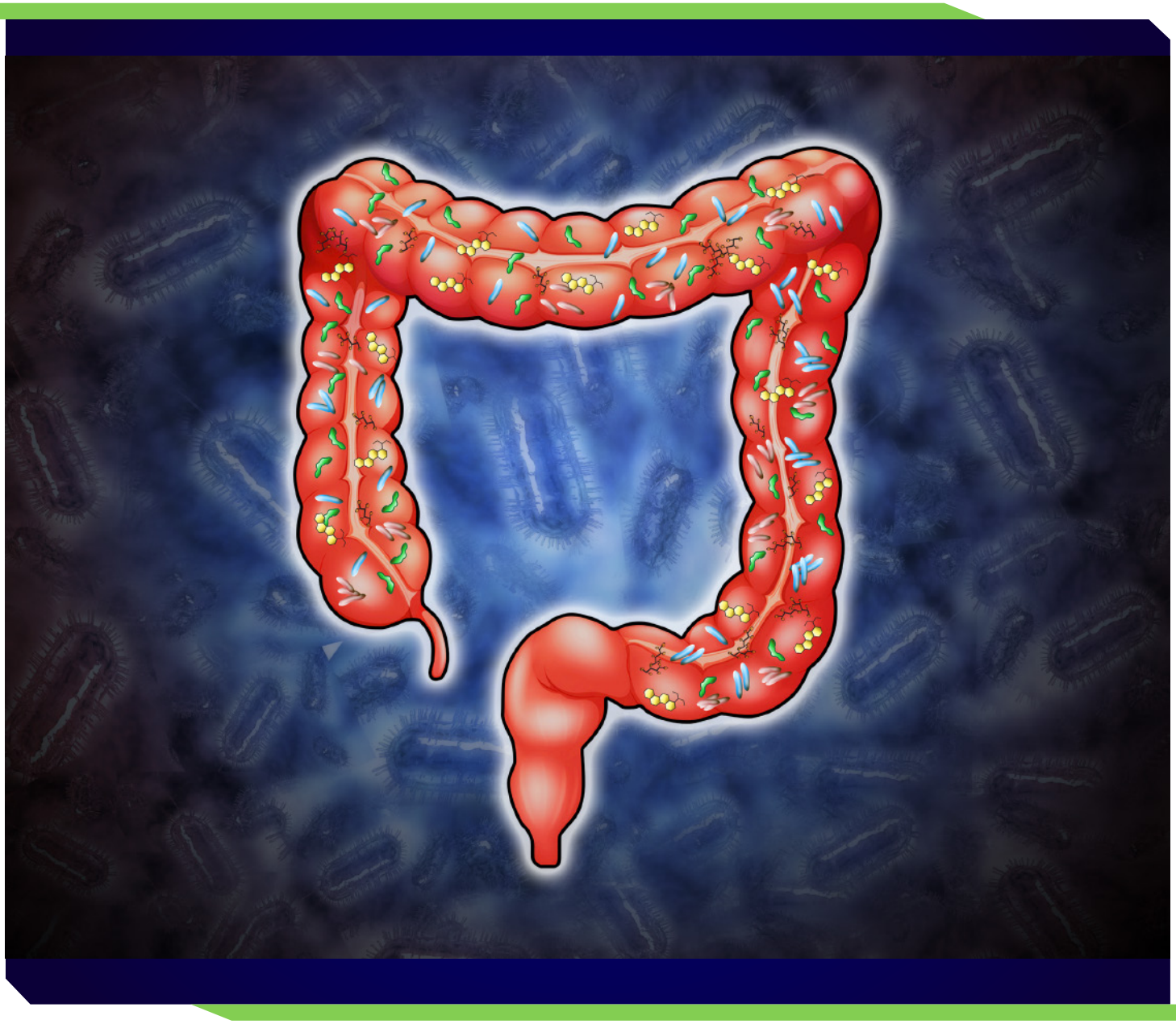
C DIFF:

I HATE MY BED ASSIGNMENT!!



APRNworld®

Disclaimer

The Nursing Continuing Professional Education materials produced by APRNWORLD® are made as an integrated review of current evidence available from multiple sources. The bulk of the information is taken from major scientific journals and other relevant publications. APRNWORLD® made every reasonable effort to cite these resources appropriately however, may have omissions made inadvertently due to the vast and generic nature of the scientific information available. APRNWORLD® does not hold copyright of any of such information. The copyright of such information belongs to the specific author/ publisher or their legal designee. Even though we made every reasonable effort in ensuring the quality and correctness of information, APRNWORLD® does not bear the responsibility of the accuracy of the information as it was taken from publicly available sources. The education material is meant for licensed professionals with a solid body of knowledge, experience and understanding of complex medical scenarios. The material presented here does not replace sound scientific and up-to-date guidelines from professional sources. Because of the dynamic nature of medical and scientific advancements, these training materials should not be used as the sole basis for medical practice. Individual practitioner should exercise their critical thinking and clinical reasoning skills in dealing with complex medical scenarios. APRNWORLD® does not bear any responsibility for the claims that the information presented through its platforms caused injury or unwanted outcomes in any clinical situations.

C DIFF:
I Hate My Bed Assignment!!

ANCC Accredited NCPD Hours: 1.3hrs

Target Audience: RN/APRN

Need Assessment

Clostridium difficile is the most common pathogen in nosocomial and antibiotics-associated diarrheal diseases. It is also responsible for diarrheal diseases in patients with no risk factors (community-acquired Clostridium difficile infection). ***The frequency of Clostridium difficile infection (CDI) and its increased morbidity, which is associated with prolonged duration of inpatient treatment and a considerable rise in the use of hygiene management, lead to a significant increase in hospital treatment costs.*** This article aims to summarize current diagnosis and treatment guidelines in order to help in making optimized diagnosis, treatment, and hygiene management comprehensive and in reducing disease burden in the long term.

Objectives

- Describe the clinical spectrum of Clostridium Difficile
- Discuss the epidemiology of Clostridium Difficile Infection
- Identify the factors leading to Clostridium Difficile Infection
- Describe the extrinsic risk factors that influence the growth of Clostridium Difficile
- Discuss the various treatment options for Clostridium Difficile Infection

Goal

The goal of this article is to discuss the incidence, prevalence and significance of hospital acquired C Diff infections exploring the current evidence regarding mortality

Introduction

Clostridium difficile is the most frequent cause of nosocomial antibiotic-associated diarrhoea. The incidence of C. difficile infection (CDI) (as shown in fig.1)has been rising worldwide with subsequent increases in morbidity, mortality, and health care costs. ***Asymptomatic colonization with C. difficile is common and a high prevalence has been found in specific cohorts, e.g., hospitalized patients, adults in nursing homes and in infants.*** However, the risk of infection with C. difficile differs significantly between these cohorts. While CDI is a clear indication for therapy, colonization with C. difficile is not believed to be a direct precursor for CDI and therefore does not require treatment.

