REVIEW ARTICLE

FROM VANCOMYCIN TO FIDAXOMICIN: SHIFTING PARADIGMS IN *CLOSTRIDIOIDES DIFFICILE* MANAGEMENT.

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Abstract

Introduction: *Clostridioides difficile* infection (CDI) is one of the leading causes of antibiotic-associated diarrhea and represents a major global public health concern. Its clinical relevance has increased due to rising incidence, greater disease gravity, high recurrence rates, and the emergence of hypervirulent strains, making CDI a persistent challenge in daily clinical practice.

Objective: to provide an updated narrative review of the epidemiology, pathogenesis, diagnostic approaches, and current therapeutic strategies for *Clostridioides difficile* infection, with emphasis on key clinical challenges and practical considerations.

Methods: a structured literature review was conducted using PubMed/MEDLINE, Scopus, and SciELO databases. DeCS/MeSH terms related to Clostridioides difficile, epidemiology, diagnosis, treatment, and prevention were combined using Boolean operators. Articles published in English and Spanish between 2020 and 2025 were included, prioritizing systematic reviews, meta-analyses, original studies, and clinical practice guidelines. The search was last updated in January 2026.

Results: CDI pathogenesis is primarily mediated by toxins A and B, which induce epithelial damage and colonic inflammation. Advances in diagnostic tools, particularly nucleic acid amplification tests and multistep diagnostic algorithms, have improved detection rates; however, inappropriate use may lead to overdiagnosis. Oral vancomycin remains a cornerstone

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of therapy, while fidaxomicin, monoclonal antibodies, and fecal microbiota transplantation have shown efficacy in reducing recurrence in selected patients.

Conclusions: effective management of CDI requires an integrated approach combining accurate diagnosis, appropriate antimicrobial therapy, and sustained preventive strategies.

Keywords: *Clostridioides difficile*, healthcare-associated infection, antimicrobial therapy, diagnostic strategies,infection prevention.

Introduction

Clostridioides difficile infection (CDI) is currently one of the leading causes of healthcare-associated diarrhea and remains a significant clinical challenge in hospitals worldwide. In recent decades, there has been a sustained increase in both its incidence and the severity of its clinical manifestations, particularly in vulnerable populations such as older adults, long-term hospitalized patients, and individuals exposed to broad-spectrum antimicrobials.[1].

Clostridioides difficile is a Gram-positive, spore-forming anaerobic bacterium whose transmission occurs predominantly via the fecal–oral route through direct contact with colonized individuals or via contaminated surfaces[2]. Its ability to form highly resistant spores allows it to persist in the hospital environment for prolonged periods and survive adverse conditions, including gastric acidity, facilitating intestinal colonization following antibiotic-induced disruption of the normal microbiota[3]. These mechanisms partly explain its close association with prior antimicrobial use and its behavior as a nosocomial pathogen.

Clostridioides difficile; formerly *Clostridium difficile*, the name change proposed in 2016 is based on phylogenetic criteria that distinguish this microorganism from other species of the genus *Clostridium*; however, the abbreviation *"C. difficile"* is still used in routine clinical practice[4]. In addition to the nomenclature aspect, the significance of *C. difficile* lies in its ability to produce a broad clinical spectrum; it is recognized as one of the main causative agents of antibiotic-associated diarrhea, ranging from self-limiting diarrhea to pseudomembranous colitis, fulminant colitis, and toxic megacolon—conditions associated with high morbidity and mortality.

It is estimated that *C. difficile* is responsible for up to 30% of cases of antibiotic-associated diarrhea and affects approximately 1% of hospitalized patients, with recurrence rates close to 20%, which complicates its management and places a significant burden on healthcare systems[5]. The emergence of hypervirulent strains, an aging population, immunosenescence, and the widespread use of antibiotics and gastric acid-suppressing agents have contributed to establishing CDI as a persistent and dynamic problem, still far from being fully controlled.

In this context, recent advances in our understanding of the pathogenesis—particularly the role of toxins A and B—as well as the development of new diagnostic tools and therapeutic strategies, have substantially altered the clinical management of this infection. However, significant controversies, diagnostic limitations, and therapeutic challenges remain, especially regarding recurrence and the effective prevention of new episodes.

