Updated Czech guidelines for the treatment of *Clostridioides difficile* infection

Jiří Beneš[1], Roman Stebel[2], Václav Musil[3], Marcela Krůtová[4], Jiří Vejmelka[5], Pavel Kohout[5]

[1]Department of Infectious Diseases, 3rd Faculty of Medicine, UK, FN Bulovka, Prague
[2]Department of Infectious Diseases of the Faculty of Medicine of the MU and FN, Brno
[3]Department of Children's Infectious Diseases, Faculty of Medicine, Faculty of Medicine, Brno
[4]Institute of Medical Microbiology 2nd Faculty of Medicine UK and FN Motol, Prague
[5]Internal Clinic of the 3rd Faculty of Medicine, UK and FTN, Prague

Address for correspondence: Prof. MD Jiří Beneš, CSc., Department of Infectious Diseases 3rd Faculty of Medicine UK, FN Bulovka, Budínova 2, 180 81 Prague 8. E-mail: benes.infekce@seznam.cz.

Content

Abstract
The updated Czech guidelines differ in some aspects from the 2021 guidelines issued by the ESCMID Study Group for *Clostridium difficile*. The key points of these Czech recommendations may be summarized as follows:
• The drug of choice for hospitalized patients is orally administered fidaxomicin or vancomycin. In outpatients with a mild first episode of *C. difficile* infection, metronidazole can also be used.
• If the patient´s response to treatment is good and there are no complications, the duration of antibiotic treatment can be reduced (e.g., to 5 days in case of fidaxomicin or to 6-7 days in case of vancomycin).
• If oral therapy is impossible, the drug of choice is tigecycline, 100 mg i.v., b.i.d., with initial shortening of the interval between the first and second doses for faster saturation. If the severity of the disease progresses during this antibiotic treatment, it is necessary to access the ileum or

cecum, i.e. to perform double ileostomy or percutaneous endoscopic cecostomy, and to instill vancomycin or fidaxomicin lavages.
• Fulminant *C. difficile* colitis should be treated with oral fidaxomicin ± tigecycline i.v. If peristalsis ceases, fidaxomicin should be administered into the ileum or cecum as described above. If sepsis develops, a broad-spectrum beta-lactam antibiotic (piperacillin/tazobactam, carbapenem) i.v. is added to topically administered fidaxomicin instead of tigecycline i.v.; at the same time, colectomy should be considered as the last resort.
• To treat first recurrence, fidaxomicin or vancomycin is administered with a subsequent fecal microbiota transplant (FMT) from a healthy donor. For second or subsequent recurrence, administration of fidaxomicin is of little benefit; the therapy of choice is oral vancomycin and subsequent FMT. Prolonged vancomycin or fidaxomicin taper and pulse treatment is appropriate only when FMT cannot be performed. The guidelines were reported and defended at the Annual Meeting of Heads of Infectious Disease Departments in the Czech Republic.

Keywords: *Clostridioides difficile* infection, vancomycin, fidaxomicin, metronidazole, faecal microbiota transplant.

Introduction

The first Czech guidelines for the diagnosis and treatment of clostridial colitis was written and defended in the spring of 2014 [1]. In 2016, the official taxonomic name of the etiologic agent was changed [2], and in 2017 and subsequently in 2021, updated guidelines were issued in the EU and the USA [3, 4, 5, 6]. We are responding to this development by creating a new Czech guidelines, in which all important news in the issue of clostridial colitis are included and discussed.

Definitions

The definitions in this chapter are the same as in the European guidelines [4].
Colitis caused by *C. difficile* (clostridial colitis): The acronym CDI, derived from the phrase "*Clostridioides difficile* infection", is used in the English and Czech literature for this disease. The diagnosis of CDI is based on the presence of clinical manifestations indicative of intestinal involvement and the detection of toxins or a toxigenic strain of *C. difficile* in the patient's stool. For detailed list of diagnostic criteria see chapter - Diagnostics.
A successful treatment (treatment response) is defined as a return to normal stool frequency and consistency that occurs during treatment and persists without any other therapeutic intervention directed at the intestinal tract ≥48 hours after the end of treatment. At the same time, it is assumed that the parameters of the severity of the disease (clinical, laboratory, radiological) will improve, and no new signs of serious disease may appear.
Refractory CDI is a disease in which the condition does not improve even after 3-5 days of recommended treatment. Refractory CDI can occur in both uncomplicated and complicated CDI.
Recurrence means the reappearance of CDI symptoms within 8 weeks after successful treatment of the previous episode. However, many experts recommend extending the follow-up period to 12 weeks (3 months or 90 days). The term "recurrence" is used because in practice it is usually not possible to distinguish a relapse (caused by the resumption of an untreated

infection) from a recurrence (a new infection caused by the same or a different strain of microbe).

Severe CDI (severe CDI) is defined by the presence of at least one of the following symptoms: fever >38.5°C; leukocytosis >15 x 10^9/l; an increase in serum creatinine levels >50% above normal values. The diagnosis of severe CDI is further supported by imaging findings that demonstrate colonic distension, destruction of pericolonic adipose tissue, or colonic wall thickening. American guidelines expand the criteria for severe CDI to include additional criteria (Table 2).

Fulminant CDI (severe-complicated CDI) is defined by the presence of at least one of the following symptoms: hypotension; septic shock; an increase in serum lactate above the physiological range; ileus; toxic megacolon; bowel perforation; rapid deterioration of the patient's general condition. At the same time, it is assumed that the mentioned symptoms are caused by a clostridial infection and have no other cause.

Etiologic agent

Clostridioides difficile is a gram-positive sporulating bacterium commonly found in nature, wastewater and surface water, as well as in the digestive tract of animals and humans. It resembles clostridia in many of its properties, which is why it was originally classified in this genus under the name *Clostridium difficile*.

The reasons for separating this bacterium into a separate genus lie in the different composition of the cell wall and different intermediate metabolism, which is manifested, among other things, in greater demands for cultivation (hence the species designation "difficile", i.e., difficult to cultivate). Another difference lies in the natural resistance of *C. difficile* to several antibiotics. Due to these properties, the bacterium was reassigned to the *Peptostreptococcaceae* family, where a new separate genus was established for microbes with similar properties [2, 7]. After a difficult search for consensus, the name *Clostridioides* was chosen for this newly created genus, while the species designation "difficile" was retained[1]. Thanks to this measure, the abbreviated name of the microbe remained unchanged - *C. difficile* [8].

Hypervirulent strains of *C. difficile*: At the beginning of this century, strains of *C. difficile*, which are characterized by increased toxin production and therefore increased morbidity and mortality were described. Another unpleasant feature of these strains is reduced sensitivity to some antibiotics, especially metronidazole. The best known and most important of these strains is referred to as NAP1/B1/027 or abbreviated as ribotype 027 [9]. Ribotypes 078 and 001 are also characterized by increased virulence. In the Czech Republic, the occurrence of ribotype 176, which is genetically very similar to ribotype 027, predominated for a long time [10]. Recently, however, a greater diversity of *C. difficile* strains has been detected in the Czech Republic, of which the epidemic ribotype 001 predominates (35%) [11].

[1] Some authors recommend keeping both the original and the new name microbe in the professional literature [12]. However, the authors of the Czech recommended procedures do not consider this solution appropriate, because the taxonomic terms should be unambiguous and uniform.

Pathogenesis of the disease

Predisposition: Factors promoting the development of CDI are shown in Table 1. The most important precipitating factor is intestinal dysmicrobia, caused by antibiotic treatment. The time required to induce CDI ranges from several days to weeks; however, the development of clostridial colitis has been described even after a single dose of antibiotics. The disease can appear during antibiotic treatment, but also several weeks after its end.

Origin of the disease: *C. difficile*, as a strictly anaerobic bacteria, cannot invade vital tissues. Under physiological circumstances, it forms only part of the intestinal microbiota. Only toxigenic strains that produce toxin B (the most important) and possibly also toxin A and binary toxin can cause the disease. Toxins B and A kill human cells, the binary toxin damages the cytoskeleton of intestinal epithelial cells, induces the formation of microtubules on the surface of the intestinal mucosa and thus facilitates the adherence of *C. difficile* to the mucosa [13, 14]. All the mentioned toxins act synergistically and in the vicinity of the microbial colony they can damage both the intestinal epithelium and the deeper layers of the intestinal wall. The development of the disease under physiological conditions is mainly prevented by the natural intestinal microbiota and also by the activity of the immune system [15, 16, 17].

From a clinical point of view, the early phase of the disease is characterized by the formation of island-like ulcerations on the colonic mucosa. The surface of these ulcers is covered with plaques. Diarrhea at this stage represents a self-cleansing mechanism that is beneficial for the patient. On the contrary, poor peristalsis or the administration of drugs suppressing intestinal motility are factors that promote the progression of the disease.