Antibiotic therapy causes alterations of the intestinal microbial composition, enabling C. difficile colonization and consecutive toxin production leading to disruption of the colonic epithelial cells. ***Clinical symptoms of CDI range from mild diarrhea to potentially life-threatening conditions like pseudomembranous colitis or toxic megacolon.*** While antibiotics are still the treatment of choice for CDI, new therapies have emerged in recent years such as antibodies against C. difficile toxin B and fecal microbial transfer (FMT). This specific therapy for CDI underscores the role of the indigenous bacterial composition in the prevention of the disease in healthy individuals and its role in the pathogenesis after alteration by antibiotic treatment. [1, Rank 5]

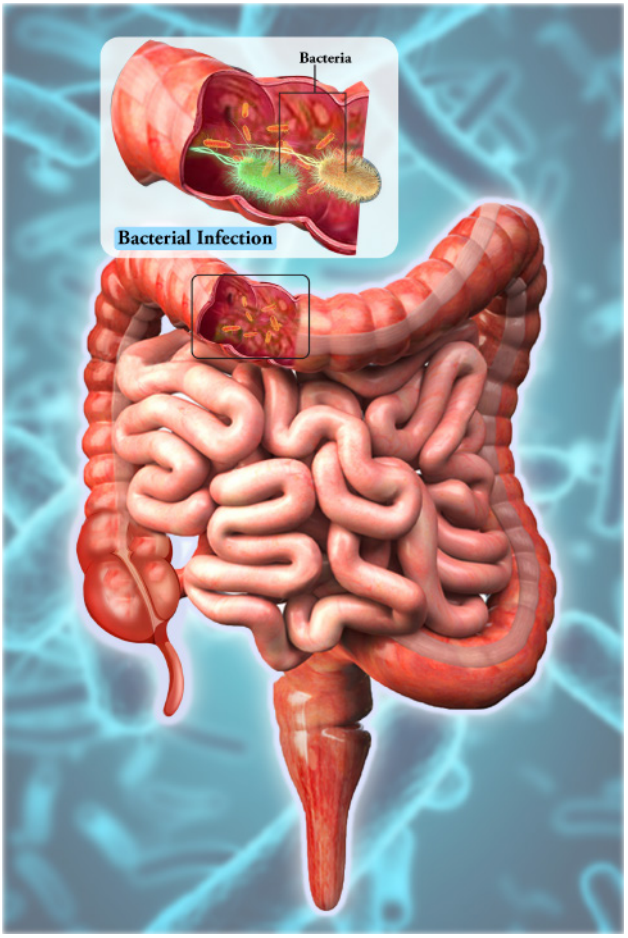


Figure 1: C. difficile infection (CDI) in the intestine

The Clinical Spectrum of Clostridium Difficile

The clinical spectrum of C. difficile (as shown in fig.2)ranges from asymptomatic colonization, mild and self-limiting disease to a severe, life-threatening pseudomembranous colitis, toxic megacolon, sepsis and death.

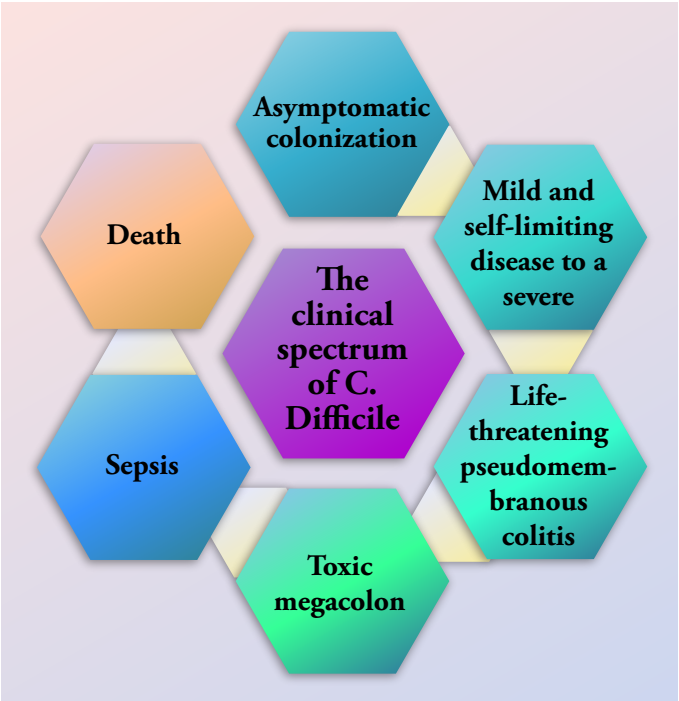


Figure 2: clinical spectrum of C. difficile

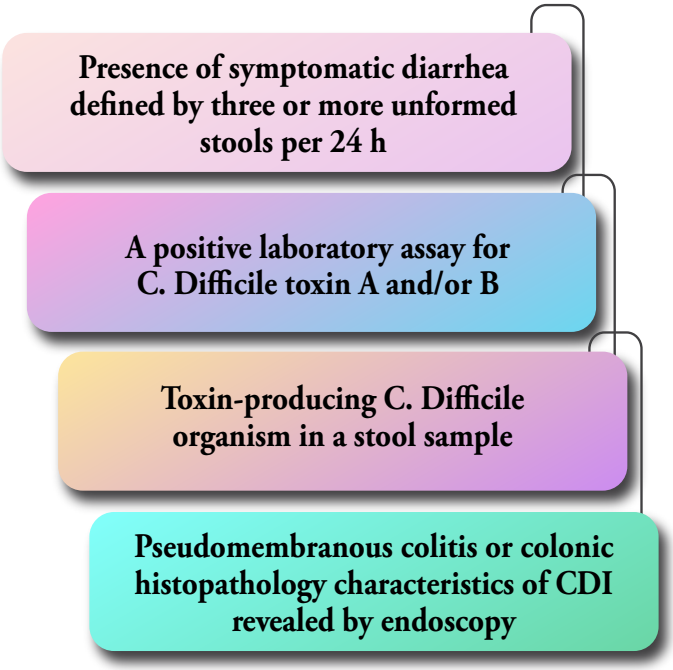


Figure 3: Characteristics for defining C. difficile infection (CDI)

CDI is defined (as shown in fig.3)when there is the presence of symptomatic diarrhea defined by three or more unformed stools per 24 h and at least one of the following criteria: a positive laboratory assay for C. difficile toxin A and/or B or toxin-producing C. difficile organism in a stool sample or pseudomembranous colitis or colonic histopathology characteristics of CDI revealed by endoscopy. ***CDI is associated with an increased abundance of toxin-producing C. difficile strains, leading to high toxin concentrations within the colon resulting in inflammation and damage of the colonocytes.*** Usually, the indigenous microbial communities provide a colonization resistance to C. difficile. However, a disruption of this microbial system can promote the development of CDI.

