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REVIEW

Therapeutics involved in managing initial and recurrent *Clostridium difficile* infection: An updated literature review

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Abstract

Clostridium difficile infection (CDI) has been increasing due to the effect of recurrent hospitalizations. The use of antibiotics has been shown to alter the gut microbiome and lead to CDIs. The treatment is limited to three major antibiotics; however, the incidence of recurrent CDIs has been increasing and drug resistance is a major concern. This aspect is a growing concern in modern medicine especially in the elderly population, critical care patients, and immunocompromised individuals who are at high risk of developing CDIs. *Clostridium difficile* can lead to various complications including septic shock and fulminant colitis that could prove to be lethal in these patients. Newer modalities of treatment have been developed including bezlotoxumab, a monoclonal antibody and fecal microbiota transplant. There have been studies showing asymptomatic carriers and drug resistance posing a major threat to the healthcare system. Newer treatment options are being studied to treat and prevent CDIs. This review will provide an insight into the current treatment modalities, prevention and newer modalities of treatment and challenges faced in the treatment of CDIs.

Key Words: *Clostridium difficile*; Antibiotics; Vancomycin; Fidaxomicin; Prevention; Bezlotoxumab; Fecal microbiota transplant

Core Tip: *Clostridium difficile* infections (CDIs) are one of the most common of hospital acquired infections and are caused by the use of antibiotics. The treatment is limited to 3 antibiotics currently. There has been a rise in recurrent CDIs. Our review aims to provide an overview of current testing and treatment modalities, prevention, new treatment options, challenges and current studies in the aspect of CDIs, which has become a growing concern to global health.

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INTRODUCTION

Clostridium difficile (*C. difficile*) infection remains a significant healthcare challenge globally, characterized by its substantial morbidity, mortality, and propensity for recurrence. Managing both initial and recurrent *C. difficile* infection (CDI) necessitates a multifaceted approach, encompassing prevention, diagnosis, and treatment strategies. In this comprehensive review, we aim to provide an updated synthesis of the literature focusing on the therapeutics involved in managing CDI, with particular emphasis on recurrent infections.

As highlighted by Song and Kim[1], recurrent CDI poses a formidable clinical challenge, requiring a nuanced understanding of risk factors, treatment modalities, and preventative measures[1]. Madoff *et al*[2] further underscores the importance of preventative strategies through their systematic review of randomized controlled trials, offering insights into interventions aimed at reducing CDI recurrence rates[2]. The advent of monoclonal antibodies, such as bezlotoxumab (BEZ), has introduced new avenues for preventing recurrent CDI in high-risk patient populations[3]. Moreover, microbiologic factors elucidated by Chilton *et al*[4] shed light on disease persistence dynamics, informing targeted therapeutic approaches[4].

Fecal microbiota transplantation (FMT) has emerged as a promising intervention in recurrent CDI management. Rokkas *et al*[5] conducted a network meta-analysis, demonstrating the efficacy of FMT in reducing CDI recurrence rates [5]. Conversely, Knudsen *et al*[6] systematically reviewed the clinical efficacy and safety of vancomycin, a cornerstone antibiotic in CDI management, particularly in recurrent scenarios[6]. The impact of FMT on patient quality of life is explored by Hammeken *et al*[7], emphasizing the multifaceted nature of CDI management[7].

The emergence of novel therapeutic modalities continues to shape the landscape of CDI management. Fein *et al*[8] investigated the use of BEZ therapy in an ulcerative colitis patient with recurrent CDI, highlighting its potential in unique clinical scenarios[8]. Innovative microbiome therapeutics, as discussed by Bloom and Young[9], represent a paradigm shift in CDI management, showcasing the evolving landscape of therapeutic innovation[9].

Furthermore, Sandhu and Chopra[10] provide insights into the safety and pitfalls of FMT, offering valuable considerations for its clinical implementation[10]. Microbiologic factors affecting CDI recurrence are further explored by Okafor *et al*[11], emphasizing the multifaceted interplay between microbial ecology and disease dynamics[11].

By synthesizing diverse perspectives and empirical evidence, this review aims to inform clinical decision-making and advance patient care in the realm of CDI management.

RISK FACTORS

CDI poses a significant threat to healthcare settings worldwide, with a complex interplay of risk factors contributing to its prevalence[12]. Understanding these factors is crucial for effective prevention and management strategies. CDI can be divided into three types based off on epidemiology: Community-onset healthcare facility–associated, community-associated CDI and healthcare facility–onset provides a framework for understanding its transmission and guiding intervention strategies[12,13].

CDI represents a predominant cause of hospital-acquired antibiotic-associated diarrhea, leading to a range of conditions marked by significant recurrence, morbidity, and mortality rates[14]. The exact mechanism by which the gut microbiota confers colonization resistance remains unclear, but it mainly involves the release of antimicrobial substances, gut barrier integrity maintenance, and utilization of bacteriophages[15]. Broad-spectrum antibiotics that include penicillins, cephalosporins and Clindamycin are very well known to cause CDI more often than the other antibiotics[16]. A 2022 meta-analysis of studies on CDI risk factors found that prior antibiotic exposure significantly increased the likelihood of developing CDI [odds ratio (OR) = 1.93] compared to those without such exposure. The meta-analysis also showed that the risk for CDI was greatest with clindamycin and lower with fluoroquinolones[17].

Gastric acid inhibitors like proton pump inhibitors and H2 receptor antagonists are other causes that have been linked to a higher risk of causing CDI. However, some studies have not found a correlation between these two factors[18], thereby casting doubt on this association. Another dimension of the research focused on pediatric populations. A 2018 study analyzing risk factors for *C. difficile*-associated diarrhea in hospitalized children older than 1 year found that a hospital stay of 10 days or more before the onset of diarrhea was an independent risk factor for *C. difficile*-associated disease in children with antibiotic-associated diarrhea[19].

In 2022, a study aimed to identify risk factors for the first recurrence of CDI, given the high incidence of recurrence in these infections. This retrospective analysis examined patient backgrounds and treatment-related factors, employing both single and multiple logistic regression analyses. The study included 134 participants, with recurrent CDI observed in 23.9% of the patients. The average age of the patients was 78 years. The findings suggested that the use of prophylactic probiotics and nasogastric tube placement might be risk factors for recurrent CDI[20].

PATHOPHYSIOLOGY OF *C. DIFFICILE*

C. difficile is a gram-positive, anaerobic bacillus, that spreads *via* the oral-fecal route and ingestion of spores. These spores are resistant and tolerant to the acidic environment of the intestine. *C. difficile* is known to colonize the large intestine of humans[21]. The normal intestinal microbiota plays a crucial role in human health by providing various advantages, such as the synthesis of essential vitamins, metabolic functions, prevention of colonization by pathogens, and stimulation of the immune response. Various antibiotics are known to play a significant role in the disruption of the intestinal microbiota such as clindamycin, fluoroquinolones, and cephalosporins. The disruption of normal colonic bacteria results in an environment that has reduced competition for resources and heightened bacterial cell lysis, thereby releasing consumable carbon sources. Within this altered environment, bacterial dynamics can become intricate[22].

The pathogen is able to capitalize on a wide range of nutrients available to it in this dysbiotic environment including carbohydrates, amino acids, and ethanolamine, allowing for its proliferation[23]. Characteristic symptoms of CDI include diarrhea and colitis, attributed to the action of clostridial glycosylation exotoxins, namely toxin A (TcdA) and toxin B (TcdB). TcdA is an enterotoxin that has a carbohydrate receptor binding site, facilitating the intracellular transport of both toxins A and B[24]. Once intracellular, these toxins deactivate pathways mediated by the Rho family of proteins, leading to damage of colonocytes, disruption of intercellular tight junctions, and subsequent colitis. Furthermore, TcdA directly activates neutrophils, while both TcdA and TcdB contribute to neutrophil chemotaxis[25].

In healthy adults with robust immune responses, the colonization often leads to asymptomatic carriers of the pathogen. Elderly individuals have an increased vulnerability due to weakened immune responses and changes in gut microbiota. Additionally, factors such as the use of proton-pump inhibitors, chemotherapy, or gastrointestinal surgery can further increase susceptibility. Moreover, the administration of broad-spectrum antibiotics significantly alters the microflora diversity and bile composition increasing the risk of *C. difficile*[26].

The host response to the pathogen involves the production of TcdA and B antibodies, interleukin-8, and activated innate lymphoid cells. Activated lymphoid cells are specifically involved in the release of IFNγ and interleukin-22. Individuals with polymorphisms of the interleukin-8 gene have an increased susceptibility to *C. difficile*. The severity of the disease also has an inverse correlation with the levels of IgG and IgA an individual possesses[27,28].

C. difficile is associated with systemic effects and complications including toxic megacolon (TM), perforation, and sepsis. The development of TM is believed to be caused by inflammation through the muscularis propria as well as the release of chemical mediators leading to an altered colon response and impaired smooth muscle contraction. It is clinically manifested as bloody diarrhea, tachycardia, and fever. Perforation is the leading cause of mortality in patients with *C. difficile* often presenting with abdominal distention, tenderness, and hemodynamic instability[29,30].

The following image displays the production of toxins A and B and the colonization of *C. difficile* causing disruption of the epithelial barrier and an inflammatory response leading to neutrophil recruitment and the development of a pseudomembrane[31] (Figure 1).

COMPLICATIONS OF CDI

The primary complication of CDI is incomplete recovery and recurrent infection, occurring in approximately 20% to 30% of cases after an initial infection and escalating up to 60% after three successive infections[32]. Extraintestinal infections caused by *C. difficile* include bacterial infection, abdominal infections (both with and without prior surgery), perianal abscesses, wound infections, and even colonization in urinary catheters. These infections, occurring primarily in hospitalized patients with substantial comorbidities, often involve polymicrobial colonization and may lead to severe outcomes, with mortality rates correlating with the severity of underlying diseases[33].

TM is one of the complications of CDI. The prevalence of TM associated with CDI is increasing with age, with an estimated incidence of 0.4%–3% before 1990 and 4.3% after 1990. Patients with fulminant infection may require surgical intervention, with colonic perforation being a significant predictor of mortality[34]. Cases of ileal perforation secondary to *C. difficile* enteritis have been reported, underscoring a rare yet potentially severe complication[35].

One of the most feared complications arising from *C. difficile*-associated colitis is the progression to sepsis, which can escalate to septic shock, characterized by a profound state of circulatory failure and organ dysfunction[36]. An observational study by Mihăilă *et al*[37] revealed that patients with CDI exhibit a distinct pattern of thrombin generation, characterized by higher mean velocity index and peak thrombin levels compared to healthy controls. These findings suggest an

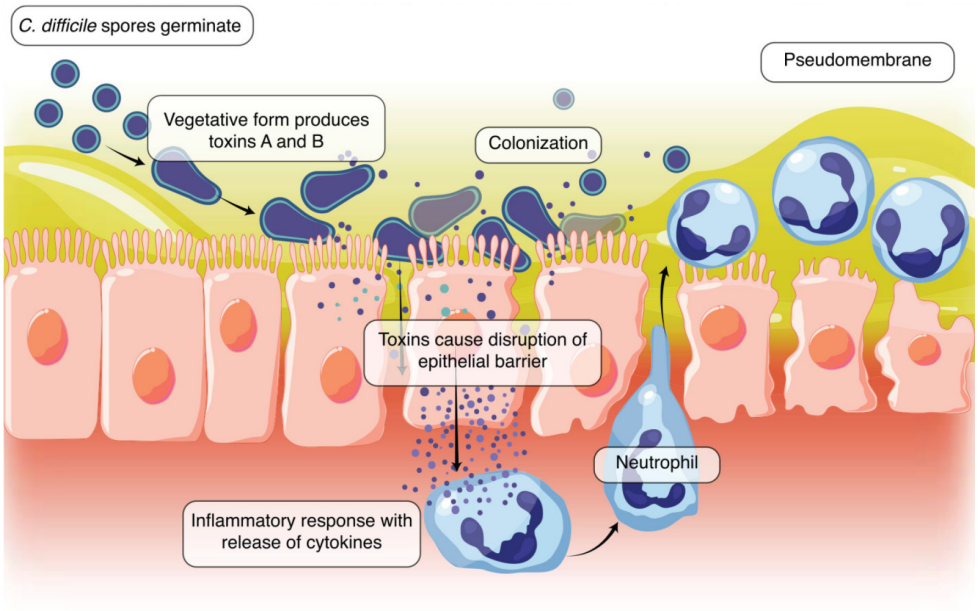

Figure 1 Production of toxins A and B and the colonization of *Clostridium difficile* causing disruption of the epithelial barrier and an inflammatory response leading to neutrophil recruitment and the development of a pseudomembrane. *C. difficile*: *Clostridium difficile*.

increased thrombotic risk in CDI patients, independent of septic shock, highlighting the potential association between CDI and venous thromboembolism[37]. Patients testing positive for CDI had a significantly higher risk of deep vein thrombosis (DVT) compared to CDI-negative patients, with an OR of 3.23 (95%CI) compared to 1.95 (95%CI), suggesting that CDI positivity doubled the risk of DVT regardless of other factors[38]. Another case report by Mastroianni *et al*[39] documented a rare complication of CDI, resulting in upper mesenteric artery thrombosis[39].

Reactive arthritis (ReA) associated with CDI is rare but has been reported in literature. Diagnostic criteria for ReA-CDI include evidence of synovitis during or immediately after colitis, presence of a toxigenic *C. difficile* strain in stool samples, and absence of other causes of colitis and arthritis. ReA-CDI tends to occur more frequently in younger patients with HLA B27-positive genotype[40]. Appendicitis occurring during CDI is exceptionally rare, with only three cases reported in the literature up to 2007. However, the authors speculate that this complication might be considerably underdiagnosed, as many cases could have been successfully managed conservatively without histological confirmation[41].

DIAGNOSIS OF *C. DIFFICILE*

CDI presents a diagnostic challenge due to varying clinical presentations and the absence of a singular definitive test[42]. Consequently, clinical guidelines emphasize a multi-step approach to accurately diagnose this prevalent nosocomial infection[43]. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America recommend testing patients with "unexplained and new-onset" diarrhea, defined as three or more unformed stools in 24 hours[44]. However, relying solely on this criterion may overlook true infections. Therefore, a comprehensive evaluation is necessary, particularly considering CDI's diverse clinical manifestations.

Diagnosing CDI primarily involves stool examination for the presence of toxins or toxigenic *C. difficile* bacillus[45]. While various techniques exist, polymerase chain reaction (PCR) has emerged as a sensitive and specific method, especially when integrated into a multi-step algorithm[46]. This approach, recommended by the IDSA, typically begins with a sensitive test such as glutamate dehydrogenase enzyme immune assay (EIA) or Nucleic Acid Amplification Testing, followed by a specific test for toxin confirmation[47]. NAAT may be used to arbitrate specimens with discrepant results, ensuring accurate diagnosis[48].

Although culture remains the "gold standard" for CDI diagnosis, its practicality in routine clinical settings is limited [42]. Therefore, a combination of molecular and immunoassay methods is preferred. However, overreliance on molecular tests may lead to overdiagnosis and unnecessary treatment, as demonstrated by studies indicating a discrepancy between PCR positivity and toxin detection. Notably, patients testing positive for *C. difficile* by PCR but negative for toxins experienced milder disease courses, suggesting potential overestimation of CDI burden with molecular testing alone[49, 50].

Diagnostic uncertainty may warrant additional investigations, such as lower gastrointestinal endoscopy, especially in cases of fulminant colitis or alternative diagnoses[51]. However, repeat testing within 7 days or testing asymptomatic patients is discouraged due to limited clinical utility and potential for false positives[48].

Ultimately, the decision on diagnostic testing for CDI involves collaboration between laboratory professionals and clinical staff. While laboratory testing aids diagnosis, clinical judgment remains paramount, particularly in patients with significant risk factors or typical clinical presentations. Therefore, a balanced approach integrating clinical assessment

with appropriate laboratory testing is essential for accurate CDI diagnosis and optimal patient management[42].

DIAGNOSIS OF RECURRENT *C. DIFFICILE*

Recurrent CDI (rCDI) is characterized by the reappearance of symptoms of CDI within a relatively brief period after the completion of treatment. Although most cases of rCDI can be managed by discontinuing antibiotics and providing additional treatment, about 25% of patients experience a recurrence within 30 days of treatment cessation[52]. First-line therapy often involves vancomycin, while fidaxomicin is recommended for patients at high risk for recurrence[53]. Current treatment guidelines for rCDI recommend the same regimen used in the initial episode[54]. Clinical evaluation is pivotal in the diagnostic process, involving a comprehensive review of the patient's medical history, prior CDI treatments, and recurrence risk factors.

