Clostridium difficile

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Introduction

Clostridium difficile is an anaerobic, spore forming Gram positive bacillus which is a worldwide enteric pathogen. It is a common cause of antibiotic associated diarrhoea and colitis and was identified as the cause of antibiotic associated pseudomembranous colitis in the late 1970s.

Since 2000, *C. difficile* infection (CDI) has had a higher profile following reports of increasing rates, mortality and morbidity, and outbreaks have presented significant challenges to many healthcare facilities. CDI was initially associated with hospital acquired infection but community acquired infections are being increasingly recognised.

Most of the literature surrounding CDI epidemiology relates to the disease in developed countries but it seems unlikely that this pathogen will not have the potential to cause problems in developing countries like South Sudan, particularly on a background of unregulated antibiotic use.

Pathogenesis

Colonization with *C. difficile* occurs following disruption of the normal intestinal flora which usually provides resistance to such colonization, particularly following antibiotic use. *C. difficile* is acquired by the faecal-oral route; the bacterial spores are not destroyed by gastric acid, enabling them to reach the intestines.

The development of active CDI requires toxin production. There are two main toxins (A and B) produced by *C. difficile*, both of which can cause symptomatic disease independently of each other. The toxins disrupt the cytoskeleton of the intestinal mucosal cells, leading to intestinal fluid secretion, damage of the intestinal mucosa and inflammation.

There are many different strains of *C. difficile* and certain strains are associated with higher virulence, particularly the North American type 1 (NAP1)/027 ribotype, first reported in 2003 from Canada [1], which has been linked to more symptomatic disease and more severe presentations.

Epidemiology

C. difficile has been isolated globally from environmental sources both in and outside the hospital. Although most

Figure 1. Pseudomembranous colitis at colonoscopy with multiple yellowish patches ("pseudomembranes") and erythematous, friable mucosa. (From Limaye *et al*, 2000].

of the research comes from industrialized countries, one study in rural Zimbabwe found toxigenic *C. difficile* in samples of soil, chicken faeces and water [2], highlighting the potential for acquisition of the organism in Africa.

Asymptomatic colonisation is common in children, reported in up to 70% of healthy neonates [3], compared to around 3% of healthy adults and 20% of hospitalized adults [4]. Some studies have indicated geographical variation in *C. difficile* colonization and infection rates, with some suggesting that the risk in Africa is lower. One study comparing HIV positive adults with diarrhoea in London, UK and Lusaka, Zambia found no patients with CDI in Lusaka, compared to 11% in London [5]. However, *C. difficile* colonisation was detected in 48.8% of Nigerian neonates and children in an earlier study [6], and another more recent Nigerian study of HIV positive patients with diarrhoea demonstrated CDI in 14% of outpatients and 43.5% of inpatients [7].

The major risk factor for developing *C. difficile* infection is receiving antibiotic therapy. Broader spectrum antibiotics are associated with a higher risk of *C. difficile*, causing

more disruption of the intestinal flora. The "four Cs" are a particular risk: clindamycin, ciprofloxacin (and other quinolones), cephalosporins and co-amoxiclav. A higher number of antimicrobial agents, doses and duration are all associated with increased CDI risk [8].

The current lack of publications demonstrating a significant CDI problem in many African countries is likely to reflect a lack of detection and reporting rather than a lack of risk, given that the organism is present in the continent and antibiotic use in many African countries is high, with uncontrolled over the counter access without prescription.

Age, co-morbidities, including malignancy and chronic renal disease, and other medications such as chemotherapy agents are also recognised factors increasing the risk of CDI. HIV infection by itself is not thought to increase the risk of CDI, although these patients are more likely to receive antibiotics leading to an increased CDI risk [4].

Presentation

Although many remain asymptomatic with *C. difficile* colonisation, toxin production results in presentations ranging from mild, transient diarrhoea to severe diarrhoea with a pseudomembranous colitis (Figure 1) which can be fatal. Abdominal pain and non-specific signs may be present, including fever, nausea, anorexia and dehydration.

Occasionally, severe disease can present without diarrhoea, with an acute abdomen, peritonitis or toxic megacolon (dilatation of the colon to greater than 6cm without obstruction with systemic signs of toxicity) which is associated with a high mortality rate.

Recurrences are common, occurring in around 20% of patients, and complications include perforation of the colon, transverse colonic volvulus and protein losing enteropathy. Extra-intestinal manifestations of CDI are rare.

Diagnosis of C. difficile

CDI diagnosis involves detecting the organism and its toxin production from diarrhoeal specimens.

One common testing strategy uses a two step algorithm in which an enzyme immune-assay (EIA) for glutamate dehydrogenase (GDH) , an enzyme with a high sensitivity for the presence of C. difficile, is performed first, followed by a *C. difficile* toxin EIA in the GDH positive samples [9]. In resource limited settings, such as South Sudan, use of the toxin EIA alone may be more appropriate given the rapid turn around and reagent availability. Other techniques include culture, tissue culture cytotoxicity
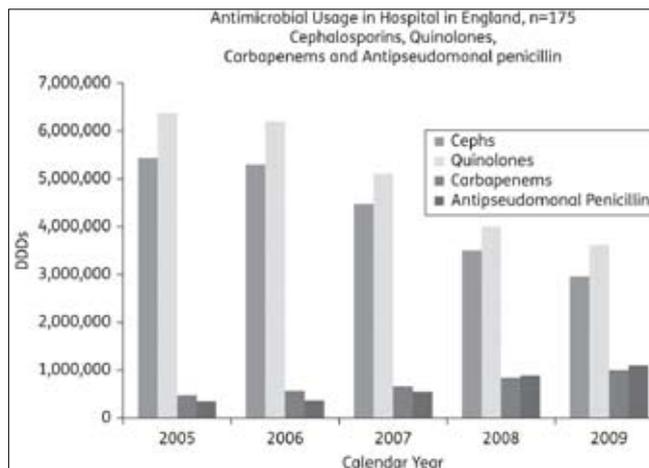
Figure 2: Antimicrobial Usage in Hospital in England 2005-2009, Cephalosporins, Quinolones, Carbapenems and Anti-pseudomonal penicillins. (From: Ashiru-Oredope et al 2012]