While the clinical presentation of CDI is distinctive, *C. difficile* colonization without any symptoms, defined as asymptomatic colonization is common, especially in neonates. [2, Rank 4]

Epidemiology of Clostridium Difficile Infection

The worldwide incidence of CDI has been rising steadily since past few years, however, susceptibility to treatment decreased. C. difficile was first reported to cause severe antibiotic-associated diarrhea and pseudomembranous colitis and has become the most common healthcare-associated infection, leading to about 500,000 cases and 29,000 deaths annually in the United States. Overall, the epidemiology data of CDI in Europe are more variable due to different reporting

> **"Clostridium difficile is the most frequent cause of nosocomial antibiotic-associated diarrhoea. The incidence of C. difficile infection (CDI) has been rising worldwide with subsequent increases in morbidity, mortality, and health care costs."**

systems within the European Union. However, by extrapolation of the data from the United Kingdom to Europe, they result in a total number of 172,000 CDI cases annually within the European Union.

The epidemic spread of CDI leads to larger nosocomial outbreaks, which are associated with increased morbidity and mortality. The economic impact of CDI is enormous, leading to additional medical costs of over one billion dollar per year in the United States and three billion euro per year within the European Union. Especially hospitalized patients and adults in long-term care facilities are at a higher risk of developing CDI. Additionally, in infants an increase of CDI was observed in the last decade. This is especially interesting since – as mentioned above – C. difficile is highly prevalent in infants, however, they usually do not show clinical signs of CDI. Nevertheless, the data regarding CDI in pediatric patients are limited. [3, Rank 3]

Asymptomatic Colonization of Pathogens Leading to Clostridium Difficile Infection

The prevalence of asymptomatic C. difficile colonization in adults varies in different population groups. In healthy adults, several studies have shown that 0–17.5% were colonized by C. difficile strains without clinical signs of CDI. The colonization rate of toxigenic strains ranges from 1 to 5% in the surveyed group. While the prevalence of asymptomatic C. difficile colonization is relatively low in healthy adults, it can rise dramatically in individuals having contact with the health system. Elderly in long-term care facilities or nursing homes have an increased rate of colonization range from 0 to 51%.

A high prevalence of asymptomatic C. difficile can also be found in patients or health-care workers. Additionally, patients in rehabilitation centers have an increased rate of asymptomatic C. difficile colonization. Furthermore, a high percentage of asymptomatic C. difficile colonization can be found in adult patients with underlying diseases, e.g., cystic fibrosis.

Risk factors for the development of the last asymptomatic C. difficile colonization(as shown in fig.4) are hospitalization within 12 months, use of corticosteroids, a previous history of CDI and antibodies

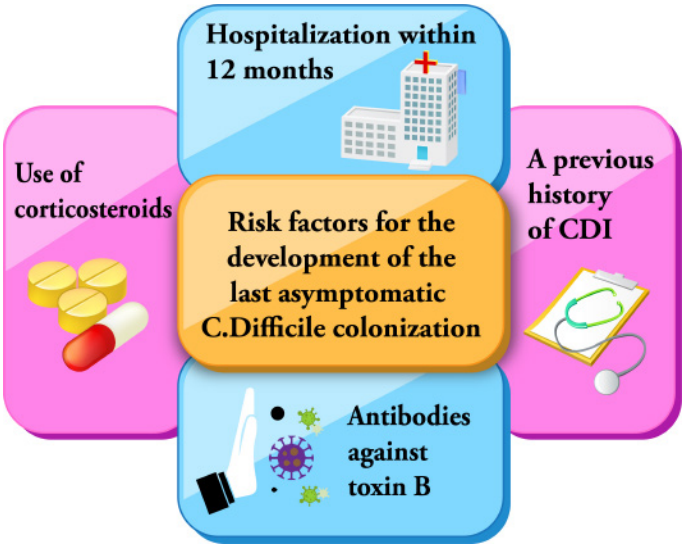


Figure 4: Risk factors for the development of the last asymptomatic C. difficile colonization

against toxin B.

In contrast to adults, a high prevalence of C. difficile colonization without clinical signs of CDI can be observed in infants and neonates. Colonization rates comparable to the rates in healthy adults were observed in infants by the age of 2 [4, Rank 2]

Factors Leading to Clostridium Difficile Infection

Intestinal Microbes

The intestinal microbiota is a complex ecosystem consisting of over a thousand bacterial species reaching its highest concentration in the colon. In adults, a healthy intestinal microbiota is dominated by the phyla Bacteroidetes and Firmicutes and shows a high diversity and richness. ***These commensal bacteria are essential for the host metabolism, nutrition function, maturation of the immune system and protection against pathogens. During human lifetime, different factors, such as the mode of delivery, diet, geography, antibiotic use and the development of gastrointestinal diseases can influence the composition of the intestinal microbiota.*** A disruption of this ecosystem, a so-called intestinal dysbiosis can have a significant influence on the structure and the function of the resident microbiota. Changes of the indigenous intestinal microbial composition result in a breakdown of the colonization resistance, which favors C. difficile germination, growth and spreading within the intestine. [5, Rank 3]

It is well known that the susceptibility of CDI is strongly associated with a previous exposure to antibiotics. The application of antibiotics, especially broad-spectrum antibiotics, can have profound and long-lasting consequences on the host by altering the intestinal bacterial composition and the metabolome. ***The first description of CDI in the setting of antibiotic therapy was in a patient after the application of clindamycin. Other antibiotics, especially cephalosporins, penicillin and fluoroquinolones have also been reported to be associated with the development of CDI.*** Moreover, it has been demonstrated that cumulative exposure to any kind of antibiotics increases the risk of developing CDI. The impact of antibi-

otic administration on the microbial composition in healthy adults has been studied extensively. [6, Rank 3]

Bile Acids

Germination of C. difficile spores is supported by changes in the composition of bile acids. A reduced number of bacteria, producing hydrolase enzymes, results in a reduction of secondary bile acids, which normally inhibit vegetative cell growth and a simultaneous increase of primary bile acids like cholate or taurocholic acid stimulates spore germination. While cholate and glycine can promote C. difficile spore formation, chenodeoxycholate was found to act as an inhibitor of spore formation. A depletion of commensals can also result in an oversupply of available nutrients, e.g., monosaccharides, which can further be utilized by C. difficile. [7, Rank 3]