CDI diagnosis is determined by diarrhea and laboratory confirmation of *C. difficile* toxins present in stool or toxigenic *C. difficile* by nucleic acid amplification testing[1,55]. Importantly, stool testing is a diagnostic approach in CDI that focuses on the detection of *C. difficile* toxins. Stool tests are typically conducted using EIA or PCR assays, with PCR offering higher sensitivity and specificity compared to EIA[56,57]. Multiple stool samples collected over time may be necessary to confirm the presence of toxins and differentiate between relapse and reinfection.

In cases where the diagnosis is unclear or when patients present with atypical symptoms, further diagnostic modalities such as colonoscopy or imaging studies may be warranted. Colonoscopy allows for direct visualization of the colon and the collection of tissue samples for analysis, aiding in confirming the presence of active infection and ruling out other potential causes of symptoms[58,59]. Imaging studies such as computed tomography scans may also be useful in assessing the extent of infection and identifying complications such as colitis or pseudomembranous colitis[60].

Stool antigen testing is not routinely recommended for the diagnosis of rCDI, as it may detect non-toxigenic strains and does not differentiate between active infection and asymptomatic carriage[61]. Instead, the diagnosis is mainly made by counting the number of diarrhea episodes, with a recurrence typically defined as the reappearance of symptoms within 8 weeks of completing treatment for a previous episode[62].

In the event of more than one recurrence of CDI, a thorough evaluation including a review of the patient's medical history, previous CDI treatments, and recurrence risk factors, is crucial to differentiate between relapse and reinfection. Distinguishing between relapse, caused by the same strain of *C. difficile*, and reinfection, caused by a new strain, may require additional testing, such as molecular typing of *C. difficile* isolates[63].

TREATMENT OF INITIAL CDI

CDI represents a significant healthcare burden globally, and its management poses considerable challenges due to the rising incidence of recurrent infections, the emergence of hypervirulent strains, and increasing antibiotic resistance[64]. Effective management strategies for both initial and recurrent CDI necessitate a nuanced understanding of the diverse therapeutic options available[65]. This section reviews the treatment modalities employed in managing initial CDI, encompassing conventional antibiotic therapy, adjunctive agents, and emerging therapeutic approaches.

The cornerstone of treatment for initial CDI involves antimicrobial therapy aimed at targeting the pathogenic organism, primarily with antibiotics exhibiting activity against *C. difficile*[66,67]. Historically, metronidazole and oral vancomycin have been the mainstays of therapy for mild to moderate and severe CDI, respectively[68]. Metronidazole, a nitroimidazole derivative, inhibits DNA synthesis in susceptible organisms, including *C. difficile*, and has been recommended as the first-line therapy for initial episodes of CDI[69]. However, concerns regarding reduced efficacy and higher rates of recurrence have led to a shift in treatment paradigms towards oral vancomycin, a glycopeptide antibiotic with potent activity against *C. difficile*[70,71]. Current guidelines recommend oral vancomycin as the preferred agent for severe CDI, initial episodes in patients at high risk of complications, or those who fail to respond to metronidazole[70-72].

In recent years, fidaxomicin, a narrow-spectrum macrocyclic antibiotic, has emerged as a promising alternative for the treatment of CDI[73]. Fidaxomicin exerts bactericidal activity against *C. difficile* while preserving the gut microbiota due to its limited systemic absorption and high fecal concentrations[74]. Clinical trials have demonstrated non-inferiority of fidaxomicin compared to vancomycin in achieving clinical cure, with significantly lower rates of recurrence[75]. Consequently, fidaxomicin is recommended as a first-line therapy for initial CDI in certain patient populations, particularly those at high risk of recurrence or with documented or suspected hypervirulent strains[76].

Adjunctive therapies play a crucial role in augmenting the efficacy of antimicrobial agents and mitigating the inflammatory response associated with CDI. Among these, probiotics have garnered attention for their potential to restore microbial balance and suppress *C. difficile* colonization[77]. However, evidence supporting the efficacy of probiotics in preventing CDI recurrence remains inconclusive, and further research is warranted to delineate their role in clinical practice. Additionally, FMT has emerged as a highly effective therapeutic option for recurrent CDI, involving the transfer of fecal material from healthy donors to restore microbial diversity and enhance colonization resistance against *C. difficile* [78,79].

Despite advances in therapeutic strategies, the management of initial CDI remains challenging, necessitating a multifaceted approach tailored to individual patient characteristics and disease severity. Ongoing research aims to elucidate the optimal treatment regimens, refine adjunctive therapies, and explore novel therapeutic targets to improve clinical outcomes and reduce the burden of CDI on healthcare systems.

TREATMENT OF RECURRENT *C. DIFFICILE*

rCDI is described as new CDI within 8 weeks of the previous occurrence, and can be from reinfection of the same strain, or by a new strain. It is estimated that 15%-30% of individuals treated for CDI with antibiotics experience rCDI, and this value increases with subsequent occurrences[1]. Given this high instance of recurrence, it is important to explore the options for treatment, and how they differ from an initial infection. Restoring the balance of the gut microbiome is an avenue that many studies have explored for the treatment of rCDI, with FMT and oral microbiome therapeutics being at the forefront[80,81].

FMT involves the transfer of donor fecal material into the recipient's gastrointestinal tract to restore the gut microbiome [82]. Different routes exist for the transplantation, including nasogastric tubes, colonoscopies, and enemas. All of these options pose their own set of risks, and require careful exploration of the patient's individual requirements. There is also extensive donor criteria that must be met, including stool testing for common Gastrointestinal pathogens[83].

The IDSA has created guidelines that shape the treatment modalities for rCDI depending on the number of recurrences a patient has had. As of 2017, in the primary recurrence, vancomycin or fidaxomicin are the first line treatment options. On secondary or further recurrences, vancomycin +/-rifampin and fidaxomicin are still the antibiotic options, while FMT is used for individuals with three or more recurrences and have failed antibiotic therapy[84]. A study published by the New England Journal of Medicine indicated that individuals who received FMT, as compared to vancomycin, had better treatment outcomes, especially those individuals with multiple recurrences[85].

In addition to FMT, many studies are aimed at evaluating the efficacy of SER-109, an oral microbiome therapeutic that is composed of firmicutes spores that are hypothesized to compete with *C. difficile* for nutrients, influence bile-acid profiles to limit the recolonization of *C. difficile*, or both[85]. A randomized clinical trial performed to determine the efficacy of SER-109 following the appropriate antibiotic regimen concluded that there were significantly less individuals in the SER-109 trial group that had rCDIs as compared to the placebo group at weeks 4, 8, 12, and 24 of the study[85].

Prophylactic treatment modalities have also been studied and shown to prevent recurrence of CDI. BEZ is a human monoclonal antibody to the *C. difficile* TcdB, and has been FDA approved for the prevention of rCDI. Use of BEZ has been shown to be an effective prophylaxis agent while also decreasing hospital readmission, and increasing quality of life in those with rCDI[86].

EPISODE

Treatment modality

First recurrence: Vancomycin 125 mg orally 4 times a day for 10 days or Fidaxomicin 200 mg orally 2 times a day for 10 days. Adjunctive therapy: BEZ 10 mg/kg IV one time dose.

Second recurrence: Tapered or pulsed vancomycin regimen or Vancomycin 125 mg orally 4 times a day for 10 days, then rifaximin 400 mg three times daily for 20 days or Fidaxomicin 200 mg orally 2 times a day for 10 days. Adjunctive therapy: BEZ 10 mg/kg IV one time dose.

Third or more recurrence: Fecal microbiota transplant. Adjunctive therapy: BEZ 10 mg/kg IV one time dose (Table 1)[87].

BEZ

BEZ is a humanized monoclonal antibody IgG1 that binds to *C. difficile* TcdB, neutralizes the toxin and prevents damage to colonic cells. Currently BEZ is approved for the treatment of recurrent CDI in adults and is available in 1000 mg/40 mL vials. Reconstituted vials are diluted with 0.9% sodium chloride or 5% dextrose to reach a concentration between 1 to 10 mg/mL. The dose is administered according to the patient's body weight with a single dose at 10 mg/kg over 60 minutes up to treatment day 14[88,89].

The hallmark trials that brought BEZ to the market were the MODIFYI/II trials which were carried out in 30 countries over 300 sites consisting of over 2000 patients. Patients who received BEZ had a lower rate of CDI recurrence compared to the placebo received standard of care antibiotics after follow-up in 12 weeks. BEZ also was found to be beneficial compared to the placebo group with minimal side effects, with the number needed to treat being 10[90]. In the 12-month follow up of the MODIFY II trial conducted by Goldstein *et al*[91] the patients who received BEZ were followed after the 12 weeks, for 9 more months, the patients who received BEZ did not have CDIs in 12 months[91].

In a recent systematic review, BEZ has shown to be effective in all the studies in the prevention of CDIs[92]. A 2021 retrospective study carried out by Mody *et al*[92] showed BEZ was proven to reduce CDIs in patient populations with comorbidities including those with history of severe CDIs, age > 65 and patients who are immunocompromised[93]. BEZ has shown to have a good safety profile with the side effects being mild to moderate infusion reactions with rare cases of heart failure exacerbation in patients already diagnosed with the same[94]. Guidelines now recommend using BEZ for the prevention of CDI, including patients with history of multiple CDIs, recurrent CDIs and multiple comorbidities, marking a significant impact in treatment strategies[95].

BEZ faces significant challenges, including its lack of cost-effectiveness and the potential for exacerbating congestive heart failure in patients already diagnosed with the condition, as indicated by some studies[94,96].

FMT

FMT has emerged as an effective treatment for recurrent CDI. This procedure involves transplanting fecal bacteria from a

Table 1 Treatment of recurrent *Clostridium difficile* infection in adults

Episode	Treatment modality
First recurrence	Vancomycin 125 mg orally 4 times a day for 10 days
	Fidaxomicin 200 mg orally 2 times a day for 10 days
	Adjunctive therapy: Bezlotoxumab 10 mg/kg IV one time dose
Second recurrence	Tapered or pulsed vancomycin regimen
	Vancomycin 125 mg orally 4 times a day for 10 days, then rifaximin 400 mg three times daily for 20 days
	Fidaxomicin 200 mg orally 2 times a day for 10 days
	Adjunctive therapy: Bezlotoxumab 10 mg/kg IV one time dose
Third or more recurrence	Fecal microbiota transplant
	Adjunctive therapy: Bezlotoxumab 10 mg/kg IV one time dose

healthy donor to restore the recipient's gut microbiota, which helps in suppressing *C. difficile* by mechanisms such as inhibition of spore germination and vegetative growth, competition for nutrients, and activation of colonization resistance [97,98]

FMT is primarily indicated for patients with recurrent CDI who have failed standard antibiotic treatments. It is generally considered for patients with at least two episodes of CDIs who do not respond to antibiotics or experience frequent recurrences[99].

Recent studies have confirmed that FMT is highly effective for treating recurrent CDI, with success rates exceeding 80% in several trials. A systematic review and meta-analysis by Baunwall *et al*[100] demonstrated that FMT significantly improves clinical outcomes in recurrent CDI, with a higher success rate compared to standard antibiotic therapy[100]. Research has elucidated the mechanisms through which FMT exerts its effects. Khoruts *et al*[97] reviewed the role of microbiota restoration in preventing CDI recurrence, highlighting how FMT reintroduces a diverse microbial community that competes with *C. difficile* and restores gut homeostasis[98]. A study by Urbonas *et al*[101] provided long-term follow-up data showing that the benefits of FMT in CDI persist beyond 1 year, with sustained resolution of symptoms and reduced recurrence rates[101]. Studies have shown that the interplay between the microbiota of the donor and the recipient plays an important role in the efficacy of FMT[102]. This research aims to optimize patient selection and improve treatment efficacy.

Studies have shown that FMT has been proven to be beneficial in the treatment of recurrent CDIs in inflammatory bowel disease (IBD), which not only decrease the probability of CDIs but also improves symptoms of IBD[103]. New approaches to FMT, including alternative delivery methods and standardized protocols, are being explored. A study examined innovative techniques to enhance the efficacy and safety of FMT, such as encapsulated microbiota and refined donor screening processes[104]. FMT is generally safe, however, there are risks of transmission of ESBL and Shiga toxin producing E Coli. These pathogens were transmitted from asymptomatic donors who were carriers to immunocompetent as well as immunocompromised individuals, which proved to be fatal. An EIA was recommended for symptomatic donors, but the utility of EIA in asymptomatic carriers is still unclear[105].

PREVENTION OF *C. DIFFICILE*

Prevention of *C. difficile* can be categorized into prevention of the spread of *C. difficile* from health care providers, prevention of spread from the environment, and risk reduction once the patient is exposed to *C. difficile*[106]. Prevention of *C. difficile* requires numerous approaches simultaneously, as it has not been found that a single approach alone is effective in prevention[107]

Contact precautions and single rooms are recommended for patients with *C. difficile*, with moderate evidence for the use of gloves[106]. The use of handwashing with soap and water, as opposed to alcohol-based hand sanitizers followed by glove usage is currently recommended for healthcare workers when treating patients with *C. difficile*[108]. Although hand washing with soap and water does not kill *C. difficile* it does remove the *C. difficile* spores from the hands of the health care workers[109].

Another recommendation with moderate quality of evidence includes limiting antibiotic therapy to only when deemed necessary. Additionally, implementing an antimicrobial stewardship program has been shown to reduce the risk of *C. difficile* up to 50%[106]. Use of any antibiotic increases the risk of *C. difficile*, but specifically broad-spectrum cephalosporins and clindamycin are seen to increase the risk of infection[108]. The gut microbiome provides a defense against infection with *C. difficile* and the use of broad-spectrum antibiotics disrupts the gut microbiome, limiting this defense [110]. When narrow-spectrum agents are substituted appropriately the risk of acquiring *C. difficile* is less. As a result, if antibiotic use is deemed necessary it is recommended that appropriate narrow-spectrum antibiotics be used[108]. Avoiding unnecessary antibiotics is the most effective prevention of *C. difficile* presently[111].

In addition, because *C. difficile* spores persist in the environment and are resistant to detergents, the use of bleach and hydrogen peroxide to clean is recommended as they are sporicidal. It is recommended that rooms of patients with *C. difficile* are cleaned daily[108].

The *American Journal of Gastroenterology* recommends against the use of probiotics concurrent with the usage of antibiotics in the prevention of *C. difficile* There is little evidence backing the claim that probiotics improve dietary health [112].

Infection with *C. difficile* can be treated with Vancomycin or Metronidazole[113]. Although oral Vancomycin is an effective treatment for *C. difficile* further research must be done to assess its efficacy in prophylactic prevention of *C. difficile* as well as proper dosing, but meta-analysis has shown oral Vancomycin as promising for prophylactic treatment of *C. difficile*[114]. Fidoxamicin prophylaxis has also been studied and shown a decrease in CDI in patients undergoing hematopoietic stem cell transplantation when compared to a placebo, but further research must be done[115].

CHALLENGES AND FUTURE DIRECTION

In the modern era, with current lifestyles posing health hazards and a higher frequency of hospitalizations, there has been an increase in the incidence of *C. difficile*. Gut dysbiosis has been observed in patients with prolonged hospital stays, likely due to the fact that the diagnostic assays are time consuming, and innovation of rapid diagnostic tools are necessary in diagnosis. Patients in the critical care unit are treated aggressively with antimicrobials, making them susceptible to *C. difficile*[116]. A major hurdle in the treatment of *C. difficile* are asymptomatic carriers. There have been cases of asymptomatic carriers of *C. difficile* after a recent hospitalization. Children under the age of 2 years are also asymptomatic carriers because they lack the receptors for the toxin to bind[117,118]. In a recent study conducted by Curry *et al*[119] in 2023, 9.9 % of patients after recent hospitalizations became carriers of asymptomatic *C. difficile* and 13.4% were diagnosed with CDI[119]. Asymptomatic carriers may result in transmission of infections at a faster rate. Even though *C. difficile* is susceptible to vancomycin, there have been recent studies in Connecticut, showing the emergence of strains with resistance to vancomycin[120].

Fidaxomicin is an alternative to treat *C. difficile*, has very little resistance reported compared to vancomycin, however the use is limited due to the drug's cost[121]. There have been some case reports to suggest that the emergence of strains of *C. difficile are* resistant even to fidaxomicin[122]. Severe acute respiratory syndrome coronavirus 2 [coronavirus disease 2019 (COVID-19)] has had an adverse impact on patients with CDI and has shown to increase the risk of fulminant CDI in a recent study conducted by Duhan *et al*[123], which can be explained by the alteration of gut microbiome caused by COVID-19 at a molecular level. COVID-19 patients are treated empirically with antibiotics, which predisposes these patients to *C. difficile*. Providers should be mindful when treating COVID 19 patients with baricitinib as there is data predisposing them to fulminant CDI[123].

