Clostridioides difficile infection in hospital and community settings: summary document of a multidisciplinary group

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ABSTRACT

Clostridioides difficile infection (CDI) affects the majority of hospital wards. In the context of a Continuing Medical Education Field Training course, a multidisciplinary group of expert healthcare professionals addressed the issue of CDI, producing a summary document to be submitted to the scientific community. The expert group was composed of healthcare professionals with an internal medicine background (Internal Medicine, Infectious Diseases, Nephrology, Gastroenterology, Geriatrics) with the contribution of a Microbiologist for the laboratory diagnostic aspects. During the draft of the document, various aspects of the problem were evaluated and developed.

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Key words: *Clostridioides difficile*; fidaxomicin; infection; vancomycin.

Contributions: all the authors equally contributed to reviewing and critically analyzing literature and writing the paper. All the authors approved the final version to be published.

Conflict of interest: F. Furfaro declares funding from Janssen and Pfizer, G. Gattuso from Angelini Acraf Italia. The remaining authors declare no potential conflict of interest.

Availability of data and material: data and materials are available by the authors.

Informed consent: the manuscript does not contain any individual person's data in any form.

Received: 11 November 2023.
Accepted: 13 November 2023.

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Licensee PAGEPress, Italy
Italian Journal of Medicine 2024; 18:1666
doi:10.4081/itjm.2024.1666

Epidemiology

CDI belongs to healthcare-related infections (HAI), already known since the seventeenth century, during which they were documented as "diseases linked to hospital stay". As far back as 1994, the World Health Organization (WHO) predicted that future challenges would be represented by the presence of new or re-emerging pathogens, hospital infections and antibiotic resistance. According to WHO data from 2005, approximately 8.7% of hospitalized patients are affected by HAI. In developed countries the risk is 5-10%, while in developing countries the risk is 2 to 20 times higher and affects an average of 25% of patients. In total, about 1.4 million people suffer from infections acquired as a result of healthcare. This frequency today oscillates between 3 and 12% of all patients, with a lethality of about 4%. An Italian survey conducted on a national scale in 1983 showed a prevalence of 6.8%. HAI are the most frequent and serious complication of healthcare. Data from the Ministry of Health showed that in Italy every year between 450,000 and 700,000 infections are recorded in hospitalized people and overall, they occur in 4-7% of hospitalizations with an increase in costs of around one billion euros. All departments are at risk of HAI, even if those in which they are registered most frequently are those considered "critical" (for various reasons) such as intensive care, surgery/orthopedics, geriatrics units.

The increase in HAI is motivated by: i) increase of populations "at risk" (immunosuppressed, elderly, premature, *etc*.): we are the oldest country in Europe, and patients over eighty have increased significantly in recent years; ii) technological implementation of care profiles; iii) poor evolution of operator behavior (hand washing, *etc*.); iv) increasing of "marginal" surgeries; v) staff understaffed and increased care burden (understaffing/overcrowding.

Risk factors for developing HAIs include: i) increased susceptibility of hospitalized patients; ii) use of invasive procedures both in the diagnostic and therapeutic fields; iii)

increase in bacterial resistance; iv) length of hospital stay; v) overcrowding of hospital wards; vi) non-compliance to hygienic rules; vii) inadequate facilities.

A high percentage of HAI is represented by CDI, the prevalence of which has increased in recent years throughout the world, especially in hospital settings. The incidence of CDI in Italy changes by region and year, but has always been relatively low compared to other countries, including the United States.

In Europe, an average incidence of 3.7 cases per 10,000 patient days was observed, as shown by a pilot surveillance study conducted in 2013 in 14 European countries.[1]

EUCLID is a prospective multicenter study on the prevalence of CDI in hospitalized patients with diarrhea,[2] in this study the authors collected data from 482 hospitals in 20 countries in Europe. The study focuses on some problems: the underestimation of diagnoses (about 40,000 new undiagnosed cases each year) and the increasing trend of prevalence rates.

Differently from what happens in other European countries and in America, in Italy there is not a national surveillance system for this infection. Data available for Italy come either from regional systems, such as the "Regional surveillance system for sentinel events" (Sentilomb) in Lombardy and the "Timely surveillance system for epidemics and sentinel events" in Emilia-Romagna, or from retrospective surveillance studies.

