8.6.24 Clostridium difficile 1115

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8.6.24 Clostridium difficile 1115 Areas of uncertainty, controversy, and future developments Tetanus continues to be a significant problem in much of the world. Considerable progress has been made towards its elimination; however, access to vaccination programmes in many communities is still limited by humanitarian, sociological, or geographical factors. While in many countries maternal and infant vaccination schemes have achieved good coverage, the provision of subsequent boosters necessary for long-term protection has been given scant attention, leaving older individuals susceptible to disease. Funding and implementing large scale booster programmes remains a major challenge for the global health community. While this is happening simple and affordable treatments are still needed that will reduce the need for expensive (and often unavail- able) intensive care unit management. FURTHER READING Borrow R, Balmer P, Roper M (2006). The immunological basis for immunisation series. Module 3: tetanus update 2006 (Vaccines and biologicals). World Health Organization, Geneva. Brüggemann H, et al. (2015). Genomics of clostridium tetani. Res Microbiol, 166, 326–31. Department of Health. Immunisation against infectious disease: chapter 30. Tetanus. https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30 Health Protection Agency (2013). HPA expert working group interim guidance on the use of tetanus immunoglobulin for the treatment of Tetanus (pp. 1–2). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400084/expert_working_group_interim_guidance_on_the_use_of_tetanus_immunoglobulin_for_the_treatment_of_Tetanus.pdf Patel JC, Mehta BC (1999). Tetanus: study of 8,697 cases. Indian J Med Sci, 53, 393–401. Rodrigo C, Fernando D, Rajapakse S (2014). Pharmacological man- agement of tetanus : an evidence-based review. Critical Care, 18, 217. Thwaites CL, Beeching NJ, Newton CR (2015). Maternal and neonatal tetanus. Lancet, 385, 362–70. 8.6.24 Clostridium difficile David W. Eyre and Mark H. Wilcox ESSENTIALS Clostridium difficile is a Gram-positive spore-forming anaerobic bacillus that is ubiquitous in nature, and particularly common in healthcare environments. Its spores are part of the colonic flora in about 2–3% of healthy adults, with colonization rates increasing, typically up to 10–20%, during hospitalization. Disease occurs when the organism shifts from quiescent spores to

replicating vegetative cells with toxin
(A and B) production; this happens when there is inhibition of the resi- dent colonic flora (gut microbiome) by prescribed antibiotics, although cases can occur when no such precipitant is identified. C. difficile in- fection is now recognized as the most important bacterial enteric pathogen in wealthier countries, epidemics, and outbreaks of which are common, most notoriously now due to the ribotype 027 (NAP-1) strain that is associated with more severe disease and poor outcomes. Clinical features—these range from trivial diarrhoea that subsides rap- idly when antibiotics are stopped to fulminant pseudomembranous col- itis, which may progress to toxic megacolon; most cases have watery and voluminous diarrhoea, possibly accompanied by abdominal cramping. Diagnosis and treatment—the condition should be suspected in any patient who has unexplained diarrhoea, particularly in as- sociation with antibiotic use. Diagnosis is established ideally by demonstrating C. difficile toxin in stool, although there has been a recent vogue for polymerase chain reaction-based detection of toxin gene, despite this being less specific. Treatment is by stopping the implicated antibiotic, supportive care, avoiding antiperistaltic agents, and giving oral vancomycin or fidaxomicin; metronidazole is less ef- fective. Bezlotoxumab (given in addition to antibiotic) has recently been approved to reduce recurrences in high risk patients. Prevention—the most important issues are controlling anti- biotic prescribing to reduce exposure overall, and particularly to fluoroquinolones, and infection control in healthcare facilities, including prompt diagnosis and isolation of patients with diarrhoea to limit spore dissemination. Table 8.6.23.3 Recommendations for wound prophylaxis Wound type Active immunization Passive immunization Clean wound Only if vaccination history incomplete (i.e. give booster if not up to date or initiate primary course as described in text) No Low risk tetanus-prone