There have been recent advancements in the treatment of recurrent *C. difficile,* one of which is BEZ. Recent studies have shown that when BEZ is used along with the normal standard of care, it has shown to prevent recurrence of *C. difficile*, and should be considered in high risk patients irrespective of age[124]. Small studies have shown that in immunocompromised patients or transplant patients who are at a higher risk of CDI or complications have a reduced rate of recurrence of infection[125]. As mentioned before, FMT has been effective in the treatment of recurrent *C. difficile,* however, a study conducted by Porcari *et al*[126] has shown that FMT has shown to have high efficacy in the treatment of patients with IBD[126].

Several antibiotics like cadazolid, LFF571, ramoplanin, and surotomycin have been studied initially for the treatment of *C. difficile,* however have failed in the later trials[127]. Many trials are being conducted on various antibiotics including ridinilazole (ongoing Phase III), MGBBP3 (completed Phase II), CRS3123 (ongoing Phase II), DNV3837/DNV3681 (ongoing Phase II), and ibezapolstat (ongoing Phase II) for the treatment of *C. difficile*. Ridinazole has shown to be superior to vancomycin in the phase II trials with a higher sustained clinical response rate with lower recurrence in 30 days after the treatment[128].

A growing field in the treatment of *C. difficile* is the application of live biotherapeutic products (LBPs) which are non-vaccine live organisms used to treat and prevent CDI. In the past 2 years, the United States Food and Drug Administration approved 2 LBPs-al microbiota, live-jslm [Rebyota (RBL)], which is a rectally administered therapeutic and live fecal microbiota spores live-brpk [Vowst (VOS)] which are administered orally[129,130]. The CLOVER trial to develop an mRNA vaccine to prevent *C. difficile* is in the phase III stage. Another field of growing interest is fecal virome transplantation for achieving homeostasis of the gut microbiome and lytic phages to kill the bacteria. However, the data is very limited and more extensive studies need to be carried out[131].

CONCLUSION

Despite advancements in medical research, CDI continues to present significant challenges in clinical management. Through this review, compelling evidence suggests that tailored therapeutic approaches, including BEZ, can substantially reduce recurrence rates by up to 40% compared to standard care alone. Additionally, FMT demonstrates remarkable success rates exceeding 90% in refractory cases, offering a promising avenue for treatment. Complications such as TM and sepsis, affecting 3%-8% and 5%-30% of CDI cases respectively, underscore the critical importance of early recognition and intervention. Diagnostic advancements, notably PCR-based methods with sensitivity and specificity exceeding 90%, enhance accuracy in identifying CDI, facilitating timely treatment initiation. By synthesizing diverse insights and

empirical findings, this comprehensive review aims to empower clinicians with the knowledge necessary to mitigate CDI-associated risks and optimize patient outcomes. However, this review underscores lingering gaps in our understanding, emphasizing the imperative for further investigation into the long-term efficacy and potential adverse effects of emerging therapies like BEZ and FMT. Additionally, the complex interplay of factors shaping CDI pathogenesis, including the gut microbiome, host immune response, and environmental influences, warrants deeper exploration. By addressing these knowledge gaps, we can refine our approach to CDI management, ultimately improving patient outcomes and reducing associated risks.

FOOTNOTES

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MINIREVIEWS

Drugs used for pain management in gastrointestinal surgery and their implications

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Abstract

Pain is the predominant symptom troubling patients. Pain management is one of the most important aspects in the management of surgical patients leading to early recovery from surgical procedures or in patients with chronic diseases or malignancy. Various groups of drugs are used for dealing with this; however, they have their own implications in the form of adverse effects and dependence. In this article, we review the concerns of different pain-relieving medicines used postoperatively in gastrointestinal surgery and for malignant and chronic diseases.

Key Words: Acute pain; Acute post operative pain; Pain score; Pain after GI surgery; Analgesia; Spinal anaesthesia; Epidural anaesthesia; Intravenous anaesthesia; Regional anaesthesia; Pain management

Core Tip: Pain is the most common symptom encountered by patients and their physicians. In the present era, there has been a change in the understanding of pain, its causes, assessment and management. Patient education and preoperative intervention are an integral part of pain management. Post-operative pain management is also an integral part of the enhanced recovery after surgery protocols in today's era. Management of pain can be pharmacological or non-pharmacological.

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INTRODUCTION

Pain is the most common symptom with which patients usually present to the emergency room[1]. Previously, it was thought to be a subjective term that could only be quantified by the patient experiencing the pain. As the 20th century advanced, there has been a change in the understanding of pain, its causes, assessment and management. The International Association for the study of pain defines it as," An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[2]. Acute pain that was once thought to be of short duration is a more complex and unpleasant experience having cognitive, emotional and sensory response to tissue trauma caused after surgery[3], which is reported by nearly 80% people in the post-operative period. Most of these patients report moderate pain, and severe or extreme pain is reported by about 20%-40% patients[4,5]. There was a time when the surgeons were afraid to conduct surgeries because of the pain it caused patients, making them apprehensive, so much so that patients feared the scalpels and avoided the dreadful yet sometimes life-saving surgeries.

CHRONICLE OF PAIN MANAGEMENT

As modern scientific knowledge brought improvement in the surgical techniques, pain management also became an area of interest. For thousands of years hashish, mandrake, opium and alcohol have been used to produce analgesia during surgical procedures. In a failed attempt in 1845, Horace Wells brought to the limelight the use of Nitrous Oxide as an anaesthetic agent. William TH Warren successfully removed a soft tissue tumour without pain from a young man's neck in 1846, making use of Ether. Soon, chloroform and ether were being used worldwide for painless surgeries. William Halsted made use of regional anaesthesia to produce field blocks for painless surgery, which was followed by the development of spinal and epidural anaesthesia by 1920. Sodium Thiopental was used to produce a similar pain-free experience by 1934. The progress in pain management became more and more significant in the coming times, making surgery a painless and pleasant experience to the patients.

Despite the advances in this field and numerous studies showing the superiority of one approach over the other, pain management in surgical patients is still not absolute, but evolving[6,7]. Acute pain must subside once the obnoxious stimulus is stopped and healing occurs, but poorly managed pain can lead to loss of function, poor mobility & recovery, increased risk of post operative complications and chronicity. Evidence based studies have led to formulation of guidelines that have been periodically updated; the guidelines include preoperative planning and patient education and perioperative pain management using pharmacological and nonpharmacological methods, while emphasizing that pain management is a complex process with significant implications over the patient's quality of life[8]. Despite all the advancements in this field, the incidence of severe acute postoperative pain has remained unchanged over the last 30 years, at about 20%[9]. Opioid use for pain management has led to an opioid abuse epidemic such as chronic pancreatitis, malignancy *etc*, thus making it even more important to make use of alternative multiple modalities in pain management. This can include non-opioid medications, neuraxial analgesic techniques, and intravenous lignocaine. Besides this, minimally invasive techniques are supposed to cause less pain compared to traditional open surgery. But the studies have not produced any consistent results favouring a particular approach[10]. The World Health Organisation has developed an analgesic step ladder where non-opioid plus optional adjuvant is used for mild pain; weak opioid plus non-opioid and adjuvant analgesic is used for mild to moderate pain; a strong opioid plus non-opioid and adjuvant analgesic is used for moderate to severe pain. It advises to move one step up when pain is intense.

SEARCH STRATEGY

The authors performed an online search on PubMed, Google Scholar and Cochrane Database for relevant articles. Further, the articles' reference lists were also searched for additional appropriate studies. The keywords used for searching were "post operative pain"; "pain management"; "Analgesia"; "acute pain"; "pain score"; "pain after GI surgery"; "spinal anaesthesia"; "epidural anaesthesia"; "intra venous anaesthesia"; "regional anaesthesia". The search

was limited to publications in English. All authors agreed that the articles selected for the minireview were relevant.

PATHOPHYSIOLOGY OF PAIN

The central nervous system receives the information about tissue damage after the nociceptors are activated due to trauma[11]. The classical mechanism of pain involves conversion of the energy from noxious stimulus into sensory receptors called signal transduction[11]. These signals are then transmitted to the spinal cord and brain where these signals are perceived as pain[12]. This results in modulation of the nociceptive response at the spinal cord level through the inhibitory or facilitatory response from the brain[13]. The neurotransmitters released, such as enkephalins and endorphins, inhibit the release of neurotransmitters involved in pain transmission. The pharmacological agents act at these different steps to produce the analgesic effects[14]. Pain management should begin before surgery with a thorough assessment of the patients, allowing the optimal pain management techniques to be used and to help to alleviate the patient's anxiety and fears about post-operative pain, as some of them might be using opioids preoperatively for complex pain syndromes[15].

PAIN ASSESSMENT

Thorough patient education and perioperative intervention (Tables 1 and 2) allows advanced planning, especially for patients with comorbidities, which could subject the patients to significant side effects of the drugs used[16]. It allays the fear of post-operative pain in the patient and allows healthcare professionals to predict the types of patients who are about to have significant pain problems after surgery. Young females who smoke and have anxiety or depression and people already using opioids before surgery are particularly at risk of having significant post-operative pain[17]. Major emergency abdominal surgeries are also a risk factor for significant post-operative pain[18]. Studies have demonstrated that all of these factors are associated with persistent post-operative pain[19].

Underassessment of the pain has been found to be the leading cause of undertreatment of pain. Therefore, the American Pain Society has included, "Pain as the 5th vital sign"[20,21]. Thus, it is as important to assess pain as the other four vital signs. Pain has also been included as the 5th vital sign in the National Pain Management Strategy by the Veterans Health Administration[22]. Various one-dimensional and multidimensional tools for pain assessment have been developed to be used in different situations. One-dimensional tools like Numeric Rating Scale, Visual Analog Scale and Categorical Scales using simple visual or verbal descriptors of pain are good for assessing the acute pain of fixed origins like post-operative pain[23]. Multidimensional tools like Initial Pain Assessment tool, Brief Pain Inventory[24] and McGill Pain Questionnaire are important tools for assessing more complex and chronic pain[25]. Clinically Aligned Pain Assessment includes comfort, change in pain, pain control, functioning and sleep, and thus can be used in the perioperative period. Pain assessment in mentally disabled people, people suffering from dementia and those unable to verbalize can be assessed with Pain in Advanced Dementia, Dolopus-2, Critical care Pain Observation Tool and Behavioural Pain Scale[26-28]. Patients should be continuously monitored for any pain worse than mild, which needs priority treatment.

PHARMACOLOGIC TREATMENT

Post-operative pain management is an integral part of the enhanced recovery after surgery (ERAS) protocols. Traditionally for abdominal surgery, Epidural Analgesia (EA) or Intravenous Patient-Controlled Analgesia (IVPCA) based on opioids has been used. It has good pain control but has a significant drug associated morbidity, which hampers the achievement of the goal of early Drinking, Eating and Moving (DrEaMing)[29]. There is no single drug with the ideal pain management properties, hence a multimodal approach towards reaching a perfect analgesia is favoured. It involves the use of various drugs acting at different levels of the pain pathway to achieve better control[30]. As in evidence-based PROcedure-SPECific Pain ManagemenT (PROSPECT) guidelines, these different drugs can be used to effectively lower the total analgesic dose and the associated side effects[31].

Pain treatment can be pharmacological or nonpharmacological in the multimodal treatment strategy[32]. Commonly used pharmacological agents are as follows:

Non opioid analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and other salicylic acid derivatives, work by inhibiting prostaglandin production responsible for pain and inflammation[33]. They could be selective cyclo-oxygenase-2 inhibitors like celecoxib or, nonspecific cyclooxygenase inhibitors like aspirin, Ibuprofen and Naproxen[34-36]. The major concerns are renal toxicity and gastritis. Paracetamol is another NSAID used for mild to moderate pain management. It has a significant opioid sparing effect in multimodal analgesia approach. When used intravenously for pain prophylaxis, it lowers the incidence of pain-associated nausea and vomiting. It has been proven safe at the therapeutic dosage in different studies[37,38]. A major concern is hepatotoxicity at higher dosages[39].

Table 1 Preoperative assessment and education of patient[20]

Establish good relationship with patients' relatives
Take pain history
Teach patient about pain assessment and management plan
Inspect concerns and handle misinterpretations regarding pain medications, adverse effects and dependence
Create a plan for postoperative analgesia in alliance with patient depending on type of surgery, anticipated severity of postoperative pain, co morbidities, the risk-benefit and expense of techniques, patient's preferences
Patient selected appropriate pain assessment tool (*e.g.*, Numeric Rating Scale, Visual Analog Scale)
Mention the patient's selected pain assessment tool
Teach patient and relatives about their responsibilities

Table 2 Postoperative assessment and education of patient[20,21]

Examine multiple indicators of pain, including (1) Patient perceptions; (2) Cognitive attempts to address pain; (3) Behavioural responses (*e.g.*, reduced mobility, sleeplessness, anxiety, depression); and (4) Physiological changes (vital signs: Tachycardia, hypertension)
Accept patients self-report, and only replace behaviour and/or physiological changes when he is unable to communicate
Assess pain at rest and during activity (*e.g.*, moving, coughing)
Measure pain frequently during the early post operative period: At regular intervals, consistent with type of surgery and severity
Document pain intensity and its response to any interventions and adverse effects
Promptly assess instances of sudden intense pain
Think of reasons or any disparities between patients' self-report of pain and behaviour. As patient may be denying pain due to casualness or worry of inadequate pain relief
Special attention to special populations, and be aware of hurdles of effective communication (*e.g.*, language issues, mental, cognitive or hearing impairments, *etc*)
Revisit the management plan, if needed
Before discharging patient, review interventions implied and their efficiency; give specific and detailed discharge instructions for pain management at home

Opioid analgesics

Mu opioid agonists (morphine like agonists) and agonist-antagonist opioids are the cornerstone of treating moderate to severe pain. They can be further classified as natural, synthetic or semi-synthetic opioids. Many people report opioid-related adverse effects (ORADE) in the immediate post-operative period, like dizziness, vomiting, nausea, constipation, dry mouth, dependence, pruritus, *etc.* Development of ORADE leads to a prolonged hospital stay. When drugs are prescribed beyond the recommended post-operative period, they can be misused and sold to other people[40]. These patients need continuous monitoring as they are liable to develop respiratory depression, drug tolerance, drug dependence and addiction when used over a long period. Patients who have a preoperative history of prolonged pain, use of benzodiazepines, anxious personality and history of drug addiction are more liable to develop drug dependence and addiction[41]. Such types of patients are liable to have withdrawal effects in the post-operative period so they should be maintained on minimal opioid dosage and supplemented with other types of analgesics and use of regional anaesthesia techniques[42].

Adjuvant analgesics or co-analgesics include a wide variety of drugs mainly used for purposes other than pain relief, but with some analgesic properties. Commonly used ones are gabapantenoids, magnesium, lignocaine IV, Ketamine, antidepressants like Selective Serotonin Reuptake Inhibitors and anti-epileptic drugs[32].

Ketamine is a dissociative anaesthetic, which when used for acute pain relief in perioperative settings may reduce morphine consumption and pain intensity[43]. It prevents the development of persistent post-surgical pain in patients. Although it is not a part of the ERAS protocols, it may reduce morphine consumption when used in multimodal analgesia [44]. Adverse effects include amnesia, psychosis, hypertension, depression, impaired coordination and judgement, depression, respiratory complications, *etc.*

Gabapantenoids act on the ascending as well as descending pathway of pain perception by decreasing nociception[45]. They have been found to be effective in post-operative pain management and have a morphine sparing effect in multimodal analgesia[43,46]. They prevent the development of persistent post-surgical pain but they have an abuse potential and can lead to addiction and death. Various other side effects include ataxia, angioedema, suicidal tendency, viral infections, nystagmus, constipation, weight gain, *etc.* They should be used with caution in patients with previous history of drug abuse or addiction[47].

Alpha-2 agonists

Drugs like Clonidine and Dexmedetomidine can be used to decrease opiate use in the perioperative period either orally, intravenously, intrathecally, or as a transdermal patch[48]. When they are used for nerve blocks, they produce prolonged analgesic effect, but they are associated with hypotension and sedation. Therefore, patients require strict perioperative monitoring when these drugs are used[49].

Lignocaine infusion

Although the current ERAS guidelines included intravenous lignocaine infusion for post-operative pain relief in colorectal surgery, there has not been sufficient evidence to support this practice anymore[50]. Studies have found insufficient evidence that it helps in post-operative pain, ileus, nausea or vomiting[51].

Magnesium

Intravenous magnesium has been found to be useful in post-operative pain management and has a morphine sparing effect under multimodal post-operative analgesia protocols[52]. It has been demonstrated to prolong the effect of nerve blocks and spinal anaesthesia[53].