Due to the action of toxin B on the smooth muscle and vegetative nerves in the wall of the colon, peristalsis will gradually stop, and ileus will develop, which further supports the multiplication of *C. difficile*. The terminal stage of the disease is characterized by an enormous distension of the colon (megacolon) and/or a gradual loss of the barrier function of the intestinal mucosa, so that various intestinal bacteria and their toxins can penetrate deeper tissues and into the bloodstream and cause a septic state.

Recurrence: Until the physiological intestinal microbial ecosystem is restored, the organism remains highly susceptible to re-overgrowth of clostridia and therefore to a new attack of the disease. It is assumed that the main cause of recurrences are spores, millions of which the patient with clostridial colitis excretes in each milliliter of diarrheal stool and contaminates his surroundings with them. The infectious dose in a susceptible individual ranges from tens to hundreds of spores. Re-development of the infection therefore occurs very easily in persons with persistent intestinal dysmicrobia[2]. Some authors suggest that the cause of recurrences may also be the persistence of *C. difficile* in the biofilm adhered to the intestinal wall [16, 18].

Clinical presentation

Colitis caused by *C. difficile* in younger people without alteration of the general condition usually arises as a result of previous antibiotic treatment and manifests as an acute diarrheal disease, which may or may not be accompanied by fever and vomiting. Diarrhea in clostridial

[2] It is important to note that in our conditions, resistance of *C. difficile* to antibiotics administered in the treatment of colitis is not the cause of recurrences. In the treatment of recurrence, it is therefore not a mistake to use the same antibiotic again as in the treatment of the previous attack of the disease.

colitis is not profuse, stools are numerous, sometimes smelly, but not voluminous. In bedridden patients (e.g., after surgery), this condition can appear as a sudden stool incontinence.
More serious forms of the disease are accompanied by abdominal pain, flatulence and gradual weakening of intestinal peristalsis leading to the development of ileus. In elderly patients, this condition may be accompanied by increase in apathy and quantitative impairment of consciousness. Fever is usually not present. In the laboratory, prominent leucocytosis is often detected, which contrasts with a slightly elevated CRP level. Clostridial colitis should be suspected especially in the situations described in Table 2. Table 3 describes the characteristics of the severe form of CDI.
CDI mortality is in the range of 3-17% [19] and depends on the proportion of old, polymorbid and otherwise disposed persons in the examined group, as well as on the frequency of occurrence of hypervirulent strains in a given locality. The most common cause of death is a toxic megacolon, a septic (fulminant) course of the disease and an exhaustion of the organism by repeated recurrences.
Toxic megacolon is the most severe form of clostridial colitis. It is characterized by the development of paralytic ileus and enormous dilatation of the loops of the large and then the small intestine. In this phase of CDI, the patient's life is immediately endangered, the mortality rate is 35-80% [20, 21]. However, it must be added that toxic megacolon can also arise from causes other than clostridial colitis; a relatively common cause is inflammatory bowel disease (IBD), especially ulcerative colitis (UC) [21, 22]. The septic course of CDI is caused by the translocation of bacteria[3] and their toxins from the intestinal lumen into the bloodstream. This condition may not be associated with intestinal dilatation, it may develop independently.
Recurrences can be lighter or more severe than the previous attack. They usually occur within 2 months of the previous attack. After the first attack, the probability of recurrence is around 20% [5, 19]. Cases with more than twenty recurrences have also been described. A patient with repeated attacks of clostridial colitis is at risk of dehydration, mineral disruption, malnutrition, and overall physical and mental exhaustion.

Diagnostics

Definition of CDI: According to the consensus of European experts [4], only a disease fulfilling at least one of the three possibilities can be considered a proven CDI:
• a clinical picture consistent with CDI and at the same time evidence of *C. difficile* toxins in stool by enzyme immunoassay (EIA, ELISA), while no other cause of diarrhoea was detected.
• a clinical picture consistent with CDI and at the same time proof of a toxicogenic strain of *C. difficile* based on culture or genetic diagnostics based on amplification and detection of selected sections of nucleic acids (NAAT, PCR), ideally with a finding of a low Ct value.
• the finding of pseudomembranous colitis at endoscopy, after colectomy or at autopsy, in combination with culture proof of a toxicogenic strain of *C. difficile*.
Recommended practices explicitly state that any positive microbiological finding is not sufficient to prove CDI; the corresponding clinical manifestations of the disease must always

[3] The penetration of intestinal bacteria into the bloodstream may not be detectable by standard blood culture because the bacteria enter the portal tract and are picked up from the blood as they pass through the liver. However, this does not prevent the release of pro-inflammatory cytokines, which induce a septic state.

be present at the same time. *C. difficile* is part of the physiological intestinal microbiota in a significant part of the human population. Therefore, a positive microbiological examination result cannot be automatically interpreted as proof of clostridial infection [23, 24, 25].

Examination of the stool, pre-analytical phase: Microbiological examination of the stool focused on evidence of CDI assumes the presence of the symptoms described in Table 1. It is not indicated in individuals with formed stool[4] and is not routinely performed even in children under 2 years of age. For microbiological examination in the case of suspected CDI, a minimum of 2 ml of stool must be collected in a sterile container. Optimally, the sample should be examined within two hours of collection; this requirement mainly concerns the detection of toxins by immunochemical method, as toxins are not stable, and a delayed examination can cause a false negative result. If it is not possible to examine the stool immediately, the sample should be kept at a refrigerator temperature of 5 °C. Then stability should be ensured for 48 hours. Freezing at -70 °C is necessary for long-term preservation of the activity of toxins and their antigenic properties.

Examination of the stool (analytical phase): Table 4 summarizes the reporting values of the tests used. Due to the different sensitivities of the various methods, according to current recommendations, a combination of two tests is preferred, i.e., examination of clostridial antigen (glutamate dehydrogenase, GDH) and clostridial toxins or at least toxin B. Both tests use the principle of immunoenzyme analysis (EIA, ELISA). As an additional examination, the gene coding for the synthesis of toxin B (possibly also toxin A) is detected using PCR. This examination is usually used for decision-making in unclear cases when a positive GDH finding is accompanied by a negative result of the A/B toxin test (Fig. 1). All tests mentioned above bring results within a few hours and thus enable timely initiation of targeted treatment.

Microbiological diagnosis of CDI should be based on the result of two different tests. It is not recommended to base the CDI diagnosis on the positivity of the PCR test alone, because this test is so sensitive that it can also react to simple colonization of the intestine by the *C. difficile* strain [25].

Stool culture for evidence of *C. difficile* should be performed in all patients where the examination of GDH and toxins did not yield a clear result, as well as in patients with a severe course of CDI. Another possible reason for establishment of cultivation is an effort to verify the sensitivity of a particular strain of *C. difficile* to antibiotics or to obtain data for epidemiological investigation (surveillance). In this context, we point out that for metronidazole susceptibility testing it is necessary to use a medium that contains heme [78].

For surveillance purposes, it is usually necessary to carry out ribotyping of isolated strains; this examination is provided by specialized workplaces (e.g., Institute of Medical Microbiology, FN Motol, Prague 5).

Stool examination, post-analytical phase: A positive finding, i.e., evidence of a toxicogenic strain of *C. difficile*, must be reported immediately to the department where the patient is hospitalized. At the same time, positive results should be automatically reported to the Department of Infection Control and Hospital Hygiene department.

[4] Clinicians should be aware that microbiology laboratory personnel are instructed that molded stools should never be accepted for CDI testing. If, exceptionally, a situation arises when the clinician indicates an examination of non-diarrheal stool, he should make refer this fact to the microbiologist in advance.

However, it is necessary to notify the clinician immediately of the positivity of the screening test itself (GDH certificate), i.e., cases where the examination of toxins by the immunochemical method came out as negative in case of GDH positivity. This information is important when deciding on the method of treatment, see Thesis A2.

Endoscopic diagnosis: In patients with a moderate to severe form of CDI, island-like coatings appear on the mucosa of the colon. Their size and density gradually increase, until eventually the mucous membrane can be entirely covered with papules. The endoscopic picture of clostridial colitis is characteristic during the period of the appearance of islet-like structures that its finding is considered pathognomonic. Critics, however, object that the endoscopic finding may not be unambiguous, as island-shaped structures can rarely form in other diseases affecting the intestine [26]. It is certainly possible to take a biopsy and wait for a histological evaluation, but this delays the establishment of the diagnosis for a period comparable to the culture examination, and moreover, even in this case, the finding may not be unambiguous [27]. Another criticism is that the description of the colonoscopy finding is subjective, the detected image is usually not recorded, and therefore there is no possibility of additional reobservation whether the description corresponded to reality. In patients with severe intestinal involvement, the risk of intestinal perforation cannot be ignored during this procedure.

Importance of imaging methods: A x-ray of the abdomen or a CT scan can demonstrate dilatation of the intestinal loops and smoothing of the haustra. Sonography or CT will show inflammatory enlargement of the intestinal wall. In addition, on CT images, after oral or rectal administration of contrast material, structures on the walls of the colon may manifest as contrast filling defects. With the simultaneous intravenous administration of a contrast agent, it is typical for clostridial colitis that the immediate surroundings of the intestinal lumen (mucosa and submucosal tissue) are saturated, but not the deeper layers of the intestinal wall. Thus, the mentioned imaging methods can significantly support the suspicion of CDI, but by themselves these findings are not considered conclusive.