1. Wounds or burns: • Requiring surgical intervention or when treatment delayed >6 h • With significant degree of devitalized tissue • Containing foreign bodies • Individuals with systemic sepsis
2. Puncture-type injury, particularly in contact with soil and/or manure
3. Open fractures Only if vaccination history incomplete (i.e. give booster if not up to date or initiate primary course as described in text) If vaccination history incomplete, one dose human immune globulin (in different site to vaccination) High-risk tetanus-prone As above but with heavy contamination with material likely to contain tetanus spores and/or extensive devitalized tissue Only if vaccination history incomplete (i.e. give booster if not up to date or initiate primary course as described in text) All one dose human immune globulin (in different site to vaccination, if given)

section 8 Infectious diseases 1116 Introduction Clostridium difficile (recently renamed as Clostridioides difficile) is an anaerobic spore-forming Gram-positive bacillus found in healthcare facilities and widely in the environment, which can colonize and prolif- erate in the human gut, especially following changes in gut microbiome after antibiotic use. The key components of the gut microbiome re- sponsible for preventing C. difficile growth are unclear, but recently secondary bile acids and Clostridium scindens have been identified as possible inhibitors. Pathogenic C. difficile strains produce exotoxins that cause acute colonic mucosal inflammation. Clinical features range from asymptomatic colonization through severe diarrhoea to ful- minant pseudomembranous colitis and occasionally toxic megacolon. C. difficile is noninvasive and so extraintestinal disease is very rare. Antibiotic-associated diarrhoea and enterocolitis have been rec- ognized throughout the antibiotic era. C difficile was initially dis- covered in 1935 as part of a survey of intestinal bacteria

of newborn children, but it was not until the late 1970s that it was established as a significant human pathogen. Within 30 years of this discovery, C. dif- ficile was established as a prominent healthcare-associated infection in developed countries, primarily as epidemic strains caused multiple outbreaks associated with poor outcomes. C. difficile infection (CDI) has therefore become a major priority for patients, healthcare professionals, and policymakers. There is also considerable activity to develop new treatment and preventative options for CDI. Aetiology, pathogenesis, and pathology C. difficile is acquired by faeco-oral transmission, usually via inges- tion of spores, given their resistance to gastric acid and ability to survive the aerobic environment outside the normal host (see Box 8.6.24.1). Stimulated by primary bile acids, spores germinate to vege- tative forms, leading either to asymptomatic colonization or disease. Asymptomatic C. difficile colonization, about 3% in healthy adults, rising to 10–20% in hospital inpatients, is relatively uncommon relative to the rates of antitoxin antibodies (up to 70%) found in adults. Presumably, therefore, most encounters lead to excretion of the bac- terium without symptoms, at least in younger individuals. Infants are frequently colonized, up to 35% in the first 1–2 years of life, falling to about 5–15% by 1–8 years and then to adult levels thereafter. It is un- known why children so uncommonly experience CDI despite such high carriage rates; lack of receptors for C. difficile toxins has been suggested but not proven. Subsequent development of antitoxin anti- bodies is an important host defence in exposed individuals. The normal gut microbiome is a key barrier to infection. Perturbation of gut bacteria, in most cases by antibiotics, allows C. difficile to colonize and/or to proliferate and cause disease. In asymptomatically colonized individuals, the composition of the gut microbiome is similar to C. difficile culture-negative patients; how- ever, in CDI marked changes in the microbiome are seen, with a significant reduction in the diversity present and marked changes in the dominant bacteria. Toxins A and B are the two principal C. difficile virulence determinants. The genes for these toxins are part of a conserved pathogen- icity locus, PaLoc, which is present in the chromosome of toxigenic strains, but absent in avirulent nontoxigenic strains. Toxins A and B enter host cells via receptor-mediated endocytosis, and irrevers- ibly inactivate Ras family small GTPases. This leads to disruption of control of the actin cytoskeleton, membrane blebbing, and eventual apoptosis of the cell. There is continuing uncertainty surrounding the relative importance of toxins A and B in human disease. Animal experiments have provided conflicting data, but this likely part re- flects interspecies differences in the role of toxins. Blocking toxin A in addition to toxin B alone has recently been shown in humans to confer no additional benefit, suggesting that the latter is more im- portant in CDI. Most strains causing disease in humans carry both toxins, but A-B + strains can cause the typical range of disease from asymptomatic colonization to severe colitis. The epidemic ribotype 027 (also known as NAP1/BI) strain carries an additional binary toxin, which also disrupts the cell actin cytoskel- eton. This strain also contains a truncation in the tcdC gene originally hypothesized to be a negative regulator with the truncation resulting in increased toxin production; however, this explanation for the increased virulence of C. difficile ribotype 027 has been recently questioned. Epidemiology Widely used surveillance definitions classify CDI into healthcare- and community-associated on the basis of the time since last healthcare exposure. Rates of healthcare-associated CDI are typically 4–10/10 000 bed-days in endemic settings, whereas rates in com- munity patients without healthcare exposure in the last 12 weeks are 8–25 cases per 100 000 person-years. CDI rates vary markedly across countries, with ascertainment bias secondary to differences in re- questing/testing rates or testing methodology important issues. Prior antibiotic exposure is a major risk factor for CDI, with second- and third-generation cephalosporins, clindamycin, and fluoroquinolones most frequently implicated. There is large vari- ation in the risks reported for different antibiotics, at least in part due to variations in