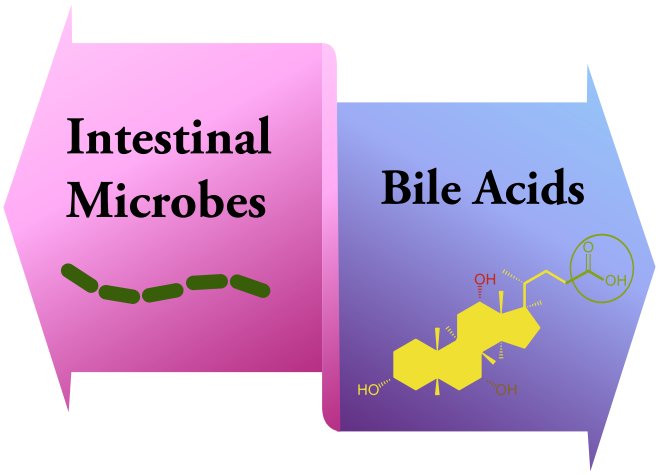


Figure 5: Factors Leading to Clostridium Difficile Infection

Extrinsic Risk Factors That Influence the Growth of Clostridium Difficile

Different studies indicate that – beneath host-mediated and pathogen-related factors – multiple extrinsic risk factors increase the development and also severity of CDI.

Antibiotics

The use of antibiotics is the most-common risk factor in the development of CDI. Antibiotics have dramatic effects on the bacterial ecosystem of the gut, which can last for a long period of time. Especially fluoroquinolones and particularly cephalosporins and clindamycin are associated with an increased frequency of CDI

Proton Pump Inhibitors

Another important risk factor for the development of CDI is the use of proton pump inhibitors (PPIs). While the normal gastric acidity provides a protective host defense, an increase of the gastric pH may prevent the gastric content from an elimination of the ingested C. difficile spores. However, the role of PPIs in the development of CDI is still controversial, since other studies could not prove an association between the gastric acid suppression and an increased risk

for the development of CDI. Since the use of PPIs is increasing globally, further prospective studies are needed in order to address the possible association with these drugs and the development of asymptomatic C. difficile colonization or CDI. [8, Rank 4]

Health Care Facilities

In hospitals or long-term care facilities, an increased exposure to C. difficile can be found due to high C. difficile contamination on surfaces, medical devices and health care personal or infected roommates. Furthermore, a high rate of polypharmacy like antibiotics and underlying co-morbidities such as malignancy or inflammatory bowel disease are closely associated with patients in health care facilities. To decrease the C. difficile transmission and infection rate in hospitals and long-term care facilities, a screening of new patients could be an option to identify toxigenic strain carriers and isolate them from other patients.

Age

Clostridium difficile is more common in advanced age, also showing a more severe outcome in this population. There are several possible mechanisms for this phenomenon. First, an inadequate innate or humoral immune response might lead to a higher incidence and also severity of CDI. Secondarily, the higher prevalence of CDI in the elderly could also be associated with the change of the intestinal microbial composition, e.g., loss of bacterial diversity during aging, which might promote C. difficile colonization. Additionally, the presence of chronic disorders and an increase in the infection rate, requiring polypharmacy, including antibiotics, is generally much higher in this age group.

Food

While the transmission of C. difficile from humans to humans is well-established, C. difficile as a foodborne disease still remains a matter of debate. In different studies, C. difficile was found in retail meat. Additionally, C. difficile was also detected in water, vegetables, pets and also piglets. Regular exposure to C. difficile in the food might lead to asymptomatic C. difficile colonization. However, since community-acquired C. difficile is relatively uncommon, it is not clear if the ingestion of C. difficile via the oral route also leads to consecutive CDI. Further studies will be needed in order to address this issue. [9, Rank 2]

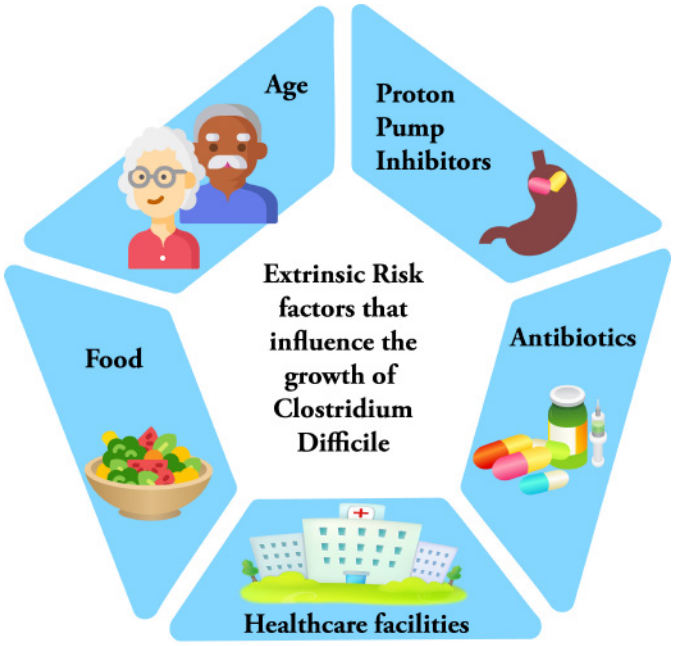


Figure 6: Extrinsic Risk Factors That Influence the Growth of Clostridium Difficile

Treatment Options for Clostridium Difficile Infection

Conventional

The mainstay in the treatment of CDI is – beneath the withdrawal of antibiotics fostering CDI – the initiation of an antibiotic therapy, e.g., vancomycin or metronidazole. However, therapy of recurrent CDI can be challenging with conventional antibiotic therapy. Recurrence of CDI is found in 20–30% of the patients with a high mortality rate in this cohort. ***Fidaxomicin, approved by the United States Food and Drug Administration for CDI treatment, shows reduced recurrence rates in patients with C. difficile. In a recent study, the use of bezlotoxumab, a human monoclonal antibody, was associated with a lower rate of C. difficile recurrent infection.*** A matter of debate for this new approach is the potential combination with fecal microbial transplantation (FMT). Further studies will be needed in order to redefine the treatment algorithm of CDI with bezlotoxumab.

Microbiota-Targeted Therapy

The intestinal microbial communities of patients with CDI differ from patients with asymptomatic C. difficile colonization. In different studies, the administration of single strain probiotics showed only limited success in the treatment of CDI. The role of probiotics in the prevention of CDI is still discussed controversial. In contrast to this, the probiotic treatment with three strains from Lactobacillus parallel to antibiotic application in hospitalized adults showed a significantly decreased CDI rate.