Neuraxial blocks

EA uses local anaesthetics along with adjuncts, such as morphine, buprenorphine, tramadol, fentanyl, hydroxymorphine, clonidine, dexmedetomidine or diamorphine. Drugs like clonidine and dexmedetomidine prolong the effect of the nerve block[54]. EA provides better analgesia after GI surgery with low incidence of ileus, pulmonary complications and analgesic requirements. It improves ileus and promotes food tolerance by reducing nausea and vomiting, thus helping the patient to achieve an early state of DrEaMing[55]. EA is associated with high failure rate as compared to IVPCA and has a high complication rates like hematoma formation, hypotension, permanent harm in about 17.4 per 100000 patients with death reported in about 6.1 per 100000 patients[56,57]. ERAS guidelines also support the use of EA in esophagectomy and colorectal surgery[58,59].

Intrathecal analgesia

A process in which the local anaesthetic agent, sometimes mixed with adjuncts, is instilled into the subarachnoid space to produce anaesthetic/analgesic effect, which can last up to 24 hours. It has high efficacy and a low complication rate compared to EA with permanent damage in about 2.2 per 100000 and death in about 1.2 per 100000 patients[57]. It reduces the opioid consumption and has low pain scores in laparoscopic colorectal surgery[58]. It can lead to respiratory depression, hence will require strict monitoring. It has been included in the ERAS protocols for colorectal surgery[60].

Abdominal wall blocks

They provide analgesia in abdominal surgery. Previously blind techniques were used but now ultrasonogram (USG) guidance has increased their popularity. They avoid the adverse effects of epidural and spinal analgesia like hypotension, motor block and the risk of neurological damage. USG should eliminate the complications, but studies have failed to demonstrate this[61]. They could be of particular importance when the neuraxial blockade is contraindicated like in sepsis, coagulopathy, preexisting neurological deficit or when the patients decide against it. Catheters for infusion can be used to prolong the blockade.

Transversus Abdominis Plane block (TAP) can be performed blindly but USG guidance increases the precision (Figure 1A and B). It can be used in a wide variety of surgeries including abdominal, urological, gynaecological, and obstetric surgeries. It has the opioid sparing effect in multimodal analgesic approach[62]. It blocks the T7-L1 nerves. The subcostal TAP block aims to block the lower thoracic nerves including T6-T9. A study has found the USG-guided posterior TAP block to be superior compared to the lateral TAP block in lower abdomen incisions[63].

Quadratus lumborum block: USG-guided quadratus lumborum block has been used in providing analgesia in midline laparotomy and laparoscopic procedures. It is a newer technique about which there is little evidence about efficacy in abdominal surgery[64].

Transversalis fascia plane: It blocks the lateral cutaneous branches of T12-L1, which are commonly missed by the TAP block. It has been successfully used in open appendectomy and inguinal hernia surgeries[65].

Erector Spinae Plane block: ESP is a new technique where the LA is injected around the tip of T5 transverse process level depositing the drug deep to the erector spinae muscle. It can have analgesic effect in laparotomies. Recently it has been reported to be used successfully in laparoscopic ventral hernia repair[66].

USG guided blocks are supposed to be safe, as the needle tip can be directly visualised while injecting the drug, but studies have found peritoneal breech while the needle tip was being visualised during the attempt to infiltrate around the nerve bundles. Thus, the needle should aim for the fascial planes rather than the nerve bundles. Systemic LA toxicity is a concern due to a large volume of the drug being used to infiltrate. The abdomen is well vascularised, so absorption is fast. Thus, less cardiotoxic alternatives should be used[67].

Nonpharmacological techniques

They have been used successfully for the management of chronic pain but recently they have been used in the acute postoperative period also. Cognitive behavioural therapy distraction techniques like music, aromatherapy, canine therapy and virtual reality have been used effectively in perioperative pain management. They decrease anxiety and help the patients in self-management[9,67]. These measures can be an area of future research for developing better methods of

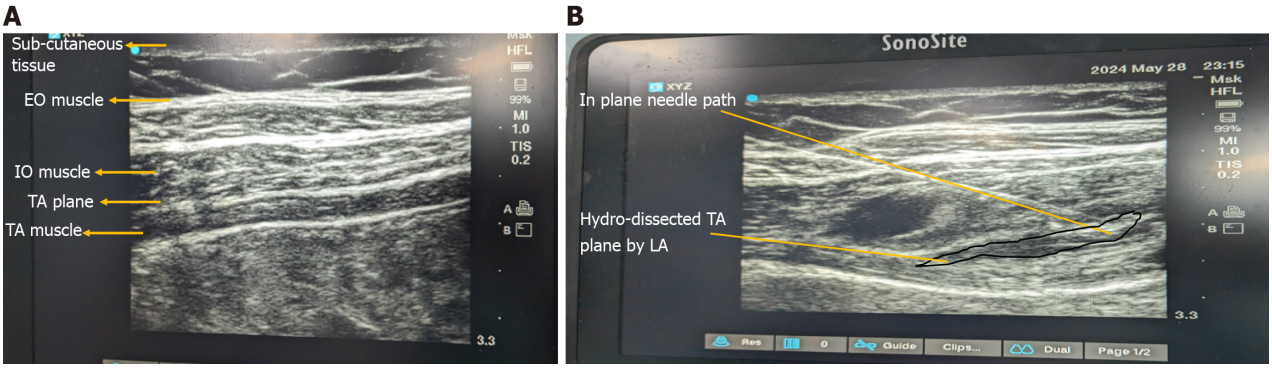

Figure 1 Transversus abdominis plane block can be performed blindly but ultrasonogram guidance increases precision. A: Ultrasonogram (USG) anatomy of abdominis plane block (TAP) block (arrows); B: USG-guided TAP block view (arrows). EO: External oblique; IO: Internal oblique; LA: Local anaesthetic; TA: Transversus abdominis.

pain relief.

CONCLUSION

Pain is the main symptom troubling patients and its management is one of the most important aspect for better outcomes and early recovery after surgery. Numerous drugs and procedures are used for the purpose of managing pain. The World Health Organisation has advocated simple and valuable use of analgesic step ladder for pain management. However, despite advances in this field and various studies, pain management in surgical patients is still not absolute and is still evolving.

FOOTNOTES

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MINIREVIEWS

Downstaging of advanced hepatocellular carcinoma followed by liver transplantation using immune checkpoint inhibitors: Where do we stand?

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Abstract

Liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) and chronic liver disease (CLD) is limited by factors such as tumor size, number, portal venous or hepatic venous invasion and extrahepatic disease. Although previously established criteria, such as Milan or UCSF, have been relaxed globally to accommodate more potential recipients with comparable 5-year outcomes, there is still a subset of the population that has advanced HCC with or without portal vein tumor thrombosis without detectable extrahepatic spread who do not qualify or are unable to be downstaged by conventional methods and do not qualify for liver transplantation. Immune checkpoint inhibitors (ICI) such as atezolizumab, pembrolizumab, or nivolumab have given hope to this group of patients. We completed a comprehensive literature review using PubMed, Google Scholar, reference citation analysis, and CrossRef. The search utilized keywords such as 'liver transplant', 'HCC', 'hepatocellular carcinoma', 'immune checkpoint inhibitors', 'ICI', 'atezolizumab', and 'nivolumab'. Several case reports have documented successful downstaging of HCC using the atezolizumab/bevacizumab combination prior to LT, with acceptable early outcomes comparable to other criteria. Adverse effects of ICI have also been reported during the perioperative period. In such cases, a 1.5-month interval between ICI therapy and LT has been suggested. Overall, the results of downstaging using combination immunotherapy were encouraging and promising. Early reports suggested a potential ray of hope for patients with CLD and advanced HCC, especially those with multifocal HCC or branch portal venous tumor thrombosis. However, prospective studies and further experience will reveal the optimal dosage, duration, and timing prior to LT and evaluate both short- and long-term outcomes in terms of rejection, infection, recurrence rates, and survival.

Key Words: Hepatocellular carcinoma; Liver transplant; Downstaging; Atezolizumab; Nivolumab; Immune checkpoint inhibitors

Core Tip: The advent of immune checkpoint inhibitors as a downstaging therapy has been followed with great interest since the results of the IMBRAVE study, especially for multifocal hepatocellular carcinoma beyond criteria and certain cases with portal vein tumor thrombosis. Multiple case reports have shown benefit but with a degree of caution. Our review aims to identify the key points and recommendations for the safe usage of these life-saving immunomodulators in the setting of liver transplantation using the current available literature.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is a leading cause of cancer-related deaths globally, especially in patients with chronic liver disease[1,2]. Liver transplantation (LT) is considered a curative treatment for HCC because it provides a definitive solution for both malignant liver tumors and the underlying liver diseases. However, the eligibility of liver transplantation has been strictly regulated by several criteria that ensure patient safety, such as tumor size, number of nodules, vascular invasion, and the absence of extrahepatic disease[3]. The Milan criteria are the pioneering guidelines and serve as the basis for the selecting LT candidates, while the UCSF criteria are the expanded version of the Milan criteria, aimed at including more patients without significantly compromising outcomes.

Despite this expansion, a distinct subset of patients, particularly those with portal vein tumor thrombosis or multinodular HCC, have been unable to receive LT. The grim prognosis of such patients and the aggressive nature of the disease make conventional downstaging therapies infeasible. Transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) are examples of locoregional therapies that downsize HCC; however, the extent of the disease in these patients hinders the efficacy of such therapies[4,5].

Recent advancements in systemic therapy for HCC have introduced new possibilities for the downstaging of advanced HCC, particularly through immunotherapy. This includes immune checkpoint inhibitors (ICI) such as atezolizumab, a programmed cell death ligand 1 (PD-1/PD-L1) inhibitor, and bevacizumab, a vascular endothelial growth factor inhibitor [6,7]. The combination of atezolizumab and bevacizumab has become the new standard of care and has shown significant benefits for overall survival[8].

Although the advent of ICIs has provided a novel approach for advanced HCC management, there is limited evidence and no robust guidelines regarding the use of ICIs to downsize advanced HCC to meet LT parameters. Pre-transplant downstaging with ICIs awaits further evidence for approval; however, there is anecdotal evidence of an ICI-induced complete pathological response before LT[9]. As shown in Figure 1, the presence of ICI [antibodies against cytotoxic T-lymphocyte associated protein 4 (CTLA-4), PD-1/PD-L1] in the chronic inflammatory or cirrhotic microenvironment has been demonstrated to establish immune exhaustion in HCC. The blockade of T-cell receptor (TCR) signaling or downstream signaling pathways of TCR impairs cytokine production, proliferative capacity, and antigen-induced killing of tumor cells by exhausted T cells. Furthermore, inhibition of TCR signaling with the major histocompatibility complex further optimizes host tumor growth. Immune exhaustion in HCC is primarily driven by the PD1/PDL1 pathway and CTLA-4 signaling[10]. In HCC, targeting these pathways through immune checkpoint inhibition, specifically blocking PDL1 and CTLA-4 increases the antitumor reaction against tumor cells, leading to significant downstaging.

This systematic review aimed to evaluate the current evidence regarding the use of ICIs for downstaging advanced HCC prior to LT. We analyzed the outcomes, safety, and challenges associated with this therapeutic approach, providing insights into its potential role in expanding eligibility for LT among patients with advanced HCC. By synthesizing data from clinical studies, case reports, and real-world experiences, this review seeks to inform future research directions and clinical practices for managing advanced HCC with ICIs.

SEARCH STRATEGY

A comprehensive literature search was conducted using PubMed, Google Scholar, and CrossRef to gather relevant studies on the use of ICIs for downstaging advanced HCC before LT. The search terms used were 'liver transplant', 'HCC', 'hepatocellular carcinoma', 'immune checkpoint inhibitors', 'ICI', 'atezolizumab', and 'nivolumab'. The search was limited to the articles published in English between January 2010 and May 2024. The reference lists of the identified

articles were also reviewed to ensure the inclusion of other relevant studies.

INCLUSION AND EXCLUSION CRITERIA

Studies were included in the review if they met the following criteria: (1) Reported on the use of ICIs for downstaging advanced HCC; (2) Included patients who underwent LT following ICI therapy; (3) Data on clinical outcomes such as tumor response, adverse effects, and post-transplant outcomes; and (4) Included case reports, case series, clinical trials, and observational studies.

Studies were excluded if they: (1) Were neither published in nor translated into English; (2) Did not provide sufficient details on the outcomes of ICI therapy; and (3) Were reviews, editorials, or opinion pieces without original data.

DATA EXTRACTION AND MANAGEMENT

Data extraction was performed independently by two reviewers. The following information was collected from each study. Study design and setting. Patient demographics and baseline characteristics. Details of ICI therapy, including the agents used, dosing, and duration. Downstaging outcomes, including tumor response rates and time to response. Adverse effects of ICI therapy, particularly immune-related adverse events. Details of liver transplantation, including the timing of post-ICI therapy, surgical outcomes, and post-transplant complications. Long-term outcomes, including recurrence rates, rejection episodes, and overall survival.

Discrepancies in data extraction were resolved through discussion and consensus between the reviewers.

QUALITY ASSESSMENT

The quality of the included studies was assessed using criteria adapted from the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for clinical trials. The following factors were considered: Selection bias: The representativeness of the study population. Comparability: Adjusting for confounding variables. Outcome assessment: Objective measurement of outcomes and follow-up duration. Reporting bias: Completeness and transparency of reporting.

DATA SYNTHESIS AND ANALYSIS

Narrative synthesis was conducted because of the heterogeneity of the included studies in terms of the study design, patient populations, and outcomes reported. Descriptive statistics were used to summarize the baseline characteristics of the study population, treatment protocols, and clinical outcomes. The key findings are tabulated and discussed in the context of the existing literature.

For quantitative outcomes, such as tumor response rates and survival data, the results were pooled using a random-effects model when appropriate. The heterogeneity of the pooled studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Sensitivity analyses were performed to explore the impact of study quality and other potential sources of heterogeneity on the pooled estimates.

ETHICAL CONSIDERATIONS

As this study involved a systematic review of published literature, no ethical approval was required. Ethical standards were maintained by accurately representing the findings of the included studies and acknowledging all sources.

Following this rigorous methodological approach, we aimed to provide a comprehensive and reliable synthesis of the current evidence regarding the use of ICIs for downstaging advanced HCC before LT, addressing both the potential benefits and challenges associated with this therapeutic strategy.

RESULTS

Eight studies with different designs, patient populations, and clinical settings were included in this systematic review. These studies provide insights into the use of ICIs for the downstaging of advanced HCC before LT (Table 1). The reviewed studies demonstrate that ICIs can significantly downstage advanced HCC, making patients eligible for LT. Tabrizian *et al*[11] reported on nine patients treated with nivolumab before LT, where the majority experienced substantial tumor necrosis, facilitating successful transplantation without severe allograft rejection or tumor recurrence. Chen *et al*[12] described a case in which toripalimab therapy was administered pre-transplantation, showing initial tumor

Table 1 Studies analysed and their key findings

Ref.	Design	Sample size	ICIs used	Key findings
Tabrizian *et al*[11]	Case series	9	Nivolumab	Significant PD-L1 expression in donor allograft may indicate a subclinical all-immune response and identify patients at high risk of rejection
Chen *et al*[12]	Case report	1	Toripalimab	The effect of PD-1 antibody leads to the failure of the graft's attempt to achieve "immune escape" by expressing PD-L1, which results in fatal acute rejection response
Nordness *et al*[13]	Case report	1	Nivolumab	Profound caution is needed when using nivolumab in patients with HCC who are either still awaiting or have previously undergone solid organ transplant. It is unclear given their mechanism of action, if a defined waiting period would be helpful before transplant
Kumar *et al*[14]	Case report	1	Atezolizumab, Bevacizumab	Atezolizumab plus bevacizumab effective as downstaging therapy for liver transplantation in HCC with PVTT
Aby *et al*[15]	Case report	1	Nivolumab	In carefully selected patients, ICI may serve as a bridge to LT
Chouik *et al*[16]	Case report	1	Atezolizumab + Bevacizumab	Complete clinical remission achieved; successful LT with no recurrence at 10-month follow-up
Kuo *et al*[17]	Case series	4	Atezolizumab, Nivolumab, Pembrolizumab	Safe washout period of 42 days recommended for LT following ICI therapy
Schnickel *et al*[18]	Case Series	5	Nivolumab	Pretransplant use of ICIs, particularly within 90 days of LT, was associated with biopsy-proven acute cellular rejection and immune-mediated hepaticnecrosis

ICI: Immune checkpoint inhibitors; PD-L1: Programmed death ligand 1; HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombosis; LT: Liver transplantation.