antibiotic resistance patterns in locally circulating C. difficile strains. There is also a distinction to be drawn between selecting for C. difficile and induction of toxin production and thus CDI. Furthermore, differing levels of exposure to C. difficile will af- fect the recorded CDI rates associated with a particular antibiotic. Repeated or prolonged exposure to antibiotics increases CDI risk, and the last antibiotic before symptom onset may be a relatively low risk agent, the issue here being cumulative damage to the normally protective gut microbiome. The exact temporal relationship between antibiotic exposure and C. difficile acquisition is not fully defined. Antibiotic exposure in the last 90 days increases risk of CDI, but exposure in the last 30 days is associated with greater risk. However, as disruption of gut flora persists beyond 90 days, patients might re- main at risk of CDI for much longer. Box 8.6.24.1 Consequences of C. difficile acquisition • Ingestion followed by excretion • Asymptomatic colonization • Diarrhoea/recurrent infection • Colitis • Pseudomembranous colitis • Pan-colitis, toxic megacolon • Death

 Multiple comorbidities and age >65 years (which is pos- sibly a proxy for the former) are important risk factors for CDI. Immunosuppressed patients, and those with renal failure or in- flammatory bowel disease have higher CDI rates, but there might be confounding here due to higher diarrhoea rates and/or anti- biotic use. Gastric acid suppressive medication, proton pump in- hibitors in particular, is a possible risk factor that is frequently cited, although recent doubt about this association due to con- founding has been reported. Transmission Molecular typing studies demonstrate infected, and to a lesser extent colonized, patients contaminate their surroundings with C. difficile. As most CDI cases occur in healthcare facilities or are admitted to them, C. difficile is widely present in hospitals. Significant healthcare CDI outbreaks occur, and serially screened hospital inpatients ac- quire C. difficile colonization and infection at rates proportional to their length of stay. These observations led to the view that most CDI was acquired from other cases in hospitals. However, whole genome sequencing of strains from CDI cases has recently demon- strated that only a third of these are sufficiently genetically similar to isolates from any previous case to support the latter as the source of infection. Overall, less than a fifth of cases were genetically related to a previous case, and had shared some form of hospital contact. These findings are contingent on appropriate infection prevention and control measures being in place (detailed next). Finding that cases are not the source for most infections has led to a search for alternative sources. Longitudinal studies show long-term C. difficile carriage is unlikely to be a significant source; carriage of toxigenic strains is protective against subsequent CDI, and most cases acquire C. difficile shortly before symptom onset. Asymptomatic patients and children are a possible reservoir. C. diffi- cile has also been recovered from domestic and production animals, retail meat and ready-to-eat food, and water supplies. Recovery from foods is usually uncommon; it is therefore difficult to study such likely sporadic contamination episodes. Different C. difficile strains have different environmental niches, such that no one source is likely to explain all CDI. For example, ribotype 027 has caused significant healthcare CDI outbreaks, but unlike many toxigenic strains, has not been found in healthy children. Similarly, ribotype 078 is strongly linked to pig farming and is an increasing cause of CDI. Clinical features The clinical features of CDI range from mild, self-limiting diar- rhoea to fulminant colitis (Fig. 8.6.24.1). The principal symptom in CDI is watery voluminous diarrhoea with ≥3 unformed stools in 24 hours, but overt gastrointestinal bleeding is rare. Diarrhoea is accompanied by evidence of colonic inflammation including ab- dominal cramps, pain, fever, nausea, anorexia, and leucocytosis. Markers of severe disease include total peripheral white blood cell count less than 15 × 109/litre, acute kidney injury with a rise in serum creatinine to 1.5-fold or less above baseline, and hypoalbuminaemia; in very severe CDIs,