The most direct and effective way in changing the patient's intestinal bacterial composition is via ***FMT. FMT is highly effective in the treatment of antibiotic-refractory CDI and recently was also shown to be cost effective.*** FMT involves installation of stool from a healthy donor into a patient, leading to a shift of the intestinal microbial communities. Despite the high effectiveness of FMT in the treatment of recurrent CDI, the long-term effects of this

therapeutic approach are still not known and might lead to an increased risk of other diseases. Furthermore, FMT is still a highly diverse biological product with several challenges in the standardization of protocols.

Another therapeutic approach is the administration of non-toxigenic C. difficile strains or a mixture of spore-forming commensals. In two phase II clinical trials testing both treatments, a significant decrease of CDI recurrence was observed. However, in another study it was observed that non-toxigenic strains had the capacity to change their phenotype to toxigenic C. difficile strains. Therefore, non-toxigenic strains can also be a predisposition in the development of CDI and have to be used with caution in the setting of C. difficile prevention. [10, Rank 3]

Risk Factors for Clostridium Difficile Infection

The main risk of acquiring CDI exists in the four weeks following antibiotic treatment (accounting for 40% to 60% of cases). A distinction can be made here between antibiotics with high colitogenic potential (clindamycin, quinolone, cephalosporin, amoxicillin/clavulanic acid) and those with low colitogenic potential (e.g. tetracyclines). Other risk factors are age (over 65), comorbidities, hospitalization in the last three months, and residence in a home for the elderly or care home. Protein pump inhibitor (PPI) treatment also increases the risk of CDI, but enteral feeding does not play a significant role. The possible risk groups include immunosuppressed or immunodeficient patients and those with chronic inflammatory intestinal diseases.

Clinical Symptoms of Clostridium Difficile Infection

It is important to distinguish between asymptomatic colonization and symptomatic CDI. ***Symptoms range from simple irritation of the mucosa, watery to soft diarrhea with a sweetish, foul odor to the full clinical picture of pseudomembranous colitis with typical endoscopic findings, preferentially in the region of the sigma and rectum.*** CDI affecting the right colon alone is rarer. Stool frequency can exceed 10 times per day, so in older patients signs of exsiccosis requiring treatment can occur swiftly. If symptoms are prolonged, hypoalbuminemia and protein-losing enteropathy can

> **“ In contrast to adults, a high prevalence of C. difficile colonization without clinical signs of CDI can be observed in infants and neonates. ”**

occur. Subfebrile temperatures are common.

On physical examination, the colon is distended in the lower left abdomen in particular. There is usually only slight local pain on palpation. Prognostically unfavorable signs of complicated CDI with ileus, toxic megacolon, perforation, or sepsis (less than 5% of cases) include absence of colonic peristalsis, sudden-onset constipation, extreme leukocytosis, and high fever. This requires further diagnostic measures such as contrast CT of the abdomen; an experienced visceral surgeon should be consulted for this. [11, Rank 5]

Methods for Diagnosis of Clostridium Difficile Infection

The international CDI diagnosis guidelines allow ***evidence-based, rapid detection of toxigenic CDI from stool samples. Multistep diagnostic procedures are recommended, combining a sensitive screening test with a confirmation test for the toxigenic infection. Only symptomatic patients should be tested.*** Repeat stool samples are not usually required. Rapid antigen tests and nucleic acid amplification tests (NAATs) are particularly important in routine diagnosis thanks to their short turnaround time (TAT), which ranges from 15 minutes to 3 hours. The toxigenic culture, i.e. the anaerobic culture in special media, combined with evidence of the toxin in the culture supernatant, is the diagnostic gold standard. Anaerobic culture is required for further special tests such as antibiotic resistance testing and ribotype testing. Cultures are not well suited to acute diagnosis, as they have a long turnaround time (more than 72 hours).

> **"The intestinal microbiota is a complex ecosystem consisting of over a thousand bacterial species reaching its highest concentration in the colon. In adults, a healthy intestinal microbiota is dominated"**

A macroscopic finding of pseudomembranous colitis is in many cases so characteristic that CDI can also be diagnosed via endoscopy or colonoscopy, though with limited sensitivity.

The Role of Hygiene Management in Clostridium Difficile Infection

C. difficile spores cannot be deactivated using conventional alcohol-based disinfectants. CDI therefore requires isolation precautions (single rooms/cohort isolation with individual sanita-

tion), lab coats and gloves, and sporicidal disinfection. During outbreaks and following contamination of the hands, washing with soap and water (mechanical removal of spores) is recommended. In addition to specific hygiene measures, antibiotic stewardship also contributes substantially to reducing CDI [12, Rank 5]

Conservative Therapy for Management of Clostridium Difficile Infection

Evidence of toxigenic CDI requires rapid, risk-adapted treatment. This usually leads to clinical improvement within 48 to 72 hours. If possible, the antibiotic treatment that has led to toxigenic CDI should be interrupted or switched to a less colitogenic drug such as tetracycline or tigecycline. Continued systemic antibiotic treatment increases the probability of a relapse. Naturally, sufficient rehydration therapy should also be administered. Motility inhibitors should be avoided and protein pump inhibitor (PPI) treatment should be discontinued if possible

Oral metronidazole, vancomycin, or fidaxomicin treatment is an evidence-based recommendation. Only metronidazole can also be administered intravenously in exceptional cases, as a result of its pharmacokinetics. There is little data based on experience with other orally administered antibiotics such as bacitracin, nitazoxanide, fusidic acid, rifaxamin, and teicoplanin. Toxin-binding drugs such as tolevamer were inferior to standard treatment in clinical trials.

There is little experience with immunotherapy using intravenously administered immunoglobulin drugs. There is good data from animal experiments, however, on active and passive vaccination. Current research on vaccination is at the stage of Phase III clinical trials. One innovative treatment is reconstitution of protective intestinal flora via the application of vital bacteria; this is known as bacteriotherapy. The use of conventional probiotics remains controversial, as most studies into this are of poor quality. This means that no overall recommendation can be provided. In contrast, numerous observational studies and one randomized controlled trial have shown complex bacteriotherapies such as microbiome transfer to be effective [13, Rank 4]

Risk-Adapted Treatment Stratification According to Treatment Guidelines

International treatment guidelines distinguish between simple, severe, and complicated infections and relapses. ***The criteria given for a diagnosis of severe infection are leukocytosis (>15 000/µL),***

hypoalbuminemia (<30 g/L), and increased creatinine levels (>1.5 mg/dL; alternatively, an increase by more than 1.5 times initial creatinine level). If there are additional risk factors, such as age over 65, immunosuppression, serious concomitant underlying illnesses, dialysis, or history of CDI, patients can be treated as for severe CDI. There is no need to modify therapy for initial treatment of specific highly virulent genotypes

Oral metronidazole is the first-line drug for simple CDI but should not be used for severe CDI. This is because in such cases the response to treatment is lower.