One of the most important retrospective studies on this issue was conducted in nine hospitals in Northern Italy where, over 6 years, 942 cases of CDI were identified with an incidence of 3.7/10,000 patient days, which was higher in internal medicine departments and in long-term care.[3] An increased incidence was also related to advanced age, previous exposure to antibiotics and use of proton pump inhibitors. Recurrent and severe cases were significantly associated with renal insufficiency (creatinine levels ≥2 mg/dl). The Italian data do not differ from those observed in other European countries.

According to data from the Integrated Antibiotic Resistance Surveillance System, 2,065 cases of CDI were reported in Italy in 2019, with an incidence rate of 3.5 cases per 100,000 inhabitants. However, it should be noted that this may only represent a fraction of the actual number of cases, due to under-reporting of CDI.

Symptomatology and diagnostics

CDI is one of the most important HAIs in industrialized countries and represents the main cause of diarrhea in hospital settings. It can present a wide range of clinical manifestations, from simple self-limiting diarrhea to very severe clinical pictures, such as pseudomembranous colitis and toxic megacolon. The severity depends mainly on the host's immune response and the virulence of the strain causing the infection.

In recent decades there has been an increase in cases of CDI with an increase in severity and mortality.[4] The diagnostic protocol must be implemented according to the time variable and the sensitivity and specificity characteristics of the available analytical methods, primarily glutamate dehydrogenase (GDH) for the search for the non-specific antigen. GDH is an excellent marker to detect the presence of *Clostridioides difficile*;[5] if the test is positive, the laboratory should proceed with the research for toxins and relative mutations. In particular, the laboratory should proceed with the search for genetic targets with molecular biology methods: toxin B (tcdB), binary toxin (cdtA), deletion of the gene (tcdC) at nucleotide 117 associated with the ribotype strain 027, a predictor of severity and mortality and hypoexpression regulator. The search for toxins is also carried out with immunoenzymatic methods and with culture, after enrichment on selective/differential media for epidemiological purposes.[6] In case of a positive result, the Microbiology Laboratory must immediately notify the healthcare personnel of the operating unit concerned of the positive results of the tests by phone.

After receiving the report, the nurse in charge of the Hospital Infections Committee carries out an accurate epidemiological investigation in the operating unit concerned and supports the staff in choosing the appropriate isolation measures to adopt. The patient must be placed in a single room equipped with toilet facilities; alternatively, if this is not possible, he can be placed in the same room as patients with a similar diagnosis (cohort isolation).

It is necessary to proceed with functional isolation, delimit the patient's area, transfer the materials, implement hand washing and dedicate the toilet service to the infected only. These isolation precautions must be maintained until 48 hours after the last diarrheal discharge.

The diagnostic protocols currently in use are multistep, with quality standards at the highest level of diagnostic performance (Figures 1-2).[7,8] In order to minimize false negative results, the correct methods for collecting, storing and transporting the sample (preanalytical phase) must be scrupulously observed. Samples of diarrheal stools, Bristol scale 5-7, must be sent to the laboratory within 1 hour of collection in a sterile jar with a scoop or stored at 4°C for no more than 48 hours, to guarantee the integrity of the toxins. The laboratory must be able to perform the test seven days a week and 24 hours a day, at least as an antigen search. Only in case of suspected *Clostridioides difficile* ileus, it is justified to carry out the research on formed stools, while it is recommended to not perform it on stool samples of asymptomatic subjects. Among hospitalized patients, subjects presenting diarrhea not linked to a known cause at the time of hospitalization should be tested, such as diarrhea that occurred within the first 48 hours in patients hospitalized in another hospital or nursing home in the previous month; diarrhea that occurred at least two days after hospitalization. Among outpatients, subjects with diarrhea discharged from a hospital for no more than four weeks or coming from nursing homes or sheltered homes should be tested. Repeating the test is only necessary in the event of a negative search for toxins A and B and in the presence of a strong clinical suspicion (possible low sensitivity of the test). In case of suspected recurrence of CDI, the test for *Clostridioides difficile* is repeated, without excluding the search for other possible causes of diarrhea. No healing confirmation test should be performed after treatment.