hypotension, elevated serum lactate, ileus, and toxic megacolon (severe dilation of the colon) can occur. Sigmoidoscopy is an uncommon route to diagnosis, but character- istically findings range from mild patchy friable erythema to severe pseudomembranous colitis (raised yellow plaques that coalescence to form confluent pseudomembranes, which might bleed when disturbed) (Fig. 8.6.24.2). Fig. 8.6.24.1 Plain abdominal X-ray showing distal colitis with proximal dilated loops of bowel. The descending colon lacks normal haustrations, resulting in a ‘lead pipe’ colon (arrows); the distal transverse colon shows mucosal thickening referred to as ‘thumb-printing’ (arrows). Fig. 8.6.24.2 Sigmoidoscopic appearances in pseudomembranous colitis: friable white/yellow plaques.

section 8 Infectious diseases 1118 Complications include recurrence, sepsis, intestinal perfor- ation, requirement for colectomy and death. All-cause mortality at 14–30 days following CDI is around 16%, varying by strain type, and is highest in CDIs due to ribotypes 027 and 078 and related strains. Differential diagnosis The main differential is antibiotic-associated diarrhoea, which can also be due to microbiome disturbance or increased peristalsis; antibiotic-associated diarrhoea generally resolves with reduc- tion in antibiotic dose or cessation. Rates of antibiotic-associated diarrhoea range from 5 to 40% depending on the agent used. CDI only accounts for a small subset of patients with diarrhoea fol- lowing antibiotics, and only 5–15% of tests submitted for C. difficile testing are positive. In hospitalized patients, diarrhoea might also be caused by other drugs, including laxatives and cytotoxics, and by enteral feeding. Other potential causes of inflammatory diarrhoea include enteric pathogens (salmonella, shigella, Campylobacter jejuni, and so on), ischaemic colitis, and inflammatory bowel disease. Concurrent CDI can exacerbate inflammatory bowel disease, while asymptomatic colonization with C. difficile might also occur alongside concurrent colitis and potentially obscure the cor- rect diagnosis. Rare cases of antibiotic-associated colitis include Staphylococcus aureus, Klebsiella oxytoca, Clostridium perfringens, and Candida spp. Clinical investigations CDI should be strongly suspected in any patient who has diarrhoea in association with current or recent antibiotic use, and considered in unexplained acute diarrhoea even without prior antibiotic ex- posure. About one-third of community-associated CDI cases have no recent history of prescribed antibiotic exposure. Diagnosis of infection depends on characteristic symptoms plus the presence of free faecal C. difficile toxin (or less commonly pseudomembranous colitis at endoscopy or histologically). An important caveat is that in life threatening CDI there can be an ileus and so lack of diarrhoea. An unexplained high white blood cell count is another potential in- dicator of CDI. Available routine tests for CDI can detect the presence of bacteria directly (e.g. by culture or via C. difficile glutamate dehydrogenase), its toxin (e.g. by cytotoxin assay or more commonly by enzyme im- munoassay, EIA), or bacteria with the potential to produce toxin (e.g. toxigenic culture or nucleic acid amplification tests, NAATs, for toxin genes). Notably, there are two reference standard tests, one for detection of bacteria with potential to produce toxin (cytotoxigenic culture), and the other for toxin detection (cell cytotoxicity assay, CTA). Only tests that detect the presence of toxin in faeces (CTA or toxin EIA) have been shown to correlate with clinical outcome. All-cause mortality is elevated in patients with positive faecal toxin assays, whereas patients with a positive NAAT, but negative toxin as- says have similar outcomes to those with negative NAAT and nega- tive toxin results. Therefore, isolated use of NAAT testing can lead to overdiagnosis of infection. Faecal culture is rarely performed for routine diagnosis of C. difficile, but might be required for surveil- lance (genotyping) studies. No ideal single test exists for detection of C. difficile toxin. CTA is technically demanding and slow (24–48 hours to result); while toxin EIAs are rapid, sensitivity is typically only 80% and false-positive re- sults occur (in