For initial treatment of severe CDI, oral vancomycin is the first-line drug; alternatively, oral fidaxomicin can be used. The lower relapse rate for fidaxomicin should be taken into account, particularly for patients with multiple risk factors, when treatment options are considered. To date there are no studies on patient groups who benefit particularly from fidaxomicin treatment. Discussion of initial therapy is dominated to a great extent by cost considerations. Although fidaxomicin reduces relapses and therefore the subsequent cost of treating relapses, regular prescription of it would lead to an increase in total treatment costs.

Complicated CDI is life-threatening and requires interdisciplinary treatment by intensive care physicians and surgeons. A particular challenge is posed by patients in whom gastrointestinal passage, and therefore the main route of application of the appropriate medication, is disrupted (toxic megacolon, ileus). For these patients, metronidazole should be administered intravenously together with intravenous tigecycline, although the therapeutic benefit of the latter has so far only been investigated in case series. As far as possible, efforts should be made to continue oral vancomycin treatment in parallel even when intestinal passage is compromised, e.g. via a nasogastric tube. As an alternative, retrograde application (colonoscopy, retention enema) is possible. [14, Rank 5]

Treatment Options for Relapsed Clostridium Difficile Infections

A first relapse of CDI should be treated using oral vancomycin or oral fidaxomicin. This means that there is little difference between treatment recommendations for a first relapse and those for initial treatment of severe CDI.

Multiple relapses usually occur within the first 14 days following the end of treatment in patients who are particularly predisposed to CDI. Each new treatment cycle swiftly leads to an improvement in clinical findings, but it is rarely possible to ensure long-term treatment success using conventional treatment cycles (10 to 14

> **"Antibiotic therapy causes alterations of the intestinal microbial composition, enabling C. difficile colonization and consecutive toxin production leading to disruption of the colonic epithelial cells. While antibiotics are still the treatment of choice for CDI, new therapies have emerged in recent years such as antibodies against C. difficile toxin B and fecal microbial transfer (FMT)."**

days). Therefore, for vancomycin, after conventional induction therapy, maintenance therapy in the form of intermittent pulse therapy or according to a tapering schedule is recommended. As an alternative, relapses can be treated with fidaxomicin. Patients in whom relapses recur despite both vancomycin and fidaxomicin treatment are candidates for stool transplantation (synonyms: microbiome transfer, fecal bacteriotherapy). [15, Rank 5]

Stool Transplantation as a Treatment Option in Clostridium Difficile Infections

Since it was first described as treatment for pseudomembranous colitis, the number of original and review articles has multiplied. This experimental form of treatment received particular attention after a randomized controlled trial in patients with multiple relapses was successfully completed early because, after patients were enrolled, stool transplantation was significantly superior to standard therapy in terms of sustained response to treatment.

Only patients with multiple relapses following established relapse treatment schedules should be offered stool transplantation. In a pooled comparison of stool transplantation, treatment response following colonoscopic transplantation was higher than that following application via a nasogastric or nasoduodenal tube. Colonoscopic stool transfer can be recommended on the strength of better acceptance and avoidance of bacterial contamination of the small intestine with fecal microbes, in addition to its higher success rate. No more than 200 mL should be applied via the upper digestive tract. For retrograde application, the response rate can be improved by using 500 mL or more of suspension. A highly diverse protective donor flora develops within two weeks following stool transplantation, predominantly natural Bacteroides species.

In a gastroenterology center with experience of selecting donors and performing the procedure, stool transplantation can be performed as an individual

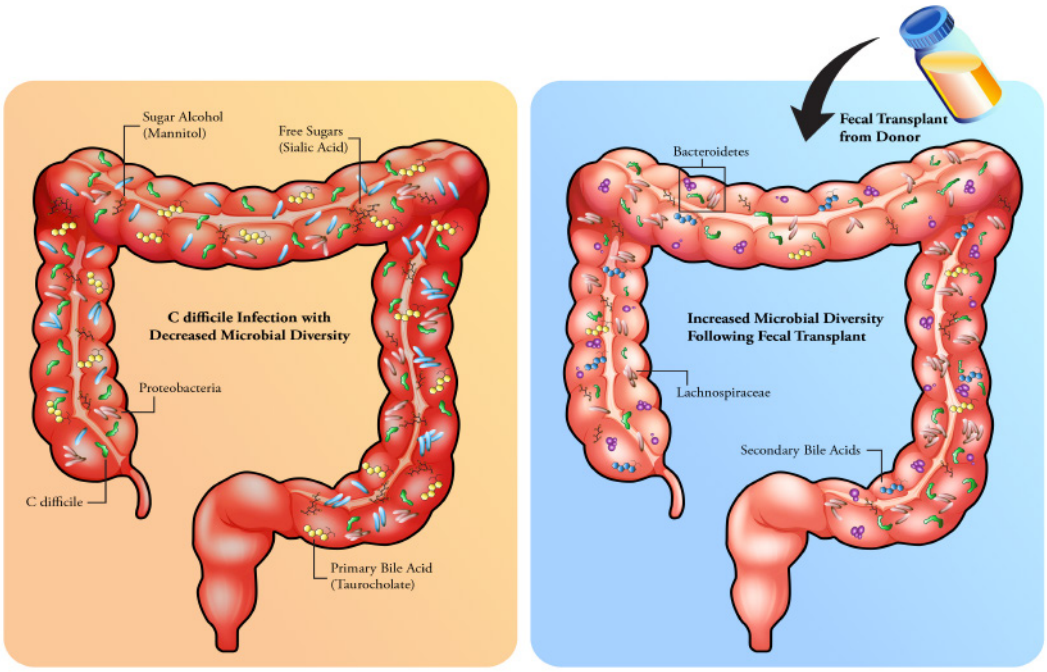


Figure 7: Clostridium Difficile Infection and intestinal microbial activity

attempt at cure, if strictly indicated. To do this, a protocol-based treatment schedule should be followed. Long-term risks that are as yet unknown must be monitored for in long-term follow-up and ruled out. There are, in fact, animal experiments that show a correlation between altered intestinal microbiome and the development of autoimmune diseases and obesity. Overall, the legal questions regarding liability have not yet been sufficiently clarified. [16, Rank 3]

> **"The clinical presentation of CDI is distinctive, C. Difficile colonization without any symptoms, defined as asymptomatic colonization is common, especially in neonates."**

Surgery as a Treatment Option for Clostridium Difficile Infection

Surgery is only necessary for complicated, fulminant CDI (1% to 4%). A pathophysiological correlate of surgery is reduction of the pathogen population and thus toxin production, in addition to removal of the damaged section of the intestine. It should be considered if CDI is fulminant and peritonitis, toxic megacolon, intestinal perforation, or systemic inflammation with organ failure develops despite suitable antibiotic treatment. In these very seriously ill patients, and in CDI patients who should undergo surgery according to general criteria for visceral surgery, 30-day postoperative mortality is reported as between 24% and 80%.