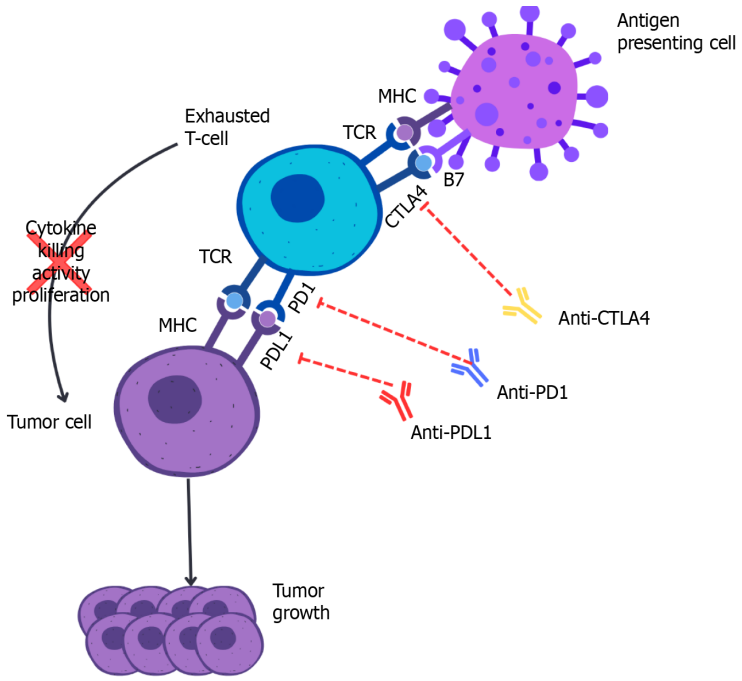

Figure 1 Mechanism of action of immune checkpoint inhibitors for downstaging of hepatocellular carcinoma. TCR: T-Cell Receptor; MHC: Major histocompatibility complex; PD1: Programmed cell death protein 1; PDL1: Programmed death ligand 1; CTLA4: Cytotoxic T-Lymphocyte associated protein 4.

control but ultimately resulting in fatal acute hepatic necrosis post-transplantation due to immune-related adverse events. Nordness *et al*[13] provided evidence of the effectiveness of nivolumab in downstaging HCC, with patients remaining within the Milan criteria for one year before LT. Kumar *et al*[14] reported the first case of successful downstaging using a combination of atezolizumab and bevacizumab in a patient with HCC and portal vein tumor thrombosis (PVTT). This combination therapy resulted in significant tumor shrinkage, enabling the patient to qualify for LT. This case underscores the potential of combining ICIs with antiangiogenic agents to enhance downstaging outcomes. Aby and Lake highlighted a case in which nivolumab successfully downstaged HCC, allowing for LT, despite the patient initially being outside the standard transplant criteria owing to PVTT[15]. Chouik *et al*[16] presented a compelling case in which a patient achieved

complete clinical remission of advanced HCC with a combination of atezolizumab and bevacizumab, followed by successful LT. This case illustrates the potential of ICIs to achieve complete tumor regression, providing a feasible pathway to curative surgery.

The time interval between the last dose of ICIs and LT is crucial for minimizing immune-related complications. Tabrizian *et al*[11] recommended a washout period of at least 30 days because their findings showed that patients receiving ICIs within this timeframe experienced no severe allograft rejection. Nordness *et al*[13] suggested that the half-life of nivolumab (approximately 25 days) necessitates careful consideration and proposed that ICIs should not be administered within six weeks before LT activation owing to the risk of prolonged immune effects. Aby and Lake reported successful LT with nivolumab cessation 16 days prior to the procedure but emphasized that individual risk factors and immune responses must guide the timing[15]. Kuo *et al*[17] conducted a study to optimize the washout period for ICIs, including atezolizumab, nivolumab, and pembrolizumab. They found that a washout period of at least four to six weeks was effective in minimizing postoperative complications and improving outcomes. This study supports the importance of individualized timing in balancing therapeutic benefits with safety.

The reviewed studies indicate promising survival outcomes for patients treated with ICIs before LT. Tabrizian *et al*[11] observed no deaths or tumor recurrences at a median follow-up of 16 months post-transplant, underscoring the potential of ICIs to improve long-term survival. Aby and Lake[15] reported that their patient remained well with normal liver function 16 months post-LT, suggesting that ICIs can contribute to favorable long-term outcomes when managed appropriately. Nordness *et al*[13] cautioned that the use of nivolumab can lead to fatal outcomes in some cases, highlighting the need for careful patient selection and monitoring. Chen *et al*[12] demonstrated that although initial tumor control was achieved, the fatal outcome in their case emphasized a balance between treatment benefits and risks. Schnickel *et al*[18] reported that none of the patients who underwent LT more than three months after the last dose of nivolumab had biopsy-proven acute cellular rejection, highlighting the importance of the interval between ICI therapy and LT in optimizing outcomes. Overall, these studies suggest that when used judiciously, ICIs can enhance the survival rates of patients with advanced HCC undergoing LT.

The use of ICIs in a pre-transplant setting for HCC is associated with significant complications, primarily immune-related adverse events (irAEs). Chen *et al*[12] reported a case of fatal acute hepatic necrosis caused by toripalimab-induced immune rejection post-LT, highlighting the severe risks involved. Nordness *et al*[13] documented a fatal outcome following pre-transplant nivolumab use, reinforcing the need for extreme caution and careful patient selection. Tabrizian *et al*[11] noted that although there were no severe allograft rejections in their cohort, one patient experienced mild acute rejection, which was manageable with increased immunosuppression. Aby and Lake[15] reported early T cell–mediated rejection in a patient who was successfully treated with high-dose steroids and thymoglobulin, indicating that prompt management of complications can lead to positive outcomes. These studies collectively underscore the importance of vigilant monitoring and aggressive management of irAEs to mitigate the risks associated with ICI therapy in patients awaiting liver transplantation.

The selection of patients for ICI therapy before LT is critical for optimizing outcomes and minimizing risks. Tabrizian *et al*[11] emphasized the importance of identifying patients who could potentially benefit from ICIs without a significant risk of severe immune-related adverse events. They highlighted that patients initially outside the Milan criteria due to tumor burden or vascular invasion could still be eligible for LT following effective downstaging with ICIs. Chen *et al*[12] discussed the need for a thorough pretreatment evaluation to identify candidates who can tolerate ICIs and benefit from their tumor-reducing effects without experiencing severe complications.

Nordness *et al*[13] underscored the necessity of individualized patient assessment, including detailed evaluations of tumor characteristics, liver function, and overall health, to ensure that the benefits of ICI therapy outweigh the associated risks. Their findings suggested that patients with significant tumor burden but otherwise stable liver function could be ideal candidates for ICI therapy as a bridge to LT. Aby and Lake[15] highlighted that patients with complex HCC, such as those with malignant PVTT, could still be considered for ICI therapy if they demonstrated a good response to initial treatments and maintained overall health stability.

Overall, careful patient selection based on comprehensive clinical evaluations and stringent criteria is essential for maximizing the efficacy and safety of ICI therapy in pre-transplant settings. This approach helps identify patients most likely to benefit from ICIs while minimizing the risk of severe complications, thereby improving the overall outcomes for patients with advanced HCC awaiting LT.

DISCUSSION

This systematic review synthesizes data from eight key studies examining the use of ICIs for downstaging advanced HCC prior to LT. The findings from these studies demonstrate the significant potential of ICIs, particularly when used in combination with agents such as bevacizumab, to effectively reduce tumor burden in patients with advanced HCC. This reduction in tumor size and extent has enabled patients who were previously deemed ineligible for LT because of extensive disease to become candidates for transplantation.

The inclusion of ICIs in pre-transplant treatment regimens represents a paradigm shift in the management of advanced HCC. Traditional downstaging methods, such as TACE and RFA, have shown limited success in patients with extensive disease. ICIs offer a novel therapeutic avenue that leverages the immune system to target and destroy cancer cells, thereby achieving significant tumor regression. The reviewed studies highlighted the transformative impact of ICIs on the treatment landscape of advanced HCC. For instance, Tabrizian *et al*[11 and Nordness *et al*[13] provided compelling evidence of tumor necrosis and successful downstaging, allowing subsequent LT without severe complications.

Moreover, the studies underscore the importance of patient selection and the timing of therapy cessation to maximize benefits and minimize risks.

ICIs have demonstrated substantial efficacy in achieving meaningful tumor regression, thereby facilitating successful LT in patients with advanced HCC. This effectiveness is crucial, as it allows patients with extensive disease to become eligible for LT. For instance, Tabrizian *et al*[11] reported significant tumor necrosis with nivolumab, enabling LT without severe complications. Similarly, the combination of ICIs with agents such as bevacizumab has been shown to enhance these outcomes by leveraging both immune activation and anti-angiogenesis mechanisms, providing a dual attack on tumor growth and vascular support. The effectiveness of ICIs in downstaging HCC is a critical advancement in this field. ICIs such as nivolumab and toripalimab have shown significant tumor reduction, which is pivotal for enabling LT in patients who were previously deemed ineligible owing to extensive tumor burden. The combination of ICIs with bevacizumab has been particularly noteworthy, as it not only enhances tumor reduction but also targets the vascular support of the tumor, making it more feasible for patients to undergo LT.

Determining the optimal timing for LT post-ICI therapy is critical for minimizing the risk of irAEs. An appropriate washout period between the last dose of ICIs and LT can mitigate perioperative risks and ensure patient safety. The reviewed studies suggested varying washout periods; however, a personalized assessment based on patient-specific factors is crucial. Kuo *et al*[17] recommended a washout period of at least 30 days and observed no severe allograft rejection within this timeframe. In contrast, Nordness *et al*[13] suggested avoiding ICI use within six weeks before LT activation due to the prolonged immune effects of nivolumab. Fisher *et al*[19] emphasized the need for individualized timing based on patient-specific factors. These insights suggest that while general recommendations can be made, personalized assessment is crucial for determining the appropriate washout period. The timing between the last dose of ICIs and LT is essential to minimize immune-related complications. Ensuring an adequate washout period is vital for balancing the therapeutic benefits of ICIs with the safety requirements of LT. Studies have suggested washout periods ranging from 16 days to several weeks, with personalized assessments being crucial for determining the most appropriate interval for each patient[11,17].

ICIs have shown the potential to significantly improve long-term survival outcomes in patients treated before LT. By facilitating significant tumor regression and enabling LT, ICIs can extend survival rates in patients with advanced HCC who would otherwise have limited treatment options. Studies have reported no deaths or tumor recurrences at a median follow-up of 16 months post-transplantation, highlighting the potential of ICIs to enhance long-term survival[11]. This suggests that when used judiciously and with appropriate patient management, ICIs can significantly improve survival rates for patients with advanced HCC undergoing LT who would otherwise have limited treatment options. The potential of ICIs to improve long-term survival outcomes for patients treated before LT is promising. Studies have reported no deaths or tumor recurrences at a median follow-up of 16 months post-transplantation, highlighting the potential of ICIs to enhance long-term survival. These findings underscore the importance of careful patient selection and monitoring to balance the benefits and risks associated with their use.

Although ICIs offer significant benefits, they are associated with irAEs that require vigilant monitoring and management. Effective strategies for managing these complications are essential for ensuring patient safety and successful transplantation outcomes. Studies have reported severe risks, including fatal acute hepatic necrosis and severe post-LT immune rejection[18]. These findings underscore the importance of aggressive irAE management and the need for standardized protocols to mitigate the risks associated with ICI therapy in patients awaiting LT. ICIs in the pre-transplant setting for HCC are associated with significant complications, primarily due to irAEs. Therefore, vigilant monitoring and aggressive management of these complications are crucial for ensuring patient safety and successful transplantation outcomes. Strategies for managing irAEs include increasing immunosuppression and careful patient selection to mitigate the risks associated with ICI therapy in patients awaiting liver transplantation.

Effective patient selection is crucial to optimize the benefits and minimize the risks of ICI therapy before LT. Comprehensive clinical evaluations and stringent criteria are essential for identifying suitable candidates for this treatment approach. Studies have emphasized the importance of selecting patients who can benefit from ICIs without a significant risk of severe irAEs. Thorough pretreatment evaluations are necessary to ensure that patients can tolerate ICIs and benefit from tumor reduction without experiencing severe complications[12]. Overall, careful patient selection based on comprehensive evaluations is critical for maximizing the efficacy and safety minimizing the risks of ICI therapy in the pre-transplant setting. Comprehensive clinical evaluation and stringent criteria are necessary to identify suitable candidates for this treatment approach. Studies have emphasized the importance of thorough pre-treatment evaluations to ensure that patients can tolerate ICIs and benefit from tumor reduction without experiencing severe complications.

The potential use of ICIs in patients with HCC and PVTT is particularly noteworthy for downstaging advanced HCC for LT. Kumar *et al*[14] reported the first case of successful downstaging using a combination of atezolizumab and bevacizumab. This combination therapy resulted in significant tumor shrinkage, enabling the patient to qualify for LT. This case underscores the potential of combining ICIs with antiangiogenic agents to enhance downstaging outcomes. Additionally, Aby and Lake[15] highlighted that patients with complex HCC, including those with malignant PVTT, could still be considered for ICI therapy if they demonstrate a good response to initial treatments and maintain overall health stability. This evidence suggests that ICIs, particularly when used in combination with other therapeutic agents, provide a viable pathway for curative surgery in patients with advanced and complicated HCC. Soin *et al*[20] described comparable findings that provided a powerful testament to the curative effects of downstaging in the treatment of advanced HCC with PVTT. Based on a similar concept, Bhangui *et al*[21] also reported acceptable long-term results after LT in an intention-to-treat strategy for HCC with PVTT if good patient selection depending on tumor biology, imaging-based downstaging with decreased tumor marker levels, and a minimum waiting period with stable disease were achieved. Traditional downstaging methods have had limited success in such complex cases; however, the advent of ICIs, particularly in combination with agents such as bevacizumab, offers a novel therapeutic approach. This strategy not only

Table 2 Recommendations

Aspect	Recommendation
Indications	HCC: Patients requiring downstaging therapy before liver transplantation. PVTT: Patients with HCC complicated by PVTT who are candidates for liver transplantation
Contraindications	Autoimmune diseases: History of severe autoimmune diseases that could be exacerbated by ICIs. Infections: Ongoing significant infections that may be worsened by immunotherapy. Liver disease: Decompensated liver disease where the risks of ICIs outweigh potential benefits
Timing of ICI initiation	Pre-transplant downstaging: Start ICIs as part of a structured downstaging protocol for HCC to shrink tumors to within transplant criteria. Advanced HCC management: Initiate ICIs in patients with advanced HCC and PVTT to control disease progression pre-transplant
Timing of ICI cessation	Before liver transplantation: Stop ICIs at least 4-6 weeks prior to planned liver transplantation to reduce the risk of graft rejection. Immune resolution: Ensure resolution of immune activation and monitoring for potential adverse effects post-ICI cessation before proceeding to LT
Monitoring and follow-up	Regular assessment: Frequent monitoring of liver function and immune response during ICI treatment. Post-ICI cessation: Close follow-up after stopping ICIs to detect and manage any late-onset immune-related adverse events and ensure patient readiness for transplantation
Immunosuppressive strategy post-LT	Standardized protocols: Implement standardized immunosuppressive regimens tailored to the patient's condition and prior ICI therapy to prevent graft rejection. Adaptive management: Adjust immunosuppression based on patient response and any emerging complications post-transplant

ICI: Immune checkpoint inhibitors; HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombosis; LT: Liver transplantation.

targets the primary tumor but also addresses the vascular component, thereby enhancing the overall efficacy of the treatment and improving patient outcomes.

Recommendations for optimizing the use of ICIs for downstaging advanced HCC prior to LT are well established (Table 2). ICIs should be considered for patients with HCC requiring downstaging therapy before LT as well as for those with HCC complicated by PVTT who are potential candidates for transplantation. Contraindications include a history of severe autoimmune diseases that can be exacerbated by ICIs, ongoing significant infections, and decompensated liver disease where the risks outweigh the benefits. ICIs should be initiated as part of a structured pre-transplant downstaging protocol to reduce tumor size within transplant criteria and control disease progression in advanced HCC with PVTT. It is crucial to stop ICIs at least 4-6 weeks before the planned LT to reduce the risk of graft rejection and ensure the resolution of immune activation. Regular monitoring of liver function and immune response during ICI treatment, as well as close follow-up after cessation, is necessary to detect and manage late-onset immune-related adverse events and ensure patient readiness for transplantation. Post-LT, the implementation of standardized immunosuppressive regimens tailored to the patient's condition and prior ICI therapy, along with adaptive management of immunosuppression based on patient response, is recommended to optimize outcomes[22,23].

Despite these promising findings, several limitations should be addressed in future studies. The heterogeneity in study designs, patient populations, and treatment protocols complicates the ability to draw definitive conclusions. The small sample sizes of some studies, particularly case reports, limit the generalizability of the results. Future research should focus on large-scale prospective studies to validate the efficacy and safety of ICIs in pre-transplant settings. Establishing standardized protocols for ICI administration, washout periods, and post-transplant monitoring is crucial. Additionally, evaluating long-term outcomes, including recurrence rates, graft survival, and overall survival, will provide a comprehensive understanding of the benefits and risks associated with this therapeutic approach. Addressing these research gaps will help optimize the integration of ICIs into the treatment paradigm for advanced HCC, ultimately improving patient outcomes. Current knowledge gaps include a lack of standardized protocols for ICI administration and variability in study design. Researchers should focus on large-scale prospective studies to validate these findings and develop uniform guidelines for ICI use in the pre-transplant setting, thereby enhancing patient outcomes.