A) Theses regarding the diagnosis of CDI:

1) The diagnosis of CDI is based on a combination of clinical manifestations (diarrhoea, abdominal pain, subileus, ileus) and laboratory detection of clostridial toxins in the patient's stool (detection of A/B toxins by enzyme immunoassay or detection of the gene encoding toxin synthesis B by PCR). A positive laboratory finding alone without clinical manifestations cannot be considered evidence of CDI.

2) If, in a patient with clinical manifestations of CDI, the GDH test is positive, the toxin test is negative, and the PCR test cannot be performed, we recommend that stool culture be performed to detect *C. difficile* and CDI treatment be started. After three days, it is possible to reassess the diagnosis based on the results of the culture and the evaluation of the effect of the treatment.

3) The typical morphological picture of the intestinal mucosa with islets of plaques, detectable during colonoscopy or during autopsy, may be so typical that it warrants the initiation of targeted CDI treatment. However, we recommend always confirming such a finding with a microbiological examination of the stool. Due to the risk of intestinal damage, we do not recommend indicating a colonoscopy to diagnose CDI.

Rationale:
Ad 1): These theses are fully in accordance with the European recommended procedures, they only specify the procedure when a quick diagnosis is necessary. All authorities agree that the diagnosis of CDI must be based on a combination of clinical signs and laboratory findings.
Ad 2): The proposed procedure shows how it is possible to solve the situation when rapid microbiological diagnostics cannot be used, or its results are ambiguous. A persistent serious clinical suspicion of CDI means that the patient meets at least two of the three conditions: a typical clinical picture of the disease; probable history of contact with *C. difficile* spores; a negative result of tests used to prove another possible aetiology of diarrhoea.
Ad 3): Colonoscopy alone is not reliable for establishing the diagnosis of CDI. Therefore, only microbiological diagnostics are mentioned in the new recommended procedures [4, 5].

Therapy - general background
The choice of treatment strategy for CDI depends on the severity of the disease, the age of the patient and the comorbidities present. Clinical and laboratory parameters defining severe CDI are shown in Table 3.
General therapeutic recommendations can be formulated as follows:
• The basis of treatment is the administration of antibiotics with proven effectiveness against *C. difficile.*
• If possible, the antibiotic treatment that led to the CDI is stopped immediately. In mild forms of CDI, this measure alone can induce recovery.
• If the antibiotic treatment of the original disease cannot be interrupted, at least in some patients it is possible to replace the antibiotic administered so far with another preparation with a narrower spectrum of effectiveness and more favourable pharmacokinetics, i.e., with a lower potential for CDI induction and progression [28].
• As needed, the patient is given rehydration and a sparing diet (i.e., a non-flatulent and non-irritating diet, with no other special restrictions). In more severe cases, parenteral nutrition is indicated.
• Drugs suppressing intestinal peristalsis (spasmolytics, opiates) are contraindicated, because the suppression of peristalsis worsens the course of the disease. In persistent diarrhoea, these drugs can be used on the condition that (1) the patient receives effective antibiotics against **C. difficile** and (2) these antidiarrheal drugs are administered in a dose that does not stop peristalsis [5].
• Drugs suppressing gastric acidity clearly contribute to the development of colitis and recurrences, but it is not clear whether the termination of this treatment favourably affects the course of CDI that has already occurred.
Preventing the spread of *C. difficile*: Patients with clinical manifestations of clostridial colitis excrete large numbers of infectious spores in their stools, and therefore must be treated in an isolation regimen. Hypervirulent strains of *C. difficile*, which spread especially in the hospital environment, pose a particularly great danger to susceptible individuals (see Table 1). On the other hand, there is no need to isolate people with a positive finding of *C. difficile* in their stool, who no longer show signs of the disease.
As part of the barrier mode of treatment, disposable gloves are used and, if necessary, also waterproof coats and dedicated examination aids (stethoscopes, thermometers, etc.). The rooms

are to be equipped with separate sanitary facilities. Sporicidal solutions must be used to disinfect contaminated objects. Commonly used disinfectant solutions based on alcohol and quaternary ammonium compounds are not effective against clostridial spores. In the prevention of transmission of *C. difficile* by the hands of patients and healthcare workers, mechanical cleaning of hands with warm water and soap followed by thorough drying is particularly emphasized [5, 29]. Detailed guidance is contained in a separate recommended procedure developed by European specialists [30]. Thorough instruction on hand hygiene and the need to use sporicidal products to clean the toilet (e.g., products with chlorine) should also be given to ambulatory patients with CDI.

Another measure reducing the risk of clostridial colitis in already colonized patients is a rational antibiotic policy. This should be managed and spread through local ATB centres [5].

Antibiotic treatment of CDI

In the current guidelines [4, 5, 6], only four antibiotics are mentioned that can be used in the treatment of clostridial colitis. Their basic characteristics are contained in Table 5.

Fidaxomicin is a new, narrow-spectrum bactericidal antibiotic that is only registered for the treatment of CDI. It is not absorbed from the GI tract, and no systemic side effects have been reported during its administration. In the intestinal contents, it reaches similarly high concentrations as vancomycin. Fidaxomicin inhibits the activity of bacterial DNA-dependent RNA polymerase, thus blocking the transcription of information from DNA to RNA. The consequence is the arrest of proteosynthesis. In the case of bacteria, this mechanism quickly stops the synthesis of toxins, and at the same time, the possibility of sporulation is also blocked. The reduced ability of sporulation together with a milder effect on the intestinal microbiota significantly reduces the risk of CDI recurrence. Thus, Fidaxomicin acts faster than vancomycin and does not cause frequent recurrences. Another advantage compared to vancomycin is a more comfortable schedule of use (2 times a day vs. 4 times a day, see table 5) and a lower risk of selection of multiresistant strains of intestinal bacteria. The main disadvantage of fidaxomicin is its relatively high price.

Vancomycin is a backup antibiotic for the treatment of serious infections caused by gram-positive bacteria. It has a slow bactericidal effect (compared to beta-lactams), and its mechanism of action does not interfere with proteosynthesis, i.e., it does not directly stop the formation of toxins. This may explain its slower onset of action compared to fidaxomicin. When administered orally, the concentration of vancomycin in the intestine reaches high values, one hundred times higher than the MIC value (Table 4). The antibiotic is not absorbed from the GI tract, so the therapy is not associated with the risk of organ toxicity in most patients. Penetration of vancomycin from the intestine into the bloodstream has only been described in isolated cases, in patients treated with doses exceeding 500 mg/day, in patients with a very severe course of CDI, extensive inflammatory bowel disease (IBD), or in combination with renal insufficiency [31]. The main adverse consequence of treatment with oral vancomycin is the deepening of intestinal dysmicrobia, which creates the conditions for the development of recurrences. High concentrations of vancomycin in the intestinal contents kill not only gram-positive bacteria, but even anaerobically growing gram-negative microbes from the Bacteroides-Prevotella group [32].

No tablet preparations containing vancomycin are registered in the Czech Republic. The drug can therefore be prepared directly in the ward by dissolving 500 mg of powder for infusion in 20 ml of water for injection; the resulting solution is drunk by the patient in four doses with an interval of 6 hours. The stability of the solution when kept at refrigerator temperature is 48 hours. Vancomycin for oral treatment can also be used in the form of enteric capsules, which are made from powder by a pharmacy as an individually prepared medicinal product.

Metronidazole works against most anaerobically growing bacteria. It was historically the first drug used in CDI therapy. It is commonly known and cheap, used in many indications. It is also the only antibiotic that can be used in both oral and parenteral forms in the treatment of CDI. When administered orally metronidazole is already absorbed in the upper parts of the intestinal tract and passes into the blood. It therefore does not reach the colon because of incomplete absorption, but via intestinal secretion, the intensity of which depends on the size and extent of the inflammation. There are two consequences: (1) the effect of the antibiotic is greater in the more severe course of the disease; (2) the same dosage scheme applies to parenteral and oral administration; the therapeutic effect is practically identical in both cases. A disadvantage of metronidazole is its lower efficacy compared to vancomycin and fidaxomicin. This can be explained by the achievement of significantly lower concentrations in the intestinal contents, see Table 5. However, the reduced sensitivity of some strains of *C. difficile* also applies, which is evident in Table 5 when comparing the MIC_{50} and MIC_{90} values. Especially with hypervirulent strains, metronidazole has an inhibitory effect only at concentrations of around 2 mg/l, which does not yet reach the official limit of resistance, but it certainly contributes to a lower effectiveness of the therapy. The consequence of both mentioned disadvantages is a slower treatment effect and a greater risk of therapeutic failure.