typical use, about one to two out of every 10 positives). This has led to the development of two-step testing strategies, adopted in UK, European, and also partly in recent US guidelines. A highly sen- sitive initial screen (e.g. glutamate dehydrogenase or NAAT), is used as a prompt rule out with high negative predictive value. Confirmatory testing is then undertaken with EIA or CTA to improve specificity. However, given the imperfect sensitivity of EIA, clinical judgement is still required, as it may be appropriate to treat a patient for CDI with a negative EIA result if there is a strong clinical suspicion of infection. Addition of a third test using a NAAT is an option but requires careful interpretation to avoid overdiagnosis; this might identify patients with diarrhoea of another aetiology concurrently carrying a toxigenic strain of C difficile (who can represent a cross infection risk), or possible false- negative toxin test results. Repeat testing is generally discouraged when a negative is obtained first (given the high negative predictive value of first step screening tests). Routine repeat testing after positive CDI tests has no value, as toxin can be detected in faeces for several weeks following clinical recovery. If symptoms recur then repeat testing should be carried out to establish whether CDI is the cause. Treatment Treatment involves, where possible, stopping any causative anti- biotic, supportive care, and specific therapy with oral vancomycin or fidaxomicin (metronidazole is less effective—below). Bezlotoxumab, a monoclonal anti-toxin B antibody that is given in addition to CDI standard antibiotic treatment, has recently been approved to reduce recurrences in high risk patients. In patients with mild disease simply stopping provocative antibiotics might resolve symptoms; however, given the potential for severe disease, usual practice is to treat all pa- tients with CDI. Older US and European guidelines have advocated 10–14 days treatment with oral metronidazole (500 mg three times daily) for patients with mild-moderate disease and oral vancomycin (125 mg four times daily) for patients with severe disease. However, two recent randomized controlled trials (RCTs) have demonstrated vancomycin is superior to metronidazole for all CDI, clinical reso- lution occurred in 81% and 73% respectively ($p = 0.02$), with the ad- vantage for vancomycin more marked in severe disease 79% versus 66% ($p = 0.06$), as previously reported. Rates of clinical cure with fidaxomicin were noninferior to vancomycin in two major RCTs, and fidaxomicin was associated with reduced risk of recurrence compared with vancomycin (15% vs. 25%, $p = 0.005$). Concurrent, non-CDI therapy antibiotics should be avoided where possible, as these are associated with longer durations of diarrhoea, reduced clinical cure, and increased recurrence rates. Antiperistaltic agents, such as loperamide, should be avoided in acute disease. Patients with severe disease where oral or nasogastric antibiotics may not reach the diseased site (e.g. with ileus), should be managed with intravenous metronidazole ± rectal vancomycin. Early surgical opinion should be sought for patients with very severe disease, as

