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Spectrum of *Clostridium difficile* infections: Particular clinical situations

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ABSTRACT

Incidence, pathogenesis, diagnostic techniques and therapeutic management of CDI have prompted abundant and adequate recent literature. However, report on clinical manifestations of CDI is frequently biased by the type of patients selected, the retrospective nature of many papers, the epidemic or endemic characteristics of the population reported. This article seeks to review some less discussed clinical and epidemiological aspects of CDI trying to include the clinical manifestations of this disease in unselected populations and also including discussion of CDI in specific groups of patients such as patients without colon and rectum, pediatric and critical care patients.

1. Introduction

Clostridium difficile infections (CDI) are becoming the main cause of nosocomial infections in many developed countries but also a significant cause of diarrhea in non-hospitalized patients which is frequently etiologically unsuspected by the attending physicians [1,2].

Incidence, pathogenesis, diagnostic techniques and therapeutic management of CDI have prompted abundant and adequate recent literature [3–9]. Onthe contrary, report on clinical manifestations of CDI is frequently biased by the type of patients selected for report, the retrospective nature of many papers, the epidemic or endemic characteristics of the population reported, the predominant causative ribotypes and other variables.

The aim of this article is to review some less discussed clinical and epidemiological aspects of CDI trying to include the clinical manifestations of this disease in unselected populations and also including discussion of CDI in specific groups of patients such as patients without colon and rectum, pediatric and critical care patients.

2. Origin and clinical manifestations of CDI in unselected populations

Large series of prospectively evaluated CDI episodes without a restrictive criteria or a selection bias, are scarce [10–14]. Our group reported in a Spanish nationwide study conducted in 2008 that 2 out of every 3 episodes went undiagnosed or were misdiagnosed owing to non-sensitive diagnostic tests or lack of clinical suspicion and request [15]. More recently, in a European multicenter study conducted in 2013 [4], it was estimated that around 40,000 in-patients with *C. difficile* infection are potentially undiagnosed every year in 482 European hospitals.

In our own institution, during a 6-month period (Jan 2013–Jun 2013), we performed a prospective study of all patients, older than 2 years, from whom unformed stools were sent to the microbiology department, with or without CDI toxin request [2]. Toxigenic *C. difficile* was detected in 249 patients, of which, 45 patients were excluded as they did not meet the clinical criteria for diarrhea. Out of the 204 cases included, twenty-six (12.7%) had no *C. difficile* request from the attending physician. Patients where *C. difficile* was not clinically suspected were significantly younger than those that had raised a clinical suspicion of CDI (median age, 29.0 vs 72.2

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years; $p < 0.001$) (Fig. 1).

Overall, 78.9% of the patients were hospitalized at the time of the diagnosis of the CDI episode and most cases (90.7%) involved patients with a non-fatal underlying disease.

The most frequent predisposing risk factors are shown in Fig. 2. Most CDI episodes (83.8%) were considered mild to moderate. No differences were found for duration of diarrhea or severity of CDI between cases that had raised a clinical suspicion and those who had not.

None of the strains corresponded to ribotype 027. The four most common ribotypes encountered were ribotype 001(35.0%), followed by 078/126 (14.7%), 014 (12.2%) and 106 (10,7%).

Of the 204 CDI episodes, 33 (16.2%) were followed by one or more recurrences (R-CDI). Only 1.5% of patients were admitted to the ICU in relation to the CDI episode and the overall mortality and attributable mortality were respectively 8.3%, and 2.5%.

Distribution of our cases, according to the potential place of acquisition was as follows: Healthcare-associated CDI (H-CDI) accounted for 74.5% of cases (8.0 CDI episodes per 10,000 patient days); 18.6% were of Community-associated (23.9 episodes/100,000 inhabitants) and 6.9% were indeterminate.

Patients with community-associated CDI (C-CDI) episodes were younger ($p = 0.002$) and more often had no underlying diseases ($p < 0.001$) than H-CDI cases. In addition, they had less malignancy and cardiovascular disease, less frequently received previous antibiotics or proton pump inhibitors. However, C-CDI had the same rate of recurrent episodes than those H-CDI. Although C-CDI is a well-recognized entity [16–19], in C-CDI cases the etiology was less frequently suspected by their clinicians and a CDI test was more frequently unrequested.