Tigecycline is a broad-spectrum parenteral antibiotic of the tetracycline series. It is resistant to most of the resistance mechanisms by which bacteria defend themselves against tetracyclines of the 1st and 2nd generation, and therefore also acts on numerous multiresistant strains of bacteria. It reaches the intestinal lumen through intestinal secretion, similar to metronidazole, the mode of action consists in inhibiting the proteosynthesis of bacteria, thus resembling fidaxomicin.

The efficacy and safety of tigecycline in the treatment of CDI have been described in numerous case reports and small studies, but have not yet been verified by sufficiently large, randomized trials. Tigecycline is therefore not mentioned as a possible drug of choice in some guidelines. Its main application comes in cases where standard oral treatment cannot be used. This is especially the case with patients with a toxic course of the disease and an interruption of intestinal peristalsis. It can also be used with advantage in case of coincidence of CDI with another bacterial infection.

Other antibiotics: Other drugs are occasionally mentioned in the literature on *C. difficile*, but their practical importance for the treatment of CDI is currently negligible. Rifaximin is an antibiotic related to rifampicin that is administered orally and is not absorbed from the GIT. It is registered for the treatment of various intestinal infections, especially mild diarrheal diseases associated with intestinal dysmicrobia (traveller's diarrhoea), but CDI is not mentioned in the list of indications. The effectiveness of rifaximin against *C. difficile* is unreliable, more than 50% of strains tested in the Czech Republic were resistant [33, 34]. Data on the efficacy of rifaximin in the treatment of CDI are insufficient [5]; some authors only admit the possibility

of using this drug in recurrent CDI (see below). Oral teicoplanin may be more effective than vancomycin, but the evidence is not sufficiently statistically supported [35]. Very little literature is available on nitazoxanide, bacitracin and fusidic acid [35]. Development of cadazolid and surotomycin was halted because these agents failed to demonstrate better efficacy than vancomycin. Ridinilazole remains in the phase of analysis of clinical trial results [4].

Therapy of individual forms of acute CDI

When assessing individual treatment options, it is necessary to separately evaluate two aspects of treatment: (1) curing the existing acute *C. difficile* infection; (2) reduction of negative impact towards the physiological intestinal microbiota, i.e., minimization of the risk of recurrence. Table 6 shows the results of randomized comparative studies.

Standard antibiotic treatment for the first episode of CDI: Of the three orally available antibiotics, fidaxomicin shows the best efficacy. A similar treatment result can be achieved by administering vancomycin, but with a significantly higher risk of subsequent recurrence. When treated with metronidazole, the treatment results are worst, especially in hospitalized patients and infections caused by hypervirulent strains [4].

According to European guidelines, this comparison indicates that fidaxomicin is the drug of first choice and vancomycin is the drug of second choice. Metronidazole can only be given in cases where fidaxomicin or vancomycin are not applicable (e.g., due to allergy) or are not available. The duration of treatment is the same when using all named antibiotics, i.e., 10 days [4].

This recommendation does not consider the price differences of the named preparations or the different priorities of antibiotic policy in individual states. It also does not account for differences in time to clinical effect, see Table 5.

B) Theses describing the recommended standard ATB treatment of the first episode of CDI:

1) The drug of choice for CDI in hospitalized patients is fidaxomicin 200 mg every 12 hours or vancomycin 125 mg every 6 hours. Both options are comparably effective in terms of treatment outcome, but the recurrence rate is lower when fidaxomicin is used.

2) Fidaxomicin is clearly preferred in two situations: (a) incipient intestinal peristalsis that can cause the development of ileus; (b) in the case of a patient in whom it is necessary to minimize the risk of recurrence.

3) In the treatment of outpatients, vancomycin 125 mg after 6 hours or metronidazole 500 mg after 8 hours can be used. The condition for the use of metronidazole is a mild course of the disease and the fact that it is the first episode of CDI. Fidaxomicin has not yet been released for outpatients in the Czech Republic.

4) The duration of antibiotic treatment for CDI can be individualized. With a good clinical response and the absence of complicating circumstances, the duration of treatment can be shortened (for example, when using vancomycin for 6-7 days and when using fidaxomicin for 5 days).

5) An essential part of the treatment is the isolation of sick persons and other principles described above in the chapter Therapy - general background.

Rationale:
Ad 1): The comparable therapeutic effect of both preparations is well documented statistically, patients treated with fidaxomicin have a lower percentage of recurrences [35, 6, 4].
Ad 2): In the first case, we consider patients whose clinical condition is critically deteriorating, and it is likely that intestinal peristalsis will stop within 1-2 days. The preference for fidaxomicin here results from its rapid action; with vancomycin administration, ileus could occur before vancomycin develops its antibacterial activity. This position is based on the consensus of clinical experts, not supported by exact data.
In the second case, the preference for fidaxomicin results from its more selective action, i.e., less destructive effect on the intestinal microbial ecosystem. Fidaxomicin is therefore preferred in patients before planned urgent medical procedures (surgery, chemotherapy) or in persons who cannot afford the risk of recurrence for other similarly urgent reasons.
Ad 3): In the Czech guidelines, access to treatment is derived from whether the patient is treated on an outpatient basis (i.e., a mild course of CDI) or is hospitalized (severe form of CDI). This simplification is possible because the care for the sick and its availability is more or less uniform throughout the state, and the decision on hospitalization is not dependent on the patients' ability to pay for treatment.

Arguments for the possibility of administering oral metronidazole as the drug of choice in outpatients:
a) Metronidazole has been administered in this indication for many years and is certainly not ineffective. Specifically, the difference in efficacy of metronidazole and vancomycin treatment is 78.1:86.9 (see Table 6). Although the difference is statistically significant, it is not significant enough to authorize a total elimination of metronidazole from the treatment of CDI. After all, iv. metronidazole in combination with locally administered vancomycin or fidaxomicin, despite all the criticism, remains the drug of choice in severe forms of CDI, where oral treatment is not possible. [4, 6].
b) Patients treated as outpatients usually have a milder course of the disease and there is also a lower probability that the cause of the infection is a hypervirulent strain of *C. difficile*.
c) Medical doctors are used to prescribing the metronidazole in the treatment of CDI in outpatient setting. It is also administratively easier since it is not necessary to apply for prescription permission from the antibiotic centre.
d) The American Gastroenterology Society (AGA) also takes a similar view towards the administration of metronidazole in uncomplicated disease course and non-risk patients [5]. The opinion that metronidazole can be used to treat mild cases of CDI was also published by German and French authors [37, 38].
Ad 4) Antibiotics used in the treatment of CDI are not perfectly selective, they always affect a certain segment of the intestinal ecosystem together with *C. difficile*. It is therefore desirable not to extend the treatment period unnecessarily, so as not to worsen dysmicrobia. It is known that a ten-day treatment period for CDI was introduced at a time when metronidazole was the drug of choice [39]. For fidaxomicin, the clinical effect is evident within 1-2 days, short-term treatment regimens lasting 5 days are already being tested, which are followed by a low-dose maintenance course designed to prevent recurrences, most often in the scheme of 1 tablet (200 mg) once a day for 10 days or 1 tablet every other day until the 25th day of treatment [40,41].

Thus, it appears that to cure CDI in uncomplicated cases, a time corresponding to approximately twice the time needed to achieve an obvious clinical effect is sufficient, see table 7. We therefore consider it permissible to shorten the duration of antibiotic treatment for CDI[5], while the condition for shortening the treatment regimen must always be proof of a good clinical response to the given treatment, i.e., the subsidence of clinical problems (diarrhoea, abdominal pain, flatulence) and at the same time the normalization of inflammatory markers, especially leucocytosis. As in point number 2, this opinion is based on the consensus of clinical experts, not supported by exact data.
Ad 5) The mentioned measures were included in the text only to remind the importance of current anti-epidemic measures.

Approach in case of insufficient effectiveness of standard treatment (refractory CDI): According to European guidelines, in these cases, the validity of the diagnosis of CDI should be re-examined. Treatment with oral fidaxomicin or vancomycin should be reliably effective. The explanation for the insufficient effect of the administered therapy may be a dual infection or the presence of another, yet unrecognized, non-infectious intestinal disease with simultaneous intestinal colonization by *C. difficile*; this is then interpreted as proof of aetiology. In patients treated on an outpatient basis, treatment failure can be caused by poor patient compliance [4].
According to the results of the studies, no benefit was found when increasing the dosage of vancomycin to 4x 500 mg or when adding iv. metronidazole or tigecycline to standard oral therapy. If the treatment with fidaxomicin or vancomycin is ineffective, it is recommended to propose a stool transplant to the patient during the treatment course [4].