There is evidence that mortality

following late surgery is similar to mortality without surgery. However, early surgery can reduce the mortality of complicated CDI. Early detection of complicated CDI, before the critical stage is reached, places particular demands on clinical monitoring and ongoing diagnostics. Emergency laparotomy is performed more frequently and more rapidly in surgery departments in cases of fulminant CDI. This can reduce mortality 3.4-fold.

In order to provide a clinical definition of fulminant CDI requiring surgery, the criteria for systemic infection and complication can be given a risk score as an aid to classification. This provides a practical basis for individual clinical decisions. Evidence of toxic megacolon, free air, or abscesses in contrast CT of the abdomen are clear indications for surgery. In contrast, if individual segments or even one half of the colon appear intact, this may be an indication for colon-preserving surgery. [17, Rank 4]

Subtotal colectomy with end ileostomy remains the standard operation for fulminant, treatment-refractory CDI. As this is a disease that primarily affects the luminal side of the colon, clearly externally demarcated areas of the colon that might indicate a part of the colon that could safely be preserved are rarely found intraoperatively.

Besides a colon-preserving diversion stoma, a blow-hole colostomy or ileostomy is another interesting approach. This can be performed laparoscopically and allows for intensive antegrade colon lavage using vancomycin. Some studies show slightly lower postoperative mortality following colon-preserving surgery. Overall long-term prognosis is poor even following successful surgery, with a five-year survival rate of less than 20%. Reversal of ileostomy appears to be possible in only 20% of patients. [18, Rank 3]

Clinical Presentation Clostridium Difficile Infection

There is a broad range of clinical manifestations from asymptomatic carriage (20% of culture positive patients) to colitis with or without pseudomembranes to fulminating colitis and toxic megacolon. A study of CDI revealed that ***"acute abdomen" was the presenting feature in 5% of patients with CDI, with 2 of 5 having no diarrhea prior to emergency laparotomy. This acute abdomen presentation without diarrhea may be particularly confusing in the postoperative patient. Onset is usually 5-10 d after antibiotic use, but ranges from 1 d up to 10 d after antibiotics are stopped. Frankly bloody diarrhea is uncommon (5%-10%). In fact, only 26% have occult blood. Fever is noted in***

> **" Changes of the indigenous intestinal microbial composition result in a breakdown of the colonization resistance, which favors C. difficile germination, growth and spreading within the intestine. "**

30%-50%, usually low grade, not to exceed 102F.

Leukocytosis, hypoalbuminemia and elevation of baseline serum creatinine are highly suggestive of CDI. Elevated white blood cell (WBC) count is common (50%-60%), as well as increased band forms (47%) and may be marked elevated. One study found a mean WBC of 15800/mm3 with 26% of patients having a WBC > 20000/mm3 and 6% > 30000/mm3. In fact, for all patients without a hematologic malignancy who had a WBC > 30000/mm3, 25% were found to have CDI. The elevation of WBC may even precede the onset of diarrhea or abdominal discomfort and may be responsible for up to 58% of cases of unexplained leukocytosis in hospitalized patients.

In a study of patients with leukocytosis who were C. difficile toxin negative, empiric treatment for CDI led to resolution of leukocytosis. CDI results in a protein losing enteropathy with resultant hypoalbuminemia. Serum albumin of < 2.5 or a fall in albumin of > 1.1 have been associated with a poor prognosis. Another study has noted that hypoalbuminemia in persons with antibiotic associated diarrhea may be a clinical clue suggesting CDI. Fecal leukocytes have been found in 28%-40% of cases. Detection of fecal lactoferrin (typically used as an indicator of inflammatory bowel disease activity) has been shown to be almost twice as sensitive (75%) as fecal leukocyte detection by methylene blue stain; however, both tests lack sensitivity and specificity and add little to the diagnostic evaluation. [19, Rank 2]

Antineoplastic agents have also been associated with CDI, including doxorubicin, cisplatin, cyclophosphamide, fluorouracil and chlorambucil, with methotrexate most commonly implicated. The proposed mechanism behind the pathogenesis of chemotherapy related CDI is two-fold. First, the antineoplastic agents have been shown to alter the gut microflora in a manner similar to antibiotics, acting as the primary predisposing factor for developing CDI. The second, these agents are capable of inducing mitotic arrest in intestinal epithelial cells, subsequently causing necrosis and desquamation of the mucosal membrane. [14, Rank 3]

Immunocompromised patients may represent a special subset of CDI for which the incidence and treatment may be more challenging to approach, in particular those with solid organ transplantation. The incidence of CDI in transplant patients has been estimated at 3%-7% for liver recipients, 3.5%-16% for kidney recipients, 1.5%-7.8% in pancreas-kidney recipients, 9% in intestinal recipients, 15% in heart recipients, and 7%-31% in lung recipients. Further fulminant colitis is noted to occur in up to 8% of immunocompromised patients and 13% of solid organ transplant recipients with the highest incidence within the first 3 months. The treatment of CDI in immunosuppressed patients should follow the same guidelines based on disease severity.

Although CDI is commonly felt to be a hospital-acquired infection, with up to 87% of infections nosocomially acquired, a significant number of cases are community acquired. In a prospective study of diarrheal pathogens, 20% of infections were community acquired. For an additional 15% of patients, CDI was acquired in the hospital, but diarrhea began after discharge at home for a total of 43% of cases with onset of symptoms at home. Suspicion should always be high for CDI whenever there is diarrhea in a resident of a long term care facility where there is a concentration of elderly, high use of antibiotics, CDI infection in other residents, or frequent exposure to hospitals. This increased risk is bidirectional: 20% of CDI with onset in the hospital are in residents of a nursing home and 67% of CDI in nursing home residents occurs in patients recently discharged from an acute care hospital. [6, Rank 4]

Conclusion

The incidence of CDI increased dramatically in the last years. While asymptomatic C. difficile colonization is common especially in newborns, the progression from asymptomatic colonization to infection is not completely understood and large, prospective studies are lacking. While many studies in adults and infants showed high C. difficile colonization rates with toxigenic as well as non-toxigenic strains, the detection of C. difficile or its toxins in feces of individuals does not immediately implicate an infection with this pathogen and therefore treatment is only indicated when there are clinical signs of CDI. Although persons with asymptomatic C. difficile colonization are potential disease carriers and therefore predispose a risk factor for themselves and other people, based on current information an eradication of C. difficile is not indicated.

