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Review

Clostridium difficile enteritis: A new role for an old foe

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ABSTRACT

Background: Small bowel involvement of *Clostridium difficile* is increasingly encountered. Data on many management aspects are lacking.
Aim: To synthesis existing reports and assess the frequency, pathophysiology, outcomes, risk factors, diagnosis and management of *C. difficile* enteritis.
Methods: A systematic review of the literature was conducted to evaluate evidence regarding frequency, pathophysiology, risk factors, optimal diagnosis, management and outcomes for *C. difficile* enteritis. Three major databases (PubMed, MEDLINE and the Cochrane Library) were searched. The review included original articles reporting *C. difficile* enteritis from January 1950 to December 2012.
Results: *C. difficile* enteritis is rare but increasingly encountered. Presentation is variable and distinct predisposing factors include emergency surgery, white race and increased age. Diagnosis generally involves a sensitive but often non specific screening test for *C. difficile* antigens. Oral metronidazole represents first line therapy and surgery may be required for complications. Outcomes are inconsistent but may be improving.
Conclusions: A high index of clinical suspicion, early diagnosis and treatment are vital. Further prospective studies are needed to determine the significance of asymptomatic small bowel *C. difficile* infections.

Introduction

The older, immunocompromised and institutionalised patient population undergoing surgery allied to increased practitioner awareness has produced a significant rise in all *Clostridium difficile* infections.[1] Although rare, small bowel involvement of *C. difficile* is increasingly identified.[2–4]

Early reports of small bowel *C. difficile* infection suggested significant morbidity and mortality rates.[4,5] However the enhanced recognition of small bowel colonisation post-operatively suggests a higher than previously thought prevalence of a milder or even asymptomatic entity.[2,6,7] Notwithstanding this a high index of suspicion is necessary allied to early intervention to maximise optimum outcomes.

Despite these features the literature on *C. difficile* enteritis is sparse comprising mainly of retrospective studies and case

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series. Unlike *C. difficile* colitis, there are no consensus guidelines to assist healthcare practitioners.[8]

Aim

To synthesis existing reports and assess the frequency, pathophysiology, outcomes, risk factors, diagnosis and management of *C. difficile* enteritis.

Methods

A systematic review of published work was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[9]

The search was performed using the Cochrane library, PubMed, MEDLINE and Embase to identify articles published between 1980 and July 2012. The Cochrane database was searched using a combination of the following terms with the Boolean AND/OR operators: 'Clostridium difficile', "*C. difficile*", 'small bowel', 'enteritis', 'pseudomembranous', 'risk factors', 'clinical presentation', 'diagnosis' and 'treatment'. For the MEDLINE and PubMed database searches, these same keywords (and variants) were used as textwords and Medical Subject Headings (MeSH terms), and were combined by using Boolean operators as follows: ('*C. difficile**') OR 'Clostridium difficile' OR 'small bowel' OR 'enteritis' AND 'epidemiology' OR 'pathogenesis' OR 'presentation' OR 'diagnosis' OR 'management' OR 'treatment' OR 'surgery' The Embase database was searched using Combinations of the following using the Boolean search term 'Clostridium difficile' 'AND'/(Emtree thesaurus term) 'small bowel'/(Emtree thesaurus term), surgery(Emtree thesaurus term)/Management/(Emtree thesaurus term).

There was no restriction on the date, language or status of publication. The search results were supplemented with hand searching of selected reviews, expert consensus and reference lists from included and excluded studies. After screening titles and abstracts, studies were included if they clearly described small bowel *C. difficile* infection and if pertinent correlation could be made from colonic *C. difficile* infection. Full-text publications of these articles were then reviewed. If two separate publications included the same cohort of patients, the larger and more complete dataset was used (see Fig. 1). The data extracted included demographics such as age and sex, presence of pre-existing gastrointestinal disease, risk factors, incidence, prevalence, previous *C. difficile* infection, recent antibiotic use, diagnostic techniques and medical or surgical treatment employed.

Incidence

Historically *C. difficile* enteritis has been considered a rare entity, although recent data suggest a significant increase in prevalence and incidence.[10]

Until 2008, fewer than 25 cases were reported.[4] Kim et al. noted an additional 29 cases in the two years from 2008 to 2010 when they performed a pooled analysis of all published

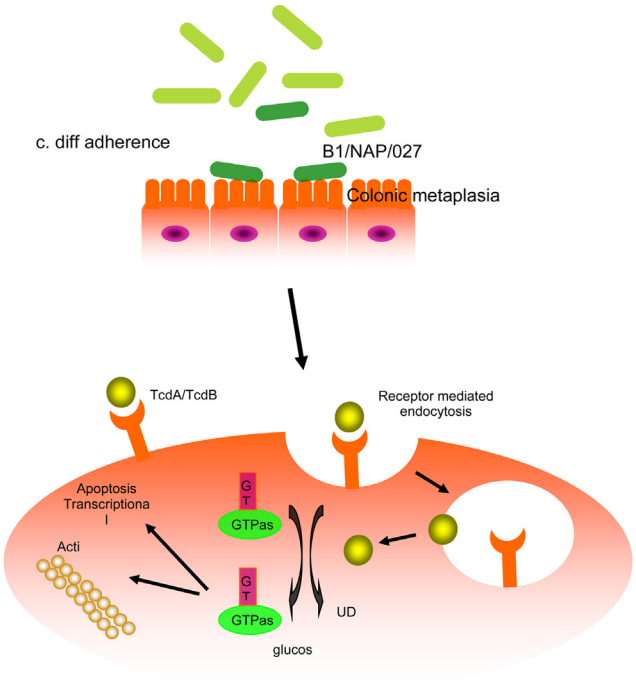

Fig. 1 – Diagramatic representation of presumed pathogenesis of small bowel *C. difficile* infection. TcdA and TcdB breach the intestinal barrier, bind to cellular receptors, inhibit GTPases and trigger mucosal inflammation and intestinal damage.

cases.[11] Diagnosis was based on positive *C. difficile* toxin in stool or ileostomy output in patients who previously had had colectomy with ileostomy (23 cases), positive *C. difficile* toxin in increased ileostomy output in patients with formation of ileostomy postoperatively (3 cases) and autopsy, surgical pathology, or biopsy showing histologic evidence of enteritis with positive *C. difficile* toxin and/or *C. difficile* isolated on culture (30 cases).[11] A total of 67 cases to July 2012 were identified in the literature. The seemingly increased population and institutional prevalence of *C. difficile*, enhanced isolation of the hypervirulent BI/NAP1/027 strain from the small bowel allied to an older more susceptible patient cohort may explain this proported increase.[12]

However accurate prevalence rate calculation is problematic due to anatomically difficulty in accessing small bowel contents, lack of awareness and underreporting of the condition.[13] Furthermore studies do not differentiate between colonisation and clinically significant infection with toxin production. Recently Tsiouris et al. suggested that ileal *C. difficile* toxin can be isolated in 16% of patients after colectomy[1] and Testore et al. showed a 3% *C. difficile* jejunal colonisation rate at post mortem in patients who died from nongastrointestinal causes.[13] There is undoubted selection bias in published reports with severe cases predominating.[10]

Collectively this data suggests the actual incidence and prevalence of small bowel *C. difficile* is probably underestimated and the proposed increase may also be due to increased testing, reporting and identification of asymptomatic carriers. Toxin producing *C. difficile* is a notifiable disease