The toxigenic *Clostridioides difficile* strains isolated in the laboratory, especially in the presence of a serious clinical picture of the disease or in situations in which an epidemic occurs, must be kept in the strain library, in order to be able to carry out typing, if necessary, even retrospectively.

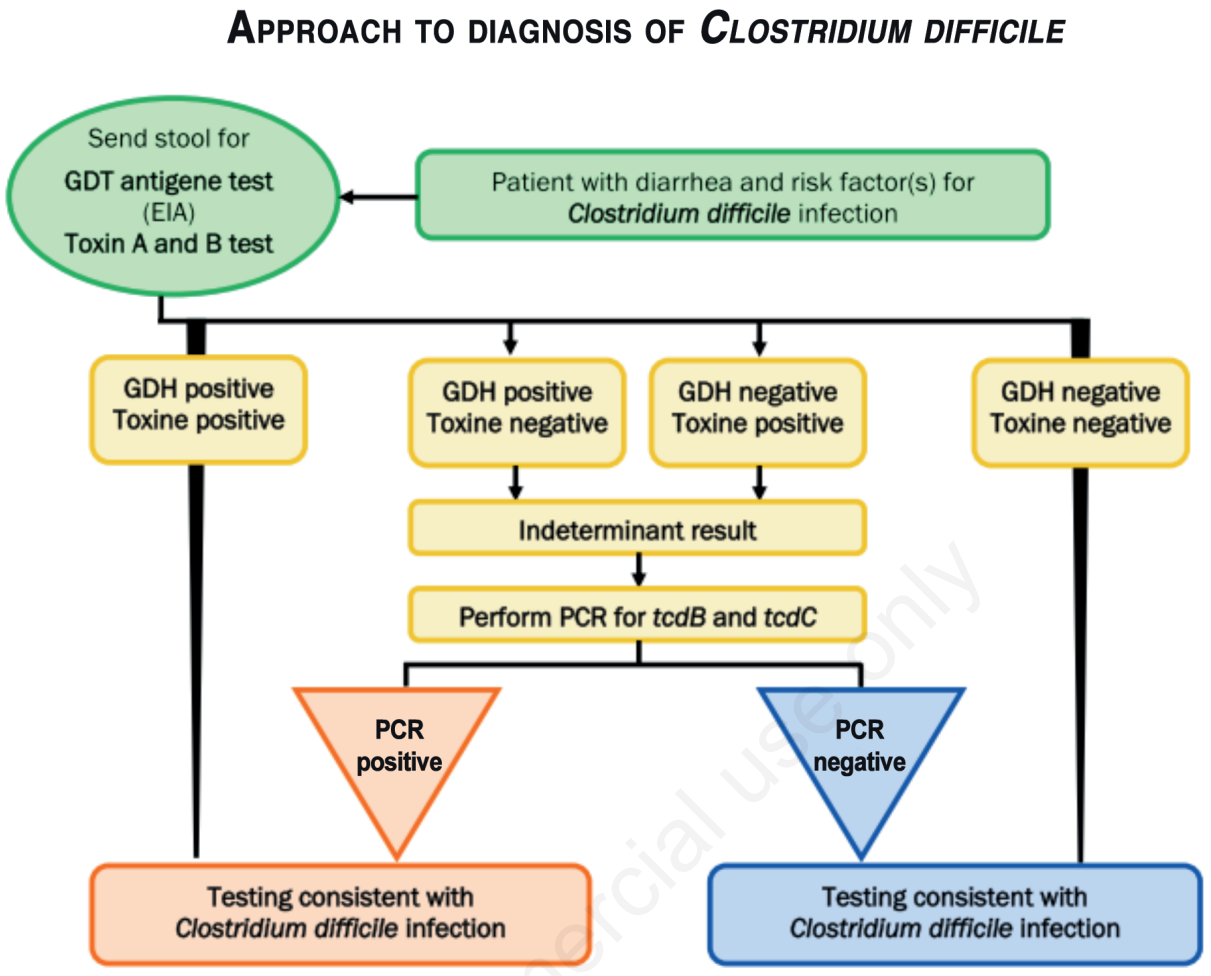

Figure 1. Diagnostic protocol.[7]

	SPECIFITY	SENSIVITY
Single step	94 - 97 %	86 - 92 %
Multi step	92 - 100 %	68 - 100 %