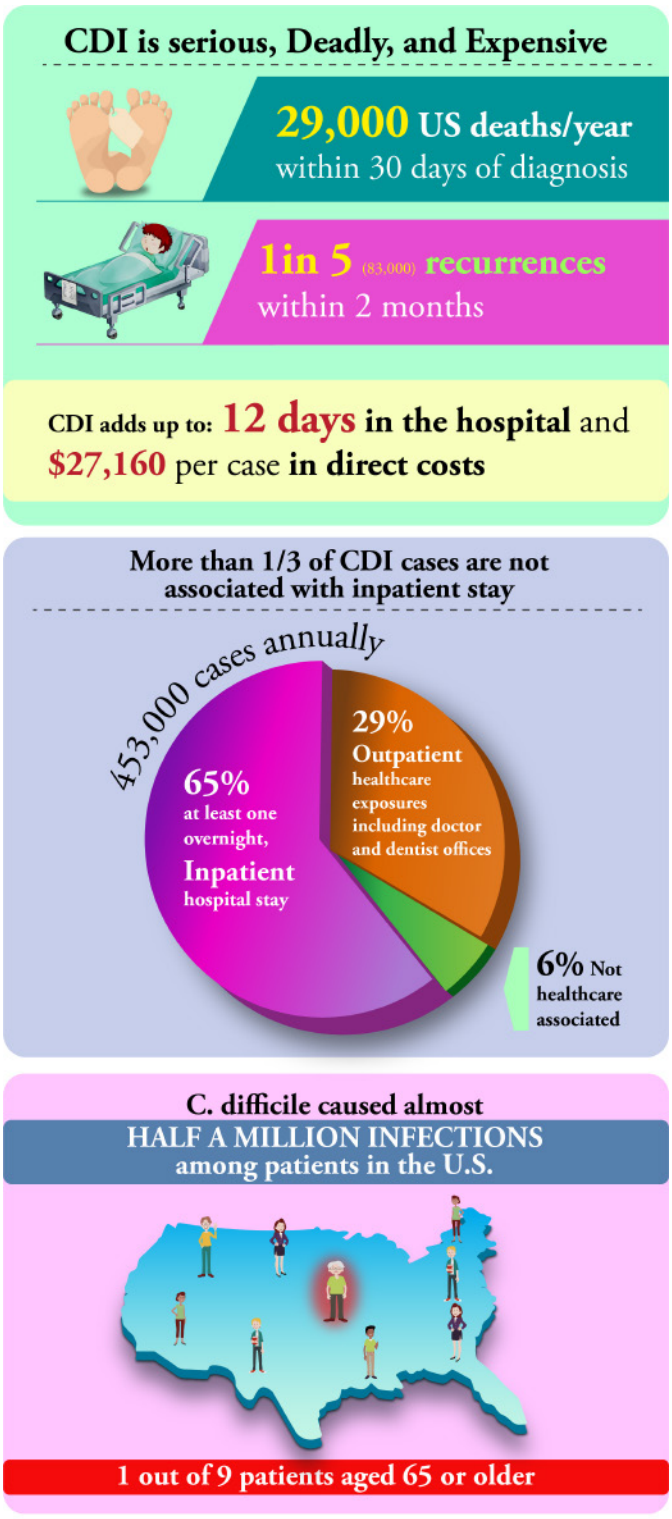


Figure8: fact on Clostridium Difficile Infection

Furthermore, several external factors like age, polypharmacy or underlying medical conditions increase the risk and severity of CDI. Due to the strong association between CDI and antibiotic exposure, therapeutic approaches that target the modulation of the intestinal bacterial composition like FMT are crucial in this clinical setting. Treatment strategies with non-toxigenic C. difficile strains are on their way, however, a change of non-toxigenic to toxigenic C. difficile strains can occur, making this therapeutic approach challenging. [20, Rank 5]

*Important information for post-test is highlighted in red letters, boxes and diagrams.

References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 pdate by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) Infect Control Hosp Epidemiol. 2015

2. Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nature Rev Microbiol. 2019

3. Behnke M, Hansen S, Leistner R, et al. Nosocomial infection and antibiotic use: a second national prevalence study in Germany. Dtsch Arztebl Int. 2016

4. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2016

5. Ott E, Saathoff S, Graf K, Schwab F, Chaberny IF. The prevalence of nosocomial and community acquired infections in a university hospital: an observational study. Dtsch Arztebl Int. 2017

6. Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial Clostridium difficile-associated diarrhoea. J Hosp Infect. 2018

7. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. New Engl J Med. 2016

8. Crobach MJ, Dekkers OM, Wilcox MH, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): data review and recommendations for diagnosing Clostridium difficile-infection (CDI) Clin Microbiol Infect. 2019

9. Debast SB, Bauer MP, Kuijper EJ. The Committee European Society of Clinical

Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2015

10. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2018

11. Hall IC, O'Toole E. Intestinal flora in newborn infants with description of a new pathogenic anaerobe, Bacillus difficilis. Am J Dis Child. 2018

12. Bartlett JG, Onderdonk AB, Cisneros RL, Kasper DL. Clindamycin-associated colitis due to a toxin-producing species of Clostridium in hamsters. J Infect Dis. 2017

13. Joost I, Speck K, Herrmann M, von Muller L. Characterisation of Clostridium difficile isolates by slpA and tcdC gene sequencing. Int J Antimicrob Agents. 2019

14. Stahlmann J, Schonberg M, Herrmann M, von Müller L. Detection of nosocomial Clostridium difficile infections with toxigenic strains despite negative toxin A/B testing on stool samples. Clin Microbiol Infect. 2016

15. Gerding DN, Johnson S, Rupnik M, Aktories K. Binary toxin CDT: Mechanism, epidemiology, and potential clinical importance. Gut Microbes. 2015

16. Heeg D, Burns DA, Cartman ST, Minton NP. Spores of Clostridium difficile clinical isolates display a diverse germination response to bile salts. PLoS One. 2018

17. Burckhardt F, Friedrich A, Beier D, Eckmanns T. Clostridium difficile surveillance trends, Saxony, Germany. Emerg Infect Dis. 2018

18. Grünewald T, Kist M, Mutters R, Ruf BR, Kern WV. Clostridium-difficile-Infektion [Clostridium difficile infection] Dtsch Med Wochenschr. 2017

19. Weiss B. Schwer verlaufende Clostridium-difficile-Infektionen: IfSG-Surveillance-

daten von 2011 und 2012. Epidemiologisches Bulletin. 2019

20 Mock M, Halfmann A, Herrmann M, von Müller L. Aktuelles zur Epidemiologie von Clostridium difficile - Bericht aus dem Konsiliarlabor C. difficile. Epidemiologisches Bulletin. 2018