Future research should address the heterogeneity in study design, patient populations, and treatment protocols to draw more definitive conclusions. In the next five years, we anticipate significant advancements in the integration of ICIs into standard treatment protocols for advanced HCC. With ongoing large-scale studies, we are likely to see the development of standardized guidelines for ICI administration and post-transplant care. Additionally, improvements in patient selection criteria and personalized treatment approaches will enhance the safety and efficacy of ICIs, potentially making liver transplantation accessible to a broader range of patients with advanced HCC. This evolution could lead to improved long-term survival rates and reduced recurrence, firmly establishing ICIs as the cornerstone for the management of advanced HCC.

CONCLUSION

The use of ICIs for downstaging advanced HCC before LT represents a significant advancement in the management of this challenging disease. Evidence from the reviewed studies indicates that ICIs, particularly in combination with agents such as bevacizumab, can effectively reduce tumor burden. This therapeutic approach expands the pool of patients

eligible for LT, offering new hope to those who were previously deemed ineligible because of extensive disease or advanced tumor characteristics. The ability to downstage tumors and facilitates LT opens up curative treatment possibilities for a broader patient population, potentially improving overall survival rates and quality of life.

However, while the potential benefits are substantial, careful consideration of the timing and management of ICI therapy is crucial for mitigating the associated risks. The timing of therapy cessation before LT is particularly important for minimizing the risk of irAEs during the perioperative period. Studies have suggested a washout period of at least four to six weeks between the last dose of ICI and LT to ensure that patients are in optimal condition for surgery. This interval allows for stabilization of the immune system and reduces the likelihood of perioperative complications.

The management of potential adverse effects also requires a multidisciplinary approach involving close monitoring and prompt intervention at the first sign of irAEs. Comprehensive pre-transplant evaluations and post-transplant care are essential to ensure patient safety and improve outcomes. As the field evolves, further research is essential to refine treatment protocols, establish standardized guidelines, and evaluate long-term outcomes, including recurrence rates, graft survival, and overall survival.

Future studies should focus on large-scale prospective trials to validate the efficacy and safety of ICIs in pre-transplant settings. Additionally, exploring the potential of combining ICIs with other therapeutic modalities and identifying biomarkers to predict responses to therapy could further enhance patient outcomes. By addressing these research gaps and continuously improving clinical practices, the integration of ICIs into the treatment paradigm for advanced HCC can be optimized, offering significant benefits to patients and advancing the fields of oncology and transplantation medicine.

FOOTNOTES

Author contributions: Pahari H and Peer JA devised the concept; Pahari H, Peer JA and Tripathi S performed the research and literature review; Tripathi S, Singhvi S and Dhir U completed the manuscript; Singhvi S and Dhir U prepared the tables and figure; Pahari H, Peer JA and Tripathi S reviewed and revised the manuscript.

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ORIGINAL ARTICLE

Observational Study

Hindi translation and validation of the English version of the gastrointestinal symptom rating scale questionnaire: An observational study

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Abstract

BACKGROUND

The gastrointestinal symptom rating scale (GSRS) is a questionnaire in English language which is designed to assess the clinical symptoms in patients with irritable bowel syndrome (IBS) and peptic ulcer disease. This validated scale has questions on around 15 items and has been validated in patients with dyspepsia and IBS.

AIM

To translate and validate the English version of the GSRS questionnaire to the Hindi version.

METHODS

The purpose of the present work was to create a Hindi version of this questionnaire for use in the Indian population. The process involved various steps as per the World Health Organization methodology including initial forward translation, backward translation, and assessment by an expert committee. Initial pilot testing was followed by testing in healthy and diseased individuals.

RESULTS
The Hindi translation was pilot tested in 20 individuals and further validated in healthy controls (n = 30, 15 females) and diseased individuals (n = 72, 27 females). The diseased group included patients with functional dyspepsia and IBS. Cronbach's alpha for internal consistency on the final translated GSRS questionnaire was 0.715 which is considered adequate. Twelve questions significantly differentiated the diseased population from the healthy population (P value < 0.05) in the translated Hindi version of the GSRS.

CONCLUSION
The translated Hindi GSRS can be used to evaluate gastrointestinal function in clinical trials and community surveys in Hindi speaking populations.

Key Words: Irritable bowel syndrome; Gut health; Dyspepsia; Symptoms; Pain; Constipation; Diarrhoea

Core Tip: The gastrointestinal symptom rating scale is a validated 15 question scale used to assess overall gastrointestinal health and has been used in irritable bowel syndrome (IBS), dyspepsia and in multiple clinical trials. We translated this questionnaire into Hindi and validated it in patients with dyspepsia and IBS. The translation will allow this scale to be used in future studies in Hindi speaking populations.

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INTRODUCTION

The gastrointestinal symptom rating scale (GSRS) is a questionnaire in the English language designed to assess the clinical symptoms in patients with irritable bowel syndrome (IBS) and peptic ulcer disease[1]. First reported in 1988, it has since been validated for the evaluation of clinical symptoms in patients with IBS and dyspepsia[2]. This validated scale has questions on around 15 items. The instrument has also been translated to multiple other languages[3]. The scale has been used in multiple clinical and research settings apart from IBS and dyspepsia, including overall gastrointestinal symptoms in diabetes, and general gastrointestinal symptoms[4]. Dyspepsia and IBS are common clinical problems that affect a large number of patients globally and have a significant mental health burden[5,6]. Therefore, the GSRS has immense value in clinical trials for these patients as it also assesses overall gastrointestinal symptoms.

The purpose of the present work was to create a Hindi version of this questionnaire for use in the Indian population. When translating a questionnaire initially established in a different nation and culture, the translation process must be able to cover all the necessary procedures to ensure that the validity and reliability of the questionnaire remain intact[7]. It is important to ensure that words in a health-related questionnaire translate accurately to the target language when translating it into a different language[8]. It is possible to decrease sample error, boost questionnaire response rates, and improve the generalizability of the results by assuring valid translation quality[9]. While the process of translating the questionnaire is included in the translation process, the process of validating the translated tool is mainly concerned with evaluating its quality[10]. The GSRS is the most relevant instrument for the evaluation of bowel function as it refers to the period in the previous week, requires a short time to complete and has easy-to-understand questions on gastrointestinal symptoms[3]. The World Health Organization (WHO) has created a standardised translation methodology in response to the growing requirement to ensure high-quality translations, particularly when it comes to cross-cultural research. Therefore, we have used the WHO-suggested methodology to create a Hindi translation of the GSRS[11].

MATERIALS AND METHODS

Study population

Ethical approval was obtained from the Institute Ethics Committee of the Postgraduate Institute of Medical Education and Research, Chandigarh (PGI/IEC-INT/2023/Study-977). All participants provided written informed consent prior to inclusion in the study.

GSRS

The GSRS is a self-administered questionnaire and has 15 items that cover the gastrointestinal system: Abdominal pain, diarrhoea, bloating, constipation, bowel movements, acidity, nausea, vomiting, abdominal rumbling, and eructation. GSRS questionnaire answers have been arranged in a 4-point Likert scale in which 0 represents no or transient and 3 represents severe symptoms[1]. The GSRS questionnaire is not copyrighted.

Forward and backward translation by an expert committee

The translation methodology was followed as suggested by the WHO including forward translation, expert panel back translation, pretesting and cognitive interviewing, and the final version[11]. The committee consisted of both the forward and backward translators, a methodologist (Padhi), and specialists with knowledge of the construct of interest. Members of the expert committee reviewed all versions of the translations and a prefinal version of the questionnaire was created.

Forward translation involved two investigators who were adept at both English and Hindi (Kumar and Sharma) who translated the questionnaire into Hindi. This translation of the questionnaire was assessed by experts fluent in both English and Hindi languages (Jearth and Sharma). They evaluated the cultural acceptability of the questionnaire for our population. After modifications to ensure cultural acceptability, the Hindi version was back-translated into English by an investigator not involved in the initial process (Jena). The back translation was compared to the original translation and modifications were made to ensure that the translation was appropriate to the original work.

Pretesting

Pretesting and cognitive interviewing were performed in 20 disease-free individuals (Figure 1). The purpose of this was to determine whether they could understand and correctly interpret the questionnaire. As they were all bilingual, they were also provided the English version so as to comment if the Hindi version captured the essence and meaning of the questionnaire. Debriefing was conducted regarding their experience with the questionnaire and if they could repeat the questions in their own words and how they chose an answer. Following this, a final version was created.

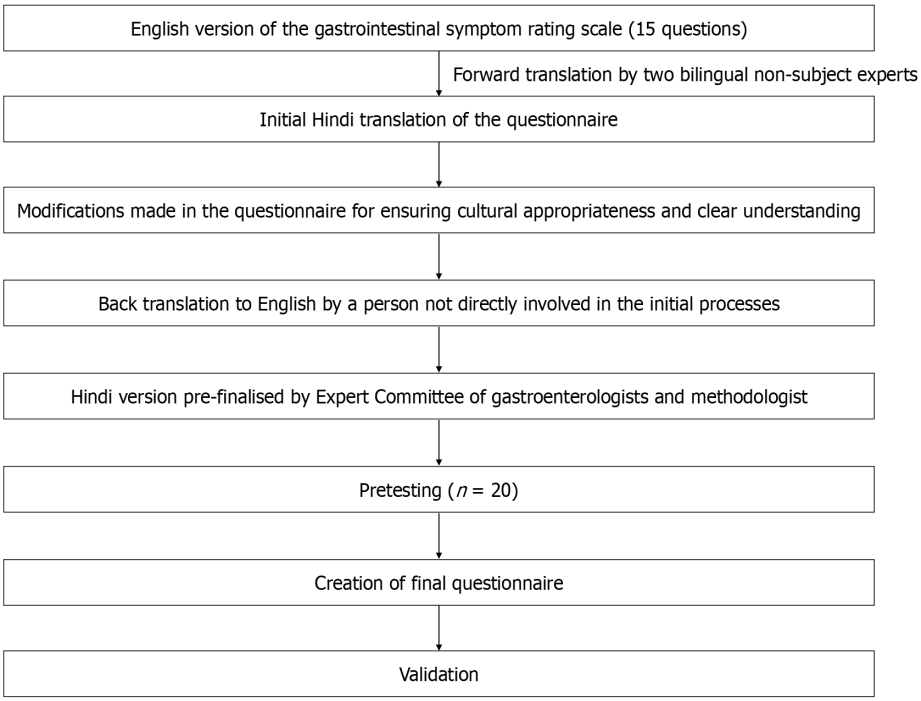

Figure 1 Flow chart showing the flow of the gastrointestinal symptom rating scale translation of the English version to Hindi and validation using the World Health Organization-suggested methodology.

Validation

Patients were enrolled in the outpatient department of gastroenterology. The final version was administered to dyspepsia patients and those with diarrhea-predominant IBS.

Inclusion criteria was based on ROME criteria for patients with dyspepsia and IBS. ROME IV criteria for functional dyspepsia were used which included the presence of one of the following symptoms: (1) Bothersome postprandial fullness; (2) Bothersome early satiation; (3) Bothersome epigastric pain; and (4) Bothersome epigastric burning and absence of any organic disease[12]. Similarly, the diagnosis of IBS was based on ROME IV criteria for IBS *i.e.* recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria: (1) Related to defecation; (2) Associated with a change in frequency of stool; and (3) Associated with a change in form (appearance) of stool[13]. The symptoms should have been present for six months and the criteria fulfilled over the past 3

months. Exclusion criteria included patients who denied consent and could not understand Hindi language, were illiterate, aged < 18 years or > 65 years.

Internal consistency

The degree of inter-correlation between the questions in the questionnaire and their consistency in measuring the same construct was indicated by internal consistency. The Cronbach's alpha coefficient, usually referred to as coefficient alpha, is frequently used to measure internal consistency[14]. Cronbach's alpha has a range of 0 to 1, with negative values occurring when there is a negative correlation between some questionnaire questions. Higher values indicate stronger interrelationships between the items, but if a negative Cronbach's alpha is still obtained after all items have been accurately scored, there are significant issues with the questionnaire's initial design. Internal consistency is absent when Cronbach's $\alpha = 0$, while complete internal consistency is represented by $\alpha = 1$. It has been recommended that an internal consistency of at least 0.70 on Cronbach's alpha scale be used in practice[15].

Test-retest reliability was not assessed as the scores were expected to change while on therapy which was initiated after the diagnosis.

Known group validity

Scores between the patients with IBS and dyspepsia were compared with controls to ascertain if the GSRS could differentiate the diseased participants from healthy participants.

Statistical analysis

The Statistical Package for the Social Sciences, 27th version (SPSS-20, IBM) and R software version were used to analyse the data. Simple descriptive statistics involved the calculation of median and interquartile range (IQR) (or mean ± SD, depending on the normality of distribution as decided by the Kolmogorov-Smirnov test) for continuous variables and frequency along with percentages for the categorical variables. Cronbach's alpha was used to assess the internal consistency of the Hindi version of the scale. The Mann-Whitney *U* test was used to compare the scores between the diseased participants and the controls.

RESULTS

Patients

A total of 117 individuals of both genders were included in the study. The group aged 16-70 years was administered the Hindi and English version of the GSRS in which 30 individuals were healthy controls (free of any known disease), 41 individuals were dyspepsia patients and 31 individuals had IBS (aged 21-66 years). Fifteen patients were excluded due to illiteracy ($n = 14$) and inability to understand Hindi language ($n = 1$). There was no disagreement or requirement for major vocabulary modifications as a result of the translation and back-translation processes (Table 1).

Internal consistency was estimated by calculating Cronbach's alpha which was 0.71 and considered adequate for the final version of the questionnaire.

Known group validity

The score for each of the questions (median and IQR) between the patients with IBS and dyspepsia (diseased group) were compared with healthy controls as shown in Table 2. Twelve questions in the questionnaire showed significant results (P value < 0.05); however, three questions (Q5, Q10, Q13) were not significant in this study, but can be evaluated for other diseases.

DISCUSSION

In this work, we have translated and validated the Hindi translation of the GSRS. The GSRS is one of the most established, validated, reliable, and responsive disease-specific instruments available for assessing gastrointestinal symptoms. Language barrier is an important concern in the native language population limiting the application of such questionnaires beyond the population where the scale was created. There are multiple reasons why we chose to translate this questionnaire: The questionnaire provides information on the overall gastrointestinal health of an individual and can be used in community surveys to identify gastrointestinal health, it can guide the further line of questioning, and the GSRS has also been translated into multiple other languages. Therefore, the GSRS is an ideal questionnaire that can be used in global collaborative studies that assess gastrointestinal heath in various studies.

In this study, we translated the English version of the GSRS into the Hindi version and validated the translated scale in dyspepsia and IBS patients. We used the standard WHO-suggested methodology to create the Hindi translation[11]. The GSRS has previously been translated and validated in the Brazilian Portuguese language for the assessment of bowel function with appropriate consistency[3]. In addition, translation into Hungarian and German languages has also been conducted[16,17]. Hindi is amongst the top five most frequently spoken languages in the world and therefore this translation of the GSRS is likely to help in research amongst a large subset of the global population.

Table 1 Characteristics of the population included in the validation cohort, *n* (%)

	Healthy controls	Diseased group	
		Functional dyspepsia	d-IBS
Number	30	41	31
Age (median, IQR) (years)	19-37 (25.5, 6.75)	16-70 (40,16.5)	21-66 (39,12.5)
Male gender	15 (50)	28 (68)	17 (55)
Duration of symptoms	Not applicable	Not applicable	Not applicable

d-IBS: Diarrhoea-predominant irritable bowel syndrome; IQR: Interquartile range.

Table 2 Median, interquartile range, and *P* value of the questions of the final version of the Hindi translation in the diseased group and healthy group

Question number	Diseased group (median, IQR)	Healthy group (median, IQR)	*P* value
Q1	1, 1	0, 1	0.02
Q2	1, 2	0, 1	0.02
Q3	1, 1	0, 1	0.04
Q4	1, 1	0, 0	0.002
Q5	0, 1	1, 1	0.66
Q6	1, 1	0, 1	0.0005
Q7	1, 2	0.5, 1	0.02
Q8	0.5, 1	0, 1	0.04
Q9	1, 2	0, 0	< 0.001
Q10	0, 0	0, 0	0.42
Q11	0, 1	0, 0	< 0.001
Q12	1, 1	0, 0	< 0.001
Q13	0, 1	0, 1	0.09
Q14	1, 1	0, 0	0.0002
Q15	1, 2	0, 0	< 0.001

IQR: Interquartile range.

