Clostridioides Difficile: A Clinical Update

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CLOSTRIDIOIDES DIFFICILE

Clostridioides Difficile (C. *Difficile*) is a gram-positive spore-forming toxin-producing anaerobic bacillus. It can survive on surfaces for a long period of time by forming heat, acid, and alcohol resistant spores. The bacteria colonise the bowel of 3-5% of the adult population and 20% of hospitalised patients. It is transmitted between individuals through a fecal-oral route. Asymptomatic carriers, infected patients and contaminated surfaces can act as a reservoir for spores. C. *Difficile* is currently one of the major nosocomial infections.[1]

PATHOPHYSIOLOGY

The pathophysiology of C. *Difficile* can be divided into three phases. The first phase of the pathogenesis involves the suppression of the normal, protective microbiota of the intestines. Clinically, this usually occurs secondary to antibiotic treatment, commonly due to clindamycin, ciprofloxacin, cephalosporin and fluoroquinolones. This allows for optimum conditions for C. *Difficile* to thrive when ingested. This leads to C. *Difficile* spore germination and toxin-producing cell formation which causes inflammation and consequently an immune response (second phase of pathogenesis).[2] The pathogen does not invade the epithelium; its virulence is through enzymes and toxins. The main toxins produced are ToxA and ToxB, which disrupt the cytoskeleton of the colonic epithelial cells. This leads to the dissociation of tight junctions between colonic epithelial cells, fluid secretion, neutrophil infiltration and cytokine production. Influx of neutrophils into the mucosa cause pseudomembrane formation, classically seen on endoscopy as yellow-white nodules or plaques. Histologically, this is seen as "volcano" lesions containing neutrophils and fibrin.[3,4] The third phase involves the potential for the infection to reoccur as a result of the antibiotic treatment for C. *Difficile*. This is when the antibiotic levels do not completely inhibit C. *Difficile* spores. Since antibiotics target both C. *Difficile* and normal gut microflora, there is a potential for spores to cause recurrent infection until the disrupted colonic microflora is recovered.[2]

RISK FACTORS

Risk factors for C. *Difficile* infection include; antibiotic use (clindamycin and 2nd/3rd generation cephalosporins), prolonged hospital stay, age over 65, previous C. *Difficile* infection, comorbidities, use of proton pump inhibitors, immunocompromised patients and inflammatory bowel disease.[5,6]

CLINICAL SIGNS

The hallmark of C. *Difficile* infection is a new onset watery diarrhea. Blood can be present, but overt bleeding is rare. Other features include abdominal pain, fever and raised white cell count (WCC). In severe cases hypotension, tachycardia, raised creatinine and lactate may develop. This is shown in Table 1.[1,7]

DIAGNOSES

C. *Difficile* infection is suspected clinically and confirmed with stool testing. The three main stool tests for C. *Difficile* detection used in the National Health Service are toxin enzyme immunoassays (EIAs), toxin gene (NAAT or PCR) and glutamate dehydrogenase (GDH) EIA.

The Department of Health recommends a two-step process for diagnoses.[8]

Step 1. NAAT or (GHD) EIA

Step 2. For samples that test positive, toxin EIA should follow, as presence of toxin detects current C. *Difficile* infection.

GRADING CRITERIA

Mild	Moderate	Severe	Life-Threatening
Normal WCC	WCC raised but <15x10(9)/l	WCC raised >15x10(9)/l	Hypotension
Stool frequently <3 per day	Stool frequency 3-5 per day	Acute rise in creatinine (more than 50% of baseline)	Partial or complete ileus
Stool consistency type 5-7 on Bristol Stool Form Scale		Temperature above 38.5°C	Toxic megacolon
		Evidence of severe colitis (examination and image)	Radiological evidence of severe disease

Table 1. Summarizing the clinical features of the different severities of C. *Difficile* infection[8]

MANAGEMENT

Updated NICE guidelines on the management of C. *Difficile* for adults aged 18 years and over were published in July 2021 and are summarised in Table 2.[9]

Treatment	**Antibiotic, dosage and course length**
First-line antibiotic for the first episode of mild, moderate or severe C. *Difficile* infection	Vancomycin 125mg orally four times a day for 10 days
Second-line antibiotic for first episode of mild, moderate or severe C. *Difficile* infection if Vancomycin is ineffective	Fidaxomicin 200mg orally twice a day for 10 days
Antibiotics for C. *Difficile* infections if first/second line antibiotics are ineffective	Seek specialist advice. Specialist may offer: Vancomycin up to 500mg orally four times a day for 10 days, with or without Metronidazole 500mg intravenously three times a day for 10 days
Antibiotic for a further episode of C. *Difficile* infection within 12 weeks of symptom resolution (relapse)	Fidaxomicin 200mg orally twice a day for 10 days
Antibiotics for a further episode of C. *Difficile* infection more than 12 weeks after symptom resolution (recurrence)	Vancomycin: 125mg orally four times a day for 10 days OR Fidaxomicin: 200mg orally twice a day for 10 days
Antibiotics for life-threatening C. *Difficile* infection	Seek urgent specialist advice, which may include surgery. Antibiotics that specialists may initially offer are: Vancomycin: 500mg orally four times a day for 10 days With Metronidazole: 500mg intravenously three times a day for 10 days

Table 2. Summary of NICE guidelines on the management of C. *Difficile* [9]

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