 fulminant CDI might require subtotal colectomy. More recently, a diverting loop ileostomy and colonic lavage has been associated with reduced morbidity and mortality. The risk of recurrent CDI (within 4–8 weeks) increases with each subsequent episode from around 25–45% to 60%. Fidaxomicin might be appropriate for the treatment of first episodes of CDI in patients at increased risk of recurrence (e.g. receiving concomi- tant antibiotics, with severe infection, older people with multiple comorbidities) or those with a first recurrent episode. There are no widely accepted prediction scores in use to identify either those at risk of severe CDI or recurrent infection. Other treatments used for recurrent CDI include tapered/pulsed doses of vancomycin, and sequential therapy with vancomycin followed by rifaximin. There is weak quality evidence that pooled intravenous immunoglobulin might be effective in patients with recurrent CDI, presumably by augmenting the host antitoxin antibody response. Faecal microbiota transplantation is very effective in patients with multiple recurrences; resolution following a single duodenal infu-

sion of donor faeces was 81% compared with 31% with vancomycin treatment in an RCT ($p < 0.001$). There remain many unanswered questions about faecal microbiota transplantation including the op- timal volume of donor faeces, the screening repertoire for donors and recipients, and the route of administration. More widespread use of faecal microbiota transplantation is currently limited by con- cerns about the long-term safety of donor faeces, including potential transmission of infectious agents to the recipient, and alteration of the gut microbiome given its far-reaching (although currently poorly understood) effects on human health and disease. Encapsulated faeces and defined populations of bacteria might overcome some of the aforementioned issues. Prevention Community and hospital antimicrobial stewardship, in particular restricting use of high risk agents such as fluoroquinolones, cephalo- sporins, and clindamycin reduces the risk of CDI. The most effective class of antimicrobial to restrict likely depends on the resistance profile of circulating C. difficile strains. Clindamycin restriction was effective at controlling an institutional outbreak caused by a clindamycin-resistant C. difficile clon e. Fluoroquinolone restric- tion has played a major role in reductions in CDI incidence in the United Kingdom in the last decade, largely driven by reductions in ribotype 027 and other fluoroquinolone-resistant lineages. Rapid identification, isolation and testing of potential cases, and prompt treatment reduces the potential for healthcare- associated transmission. Contact precautions and hand washing with soap and water (C. difficile spores are resistant to alcohol gels that are widely used for hand hygiene) should be implemented on suspicion of CDI. These should be continued until at least reso- lution of diarrhoea, and longer if resources allow (as excretion of viable C. difficile can continue beyond the end of symptoms). Environmental cleaning around cases should be with chlorine- releasing agents with activity against C. difficile spores; vaporized hydrogen peroxide is used in some settings. Coordinated infec- tion control programmes are required, complemented by active monitoring of CDI incidence, and staff, patient, and visitor edu- cation programmes. Areas of uncertainty, controversy, and future developments Preventing CDI is a major focus for researchers. Although all based on C. difficile toxins A and B as immunogens, three distinct vaccines have completed phase 2 clinical trials; one has been terminated mid- phase 3 for unclear reasons. Other approaches to prevention include an orally delivered β-lactamase that aims to degrade β-lactams on the large intestine, and so avoid the deleterious effects of these anti- biotics on the gut microbiome. A charcoal-based absorbent is also being investigated as a way of blocking the harmful effects of anti- biotics on gut bacteria. The diagnosis of CDI could be improved if rapid highly sensitive toxin tests were available. The absence of commercially available antitoxin antibody tests is a hindrance to identifying (those with low levels) who are at increased risk of CDI. Similarly, biomarkers that can accurately predict CDI severity and outcome would be valuable adjuncts to targeting therapies optimally. It remains unclear if C. difficile could have a pathogenic role in infants; high colonization rates tend to obscure any possible such role. Studies to date have typically failed to examine sufficiently wide repertoires of alternative potential pathogens in infants harbouring C. difficile. Whole genome sequencing has already proved a valuable tool for deepening our understanding of CDI epidemiology. The growing suspicion that foods might be an important source of C. difficile will require large prospective studies, noting that contamination is likely to be sporadic, and highly discriminatory fingerprinting to determine if such theories are true. FURTHER READING Bartlett JG (2006). Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. Ann Intern Med, 145, 758–64. Cohen SH, et al. (2010). Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol, 31, 431–55 (2010). Davies KA, et al. (2014). Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point- prevalence study of

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