Apart from the use of standard methodology including lingual and subject experts in the translation, the translation also demonstrates excellent internal consistency. The correlation between the questions was found to be adequate *i.e.* Cronbach's alpha was 0.71. There were twelve questions with significantly different responses in the diseased group (*P* value < 0.05). Nonetheless, three items (Q5, Q10, Q13) can be examined for different illnesses as they are not significant in this study (Table 2). Furthermore, the questions also identified the diseased population from the healthy population, suggesting the usefulness of the scale in field/community surveys. The Hindi translated version of the GSRS is therefore useful in an Indian population for the assessment of dyspepsia and IBS by clinicians. In spite of these strengths, the study has some limitations: This is a single centre study, the diseased population included only patients with dyspepsia and IBS and we could not perform test-retest reliability. Nevertheless, future studies in larger datasets would clarify the utility of this translation in various other clinical and community settings.

CONCLUSION

In conclusion, a culturally appropriate Hindi translation of the GSRS with suitable internal consistency and reliability has been created.

FOOTNOTES

Author contributions: Sharma V conceptualised the study; Jindal N and Jena A collected and interpreted data; Kumar K, Padhi BK and Sharma R translated the questionnaire; Jena A, Jindal N and Sharma V helped in the cultural adaptation; Padhi BK, Kumar K and Sharma V ensured appropriate methodology; Jearth V, Dutta U and Sharma V provided infrastructural support and critical comments on the methodology; Jindal N wrote the initial draft which was critically revised by all authors; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of KiwiBiotic on functional constipation and related symptoms: A prospective, single-center, randomized, comparative, crossover study

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Abstract

BACKGROUND

Functional constipation (FC) is a common gastrointestinal disorder characterized by abdominal pain and bloating, which can greatly affect the quality of life of patients. Conventional treatments often yield suboptimal results, leading to the exploration of alternative therapeutic approaches.

AIM

To evaluate the efficacy of KiwiBiotic in the management of FC and related symptoms.

METHODS

This prospective, interventional, single-center, crossover study compared the safety and effectiveness of KiwiBiotic® *vs* psyllium husk in managing FC, abdominal pain, and bloating. Participants diagnosed with FC were randomly assigned to receive KiwiBiotic or psyllium husk during the two treatment periods, with a 14-day washout period between them.

RESULTS

Seventy participants were enrolled, 32 of whom received KiwiBiotic followed by psyllium husk, and 33 received KiwiBiotic. KiwiBiotic showed superiority over psyllium husk in alleviating abdominal pain and bloating, as evidenced by significantly lower mean scores. Furthermore, KiwiBiotic resulted in more than

90.0% of patients experiencing relief from various constipation symptoms, while psyllium husk showed comparatively lower efficacy.

CONCLUSION
KiwiBiotic is an effective treatment option for FC, abdominal pain, and bloating, highlighting its potential as a promising alternative therapy for patients with FC and its associated symptoms.

Key Words: KiwiBiotic; Psyllium husk; Constipation; Abdominal pain; Bloating

Core Tip: Functional constipation (FC) significantly affects the quality of life of patients due to symptoms such as abdominal pain and bloating. Conventional treatments often fail, necessitating alternative therapies. Phytotherapeutic product KiwiBiotic has emerged as a promising alternative treatment for FC, abdominal pain, and bloating, offering superior efficacy, improved quality of life, and higher patient satisfaction than conventional options such as psyllium husk. Its effectiveness in symptom relief, demonstrated in more than 90% of patients, highlights its potential as a safe and comprehensive therapeutic option.

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INTRODUCTION

Constipation is characterized by a decrease in the regularity of bowel movements or challenges in stool discharge. Symptoms commonly linked to this condition include hard stool, effortful strain, blockage sensation in the anal region, sense of incomplete bowel emptying, abdominal pain, and swelling[1]. This condition is divided into several categories, including functional, chronic idiopathic, and secondary constipation, all of which are distinguished by specific causes and clinical characteristics[2]. Functional constipation (FC) is a type of functional bowel disorder characterized by symptoms such as difficulty in defecating, infrequent bowel movements, or a feeling of incomplete bowel evacuation, with a prevalence of approximately 20% in adults[3,4]. Constantly constipated patients are associated with higher all-cause mortality and are at higher risk of mental health issues[5]. Risk factors for constipation include living conditions, dietary patterns, and unhealthy lifestyle choices[6].

Many people with FC resort to self-medication, which can affect the ideal timing of treatment and worsen their condition[7]. Due to variables such as decreased mobility, polypharmacy, and coexisting medical diseases, older people frequently have poor tolerance to non-pharmacological treatments such as lifestyle changes (*e.g.*, exercise, high-fiber foods, and increased fluid intake)[8,9]. The underlying causes of FC are complex and involve multiple factors, including genetics. However, specific genes linked to this condition have not been identified. This absence of genetic markers leads some experts to propose that lifestyle and environmental influences within certain families could actually explain the observed patterns of constipation rather than hereditary factors[10]. The quality of life and psychological well-being of patients are significantly affected by repeated consultations, unnecessary investigations, and prolonged disease duration, which impose substantial financial burdens and pose considerable challenges in managing the condition[11].

Bulk-forming drugs are usually recommended as first-line treatment for constipation. These substances absorb water to increase the amount of feces and facilitate bowel movements. Adequate fluid intake is crucial when using bulk-forming medications to prevent bloating and, more importantly, reduce the likelihood of intestinal obstruction associated with dehydration[12]. In addition to bulk-forming medications, various drugs are used to treat constipation, including stimulants, stool softeners, and osmotic agents, depending on the severity of the condition[13-16]. Although conventional treatment is established and considered safe, it often does not provide satisfactory improvement in many patients, leading them to explore alternative therapeutic approaches[17]. Complementary and alternative medicines are gaining popularity due to their perceived safety and efficacy[18].

Consequently, there is an incentive to consider medications from complementary and alternative medical systems as potential treatment options for constipation. The formulation used in the current study, KiwiBiotic, was in liquid form and contained mainly kiwi pulp. This study aimed to evaluate the safety and effectiveness of KiwiBiotic compared to psyllium husk in the management of FC, abdominal pain, and bloating.

MATERIALS AND METHODS

Study design

In this prospective, interventional, single-center, crossover study, participants diagnosed with FC were randomly assigned to groups in a 1:1 ratio. The trial was carried out at Healing Hands Clinic Pvt. Ltd., DP Road, Pune, Maharashtra, India. The study was registered with the Clinical Trial Registry of India (CTRI/2023/09/058081, dated 27th September 2023) and the Institutional Ethics Committee of the Healing Hands Clinic, DP Road, Pune-411001 (HHCRS/HH&HPL-002/23-24). This study complied with the ethical guidelines of the 1975 Declaration of Helsinki.

Study products

The phytotherapeutic products, KiwiBiotic® and psyllium husk, were provided by Healing Hands and Herbs Pvt. Ltd., located in Pune, India, www.myhealinghands.in. KiwiBiotic was manufactured and marketed by Healing Hands and Herbs Pvt., Ltd.

Participants

Eligible participants were aged ≥ 18 years and diagnosed with FC, abdominal pain, or bloating according to the ROME IV criteria[19,20]. Participants are only included if the participants, their parents, or any legal guardian are willing to give their written informed consent or parental consent or consent form and if they are willing to strictly adhere to the investigator's prescription. Patients were excluded if they had taken any medication that could interfere with the action of the medication before or during the start of the study. Furthermore, patients with pre-existing conditions that could compromise their safety or participation in the study were excluded.

Randomization

Participants were randomly assigned in a 1:1 ratio to receive KiwiBiotic (50 mL orally twice daily) during period 1, followed by psyllium husk (1.82 g orally once daily) during period 2 (sequence 1), or psyllium husk during period 1, followed by KiwiBiotic during period 2 (sequence 2).

Procedures

During the screening visit, the participants underwent assessments of their medical history and concomitant medications, along with physical examinations. The patients were randomly assigned to undergo two treatment periods of 14 days each, with a 14-day washout period between them. Vital signs, such as body temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate, were assessed at each visit (days 0, 14, 28, 42, and 49) to ensure safety. The last follow-up visit, scheduled for day 49, aimed to confirm whether symptoms had recurred after the completion of the final treatment on day 42 (Figure 1). Participants were assessed for efficacy following the administration of the study products. This includes an assessment of FC according to the ROME IV criteria and an assessment of abdominal pain and bloating using a visual analog scale. At the end of each treatment period, quality of life was evaluated using the gastrointestinal quality of life questionnaire, and the overall treatment evaluation score was measured.

Outcomes

The primary efficacy endpoint was changes in FC symptoms, abdominal pain, and bloating. Secondary endpoints included the assessment of gastrointestinal quality of life using the gastrointestinal quality of life index (GIQLI), overall treatment evaluation scores by physicians, and incidence of adverse events, with data collected up to the 5th visit.

Statistical analysis

The trial sample size was determined to detect a standardized difference of 0.6 with 90% power and significance level α = 5%, which represents a 10% dropout rate, resulting in the recruitment of 70 participants. Demographics and baseline characteristics of the participants were summarized using mean, SD, and range for continuous variables, and frequencies and percentages for categorical variables. Equivalence tests were conducted to compare abdominal pain and abdominal bloating at a significance level of 5%. For the symptoms of FC, we used a two-sided McNemar's test, with a P-value < 0.05 indicating statistical significance. Two-sided paired t-tests were used to compare the overall GIQLI scores and their domains.

RESULTS

Between October 20, 2023 and February 12, 2024, a total of 70 patients were recruited. Of the initial 70 patients, 35 were randomly assigned to receive KiwiBiotic during period 1, followed by psyllium husk during period 2; the remaining 35 received psyllium husk during period 1, followed by KiwiBiotic during period 2. In this study, 44 females (62.86%) and 26 males (37.14%) were enrolled, with a mean age of 43.61 years (SD = 13.41). The average weight of all participants was 60.65 kg (SD = 8.09) and the average height was 163.42 cm (SD = 7.2). The mean body mass index of the entire cohort was 22.68 kg/m² (SD 2.48) (Table 1). During the second visit, three patients from sequence 1 and two patients from sequence 2 were excluded due to loss of follow-up. Thirty-two patients in the KiwiBiotic group and 33 patients in the psyllium husk group completed the study. At the 5% level of significance, no significant differences were observed between the groups, as P > 0.05.

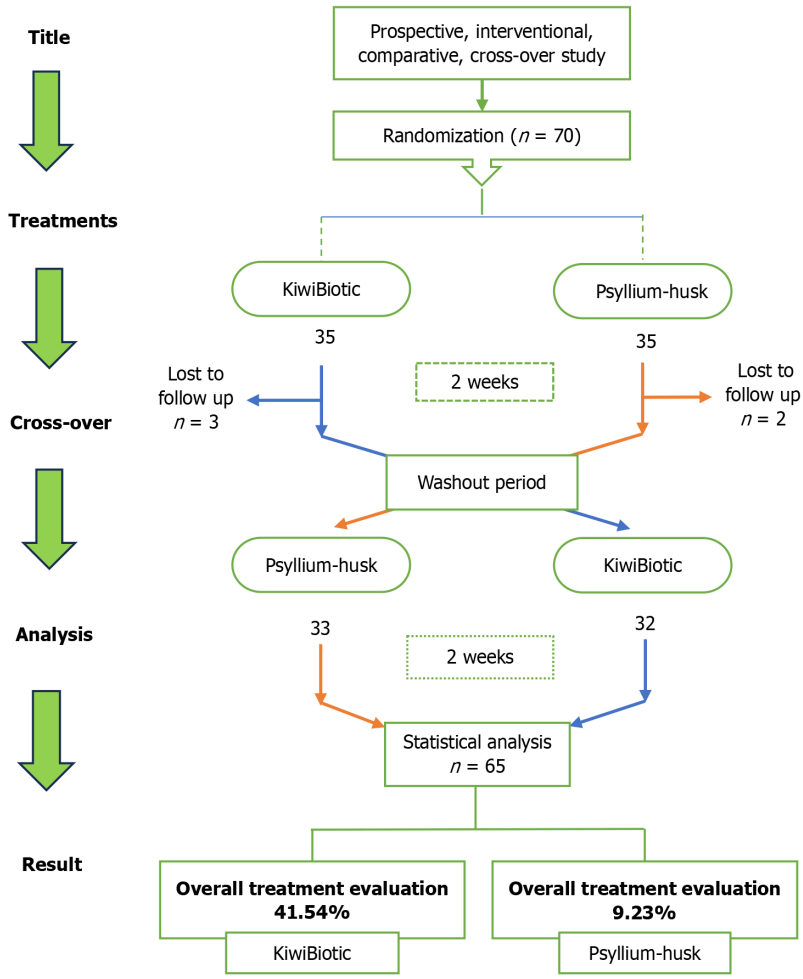

Figure 1 Trial profile.

Changes in abdominal pain

The results showed that for the KP sequence, the mean score of abdominal pain was 1.4688 (SD = 0.87931) at visit 2 in period 1 and 6.2188 (SD = 2.4591) at visit 4 in period 2. In contrast, for the PK sequence, the mean score was 7.2121 (SD = 2.342) at visit 2 in period 1 and 1.6667 (SD = 1.0206) at visit 4 in period 2 (Table 2) (Figure 2A). These findings indicate that KiwiBiotic is more effective than psyllium husk in reducing abdominal pain.

The crossover effect and analysis of abdominal pain showed that the estimated carryover effect was -1.1913 with a corresponding *P*-value of 0.092, exceeding = 0.05, indicating that the carryover effect was not statistically significant. Conversely, the estimated treatment effect was -5.1477, with a *P*-value of 0.000, demonstrating statistical significance at the 0.05 level and indicating that one treatment has a superior effect compared to the other. Furthermore, the estimated period effect was -0.39773, but the *P*-value of 0.175 exceeded = 0.05 (Table 3) (Figure 3A), indicating that the period effect was not statistically significant.

Changes in abdominal bloating

The findings revealed that the average abdominal bloating score for the KP sequence was 1.3125 (SD = 0.7378) during visit 2 in period 1 and 4.9375 (SD = 1.7949) during visit 4 in period 2. The mean score for sequence PK was 5.4848 (SD = 1.8392) at visit 2 in period 1 and 1.4545 (SD = 0.6657) at visit 4 in period 2 (Figure 2B) (Table 4). Ultimately, these results suggest that KiwiBiotic showed a more substantial improvement in abdominal bloating than psyllium husk.

The crossover effect and analysis of abdominal bloating show that the determined carryover effect was -0.68939. However, the *P*-value (0.178) exceeded = 0.05, indicating a lack of statistical significance for the carryover effect. The estimated treatment effect was -3.8277, with a *P*-value of 0.000, indicating statistical significance at the 0.05 level. This notable treatment effect implies that one treatment showed superior efficacy over the other. The estimated period effect was -0.20265 with a *P*-value of 0.382 (Table 5), surpassing = 0.05, making the period effect statistically insignificant.

A one-sided *t*-test (5% level of significance) was performed for abdominal pain and abdominal bloating to determine the significant differences between treatments. The mean response to abdominal pain was 1.5692 for KiwiBiotic treatment and 6.7231 for psyllium husk treatment. Similarly, for abdominal bloating, the mean response was 1.3846 for KiwiBiotic treatment and 5.2154 for psyllium husk treatment (Table 6) (Figure 3B). These findings indicate a significant difference between the two treatments ($P < 0.05$).

Table 1 Patient characteristics at baseline (*n* = 70), *n* (%)

Demographics	KiwiBiotic	Psyllium husk	Total	*P* value
Gender				0.138[a]
Female	25 (71.43)	19 (54.29)	44 (62.86)	
Male	10 (28.57)	16 (45.71)	26 (37.14)	
Age (year)				0.156
Mean (SD)	41.4 (10.96)	45.83 (14.84)	43.61 (13.14)	
Range	18-65	23-73	18-73	
Weight (kg)				0.064
Mean (SD)	58.89 (7.88)	62.41 (8.03)	60.65 (8.092)	
Range	42-80.9	47-79.3	42-80.9	
Height (m)				0.123
Mean (SD)	162.1 (6.68)	164.73 (7.54)	163.42 (7.2)	
Range	152-176.7	152-177	152-177	
BMI (kg/m^2)				0.291
Mean (SD)	22.37 (2.40)	23.00 (2.56)	22.68 (2.48)	
Range	17.3-28.8	17.3-28.3	17.3-28.8	

[a]Chi-square test.
BMI: Body mass index.