C) These describing the recommended procedure in case of insufficient effectiveness of standard treatment:
1) Insufficient effectiveness, or clinical failure of antibiotic treatment, can be noted for fidaxomicin as soon as during the third day of therapy, for vancomycin during the fourth day and for metronidazole during the day five to six.
2) It is unlikely that *C. difficile* is resistant to the given antibiotic as the cause of treatment failure. If peristalsis is preserved, it makes no sense to try to increase the effectiveness of the treatment by increasing the doses, in practice especially by increasing the dosage of vancomycin to 4x 500 mg, or by administering a combination of antibiotics. We recommend reassessing the diagnosis of the disease and looking for another cause (dual infection, current undiagnosed non-infectious intestinal disease, etc.) using interdisciplinary cooperation. If the patient is treated in the department of infectious diseases a gastroenterologist should be consulted in this situation; if the patient is treated in the department of internal medicine, it is

[5] We consider it necessary to emphasize that shortening the duration of treatment must be approached selectively and not routinely. This is a change in the doctor's approach to therapy. The purpose of individualizing treatment is that an experienced doctor is given the right to shorten or, on the contrary, extend the duration of treatment, depending on the overall condition of the patient, the speed of response to treatment and the presence or absence of risk factors. At the same time, we add that the individualization of treatment gives treating doctors room not only to shorten, but also to extend the antibiotic course. For example, the American Gastroenterology Society recommends extending the administration of oral vancomycin for 14 days in patients with idiopathic inflammatory bowel disease (IBD) [5].

advisable to consult an infectious disease specialist. For outpatients, we recommend examining whether the patient has really taken the prescribed treatment.
3) If the clinical failure of properly administered CDI antibiotic treatment is indeed detected, it is recommended to suggest a stool transplant to the patient as a treatment measure in addition to switching the preparations. The *C. difficile* strain (stool sample if culture is not possible) should be sent for ribotyping.

Rationale:
Ad 1): This statement follows from the data contained in Table 5. Individual antibiotics used in the treatment of CDI differ in the speed of achieving a clinical effect.
Ad 2): *C. difficile* strains are still very sensitive to the recommended antibiotics, the occurrence of resistance to metronidazole, vancomycin and tigecycline is at the level of 1%, in the case of fidaxomicin even <0.1% [43]. According to another study, resistance of *C. difficile* to vancomycin in EU countries is below 5%, and resistance to fidaxomicin is quite exceptional [44, 45]. In case of uncertainty, it is possible to send an isolated strain of *C. difficile* to a specialized laboratory (Institute of Medical Microbiology, FH Motol, Prague 5).
A comprehensive justification of the mentioned measures is contained in the European guidelines [4]. A colonoscopy is usually part of the examination procedure; due to the fragility of the intestine, this examination can be postponed until after the acute phase of the disease has been managed.
Ad 3): Clinical treatment failure (persistent diarrhoea) can be caused not only by the clostridial infection itself, but also by severe dysmicrobia that persists after the clostridial infection has been managed. In such a case, stool transplantation is an appropriate treatment measure. Experience with the use of FMT in this indication is still scarce [46, 47], however, European guidelines allow this procedure [4].

Approach when oral treatment is not possible: in these cases, there is not enough data to determine the optimal procedure [4, 5, 6]. According to European guidelines, it is advisable to try to administer vancomycin or fidaxomicin intraluminally, i.e., by operatively creating a double-barrel (two-hole) ileostomy and lavage the intestines with an antibiotic solution. It is possible to add parenteral treatment with metronidazole in a dose of 3x 500 mg or tigecycline 2x 50 mg, after an initial loading dose of 100 mg [4].
US guidelines also allow vancomycin enemas (500 mg in 100 ml saline every 6 hours); however, the benefit of this method of treatment is inconclusive [5].

D) Theses describing the recommended treatment of CDI when oral therapy is not possible:
1) If we exclude the fulminant course of CDI, it is advisable to start the treatment by administering iv. tigecycline. Tigecycline dosage in this indication should be increased to 100 mg every 12 hours (200 mg/day), while rapid saturation can be achieved by shortening the interval between the first two doses to 6 hours.
2) If tigecycline is not available, it is possible to give iv. metronidazole, in a standard dosage of 500 mg every 8 hours.

3) The surgical solution must be considered when the severity of the disease progresses during this antibiotic treatment. The procedure of choice is the creation of a double-barrel ileostomy or percutaneous endoscopic cecostomy. Lavages containing vancomycin or fidaxomicin are applied to the entrances created in this way.

Rationale:
Ad 1) Antibiotic treatment is significantly gentler for the patient than surgery and bowel lavage. From the point of view of choosing an antibiotic, we prefer tigecycline to metronidazole because it stops the bacterial proteosynthesis and thus the production of the toxin, and because it more effectively stops the multiplication of *C. difficile* (lower MIC value) when reaching the same concentrations in the intestinal contents, see table 5. We consider this argument justified, although there is not yet enough data from clinical trials to confirm these theoretical conclusions. Increased dosage of tigecycline in severe infections has been tried in other indications and is well tolerated [48, 49].
Ad 2) Metronidazole dosage cannot be escalated due to the increasing risk of adverse effects.
Ad 3) Only the creation of a double-barrel terminal ileostomy is recommended as the procedure of choice by European guidelines [4]. Percutaneous endoscopic cecostomy is a simpler method, suitable for patients with a very high surgical risk [50, 51]. There are no accepted rules for the preparation of lavage. The daily doses of the antibiotic given in this way should be the same as with the standard method of administration. The authors describing this treatment method used vancomycin, which is why European guidelines recommend it as the drug of choice [4]. Fidaxomicin is mentioned in these guidelines as a possible alternative for lavage preparation, with a theoretical rationale based on its higher efficacy, but without confirmation by reliable clinical experience. Fidaxomicin is distributed in the form of coated tablets, from which it is possible to prepare a suspension.

Treatment of fulminant CDI: There is no reliable guide for the successful treatment of this form of the disease. The patient should be hospitalized in the ICU with continuous monitoring of vital functions. European guidelines are based on the greater effectiveness of antibiotics administered directly into the digestive tract and therefore recommend the administration of oral vancomycin or fidaxomicin if possible. If oral treatment is not feasible, it is recommended to create a double-barrel ileostomy and administer antibiotics through this route [4].
It is important to consult a surgeon early. By performing an ileostomy in time, it is possible to prevent the progression of the disease, which can then only be resolved by total colectomy, with a mortality rate of 35-40% [4, 5].
Intraluminal application of antibiotics against *C. difficile* can be supported by iv. administration of tigecycline or metronidazole. [4]; however, the available literature does not contain studies that would reliably demonstrate the benefit of this combination.

E) Theses describing the recommended treatment of fulminant CDI:
1) If the patient can receive oral treatment and has at least partially preserved peristalsis, fidaxomicin is the drug of choice in the standard regimen. If the patient is unable to take drugs orally, we recommend creating conditions for administration of antibiotics into the ileum or cecum.

2) To strengthen the effect of this treatment, especially in case of imminent ileus, we recommend simultaneously giving iv. tigecycline in a dosage of 100 mg/dose. The interval between the first and second dose is 6 hours, then after 12 hours.
3) If the patient shows signs of sepsis, we recommend using the broad-spectrum beta-lactam antibiotic iv., i.e., piperacillin/tazobactam or a carbapenem instead of iv. tigecycline. At the same time, partial or total colectomy should be considered as a last resort.

Rationale:
Ad 1) Fidaxomicin has the fastest effect of all three orally applicable antibiotics, see Thesis B2, therefore we consider it the drug of choice for life-threatening infections. The concentration of fidaxomicin in the intestinal contents is high enough (see Table 5) that it is not necessary to use a loading regimen. Creating access to the ileum or cecum is described in the previous chapter.
Ad 2) We prefer the administration of tigecycline because it has more favourable pharmacodynamic properties than metronidazole. Due to the severity of the disease, tigecycline dosage should be at the upper limit of the therapeutic range, i.e., 200 mg/day, see Thesis D1.
Ad 3) The septic course of CDI usually indicates severe damage to the intestinal wall, loss of its barrier function and translocation of intestinal bacteria into the internal tissues of the body, including the bloodstream. If this complication is suspected, we therefore consider the administration of an intravenous bactericidal antibiotic with a spectrum of action affecting common intestinal aerobically and anaerobically growing bacteria, i.e., piperacillin/tazobactam or meropenem. These antibiotics are effective not only against most potentially invasive intestinal bacteria, but also against *C. difficile* [43]. At the same time, it is necessary to decide on an urgent colectomy in cooperation with the surgeon. It is a mutilating procedure that poses a significant burden to a critically ill patient; on the other hand, at this stage of the disease, it is the only effective method that leads to the removal of the source of sepsis. If it is to be performed, it must be performed without delay, because every hour of delay worsens the patient's prognosis.

Treatment of recurrent CDI
A patient who experiences recurrent CDI is always at risk of another recurrence. Treatment of recurrent CDI therefore consists of two components: management of the current clostridial infection and prophylaxis of further recurrence.