Figure 2. Modified and adapted diagnostic protocols specificity and sensitivity.[8]

Guidelines and therapy

New guidelines on the management of CDI have recently been published by scientific societies and bodies such as: Infectious Diseases Society of America (IDSA)/ Society for Healthcare Epidemiology of America (SHEA), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), American College of Gastroenterology (ACG), and National Institute for Health and Care Excellence (NICE).[9-12]

From a methodological point of view, the Grading of Recommendations Assessment, Development, and Evaluation system was used in all the guidelines to determine the strength of the recommendations and the quality of the scientific evidence.[13]

The two universally recommended criteria for defining a severe form of the disease are: leukocytosis and worsening of renal function (Table 1); the presence of fever is a severity criteria only for ESCMID. Similarly, a picture of sepsis (hypotension or shock) or severe gastrointestinal involvement (paralytic ileus, toxic megacolon) are indicative of a fulminant (or severe-complicated) form; a significant lactates increase is also highlighted in the ESCMID guidelines.

Stratification of recurrence risk,[14] and severity are recommended for appropriate therapeutic choice.[15] Recent guidelines have placed particular emphasis on the risk of relapses.

The main drugs taken into consideration are metronidazole, vancomycin, and fidaxomicin.

Based on literature data, with metronidazole the cure rate is about 70-75% and the relapses rate is 20-30%. The inferiority compared to vancomycin in both severe and mild/moderate forms has led to the withdrawal of metronidazole from the recent guidelines,[16] although some controversy remains since, in addition to the lower cost, some authors suggest the use of metronidazole in selected groups,

such as in severe forms with ileus/megacolon; in these cases, metronidazole is parenterally administered in association with vancomycin per os.

Treatment with vancomycin, on the other hand, is still widely used in CDI, with a cure rate of 80% even in severe forms. Vancomycin is an adequate alternative to fidaxomicin in terms of therapeutic success, despite a higher risk of relapses; the debate in scientific societies regarding the best "cost/effectiveness" ratio is large.

Limitations of vancomycin are the poor antibacterial selectivity and the greater impact on the intestinal microbiota, which is partly responsible for the relapses; it can also favor the selection of vancomycin-resistant Enterococcus and Candida. The standard therapeutic schedule is 125 mg x 4/day orally for 10 days; at this dosage, the risk of systemic effects is very low, given the modest absorption of the drug. Some authors recommend higher doses (500 mg x 4/day) in severe forms or in the absence of response to the standard dose, but controlled studies are lacking. In patients with paralytic ileus, vancomycin can be administered rectally. In relapses, this drug is still a frequent choice; the suggested scheme is "pulsed-tapered", the efficacy of which was found to be 83%.[17] At first relapse of CDI treated with metronidazole or fidaxomicin, the vancomycin regimen is the standard one.

Fidaxomicin has been available since 2011 and until a few years ago it was mostly used in relapses, also due to its high cost; currently, it is considered the first choice drug (in relation to the available resources) also at first infection; this after the results of randomized clinical trials comparing vancomycin (Table 2).[18] The standard therapeutic scheme is 200 mg twice a day for 10 days. Even the "extended" scheme, evaluated in a randomized clinical trial with vancomycin, showed the superiority of fidaxomicin in terms of sustained healing. According to some authors, certain aspects in clinical trials remain to be clarified: for example, fidaxomicin *vs.* vancomycin in severe-complicated CDI, efficacy of fidaxomicin + bezlotoxumab in preventing relapses, when to consider fecal microbiota transplantation as an alternative to fidaxomicin.

Based on the various positions of the three corporate guidelines on how to treat the initial form and the first relapse of CDI (Table 3), the drugs to be used as first-line should be fidaxomicin or vancomycin, while the drug to be used on the first relapse should be fidaxomicin.