Objetive

To critically analyze the available scientific evidence on the pathogenesis, diagnosis, treatment, and prevention strategies for *C. difficile* infection, highlighting recent advances, current controversies, and their clinical implications in the hospital setting.

Method

A narrative review of the scientific literature from 2020 to 2025 on *C. difficile* infection was conducted. The search was conducted in the PubMed, Scopus, and Google Scholar databases, using terms related to the epidemiology, pathogenesis, diagnosis, treatment, recurrence, and prevention of *C. difficile* infection (CDI). The following health sciences descriptors were used (DeCS/MeSH): *Clostridioides difficile*; Healthcare-associated infection; epidemiology; Antimicrobial therapy; Diagnostic strategies; Infection prevention, combined using Boolean operators. Articles published in English and Spanish were included, covering the period from 2020 to 2025. The search was last updated in January 2026, prioritizing original studies, meta-analyses, systematic reviews, and relevant clinical guidelines.

Original articles, systematic reviews, clinical trials, observational studies, and relevant clinical guidelines published in English and Spanish were included, with no geographic restrictions, prioritizing those with the greatest clinical and methodological impact. Isolated case reports,

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duplicate studies, and publications with redundant information or without direct clinical relevance were excluded.

The information obtained was critically analyzed and organized into thematic areas, with an emphasis on consistent findings, areas of controversy, and practical implications for the clinical management and prevention of *C. difficile* infection.

Results

Current evidence on pathogenesis and virulence factors

The pathogenesis of *C. difficile* infection is closely linked to the production of its main virulence factors: toxins A (TcdA) and B (TcdB). Both toxins are glycosyltransferases that inactivate Rho-GTPases in the actin cytoskeleton of intestinal epithelial cells, causing disruption of tight junctions, increased epithelial permeability, local inflammation, and cell death[6].

Although toxin A was historically considered the primary determinant of disease, the most recent experimental and clinical evidence has shown that toxin B plays a central role in the bacterium's virulence[7]. Studies using isogenic mutants have shown that strains producing exclusively toxin B retain the ability to induce significant tissue damage, while those expressing both toxins exhibit greater virulence, suggesting a synergistic effect in disease development[7].

These findings have had direct implications for the development of new therapeutic strategies, particularly those aimed at neutralizing toxin B, and have helped redefine the classical understanding of the pathogenesis of CDI.

Additionally, the emergence of hypervirulent strains, such as NAP1/BI/027, has been associated with increased toxin production, greater sporulation capacity, and higher rates of recurrence and mortality[8]. However, the distribution and actual impact of these strains in Latin America remain poorly characterized, which limits the direct extrapolation of data from North America and Europe.

Clinical manifestations and disease severity

C. difficile infection presents with a broad clinical spectrum ranging from mild watery diarrhea to severe conditions such as pseudomembranous colitis, fulminant colitis, and toxic megacolon[9]. Diarrhea remains the cardinal symptom; however, the severity of the clinical presentation depends on multiple factors, including bacterial load, toxin production, the host's immune status, and the presence of comorbidities[10].

In mild to moderate cases, patients present with diarrhea, abdominal pain, and nonspecific systemic symptoms[11]. In contrast, severe forms are characterized by marked leukocytosis, compromised general condition, fluid and electrolyte imbalances, and a high risk of life-threatening complication[11]. In fulminant cases, transmural inflammation of the colon can lead to paralytic ileus and cessation of diarrhea, which delays diagnosis and worsens the prognosis[12].

Available evidence confirms that advanced age, recent antibiotic exposure, and prolonged hospitalization are consistently associated with greater disease severity and a higher probability of recurrence, establishing CDI as a condition of particular relevance in high-risk hospital populations[12]. The clinical manifestations of CDI can be grouped into distinct clinical phenotypes with different prognostic implications (Table 1).

Diagnostic advances and limitations of available tests

The diagnosis of CDI is based on the integration of clinical criteria with laboratory tests aimed at detecting toxigenic strains or their toxins in stool samples[13]. Available evidence demonstrates that no single diagnostic test offers optimal performance in all clinical scenarios, which has driven the use of combined diagnostic algorithms[14].