Treatment of the first recurrence of CDI: European guidelines [4] advise giving fidaxomicin to all patients who were treated with vancomycin or metronidazole during the previous (=first) attack of CDI. Fidaxomicin in this indication can be administered in the usual regimen, i.e., 200 mg every 12 hours for 10 days, or in an alternative regimen, i.e., 200 mg every 12 hours for 5 days and then 200 mg every 48 hours for 12 days, i.e., on days 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25. This prolonged administration schedule may reduce the risk of recurrence [40]. Its disadvantage is the extended treatment time and, theoretically, the creation of conditions supporting the spread of resistance to fidaxomicin.
Patients who have CDI recurrence after treatment with fidaxomicin can be given standard therapy (vancomycin or fidaxomicin again) along with an intravenous infusion of an anti-toxin

B monoclonal antibody (bezlotoxumab). In this context, it is recommended to consider the prolonged administration of vancomycin in a gradual withdrawal regime (taper and pulse), i.e., 2 weeks 4x 125 mg, then 1-week 2x 125 mg, then 1 week 1x 125 mg, then 1 week 125 mg every 48 hours, finally 1 week 125 mg every 72 hours. The total duration of the antibiotic treatment thus comes to 6 weeks[6]. The effectiveness of this method of treatment is demonstrated by a meta-analysis [52], the disadvantages are similar to those of prolonged administration of fidaxomicin.

Treatment of second and subsequent recurrences: In these cases, two possible procedures are recommended [4]: (a) standard antibiotic treatment (fidaxomicin or vancomycin for 10 days) followed by stool transplantation (FMT), or (b) standard antibiotic treatment along with an intravenous infusion of a monoclonal antibody against toxin B (bezlotoxumab). As in the previous case, it is possible to give vancomycin or fidaxomicin in an extended regimen.

F) Theses describing the recommended treatment of recurrent CDI:

1) In the treatment of the first recurrence, we recommend either giving fidaxomicin or using vancomycin followed by stool transplantation (FMT). If FMT is not feasible in a given patient, fidaxomicin is the drug of choice. For the dosing of antibiotics, see Thesis B.

2) From the second recurrence, we do not recommend treating patients with fidaxomicin. We consider oral administration of vancomycin followed by FMT to be the procedure of choice.

3) Faecal filtrate can be administered into the duodenum/jejunum by probe or the working channel of the endoscope, or into the colon by rectal enema or colonoscope. Another possible way is to use enteric capsules. Patients with an ileostomy or cecostomy can be given the filtrate via this route. It is the responsibility of the attending physician to choose the procedure that is optimal from the point of view of the patient and at the same time from the point of view of the possibilities of the given workplace.

4) We recommend considering the gradual withdrawal of vancomycin or fidaxomicin for multiple recurrences only if it is not possible to perform FMT. We do not recommend their routine use.

Rationale:

Ad 1) Bezlotoxumab is registered in the Czech Republic (as part of pan-European registration), but it is not traded, i.e., it is not available, it can only be obtained through special importation. Therefore, it cannot be listed in the Czech guidelines as a standard solution. We consider the submission of FMT to be a high-quality and easily accessible alternative. The risks associated with FMT can for the most part be eliminated by appropriate selection of donors. For this reason, we consider FMT to be a procedure that, with the patient's consent, is already fully indicated for the first recurrence of CDI. In persons highly predisposed to a recurrent course, FMT may be considered even after the first attack of the disease. The conditions for the correct performance of FMT are described in a separate guideline [53].

[6] The fidaxomicin or vancomycin taper regimen can be divided into two phases. The first of them is the actual treatment course, the second is the continuous prophylaxis of recurrence. It is worth noting that in the case of fidaxomicin there is a tacitly accepted principle, according to which it is possible to shorten the duration of treatment with a good clinical response. This corresponds well with the polemic described above (Thesis B4).

Ad 2) At the second recurrence, the intestinal microbial ecosystem is so disrupted that the narrow spectrum of fidaxomicin and its selective effect lose significance [54, 55].
Ad 3) Administration of stool filtrate into the duodenum/jejunum or into the colon are standard methods described in the aforementioned guidelines [53]. The use of enteric capsules is an alternative method with very good efficiency (74-96%), which has so far found popularity especially in the USA [5, 56, 57]. If peristalsis fails and access to the ileum or cecum is artificially created, it is possible to administer stool filtrate through this route as well [56].
Ad 4) Above mentioned regimens with gradual reduction of antibiotic doses, over several weeks, undoubtedly reduce the risk of recurrences. However, it is important to note that the studies demonstrating this fact [52] contain a bias: requiring long-term antibiotics according to a changing template automatically excludes patients who are non-compliant for any reason from insufficient diligence to technical difficulties in providing ambulatory medical care. This may distort the results of the studies. We consider the fact that the regimes are in direct contradiction to the general principle of antibiotic policy, according to which antibiotics should be administered in as high doses as possible and for a short time [58]. The urgency of this principle derives from the increasing resistance of bacteria to antibiotics. It is true that it has not yet been possible to reliably prove that treatment of CDI with orally administered vancomycin leads to the selection of multiresistant enterococci [59, 60], however, the emergence of selection pressure supporting the spread of resistant strains is indisputable when using the mentioned regimens.

Notes on CDI prophylaxis
We differentiate between primary CDI prophylaxis (measures to prevent the onset of the disease in predisposed persons) and secondary prophylaxis (measures to prevent the development of recurrence after the disease has been experienced).
In this chapter, the most important measures that can protect disposed persons are discussed.

Regime measures: These include early mobilization of the sick, high-quality nutrition, measures to reduce the risk of *C. difficile* spores appearing in the vicinity of people susceptible to infection, etc. Antibiotic treatment should be limited to the necessary minimum in predisposed persons, and if it is necessary, preparations should be preferred that disturb the intestinal microbiota as little as possible [28]. The mentioned measures are generally accepted, but their importance is not supported by the results of the studies.

Fecal transplantation (FMT): It is a proven effective method used to restore the physiological intestinal microbiota. It is mainly used for the prophylaxis of recurrences, but it can also be used for treatment (Thesis C2). In both European and American guidelines, it is only recommended for the second and subsequent recurrences, not before. This restrained approach results from an analysis of the risks of FMT: it is mainly about the possibility of transmission of various intestinal pathogenic microbes, then the risk of the spread of multi-resistant bacteria and finally the risk of transmission of microbes that can influence intercellular signalling in the recipient's organism and in this way induce the development of obesity, diabetes, autoimmune diseases, or tumours [4, 5, 6]. These risks can be minimized by careful selection of donor.

Prophylactic (suppressive) vancomycin administration: Several retrospective observational studies have recently been published that report a 5% to 30% reduction in the incidence of CDI with oral vancomycin prophylaxis during other broad-spectrum ATB therapy. The current European guideline recognizes the potential benefit of such prophylaxis in polymorbid immunocompromised patients, typically individuals after organ transplants or burdened with oncological diseases, during the administration of broad-spectrum antibiotics [4]. In addition, American guidelines propose the possibility of long-term suppressive prophylaxis with vancomycin (usually 125 mg p.o. once a day) as an ultimum refugium in patients who are at an extremely high risk of a severe course of CDI, and at the same time other methods of prophylaxis have failed or could not be used [5]. In similar exceptional situations, antibiotic prophylaxis of CDI is justified, but it is not possible to recommend it for routine use with regard to the principles of antibiotic policy, see Thesis F4.

Bezlotoxumab: This is a human monoclonal IgG antibody that neutralizes clostridial toxin B. It is registered specifically as an agent for the prophylaxis of recurrences, not for the treatment of active CDI. It is administered as a single iv. infusion with a biological half-life of approximately about 19 days. It enters the intestinal lumen by secretion during inflammation. According to the results of registration studies, administration of bezlotoxumab reduces the incidence of CDI recurrence by 10-20% [4, 61]. Based on a more detailed analysis, groups of patients were identified in which the effect of bezlotoxumab administration in the prophylaxis of CDI recurrence was the best. These were patients over 65 years of age, patients with a history of CDI in the previous 6 months, immunocompromised individuals, and patients after a severe episode of CDI and after disease caused by hypervirulent ribotypes of *C. difficile* [4, 5].

Probiotics: The use of probiotics in the prevention and treatment of CDI has a long tradition, but the clinical experience is ambiguous. Recently, two large meta-analyses [62, 63] were published, the conclusions of which were in favour of probiotics in the prevention of CDI. However, the authors of European and American guidelines [4, 5] subjected these meta-analyses to harsh criticism and evaluated them as unconvincing. Individual published studies are also not very convincing. Therefore, European, and American guidelines generally do not recommend probiotics for routine treatment or prophylaxis of CDI [4, 5].
A more detailed survey of literary sources yields conflicting information. Preparations containing *Saccharomyces boulardii* seem to show some protective effect against CDI [64]. This yeast produces a protease that inactivates the receptor for clostridial toxin A; on the other hand, it is known that *S. boulardii* can cause severe infection by itself in debilitated individuals [5, 65, 66]. Preparations containing lactobacilli and bifidobacteria are not very effective in the prophylaxis and treatment of CDI [67, 5]. A study demonstrating a slower restoration of the physiological microbiota after the administration of probiotics was also published [68]. These negative reports are opposed by individual clinical observations that demonstrate the beneficial effect of probiotic treatment. These observations suggest that probiotics could have a beneficial effect on the gut microbiota under certain circumstances[7].