If the criteria for a high risk of recurrence already exist at the first episode, fidaxomicin should be considered immediately. In fact, the greater ability of fidaxomicin in preventing relapses, both in the initial form and in relapses, means that it is currently to be considered the first-line drug in severe and non-severe disease. However, vancomycin remains a recommended therapy, while intravenous metronidazole maintains a role in the treatment of severe-complicated forms, albeit on the basis of expert opinion. In addition to the standard

Table 1. Diagnostic criteria of severe or fulminant disease, modified from Bishop *et al.*[13]

	IDSA/SHEA 2021	ESCMID 2021	ACG 2021	NICE 2021
Severe	White blood cells >15 x10^9/L or serum creatinine ≥1.5 mg/dl	White blood cells >15 x10^9/L or increase of serum creatinine >50% from baseline, or body temperature >38.5°C	White blood cells >15 x10^9/L or serum creatinine ≥1.5 mg/dL	White blood cells >15 x10^9/L or serum creatinine ≥1.5 mg/dL or body temperature >38.5°C or evidence of severe colitis
Fulminant	Presence of hypotension or shock, paralytic ileus, or toxic megacolon	Presence of one of the following: hypotension, shock, increased lactate, paralytic ileus, or toxic megacolon, intestinal perforation, any fulminant course (*e.g.* rapid patient deterioration)	Presence of hypotension or shock, paralytic ileus, or toxic megacolon	Presence of hypotension or paralytic ileus, or toxic megacolon

IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ACG, American College of Gastroenterology; NICE, National Institute for Health and Care Excellence.

Table 2. Results of controlled clinical trials comparing fidaxomicin *vs.* vancomycin.

Therapeutic success rate (primary endpoint in non-inferiority studies) in first CD infection. Non-inferior in the group treated with fidaxomicin *versus* vancomycin (approximately 88-90% *vs.* 86-89% in the ITT and PP analyses).
Relapse rate (secondary endpoint): significantly reduced in the fidaxomicin *versus* vancomycin group (13-14% *vs.* 25-27%). In agreement with this result, also the secondary end-point defined as "global cure" (clinical healing and absence of relapse) was significantly better in the group treated with fidaxomicin (74-76% *vs.* 63-64%). In terms of safety, there were no differences between the two treatment groups.
Pooled trial data analysis and subgroup analysis. Treatment with fidaxomicin had better outcomes, compared to vancomycin, in patients with concomitant antibiotic therapy (higher frequency of healing and fewer relapse), with neoplasia (higher frequency of healing), with previous CD infection (lower frequency of second relapse, about 20% *vs.* 36%).
Trial extend (open RCT comparing fidaxomicin with a "pulsed" regimen *vs.* vancomycin 125 mgx4/day for 10 days in patients aged >60 years). Fidaxomicin schedule: 200 mg twice/day on days 1-5, then 200 mg/day every other day from days 7 to 25. Sustained clinical healing 30 days after the end of treatment (primary endpoint) significantly greater in the fidaxomicin group (70% *vs.* 59%). In subgroup analysis, the superiority of fidaxomicin was independent of age, previous CD infection, ribotype 027 infection, severity of CD infection, or the presence of cancer.

CD, *Clostridioides difficile*; ITT, insulin tolerance test; PP, pulse pressure; RCT, Randomized controlled clinical trials.

modalities (fidaxomicin 200 mg bid or vancomycin 125 mg qid, both for 10 days) the guidelines contemplate the possibility of using "extended-pulsed" fidaxomicin (200 mg bid for 5 days, then 200 mg every other day for 20 days) or tapered-pulsed vancomycin (125 mg qid for 14 days, bid for 7 days, qd for 7 days, then every 3 days for 1 week). Only NICE guidelines recommend vancomycin in the initial episode (fidaxomycin in the second line in case of therapeutic failure):[12] at the basis, there are rigid economic assessments, for which the two strategies are not cost-effective from the perspective of the British National Health System.

In view of what the latest guidelines state regarding the need to use fidaxomicin as a first line in CD infection and relapses, in clinical practice the high cost limits its use, favoring less expensive second-line therapies. Despite the latest guidelines state recommend the use of fidaxomicin as a first-line drug in CD infection and relapses, in clinical practice the high cost limits its use, favoring less expensive, second-line therapies.

Second-line therapies include vancomycin and, in rare situations, metronidazole, which find a role both in the case of scarce availability or scarce economic resources, and in particular clinical situations for which controlled studies are not available.