Molecular tests, such as polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP) techniques, have demonstrated high sensitivity and rapid diagnostic performance; however, their main limitation lies in their inability to distinguish between colonization and active infection, which can lead to overdiagnosis in asymptomatic patients[15]. The main tests used for the diagnosis of CDI have advantages and limitations that determine their clinical utility (Table 2).

On the other hand, toxin detection assays using enzyme-linked immunosorbent assay (ELISA) offer greater clinical specificity, although with limited sensitivity, which increases the risk of false negatives. The cytotoxicity assay continues to be considered a gold standard, but its technical complexity and the time required to obtain results have limited its use in daily clinical practice[16].

Glutamate dehydrogenase (GDH) is a constitutive enzyme produced by all strains of *C. difficile*, both toxigenic and non-toxigenic; therefore, its detection is used as an initial screening

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Clinical presentation	
1. Colitis without pseudomembrane formation	Severe diarrhoea, abdominal pain and abdominal distension. Systemic symptoms may include fever, nausea and dehydration. Stools may contain leukocytes and occult blood, whereas overt gastrointestinal bleeding is uncommon. Colonoscopy typically demonstrates diffuse or patchy mucosal inflammation.
2. Pseudomembranous colitis	Similar to the above presentation, although symptoms are more severe and leukocytosis is common. Colonoscopy reveals the characteristic pseudomembranes*, appearing as raised cream-yellow plaques on the colonic mucosa.
3. Fulminant colitis	In rare cases, CDI may present as fulminant colitis, with marked deterioration in the patient's general condition. Clinical features include severe abdominal pain, abdominal distension and severe systemic manifestations. Transmural intestinal inflammation may result in intestinal paresis and colonic dilatation with paralytic ileus, leading to cessation of diarrhoea.
4. Toxic megacolon	An uncommon but severe complication triggered by progressive inflammation involving the colonic wall, resulting in secondary dilatation of the intestinal lumen. Clinical manifestations vary but generally include severe abdominal pain, abdominal distension, high fever, tachycardia, dehydration and altered mental status. The resulting inflammation and oedema may lead to colonic perforation, sepsis and septic shock.

Notes: CDI exhibits a broad clinical spectrum, ranging from mild colitis to severe and potentially life-threatening disease. The clinical manifestations described above may overlap, and disease severity depends on host-related factors, bacterial burden and the inflammatory response. * The endoscopic findings described, including pseudomembranes, are not pathognomonic of Clostridioides difficile infection and should be interpreted within the patient's overall clinical and microbiological context. Source: Prepared by the authors.

Table 1. ***Clinical phenotypes and associated manifestations of Clostridioides difficile infection (CDI).***

test due to its high sensitivity, although with limited clinical specificity[17].

Therapeutic evidence and emerging strategies.

Historically, metronidazole was considered the first-line treatment for mild to moderate cases of *CDI*. However, accumulating evidence has shown that it is less effective in real-world clinical settings, particularly when compared with oral vancomycin, with lower rates of clinical resolution and a higher risk of recurrence. This finding has been consistent across observational studies and clinical trials, especially in patients with moderate to severe disease[18].

Additionally, an increase in the minimum inhibitory concentration (MIC) of metronidazole has been documented in some strains, suggesting a progressive decline in bacterial susceptibility, although the mechanisms of resistance are not fully defined. This phenomenon, coupled with its lower clinical efficacy, has contributed to the displacement of metronidazole as the preferred therapeutic option[19]. In this context, the updated guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (2021) recommend oral vancomycin or fidaxomicin as first-line treatment, relegating metronidazole to specific situations where no other alternatives are available[19].

The guidelines from the *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America* (2021) recommend tapering and/or pulsing regimens for vancomycin, which have been shown to reduce the likelihood of recurrence by enabling more effective eradication of residual spores. These regimens consist of progressively spaced administration of the antibiotic following a standard course, promoting the recovery of the gut microbiota. A common regimen includes 125 mg every 6 hours for 10–14 days, followed by a gradual dose reduction and administration every other day or every 2–3 days for several weeks[20].