[7] The difference between the difficult-to-proven benefit of probiotics in the prophylaxis and therapy of CDI on the one hand and the high efficiency of FMT on the other can be justified by the order of magnitude of lower

Specifics of CDI treatment in paediatric patients

The paediatric population accounted for about 2% of the total number of reported CDI cases in the Czech Republic in 2017 [69]. Paediatric issues are not mentioned in the European guidelines [4].

Diagnosis: Due to the higher percentage of colonization by toxicogenic strains of *C. difficile* and the low morbidity in children under one year of age, it is not recommended to routinely test diarrheal stools for *C. difficile*; for diarrhoea and/or abdominal pain in these children, it is advisable to look primarily for another cause, infectious or non-infectious [3, 70].

Therapy: In the aforementioned guidelines [3, 71], oral metronidazole is evaluated as a useful alternative to vancomycin in the treatment of an initial episode of non-severe CDI or a first recurrence. For severe CDI as well as for repeated recurrences, vancomycin is preferred in these guidelines; in case of peristalsis disorders, it is recommended to combine vancomycin with intravenously administered metronidazole. This approach to treatment corresponds to the knowledge in 2010-2015, when experience was just being gathered in the treatment of CDI caused by hypervirulent strains of *C. difficile*; fidaxomicin was also launched at this time.

Fidaxomicin was approved for CDI therapy in paediatric patients based on a multicentre, randomized trial in 142 patients [72]. Similar to the adult population, fidaxomicin showed a slightly higher success compared to vancomycin in terms of clinical cure, and its administration was associated with a significantly lower risk of recurrence. The overall difference in treatment success was 68.4% vs. 50.0%. Based on these results, fidaxomicin is now considered the drug of first choice for paediatric patients [73].

G) Theses regarding the treatment of paediatric patients:

1) Testing for evidence of *C. difficile* is indicated in children under 1 year only in the case of specific intestinal motility disorders (e.g., Hirschsprung's disease, conditions after intestinal surgery), with proven exposure (contact with CDI in a hospital facility), or in patients in severe immunosuppression with impairment of intestinal immunity (e.g., oncology patients on cytostatic treatment). In older age groups, testing is recommended similarly to adults, i.e., for prolonged or worsening intestinal problems in individuals with a significant risk factor (e.g., IBD, severe immune disorder, contact with CDI or recent antibiotic therapy). In general, in preschool children, it is necessary to consider that a positive CDI test result is probably due to colonization of the intestine by *C. difficile* alone, while other bacterial or viral pathogens are the actual cause of diarrhoea.

2) In the treatment of CDI in children, we recommend the same principles as in adult patients, only with a higher preference for fidaxomicin and, conversely, a lower support for metronidazole. Dosing follows the rules described in Table 8.

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number of live bacteria in probiotic preparations and at the same time by their minimal species diversity; with FMT, an entire complex ecosystem is delivered to the recipient's intestinal tract. Another reason may be individual differences in the composition of the intestinal microbiota; it was originally proposed to divide the human population according to so-called enterotypes [77]. It is now clear that this issue is more complex, but there is no doubt that a probiotic that will help one person may not be effective in another, and we do not yet have a detection system that can determine in routine practice which patients could benefit from the administration of probiotics, nor what composition of probiotics or prebiotics would be suitable for a particular patient.

Rationale:

Ad 1) Compared to the adult population, the occurrence of CDI in children is significantly less frequent. If it occurs, then the cause is usually other than the previous administration of common antibiotics. The list of predisposing diseases and other circumstances is taken from the literature [3, 71]. A panel of experts emphasizes the high probability of an infection other than clostridial, or of a combination of two infections [73].

Ad 2) Fidaxomicin for use in paediatrics is certified in the Czech Republic in the form of an oral suspension (DIFICLIR 40 mg/ml), but it is not yet marketed. Given the proven efficacy and safety of fidaxomicin in adult patients, a similar use can be recommended for children as well. Since this drug is not absorbed from the GIT, the risk of side effects is very low. It has already been included in the therapeutic arsenal in some foreign review works [74].

Faecal bacteriotherapy (FMT) has been performed in dozens of paediatric patients, showing comparable efficacy and safety to adults [75, 76].

Conclusions

The deviation of Czech guidelines from European guidelines results from two circumstances. Above all, it is tailored to the current conditions in the Czech healthcare system (unavailability of bezlotoxumab; a uniform level of care that allows metronidazole to be kept as a usable drug for ambulatory patients with a mild course of the first episode of CDI; the tradition of choosing stool donors among the patient's relatives during the treatment of recurrent CDI).

The second difference lies in the way literary sources are used. The European guidelines were written by a number of experts from different countries, with different traditions in the management of treatment. For these guidelines to be acceptable to all European countries, they had to be formulated very correctly, with maximum emphasis on evidence-based medicine (EBM). The results of clinical studies, if possible prospective and randomized, are recognized here as the only reliable criterion. The authors of the Czech text agree with the opinion that the results of well-organized clinical studies provide the best data, but at the same time point out that in many cases high-quality clinical studies are not available. A typical example is the question of individualizing the duration of CDI treatment or solving a fulminant ongoing infection. We believe that in these cases it is acceptable to use rational reasoning based on knowledge of pathogenesis and pathophysiology, and of course also on pharmacokinetic and pharmacodynamic data on the drugs used. The initial data are based on precise observations and measurements and are therefore also evidence based. A national guideline does not have to take the form of a scientific paper, every part of which can be substantiated by observation or experiment. It is a guide on how to solve clinical situations in practice, approved by representatives of the medical field.

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Tab 1: Factors predisposing to the development of clostridial colitis (CDI)

Predisposing factor	**Typical examples**
intestinal dysmicrobia	antibiotic treatment (especially aminopenicillins including combined drugs containing beta-lactamase inhibitors, 2nd and 3rd generation cephalosporins, clindamycin and ciprofloxacin)
disorder of GIT mucosal immunity	insufficient production of mucosal IgA; protein deficiency; malignant tumours; cytostatic treatment; idiopathic inflammatory bowel diseases (ulcerative colitis, Crohn's disease)
intestinal immobility	conditions after surgery in the abdominal cavity; administration of drugs suppressing peristalsis; pregnancy; tumours limiting peristalsis mechanically
immobility in general	long-term bed rest; surgery under general anaesthesia; rheumatic and nervous diseases limiting mobility
hospitalization	especially stay in ICU and hospital for long-term sickness; the risk of infection is higher in wards where clostridial colitis has already occurred in the past
higher age	incidence and the severity of the disease increases substantially from the age of ≥ 65 years

Tab. 2: Clinical suspicion of clostridial colitis

Medical history	• acute diarrheal illness that occurred in people taking antibiotics (or within 2 weeks after an antibiotic course); these are mainly co-aminopenicillins (Augmentin, Amoksiklav), 2nd and 3rd generation cephalosporins, clindamycin and ciprofloxacin. • acute diarrheal illness that arose in the hospital, especially when it comes to - elderly (≥65 years) and immobile persons - patients with pre-existing bowel disease (IBD, conditions after bowel surgery, diverticulosis; PPI use) - patients after cytostatic/immunosuppressive treatment (malignant disease, conditions after organ transplantation) - patients hospitalized in the ICU now or recently - in the ward where the patient developed diarrhoea, CDI occurred during the previous 12 months • recurring diarrheal disease
Clinical manifestations	acute or recurrent diarrheal disease accompanied • the typical stool odour • abdominal pain • meteorism, subileus or ileus • increasing leucocytosis • an unreasonably depressed state or impaired consciousness

IBD – inflammatory bowel diseases (ulcerative colitis, Crohn's disease); PPIs – proton pump inhibitors

Tab. 3: Symptoms indicative of severe clostridial colitis (Kelly, McDonald)

Symptom	Comentary
hypotension and shock	alarming clinical manifestations
subileus and ileus	alarming clinical manifestations
colon span (>80 mm in the cecum region or >60 mm on the transverse and descending)	bowel distension demonstrated by imaging (abdominal X-ray, CT)
fever >38.5°C chills and chills	in CDI are a sign of a serious course, but they occur very rarely
leucocytosis >15 x 10^9/l	increasing leucocytosis is alarming
shift to the left (>20% rods in leukocyte differential) and/or absence of eosinophils in the peripheral blood	typical haematological manifestations of sepsis
rise in serum creatinine (>50% above normal value)	if baseline creatinine level is not known, >133 umol/l can be used with less reliability
hypalbuminaemia <30 g/l	can have various causes, but always indicates an alteration that worsens the prognosis of CDI
serum lactate level >2 mmol/l	biochemical marker of septic shock
faecal calprotectin level >2000 ug/g	not a commonly used test
detection of a hypervirulent strain of *C. difficile*	not a commonly used examination

Note: Patients aged ≥65 years, with severe comorbidities and/or with a severe immune disorder should be treated in the same regimen as patients with a severe course of clostridial colitis. The same applies to patients admitted to the ICU.