Among the therapies for recurrences or special cases of CDI, in addition to the already described standard regimen treatments with fidaxomicin and vancomycin, and specific therapeutic schemes ("pulsed-tapered" vancomycin and

Table 3. Recommended drug therapies, modified from Bishop *et al.*[13]

	IDSA/SHEA 2021	ESCMID 2021	ACG 2021	NICE 2021
Non-severe initial episode	FDX-STD Alternative: VAN-STD Alternative: MET-STD if both previous ones are unavailable	FDX-STD Alternative: VAN-STD if FDX unavailable Alternatives: MET-STD only if both previous ones are unavailable Alternatives: FDX-EP if increased risk of recurrence (1) Alternatives: VAN-STD + BEZ if increased risk of recurrence (1) and FDX unavailable	FDX-STD VAN-STD Alternative: MET-STD in low-risk patients (young patients with minimal comorbidities)	VAN-STD Second line: FDX-STD
Severe initial episode	FDX-STD Alternative: VAN-STD	FDX-STD VAN-STD	FDX-STD VAN-STD	VAN-STD Second line: FDX-STD
First relapse	FDX-STD o FDX-EP (+ BEZ if initial episode <6 months) Alternative: VAN-STD (if MET-STD used for initial episode) or VAN-TP (+BEZ if initial episode <6 months)	FDX-STD (if FDX not used for the initial episode) VAN-STD + BEZ (if FDX used for the initial episode) FDX-STD + BEZ (if FDX used for initial episode) Alternative: VAN-TP if FDX e BEZ unavailable	VAN-STD (if FDX, VAN or MET for initial episode) (+ BEZ if age >65 years and immunocompromised or initial episode <6 months) FDX-STD (if VAN or MET for initial episode) (+ BEZ if age >65 years and immunocompromised or initial episode <6 months)	FDX-STD VAN-STD (if first episode >12 weeks)
Further relapse	FDX STD o FDX-EP (+ BEZ if initial episode <6 months) VAN-TP (+ BEZ if initial episode <6 months) VAN-STD followed by RX (+ BEZ if initial episode <6 months)	FDX-STD + BEZ VAN-STD + BEZ	VAN-STD (+ BEZ if age >65 years and immunocompromised or initial episode <6 months)	FDX-STD VAN-STD (if initial episode >12 weeks)
Severe relapse	FDX-STD Alternative: VAN-STD	FDX-STD VAN-STD	FDX-STD (+ BEZ if age >65 years) VAN-STD (+ BEZ if age >65 years)	FDX-STD VAN-STD (if initial episode >12 weeks)
Fulminant (severe-complicated)	VAN-500 + MET-EV	FDX-STD VAN-STD	VAN-500 + MET-EV	VAN-500 + MET-EV

Age >65 plus at least one additional factor of healthcare-related illness, hospitalization in the previous 3 months, previous episode of CDI, PPI therapy during/after diagnosis of CDI, concomitant use of antibiotics. IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ACG, American College of Gastroenterology; NICE, National Institute for Health and Care Excellence; FDX-STD, Fidaxomicin 200 mg bid for 10 days; FDX-EP, Fidaxomicin 200 mg bid for 5 days, then 200 mg qd every other day for 20 days; VAN-STD, Vancomycin 125 mg qid for 10 days; VAN-TP, Vancomycin 125 mg qid for 14 days, bid for 7 days, qd for 7 days, then every 3 days for 1 week; VAN-500, 500 mg qid for 10 days; MET-STD, Metronidazole 500 mg td for 10 days; METH-IV, Metronidazole 500 mg IV td for 10 days; RX, Rifaximin 400 mg tid for 20 days; BEZ, Bezlotoxumab 10 mg/kg IV single dose during course of antibacterial therapy.

"extended" fidaxomicin), also the antibody monoclonal anti-toxin B (bezlotoxumab), fecal microbiota transplantation and surgery should be considered.