DDDs: defined daily doses

testing and toxin gene detection by polymerase chain reaction.

Treatment

Treating CDI involves firstly stopping any non-essential systemic antibiotics and secondly using a specific agent against *C. difficile*. The two agents with most evidence for successful treatment of CDI are metronidazole and vancomycin. Metronidazole is used in non-severe cases of infection and is normally administered orally or can be given intravenously if there is a reason for the oral drug not reaching the affected bowel, e.g. intestinal obstruction.

Vancomycin is usually used for more severe infections, although the new agent fidaxomicin is now being used in some centres. Vancomycin is given orally as intravenous vancomycin is not secreted into the intestinal lumen. Patients with unresponsive or recurrent disease can be difficult to treat and approaches include tapering courses of vancomycin, intravenous immunoglobulin, and donor "faecal transplant" therapy, for which there is a growing body of evidence.

Prevention

Strategies to prevent CDI include controlling the spread of *C. difficile*, particularly within healthcare facilities, and minimizing antibiotic exposure, thereby avoiding the disruption of colonic flora which leaves the patient at risk of *C. difficile* colonization. Preventing the spread in hospitals involves side room isolation of patients with suspected or confirmed CDI with barrier nursing, effective cleaning of the patient's environment and careful hand hygiene practices by healthcare workers, with soap and water.

CDI reduction has been a key factor in driving the development of antimicrobial stewardship programmes around the world, along with increasing antimicrobial resistance. Restricting the use of antibiotics, both by minimizing overall antibiotic consumption and by selecting the narrower spectrum lower risk agents is therefore an important method in reducing the problem. In the UK, rates of CDI and mortality from CDI have declined significantly, following improvements in infection control and increased antibiotic stewardship. Figure 2 illustrates the decrease in England in prescription of cephalosporins and quinolones (high risk antibiotics), which is mirrored by a decrease in reported CDI cases over a similar time period (Figure 3).

In summary, CDI is an important cause of diarrhoea, particularly antibiotic associated, which can result in severe disease. Countries without effective control of antibiotic use have a high potential for problems with this organism and it should be considered in the differential diagnosis of patients with diarrhoea.

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- Figure 1. Limaye AP et al. Case reports: Pseudomembranous Colitis Caused by a Toxin A2 B1 Strain of Clostridium difficile. *J Clin Microbiol.* 2000; 38(4): 1696–1697.

- Figure 2. Ashiru-Oredope D et al. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart—Then Focus. *J Antimicrob Chemother.* 2012; 67 Suppl 1: i51–i63
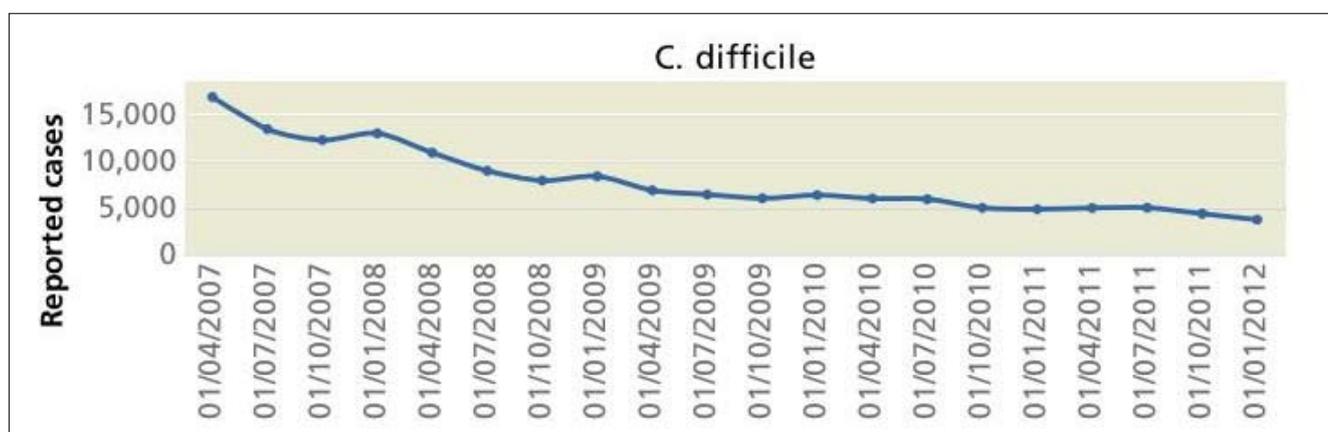

Figure 3: Decline in reported C. difficile cases in England 2007-2012. [From: Davies, SC. Annual report of the chief medical officer. Volume 2, 2011. In: Infections and the rise of antimicrobial resistance. London: DoH, 2013]