Tab. 4: Tests used in the diagnosis of CDI [5, 23]

Test	Sensitivity/specificity (%)	PPV/NPV (%)	Evidence of toxin production	Evidence of active infection	Notes
Evidence of GDH (EIA)	94-96/≥90	34-38/100	no	no	screening test

Evidence of toxin A/B (EIA)	57-83/99	69-81/99	yes	yes	toxins are unstable
NAAT (PCR)	95-96/94-98	46/100	yes	no	detection of *C. difficile* toxin-producing genes
Cultivation method[a]	94/99	-	yes	no	results only after 3 days
CCNA, CTA	93/98	-	yes	yes	used for research only

PPV – positive predictive value; NPV – negative predictive value; GDH – glutamate dehydrogenase (an enzyme produced by *C. difficile*); EIA – enzyme immunoassay (usually ELISA test); NAAT – nucleic acid amplification test (usually PCR or LAMP test); CCNA – cell cytotoxicity neutralization assay; CTA – cytotoxicity assay. [a] the cultivation is followed by an EIA test demonstrating the formation of A/B toxins in the isolated strain of *C. difficile* or PCR. From the comparison of the second and third columns of the table, it can be seen that the detection of toxins using EIA has a low sensitivity compared to other examinations, but a high positive predictive value; therefore, it is suitable for confirmation.

Tab. 5: Pharmacokinetics and pharmacodynamics of antibiotics used in the treatment of CDI (Beneš 2016)

Antibiotic	**Method of application**	**Inhibition of toxin formation**	**Efficacy against *C. difficile*** (*in vitro*)		**Stool concentration**[a] (μg/g)	**Achievement of a clinical effect** (days)
			MIC_{50} (μg/ml)	**MIC_{90}** (μg/ml)		
metronidazole	p.o., i.v.	±[b]	0,25	2	3-9	4-5
vancomycin	p.o.	-	1	2	200-2000	3
fidaxomicin	p.o.	+	0,06	0,125	800-3900	1-2
tigecycline	i.v.	+	0,06	0,06	3-14(Nord)	NA

[a] Stool does not represent a homogeneous environment comparable to an aqueous solution. It seems that only an antibiotic which concentrations exceed the MIC value by a hundredfold will achieve reliable effectiveness in such an environment. On the other hand, it is necessary to take into account the fact that the mentioned concentrations of metronidazole and tigecycline in the intestinal contents correspond to a resting state and will increase during an inflammatory reaction.

[b] The effect of metronidazole in the bacterial cell is non-selective. The antibiotic in the bacterium damages various macromolecules, so it can disrupt proteosynthesis, but this effect is not dominant.

Tab. 6: Comparison of the success of individual antibiotics in the treatment of CDI (Prehn)

Compared ATB	% cured	% recurrences	Commentary
metronidazole: vancomycin	78,1: 86,9	17,2: 18,0	VAN: significantly more effective treatment of CDI
vancomycin: fidaxomicin	84,0: 86,6	26,0: 15,9	FDX: significantly fewer recurrences

Tab. 7: Recommended dosage of orally administered antibiotics, duration of CDI treatment

Antibiotic (p.o. treatment)	**Recommended dosage** (adults)	**Total daily dose**[3]	**Recommended duration of treatment according to the EU** (days)(Prehn)	**Achievement of a clinical effect** (days) (Beneš 2016)	**Recommended duration of treatment in the Czech Republic** (days)
metronidazole	3x 500 mg	1500 mg	10	4-5	10
vancomycin	4x 125 mg	500 mg	10	3	6-7
fidaxomicin	2x 200 mg	400 mg	10	1-2	5

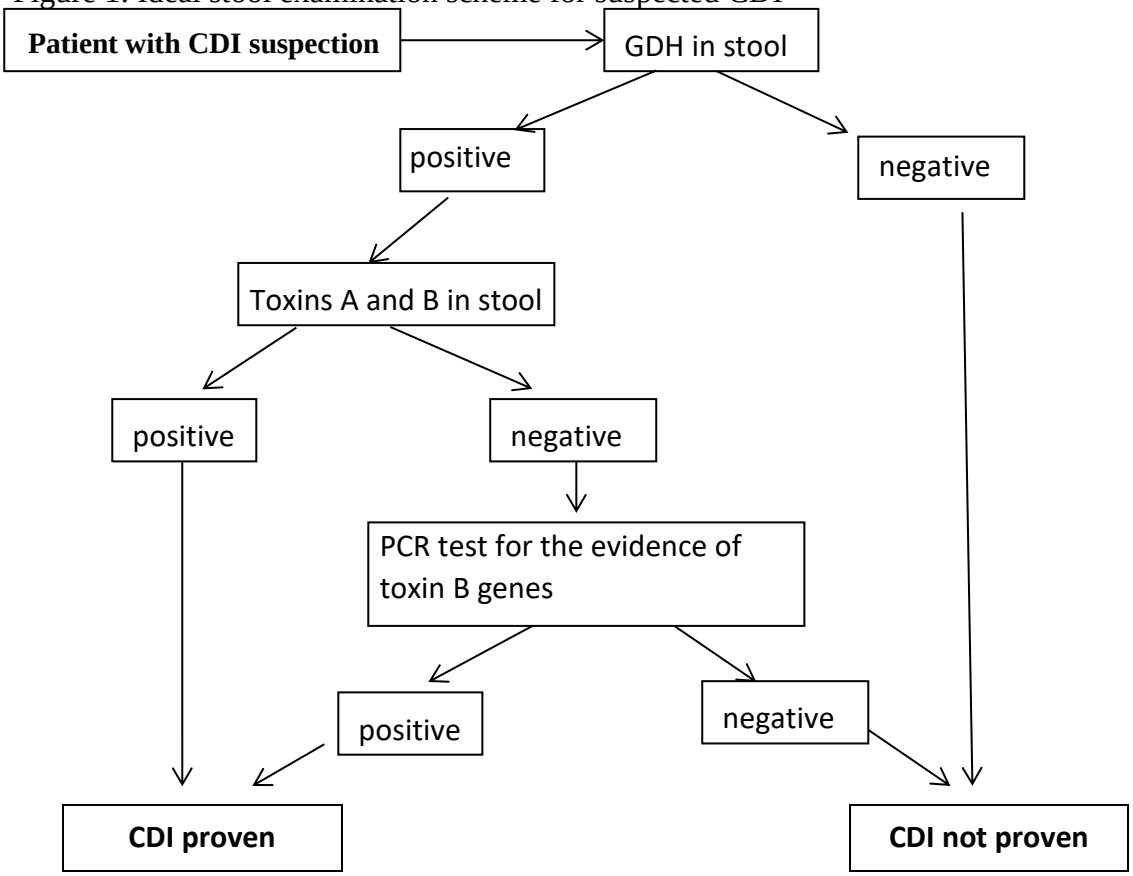
[3]Vancomycin and fidaxomicin have similar oral pharmacokinetics. So, the question arises whether it would not be possible to administer vancomycin in a more comfortable regimen of 2x 250 mg. However, without a clinical study, such a regimen cannot be officially recommended.

Tab. 8: Overview of recommended paediatric antibiotic dosing for the treatment of CDI

Antibiotic	Dosage
Metronidazole [3]	7.5 mg/kg 3-4 times a day up to a maximum dose of 500 mg 3 times a day i.v. or p.o.
Vancomycin [3]	10 mg/kg 4 times a day up to a maximum dose of 125 mg 4 times a day perorally or 10 mg/kg 4 times a day up to a maximum dose of 500 mg 4 times a day per rectum (for ileus)
Fidaxomicin [69]	dosage according to weight: <4kg → 40 mg once a day; 4-6.9 kg → 80 mg once a day; 7-8.9 kg → 120 mg once a day; 9-12.4 kg → 160 mg 2 times a day; >12.5 kg → 200 mg 2 times a day

Note: The dosage of fidaxomicin applies to the form of granules for the preparation of an oral suspension. This medicinal form is registered in the Czech Republic but is not yet marketed.

Figure 1: Ideal stool examination scheme for suspected CDI



GDH – glutamate dehydrogenase is an enzyme that *C. difficile* creates and secretes into its environment. In the first step, a highly sensitive GDH test is used, the negativity of which with high probability excludes the presence of *C. difficile* in the examined sample. Positive findings are subsequently confirmed using a test with high specificity. The confirmatory test is usually an enzyme immunoassay (ELISA), which demonstrates the presence of toxins A and B in the stool. However, toxins are not very stable, they break down quickly, and therefore the test result can be falsely negative, especially if the stool is examined with a gap after defecation. The text describes possible solutions if the result of the microbiological examination is negative, and yet the clinical suspicion of CDI persists.

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