Bezlotoxumab is a monoclonal antibody that binds to CD toxin B, preventing its harmful action on the intestinal epithelium.[9-11] Associated with standard therapy, it reduces recurrence of CDI and is approved for the prevention of recurrence of CDI in high-risk adult patients.[19] The monoclonal antibody bezlotoxumab is recommended in addition to fidaxomicin or vancomycin in relapses as a possible option in all patients (ESCMID),[10] or in case of an initial episode less than 6 months ago (IDSA/SHEA, ACG),[9,11] or in immunosuppressed subjects (GCA).[11] Only the NICE guidelines do not include the use of bezlotoxumab among the recommendations:[12] also in this case, rigid economic assessments are the basis. The prescription takes place after completing the AIFA monitoring form, which limits its use to patients with CDI and at least one of the following risk factors for recurrence: age over 65, serious infection, or immunosuppression. Bezlotoxumab is administered in a single intravenous dose at the dosage of 10/mg/kg and, as a drug with only prophylactic action, it should be used in association with CDI therapy. In patients with congestive heart failure, it is necessary to evaluate the risk/benefit ratio for the risk of exacerbation. The results of the various clinical studies are reported in Table 4.[19] The comparison remains to be evaluated the fidaxomicin *vs*. bezlotoxumab in terms of prevention of recurrences, since in the related studies only 4% of patients had been treated with fidaxomicin.

Fecal microbiota transplantation is an approved ancillary treatment for multiple relapses; efficacy is reported in 83-94% of cases, therefore superior to vancomycin and fidaxomicin in patients with multiple relapses.[20] The American scientific societies have limited the transplantation of fecal microbiota to the third and subsequent relapse, after cases of transmission of enteropathogenic Escherichia coli in recipients. Transplantation is indicated in patients with multiple recurrent CDI (therefore from the third episode), refractory to standard antibiotic therapy.[9,11,21] Its action consists of restoring the normal intestinal microbiota by creating an unfavorable environment for the multiplication of *Clostridioides difficile*. It is obtained from the feces of a healthy individual, feces are treated in order to obtain a suspension to be administered with colonoscopy or alternatively by rectoclysis or by naso-gastric or naso-jejunal tube.[22,23] Given the risk of transmission of pathogens, rigorous screening of the donor is recommended to prevent the transmission of infections;[9] it is considered and managed as a real organ transplant.

Surgical therapy is reserved for severe or fulminant CDI, which represent 5-20% of cases and are associated with high mortality (15-25% of cases, 30-35% in patients admitted to the intensive care unit). They are characterized by systemic complications (sepsis, hypotension/shock), and gastrointestinal complications (pseudomembranous colitis, paralytic ileus, toxic megacolon, intestinal perforation); they require intensive supportive care and in about 25% of cases surgery with a post-operative mortality of about 30-50%. A meta-analysis showed that surgery improves mortality in patients failing medical therapy, but the studies analyzed did not define specific inclusion criteria or best therapeutic window. Surgical techniques are loop ileostomy and total colectomy (indicated in case of abdominal compartment syndrome, necrosis, perforation).

Other therapies include: i) rifaximin: after standard antibiotic therapy it can reduce relapses rates; it is approved for patients with more than one recurrence (weak recommendation); ii) tigecycline: approved by ESCMID as combination therapy for severe-complicated CDI; iii) probiotics: in accordance with the main guidelines, there are not enough data to recommend their use in primary prevention of CDI in patients on antibiotic treatment or for the prevention of relapses of *Clostridioides difficile* infection.[9,11,21] They have been evaluated in many studies, but the high heterogeneity of doses and types and the numerous limitations do not provide enough data to recommend probiotics for primary prevention.[24]

General indications: other generic therapeutic/managerial suggestions are the suspension of antibiotics and proton pump inhibitors, when possible. All antibiotics can alter the intestinal microbiome favoring the proliferation of CD, but some of them such as fluoroquinolones, clindamycin, broad-spectrum penicillin and cephalosporins are more frequently associated with the development of the infection. To reduce the incidence of CDI, it is recommended to implement antibiotic stewardship in order to reduce, where possible, the frequency and duration of therapy with high-risk antibiotics and reduce the number of antibiotics prescribed.

Antibiotic prophylaxis: only in selected cases (patients with recurrent CDI who are not eligible for fecal microbiota transplantation or who recur after transplantation and who require long-term antibiotic therapy or frequent courses of antibiotic therapy), after consultation with an infectious disease specialist, it is possible to consider prophylaxis with oral vancomycin concurrently with antibiotic treatment to prevent further episodes of CDI.

Table 4. Results of randomized controlled trials comparing standard therapy *versus* standard therapy + bezlotoxumab.