Fidaxomicin has emerged as a relevant therapeutic alternative, especially in patients at high risk of recurrence[21]. Several studies have documented significantly lower recurrence rates compared to vancomycin, which is attributed to its lesser impact on the gut microbiota. In cases of multiple recurrences, fecal microbiota transplantation (FMT) has established itself as one of the most effective therapeutic strategies. Its rationale lies in the restoration of gut microbial diversity, which is altered following antibiotic exposure. From a methodological standpoint, FMT involves rigorous donor selection, clinical and microbiological screening, as well as standardized stool processing; the stool can be administered via colonoscopy, enema, nasogastric tube, or oral capsules[21].

Accumulated evidence, including clinical trials and real-world studies, has reported resolution rates exceeding 80–90% in recurrent infections, establishing it as a standard-of-care option in this setting. However, challenges remain regarding protocol standardization, long-term safety, and regulatory oversight[22].

In this context, regulatory-approved microbiota-based therapies have emerged, such as Rebyota (a rectal suspension

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Test	Sensitivity	Specificity	Remarks
Glutamate Dehydrogenase (GDH) Enzyme Immunoassays	Very high	Low	Detect the presence of the GDH enzyme, which is produced by all *Clostridioides difficile strains*. A positive GDH result indicates the presence of the organism but does not confirm toxin production. These assays are useful as an initial screening method owing to their high sensitivity.
Enzyme Immunoassays (EIA)	Moderate	High	Detect toxins A and B produced by *Clostridioides difficile* in stool samples. They employ toxin-specific antibodies and provide rapid, easily interpretable results. However, their sensitivity is limited, which may result in false-negative findings.
Nucleic Acid Amplification Tests (NAATs)	Very high	Moderate	Detect *Clostridioides difficile*-specific genetic material in stool samples. These tests are highly sensitive and specific and can provide rapid results. They identify toxigenic strains but do not determine whether toxins are being actively produced at the time of testing (biological activity). They are rapid, sensitive and suitable for use in resource-limited settings.

Notes: Diagnostic tests for CDI vary in sensitivity and specificity; therefore, results should be interpreted in conjunction with clinical findings. In clinical practice, the use of stepwise diagnostic algorithms combining tests with high sensitivity and specificity is recommended in order to reduce overdiagnosis and optimise the identification of clinically relevant cases. **Source:** Prepared by the authors.

Table 2. ***Main diagnostic tests for Clostridioides difficile infection (CDI): advantages and limitations.***

of fecal microbiota) and Vowst (an oral preparation of purified spores), both approved by the Food and Drug Administration for the prevention of *CDI* recurrence. These therapies represent an evolution toward standardized products with controlled safety profiles and regulated manufacturing processes, overcoming some of the limitations of conventional FMT[23]. Recent data from Europe support the use of these strategies, highlighting a significant reduction in recurrence and adequate tolerability, which reinforces their emerging role within the current therapeutic arsenal[23].

Other innovative strategies include the use of monoclonal antibodies, such as bezlotoxumab, directed against toxin B, which have been shown to significantly reduce recurrence rates when used as adjuvant therapy. Furthermore, therapies aimed at preserving the gut microbiota during antibiotic use represent a promising line of research in the primary prevention of CDI[24].

Colonization, risk factors, and prevention strategies.

Asymptomatic colonization by *C. difficile* is a common phenomenon, particularly in hospital settings and among at-risk populations. It is estimated that 3–8% of healthy adults may be carriers, a figure that can rise to 20–50% among hospitalized patients or residents of long-term care facilities. Although these individuals do not exhibit clinical symptoms, they act as potential reservoirs for the transmission of the microorganism[25].

The progression from colonization to clinical infection depends on multiple host and environmental factors. Key risk factors include prior exposure to broad-spectrum antibiotics, advanced age, prolonged hospitalization, the presence of comorbidities, immunosuppression, and the use of proton pump inhibitors. These factors contribute to alterations in the gut microbiota and reduce resistance to colonization[26].