Table 2 Descriptive statistics for abdominal pain at visit 2 and visit 4

	Sequence	*n*	Period 1		Period 2	
			Mean	SD	Mean	SD
Abdominal pain	KP	32	1.4688	0.87931	6.2188	2.4591
	PK	33	7.2121	2.342	1.6667	1.0206

KP: KiwiBiotic during period 1 and psyllium husk during period 2; PK: Psyllium husk during period 1 and KiwiBiotic during period 2.

Table 3 Cross-over effects and analysis details for abdominal pain

	Effect	SE	DF	*T* value	*P* value	95%CI	Significance
Carryover	-1.1913	0.69641	63	-1.7106	0.092	-2.5830, 0.20038	No
Treatment	-5.1477	0.28995	63	-17.754	0.000	-5.7271, -4.5683	Yes
Period	-0.39773	0.28995	63	-1.3717	0.175	-0.97714, 0.18169	No

DF: Degrees of freedom; CI: Confidence interval.

Evaluation of FC using the Mcnemar test

After KiwiBiotic treatment, 39 patients reported no straining, while only one patient experienced the same result after psyllium husk treatment. Regarding the presence of lumpy or hard stool, 39 patients achieved complete relief with KiwiBiotic treatment, compared to only one patient with psyllium husk treatment. Similarly, for the feeling of incomplete evacuation of more than one-fourth (25%) of defecations, 37 patients found complete relief with KiwiBiotic treatment, while only one patient did so with psyllium husk treatment (Table 7).

In the evaluation of anorectal obstruction or sensation of blockage, nearly 33 patients experienced total relief after KiwiBiotic treatment, while none experienced relief after psyllium husk treatment. Concerning manual maneuvers to facilitate more than 25% defecation, 33 patients achieved complete relief with KiwiBiotic treatment, compared to only one patient with psyllium husk treatment. Similarly, among individuals who experienced fewer than three spontaneous

Table 4 Descriptive statistics for abdominal bloating at visit 2 and visit 4

	Sequence	*n*	Period 1		Period 2	
			Mean	SD	Mean	SD
Abdominal bloating	KP	32	1.3125	0.7378	4.9375	1.7949
	PK	33	5.4848	1.8392	1.4545	0.66572

Table 5 Cross-over effects and analysis details for abdominal blotting

	Effect	SE	DF	*T* value	*P* value	95%CI	Significance
Carryover	-0.68939	0.50583	63	-1.3629	0.178	(-1.7002, 0.32143)	No
Treatment	-3.8277	0.22994	63	-16.646	0.000	(-4.2872, -3.3681)	Yes
Period	-0.20265	0.22994	63	-0.88131	0.382	(-0.66216, 0.25686)	No

DF: Degrees of freedom; CI: Confidence interval.

Table 6 *T*-test for abdominal pain and abdominal bloating (one-sided)

	Mean (KiwiBiotic)	Mean (Psyllium husk)	SE	DF	*T* value	*P* value	Significance
Abdominal pain	1.5692	6.7231	0.28995	63	-17.754	< 0.05	Yes
Abdominal bloating	1.3846	5.2154	0.22994	63	-16.646	< 0.05	Yes

DF: Degrees of freedom.

Table 7 Assessment of functional constipation

Symptoms of functional constipation	Number of subjects experiencing symptom relief from functional constipation after consuming KiwiBiotic but not after psyllium husk	Number of subjects experiencing symptom relief from functional constipation after consuming psyllium husk but not after KiwiBiotic	*P* value for MC-Nemar's test
Straining during more than ¼ 25% of excretion	39	1	< 0.05
Lumpy or hard stools (BSFS type 1 or 2) more than 25% of defecations	39	1	< 0.05
Sensation of incomplete evacuation of more than one-fourth (25%) of defecations	37	1	< 0.05
Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations	33	0	< 0.05
Manual manoeuvres to facilitate more than ¼ (25%) of defecation	33	1	< 0.05
Fewer than three spontaneous bowel movements per week	11	2	< 0.05

bowel movements per week, 11 patients achieved complete relief with KiwiBiotic treatment, while only one patient reported complete relief with psyllium husk treatment (Table 7).

Rejecting the null hypothesis implies that one treatment is superior because it has more successful patient outcomes. McNemar's test, which yields a two-sided *P*-value of < 0.05, for all FC symptoms, rejects the null hypothesis of no difference between treatments with KiwiBiotic and psyllium husk. Consequently, the test results significantly favored KiwiBiotic, as it was more effective in alleviating FC symptoms.

Table 8 indicates that patients treated with KiwiBiotic experienced relief of symptoms that exceeded 90% in various symptoms related to FC, exceeding the relief observed in patients treated with psyllium husk.

Table 8 Percentage of subjects improved their symptoms of functional constipation

Symptoms of functional constipation	After the KiwiBiotic treatment (%)	After the psyllium husk treatment (%)
Straining during more than ¼ 25% of excretion	91.0	32.0
Lumpy or hard stools (BSFS type 1 or 2) more than 25% of defecations	91.0	32.0
Sensation of incomplete evacuation of more than one-fourth (25%) of defecations	91.0	35.0
Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations	95.0	45.0
Manual manoeuvres to facilitate more than ¼ (25%) of defecation	94.0	45.0
Fewer than three spontaneous bowel movements per week	97.0	83.0

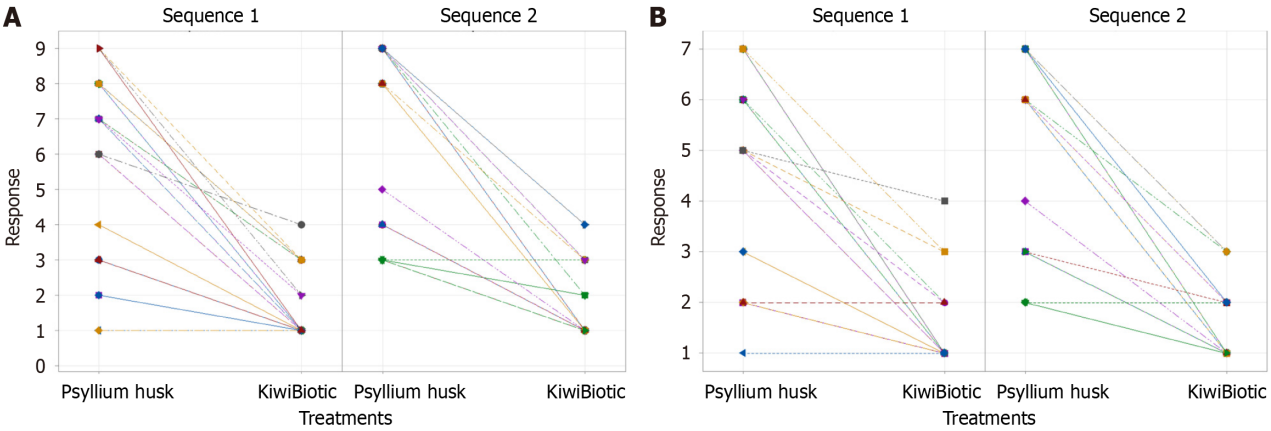

Figure 2 Graphical representation of change in abdominal pain and abdominal bloating for sequence 1 (KP) and sequence 2 (PK). A: Abdominal pain; B: Abdominal bloating.

Assessment of the GIQLI

Following treatment with KiwiBiotic, the overall score of the gastrointestinal symptom questionnaire was -39.69 (SD = 6.3), compared to -10.78 (SD = 15.7) after psyllium husk treatment. Regarding the psychological questionnaire, the mean score was -10.19 (SD = 2.2), compared to -0.415 (SD = 5.5) after psyllium husk treatment. After KiwiBiotic treatment, the mean score for the physical questionnaire was -16.71 (SD = 3.3) and for the social questionnaire, it was -2.37 (SD = 3.6). On the contrary, after psyllium husk treatment, the mean scores were -3.23 (SD = 7.1) for the physical questionnaire and -0.077 (SD = 2.0) (Table 9) for the social questionnaire. The overall mean score for the KiwiBiotic treatment was -68.95 (SD = 10.5) and for the psyllium husk treatment, it was -14.51 (SD = 26.8) (Table 9) (Figure 4). These findings suggest that KiwiBiotic generally provides a greater improvement in GIQLI and its domains, such as gastrointestinal symptoms and psychological, physical, and social well-being, compared to psyllium husk treatment, as evidenced by the statistically significant differences in mean scores.

Overall treatment evaluation

Approximately 53.38% of the patients experienced a complete resolution of the condition, 41.54% of the patients reported a significant improvement in their condition, and only 3.08% of the patients reported a slight improvement in their condition after KiwiBiotic treatment (Table 10). Overall, the table shows that a higher percentage of patients experienced positive outcomes, including resolution and significant improvement, when treated with KiwiBiotic than with psyllium Husk.

DISCUSSION

In this single-center study conducted in a single center, the findings underscore the safety and efficacy of KiwiBiotic in managing symptoms associated with FC, abdominal pain, and bloating compared to psyllium husk. This study revealed significant improvements in various parameters, including symptom relief, quality of life, and overall treatment evaluation, in patients treated with KiwiBiotics. More than 90.0% of the patients experienced symptom relief from FC following treatment with KiwiBiotic. Generally, most of the participants exhibited good tolerance to treatment.

Table 9 Effect of treatments on gastrointestinal quality of life index and its domain and estimation for paired differences (two-sided)

	KiwiBiotic			Psyllium-husk		
	Estimation for paired difference					
GIQLI domains	Mean (SD)	95%CI	*P* value	Mean (SD)	95%CI	*P* value
GI-symptoms	-39.69 (6.3)	-41.264, -38.121	< 0.05	-10.78 (15.7)	-14.67, -6.90	< 0.05
Psychological	-10.19 (2.2)	-10.744, -9.626	< 0.05	-0.415 (5.5)	-1.787, 0.956	0.547
Physical	-16.71 (3.3)	-17.533, -15.883	< 0.05	-3.23 (7.1)	-4.999, -1.463	0.001
Social	-2.37 (3.6)	-3.262, -1.476	< 0.05	-0.077 (2.0)	-0.571, 0.417	0.757
Overall	-68.95 (10.5)	-71.56, -66.35	< 0.05	-14.51 (26.8)	-21.15, -7.86	< 0.05

CI: Confidence interval; GI: Gastrointestinal; GIQLI: Gastrointestinal quality of life index.

Table 10 Overall treatment evaluation score

Condition	KiwiBiotic (%)	Psyllium-husk
Resolved	55.38	0.00
Much better	41.54	9.23
Little better	3.08	13.85
The same	0.00	33.85
Worse	0.00	43.08

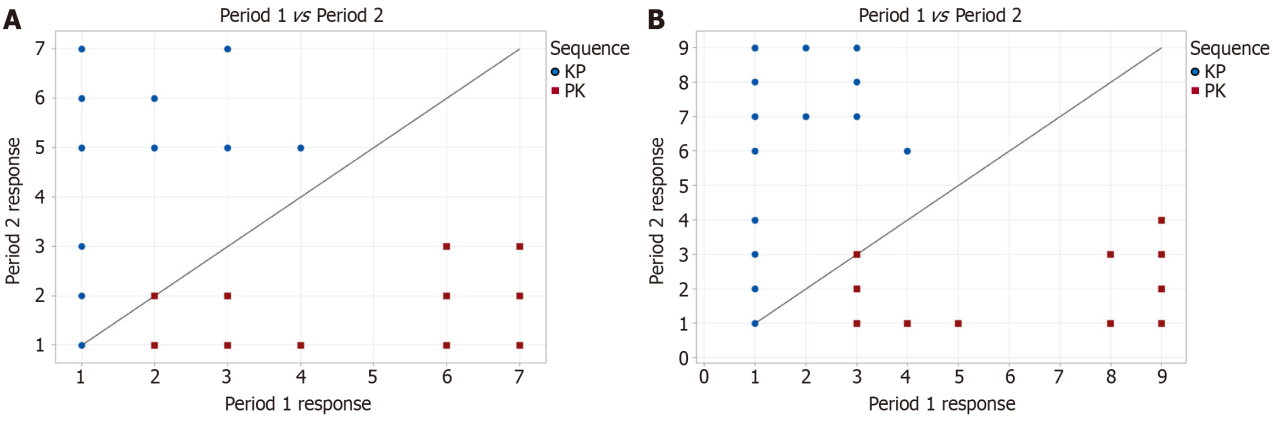

Figure 3 Period-wise change in abdominal pain and abdominal bloating for sequence 1 (KP) and sequence 2 (PK). A: Abdominal pain; B: Abdominal bloating.

The inherent properties of kiwifruit have shown their effectiveness in reducing symptoms such as constipation, abdominal pain, and discomfort[21-23]. KiwiBiotic contains mainly kiwi pulp and a required quantity of excipients. KiwiBiotic demonstrated a marked decrease in abdominal pain and bloating, supported by notably lower mean scores of 6.2188 and 4.9375, respectively, at visit 4. The analysis of crossover effects indicated statistically significant treatment effects for both abdominal pain and bloating, with a *P*-value of 0.000 for each, further highlighting the superior efficacy of KiwiBiotic compared to psyllium husk in relieving these symptoms. In the management of FC, more than 90.0% of the patients found relief from symptoms such as straining, lumpy or hard stools, the feeling of incomplete evacuation, the feeling of anorectal obstruction or blockage, the need for manual maneuvers, and fewer than three spontaneous bowel movements per week after treatment with KiwiBiotic. In contrast, after psyllium husk treatment, only 32.0% of the patients experienced relief from straining and lumpy or hard stools, 35.0% from the sensation of incomplete evacuation, 45.0% from the sensation of anorectal obstruction or blockage and the need for manual maneuvers, and 83.0% from fewer than three spontaneous bowel movements per week.

Importantly, the evaluation of GIQLI and its domains revealed that KiwiBiotic significantly improved overall gastrointestinal symptoms, psychological well-being, physical health, and social aspects compared to psyllium husk. These findings underscore the extensive benefits of KiwiBiotic in enhancing the patient's quality of life beyond symptom

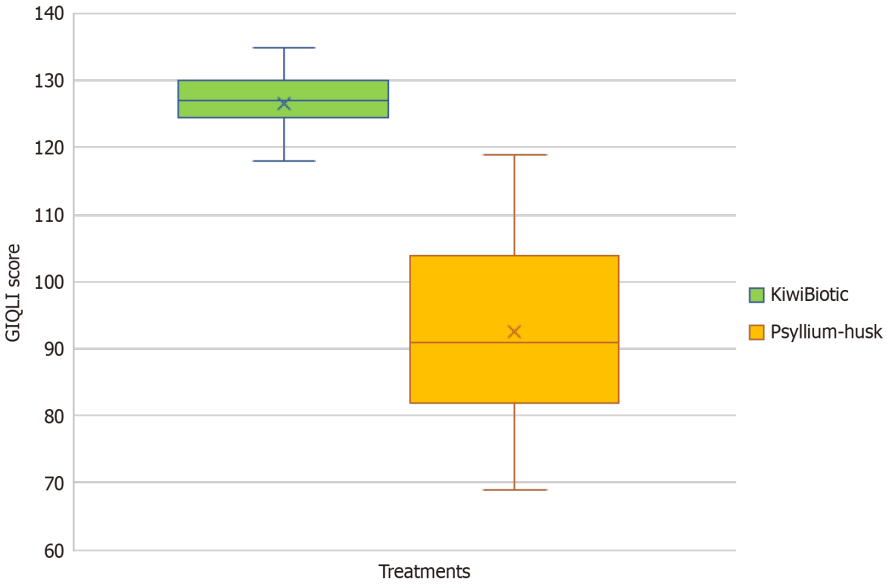

Figure 4 Box-plot for overall gastrointestinal quality of life index after treatment.

relief alone. Furthermore, the overall treatment showed a substantially higher percentage of patients experiencing resolution or significant improvement with KiwiBiotic than with psyllium husk. Collectively, these results suggest that KiwiBiotic is a promising treatment option for managing constipation, abdominal pain, and bloating, offering superior efficacy and patient satisfaction compared to psyllium husk.

CONCLUSION

In conclusion, our study demonstrates that KiwiBiotic is a safe and effective treatment option for managing symptoms of FC, abdominal pain, and bloating. Its superior efficacy, favorable impact on the quality of life, and high patient satisfaction make it a promising alternative to conventional treatments such as psyllium husk. Further research, including larger sample size and long-term follow-up studies, is warranted to validate these findings and establish KiwiBiotics as a standard therapeutic option for individuals with FC and related symptoms.

FOOTNOTES

Author contributions: Porwal AD, Gandhi PM, Kulkarni DK and Bhagwat GB conceptualized and designed the study; Kamble PP and Bhagwat GB wrote the manuscript; Porwal AD and Bhagwat GB revised the manuscript; Kamble PP, Bhagwat GB and Porwal AD confirmed the authenticity of the data. All authors have read and approved the final manuscript. Porwal AD and Gandhi PM contributed equally to this work as co-first authors.

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