MODIFY I and MODIFY II studies, randomized controlled trials comparing bezlotoxumab + standard therapy *vs.* standard therapy in patients with first or relapsed CD infection:
The 12-week relapse rate was significantly lower in the bezlotoxumab group (129/781, 16.5% *vs.* 206/773, 26.6% in the placebo group.
The number of treatments needed to prevent an episode of rCDI was 10 in the total group, 6 in the subgroups ³65 years and in those with previous CD infection.
Mild ADRs: nausea/vomiting, abdominal pain, diarrhea, asthenia, fever, headache.
Severe ADRs (rare): sepsis, pneumonia, ARF, UTI, CHF (the latter is a limitation of use due to a higher rate of death in the bezlotoxumab group compared to placebo).
Subsequent studies (mostly multicenter retrospective, in patients with co-morbidities, with first or second recurrence of CD infection, in bone marrow transplant patients and other series, real-world experience studies, systematic review of bezlotoxumab studies) confirmed low relapse rates.

Bezlotoxumab scheme: dose 10 mg/kg iv in 60', in a single administration within the 14th day of treatment. CDI, *Clostridioides difficile* infection; rCDI, recurrent *Clostridioides difficile* infection; ADRs, adverse drug reactions; ARF, acute renal failure; UTI, urinary tract infection; CHF, congestive heart failure.

Pharmacoeconomics

Treatment and management of CDI can be complex, and cost considerations are becoming increasingly important in healthcare decision-making. Most pharmacoeconomic studies have been conducted in the United States, with a few studies in Europe and Asia. Published studies have evaluated the cost-effectiveness, and cost-utility of different interventions for the management of CDI.

Many studies evaluated the economic burden of CDI, including healthcare costs, lost productivity, and decreased quality of life. The estimated cost of CDI varies widely, from $3,000 to $30,000 per episode.[25] Antibiotic treatment is the primary management strategy for the infection, and several studies have compared the cost-effectiveness of available antibiotic regimens. Most studies suggested that fidaxomicin is more cost-effective than vancomycin or metronidazole due to lower recurrence rates and, therefore, lower hospital admissions in patients treated with this therapy.[26,27]

Studies on the analysis of the costs of the various elements during hospitalization for CDI, showed that the most important economic factor is not the type of therapy chosen, but the length of hospital stay.[28] It can therefore be stated that the cost-effectiveness assessment must not be limited to the cost of the drug, but must take into consideration all the other factors that impact the choice of therapy.

Control and prevention strategies

CDI prevention strategies must aim at the diagnosis, treatment and timely isolation of cases of infection, the reduction of environmental contamination and the correct management of antibiotic therapy.[29]

The measures to be implemented for prevention are therefore: i) active surveillance of cases (important to understand the local epidemiology and evaluate the control measures adopted against the infection); ii) timely diagnosis and treatment; iii) isolation and contact precautions; iv) hand hygiene (prefer washing with water and detergent solution or antiseptic detergent to alcoholic rub, because the only antiseptics act only on the vegetative forms and not on the spores of CD); v) environmental hygiene (the vegetative forms of CD survive in the environment for about 15 minutes, but the spores can also survive for months); vi) proper management of antibiotics (antibiotics, together with age, are considered the major risk factors for CDI); vii) training and information for healthcare professionals.

Conclusions

CDI remains a major public health problem. It is certainly necessary to have epidemiological data available on the real frequency of CDI in Italy, on the most affected population groups/care settings, on the type of circulating strains, on the frequency and characteristics of epidemic events in order to increase the perception of the problem and to activate effective intervention. New drugs such as fidaxomicin are changing the natural history of the disease, particularly in the prevention of relapses; moreover, from a microbiological point of view, many progresses have been made: in fact, diagnostics can now also be performed at the genotype level, which makes it possible to decide on the targeted use of the available therapies. For the near future, efforts should be made to implement clinician-biologist interactivity throughout the use of dedicated platforms.

The goal, however, is not to treat but to prevent healthcare-associated infections. Antibiotic stewardship is certainly essential to reduce intestinal dysmicrobism and the consequent risk of CDI.

Prevention passes through the adoption of good healthcare practices, given that 20-40% of hospital infections are caused by microorganisms transmitted by hands; the isolation of the patient, the rational management of the antibiotics, the control of the environments with adequate hygiene of the spaces and the improvement of the microbiological diagnostics represent the milestones of the management of this infectious problem.

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