From a pathophysiological perspective, intestinal dysbiosis resulting from the use of antimicrobials allows *C. difficile* spores to germinate and toxin A- and B-producing vegetative forms to proliferate. These toxins induce epithelial damage, disruption of tight junctions, and a local inflammatory response that leads to the development of clinical symptoms[26].

Prevention strategies are based on interrupting transmission and preserving the intestinal microbiota. Key measures include the rational use of antimicrobials through optimization programs (PROA in Spanish), hand hygiene with soap and water, isolation of symptomatic patients, and environmental disinfection with sporicidal agents. Additionally, the implementation of appropriate diagnostic protocols helps prevent overdiagnosis and unnecessary treatment.

Epidemiological implications and the burden on health care systems

Available epidemiological evidence confirms a sustained increase in the incidence and prevalence of CDI globally, particularly in hospital and long-term care settings[27]. This increase is associated not only with higher morbidity and mortality but also with a considerable economic impact, resulting from prolonged hospital stays, frequent readmissions,

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and costs associated with managing recurrences and serious complications[27].

In Europe, *C. difficile* infection continues to represent a significant cause of healthcare-associated infection. In Spain, multicenter studies have documented variable incidence rates across hospitals, attributed to differences in diagnostic algorithms, microbiological surveillance, and antimicrobial use policies[27]. Recent data indicate that the infection predominantly affects elderly, hospitalized patients with prior exposure to antibiotics or proton pump inhibitors. Furthermore, an increase in the identification of community-acquired cases and a significant persistence of recurrences have been reported, which keeps this infection a current clinical and epidemiological problem in Spain[28].

In the Spanish context, the gradual implementation of antimicrobial optimization programs (PROA) and infection control measures has helped strengthen the preventive approach, although diagnostic challenges and interhospital heterogeneity persist.

Complementarily, the European Society of Clinical Microbiology and Infectious Diseases has published updated recommendations that agree on prioritizing fidaxomicin and vancomycin over metronidazole as initial treatment. However, the ESCMID guidelines take a more conservative approach to the use of fecal microbiota transplantation, reserving it primarily for carefully selected cases of multiple recurrences, while also emphasizing the need for individualized assessment based on clinical severity, therapeutic availability, and the local epidemiological context[29].

In contrast, the recommendations from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America advocate for earlier incorporation of therapies aimed at preventing recurrences, including monoclonal antibodies and microbiota-based products.

These findings underscore the need to implement comprehensive strategies for prevention, prudent use of antimicrobials, and infection control, with the aim of reducing both the clinical burden and the economic impact of CDI on healthcare systems[30]. Various factors have been associated with both the development of the first episode and the recurrence of CDI, with notable differences between the two scenarios (Table 3).

Discussion

CDI continues to represent a significant clinical and epidemiological challenge, not only due to its high incidence in hospital settings but also because of the complexity inherent in its diagnosis, treatment, and prevention. The evidence analyzed in this review confirms that CDI is no longer a secondary complication of antibiotic use but has established itself as a distinct entity with its own dynamics, influenced by microbiological, clinical, and organizational factors.

One of the main conceptual contributions of recent studies has been the redefinition of the role of toxins in the pathogenesis of the disease. The classical notion of toxin A as the primary determinant of virulence has been superseded by solid experimental evidence that identifies toxin B as an essential factor in tissue damage, and even a dominant one in certain contexts[20]. This evolution in the understanding of pathogenesis is not merely academic but has had direct repercussions on the development of targeted therapies, such as monoclonal antibodies against toxin B, which have been shown to significantly reduce the recurrence of infection.

In the diagnostic realm, the current discussion focuses less on the availability of tests and more on their correct clinical interpretation. Molecular techniques, while having significantly improved diagnostic sensitivity and reduced turnaround times, have introduced the risk of overdiagnosis by failing to adequately distinguish between colonization and active infection. This phenomenon is particularly relevant in hospital settings with a high prevalence of asymptomatic carriers, where the indiscriminate use of highly sensitive tests can lead to unnecessary treatments and increased selective pressure on the gut microbiota. In this context, combined diagnostic algorithms emerge as the most reasonable strategy for balancing sensitivity and specificity, reinforcing the need to integrate laboratory findings with clinical judgment.

