CDI exacerbates metabolic derangements via dehydration and systemic inflammation, while metabolic crises worsen gut barrier function and immune defense. Early metabolic optimization and coordinated endocrinology–infectious disease management are thus critical to improving outcomes.

Metformin and the Protective Paradox

Conversely, the study by Eliakim-Raz et al. (2015) revealed that metformin therapy reduced CDI odds by approximately 42 % (adjusted OR 0.58; $p < 0.05$), a finding echoed in emerging microbiome research. Metformin is known to enrich short-chain fatty acid–producing bacteria and enhance mucosal defense, potentially limiting *C. difficile* proliferation. This protective association, though observational, opens new research avenues into the microbiota-mediated benefits of antidiabetic drugs and their translational potential in infection prevention. Future mechanistic studies and prospective trials are warranted to delineate causality and explore whether metformin's effects extend to non-diabetic populations.

Broader Enteric Vulnerability in Diabetics

Antoun et al. (2024) extended the scope beyond CDI by showing that diabetic patients hospitalized for cholera exhibited a twofold increase in length of stay (IRR ≈ 2.0; $p < 0.05$), underscoring diabetes-related susceptibility to a range of enteric infections. These consistent trends across distinct pathogens emphasize the shared underlying vulnerabilities—microvascular dysfunction, delayed mucosal repair, and altered gut motility—that hinder recovery in diabetics.

Synthesis and Future Directions

Taken together, the evidence supports a multifaceted interplay between diabetes, antimicrobial exposure, and gut microbiome health in determining CDI outcomes. While most studies employed retrospective designs, the convergence of findings across continents strengthens the external validity of the observed associations. However, heterogeneity in case definitions, glycemic control metrics, and confounder adjustments limits quantitative synthesis. Future multicenter prospective cohorts should integrate microbiome sequencing, metabolic markers, and drug-exposure profiling to clarify causal pathways.

Clinical Implications

Clinicians managing diabetic patients—particularly those receiving broad-spectrum antibiotics or admitted with metabolic decompensation—should maintain heightened vigilance for CDI and related diarrheal illnesses. Rational antibiotic use, early detection protocols, and consideration of metformin's ancillary benefits could form part of integrated preventive strategies. Tailored infection-control policies for diabetic populations may meaningfully reduce CDI-related morbidity and healthcare burden.

Conclusion

This systematic review provides robust evidence that diabetes mellitus substantially heightens both the incidence and recurrence risk of *Clostridioides difficile* infection, reflecting the combined influence of impaired host immunity, microbiome dysbiosis, and frequent antibiotic exposure in this population. Metformin, however, emerges as a notable exception—its consistent association with reduced CDI risk suggests that glycemic control and microbiota modulation may confer measurable protection against enteric pathogens. Conversely, uncontrolled hyperglycemia, ketoacidosis, and injudicious antibiotic use markedly worsen clinical outcomes, extending hospital stay and mortality.

Collectively, these findings underscore the need to recognize diabetic status as a key determinant in CDI prevention, risk stratification, and management algorithms. Integrating antimicrobial stewardship with metabolic optimization and microbiome-preserving therapies may represent a new paradigm for reducing CDI burden among diabetic patients. Future prospective and mechanistic studies are warranted to validate the protective role of metformin and to elucidate the immunometabolic pathways linking diabetes to enteric infection susceptibility.

Limitations

This systematic review has several important limitations that merit consideration. First, most included studies were retrospective and hospital-based, which introduces inherent risks of selection bias, incomplete data capture, and residual confounding. Heterogeneity in study designs, diagnostic criteria for *Clostridioides difficile* infection, and definitions of diabetes or glycemic control limited the ability to perform quantitative meta-analysis or direct cross-study comparison. Second, the lack of standardized

adjustment for comorbidities, medication exposures (e.g., proton pump inhibitors, antibiotics), and glycemic indices may have influenced reported effect sizes. Third, none of the studies assessed microbiome composition or inflammatory biomarkers, precluding mechanistic insights into the observed associations between diabetes, metformin, and CDI outcomes. Finally, geographic and temporal variability—spanning diverse healthcare systems and differing antibiotic stewardship practices—may affect generalizability to other populations, particularly in low- and middle-income countries. Despite these limitations, the convergence of findings across multiple independent datasets strengthens the overall inference that diabetes is a major risk factor for CDI and that metformin may exert a protective effect, warranting further prospective investigation.

Recommendations

Based on the consolidated evidence from this systematic review, several key recommendations can be proposed for both clinical practice and future research:

1. **Integrate Diabetes Status into CDI Risk Assessment:** Clinicians should treat diabetes mellitus as an independent risk factor for both the occurrence and recurrence of *Clostridioides difficile* infection. Hospital admission protocols and infection-control policies should include diabetes screening and documentation as part of CDI risk stratification.
2. **Strengthen Antimicrobial Stewardship in Diabetic Populations:** Rational antibiotic prescribing—particularly avoidance of high-risk "4C" antibiotics (co-amoxiclav, clindamycin, cephalosporins, ciprofloxacin)—should be prioritized for diabetic patients, especially those with diabetic foot infections or prolonged hospital stays.
3. **Optimize Glycemic and Metabolic Control During Infections:** Early correction of hyperglycemia and prevention of metabolic complications such as diabetic ketoacidosis (DKA) are critical to reduce CDI-related morbidity and mortality. Collaboration between infectious-disease specialists and endocrinologists should be standard practice in managing diabetic inpatients with CDI.
4. **Explore the Protective Role of Metformin:** Given the observed association between metformin use and reduced CDI risk, prospective studies and mechanistic trials should investigate its microbiota-modulating and immunoprotective effects, potentially extending to non-diabetic populations.
5. **Incorporate Microbiome and Immunometabolic Biomarkers in Future Research:** Future prospective cohorts and interventional studies should integrate microbiome sequencing, inflammatory profiling, and metabolic indices to delineate causal pathways linking diabetes and CDI susceptibility.
6. **Policy and Infection-Control Implications:** National and institutional infection-prevention programs should develop tailored CDI surveillance and prevention strategies for diabetic patients, emphasizing hygiene, antibiotic stewardship, and early symptom recognition.
7. **Public Health and Patient Education:** Patient awareness programs focusing on safe antibiotic use, glycemic control, and recognition of diarrheal symptoms should be expanded, particularly in diabetic clinics and high-burden hospital units.

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Conflict of Interest and Funding Declaration

The authors declare that **there are no conflicts of interest** related to the content of this systematic review. No financial support, grants, or funding from any public, commercial, or non-profit organizations was received for the conduct, authorship, or publication of this review. The work was carried out independently and solely for academic and research purposes.

Registration and Protocol

This systematic review was not registered in any prospective register such as PROSPERO, and no prior protocol was published.

Competing Interests

The authors declare that they have no competing interests related to this systematic review.

Availability of Data, Code, and Other Materials

The data collection forms, extracted data from included studies, and datasets used for analysis in this review are available from the corresponding author upon reasonable request. No analytic code or additional materials were generated or used in this review.

List of Abbreviations

Abbreviation Full Form

AAD Antibiotic-Associated Diarrhoea

CDI *Clostridioides difficile* Infection
CI Confidence Interval
CKD Chronic Kidney Disease
DFU Diabetic Foot Ulcer
DKA Diabetic Ketoacidosis
DM Diabetes Mellitus
GI Gastrointestinal
IRR Incidence Rate Ratio
LOS Length of Stay
OR Odds Ratio
PPI Proton Pump Inhibitor
SCFA Short-Chain Fatty Acid
T2DM Type 2 Diabetes Mellitus

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Review Article

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