From a therapeutic standpoint, the available evidence consistently supports replacing metronidazole as the first-line option with oral vancomycin, particularly in moderate-to-severe cases. This change reflects a shift toward treatment regimens based on more robust clinical outcomes rather than solely on historical or economic considerations. Fidaxomicin, for its part, represents a significant advance in reducing recurrences, although its widespread use remains limited by cost and availability factors, especially in health systems with limited resources.

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Managing recurrence remains one of the greatest challenges in CDI. In this context, fecal microbiota transplantation has demonstrated greater efficacy than conventional antibiotic regimens, establishing itself as a key therapeutic intervention in selected cases. However, its large-scale implementation faces logistical, regulatory, and standardization barriers, underscoring the need for more uniform protocols and studies evaluating its long-term safety.

The discussion on CDI prevention transcends the individual patient level and extends to an institutional dimension. Evidence suggests that environmental control strategies, the use of sporicidal disinfectants, and the adoption of contactless disinfection technologies are effective in reducing nosocomial transmission. However, their actual impact depends on adequate adherence to protocols and an organizational culture that prioritizes patient safety. In this sense, the prevention of CDI cannot be understood solely as a technical intervention, but rather as an indicator of the quality of healthcare systems.

Finally, significant gaps in knowledge remain, particularly regarding the regional epidemiology of hypervirulent strains and the impact of new therapeutic strategies in settings other than high-income countries. The indiscriminate extrapolation of data from North America and Europe may not accurately reflect the epidemiological reality of regions such as Latin America, highlighting the need for local studies to inform prevention and treatment policies tailored to each context.

Conclusions

CDI constitutes a persistent and complex problem in modern hospital settings, with a significant impact on patient morbidity and mortality and on the economic burden on health systems. The evidence reviewed confirms that effectively addressing this issue requires a comprehensive understanding of the mechanisms of pathogenicity, particularly the central role of toxins A and B, as well as the clinical and epidemiological factors that determine the severity and recurrence of the disease.

Advances in diagnosis have enabled faster and more sensitive detection of the infection; however, these benefits must be balanced with careful clinical interpretation to avoid overdiagnosis and unnecessary treatment. In the therapeutic setting, oral vancomycin has established itself as the first-line treatment, while fidaxomicin, monoclonal antibodies, and

Risk factors for initial episode	Risk factors for recurrent episode(s)
Advanced age (≥65 years)	Advanced age (≥65 years)
Antibacterial therapy	Antibacterial therapy
Cancer chemotherapy	Gastric acid suppressive agents (proton pump inhibitors)
Enteral feeding and gastrointestinal surgery	Exposure to healthcare settings
Gastric acid suppressive agents (proton pump inhibitors)	Impaired immune response
Exposure to healthcare settings	Previous episode(s) of Clostridioides difficile infection (CDI)
Impaired immune response	Underlying chronic comorbidities
Smoking and history of smoking	
Underlying chronic comorbidities	

Notes: Risk factors for *Clostridioides difficile* infection include host-related conditions, exposure to antimicrobial agents and contact with healthcare environments. Disease recurrence is associated with additional factors, such as persistent alterations in the intestinal microbiota and impaired immune response, which increase clinical complexity and the risk of further episodes.
Source: Prepared by the authors.

Table 3. ***Risk factors associated with the initial episode and recurrence of Clostridioides difficile infection.***

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fecal microbiota transplantation represent effective strategies for reducing recurrence in selected patients.

Preventing CDI requires interventions that go beyond individual treatment and integrate institutional policies for infection control, rational use of antimicrobials, and strengthening of the patient safety culture. Likewise, there is a clear need to generate regional evidence that allows diagnostic and therapeutic recommendations to be adapted to contexts with limited resources and distinct epidemiological realities.

Overall, the management of C. difficile infection requires an interdisciplinary and dynamic approach, grounded in the integration of scientific evidence, clinical judgment, and sustained preventive strategies, as the only way to mitigate the impact of this infection on contemporary healthcare systems.

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