The awareness of CDI should be extended to diarrheic patients without known risk factors for CDI. Our data show that in order to detect all CDI cases, laboratories should routinely test diarrheic stool samples for CDI. This approach seems to be cost-effective, since the diagnosis of CDI episodes triggers both infection control strategies (resulting in a reduction in the number of secondary CDI cases) and appropriate therapeutic interventions that can prevent costly complications.

3. High white blood count as a warning of CDI

C. difficile infection is a prominent cause of leukocytosis and this diagnosis should be considered for patients with white blood counts (WBC) counts of ≥15,000 cells/mm^3, even in the absence of diarrheal symptoms [20–22].

A retrospective study reported that patients with CDI were more likely to have leucocytosis than those with *C. difficile* negative

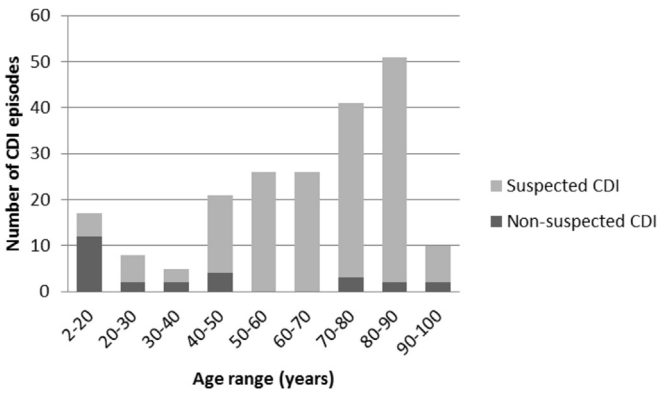

Fig. 1. Age distribution of unselected patients with CDI. Gregorio Marañón Study [2].

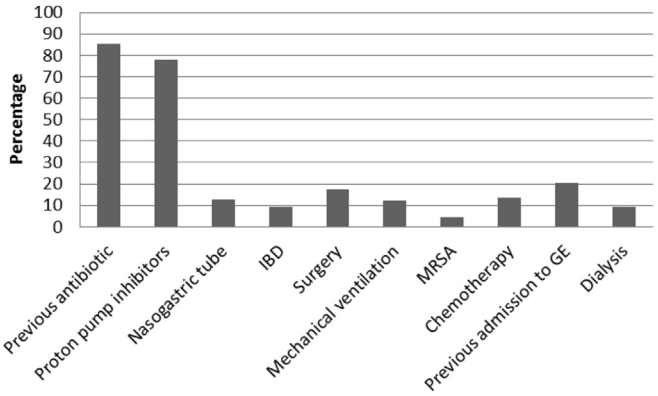

Fig. 2. Risk factors of unselected patients with CDI. Gregorio Marañón Study [2].

diarrhoea (Mean 15,800/mm3 vs. 7700/mm3 $p = 0.01$) [22]. Three patterns of leucocytosis in patients with CDI were reported, namely a sudden WBC increase coinciding with the onset of symptoms suggestive of CDI, patients that initially presented with leucocytosis which preceded the diarrhea and lastly patients where pre-existing leucocytosis deteriorated. This was the first time in which leukocytosis was pointed out as a sign preceding diarrhea due to toxigenic *C. difficile* [23].

In 2002 Wanahita et al. [21] signaled CDI as an important condition associated to leukocytosis. In this study, one or more infections were observed in 207/400 patients with WBC counts ≥15,000 cells/mm, out of which 34 (16%) had CDI. CDI was present in 25% of patients with WBC counts of >30,000 cells/mm^3 who did not have hematological malignancy.

In another paper from the same authors [20], they prospectively identified 60 patients who had unexplained leukocytosis and compared them with 25 hospitalized patients without leukocytosis. Overall, 35 (58%) of the patients with unexplained leukocytosis had *C. difficile* toxin in at least one fecal specimen as compared with 3 (12%) of the controls. Fever, may not be present when leukocytosis is first noted, especially in debilitated or elderly patients, and diarrhea or abdominal pain may be mild or absent.

Therefore, unexplained leukocytosis in hospitalized patients should prompt a search for symptoms and signs consistent with *C. difficile* infection including a study to detect toxigenic *C. difficile,* even in the absence of diarrheal symptoms.

Leukocytosis measured on the day of diagnosis, together with renal failure, is also a predictor of a complicated course of CDI [24].

4. CDI in patients without colon and rectum

CDI is typically described as a colonic disease, however, other areas of the intestine (*C. difficile* enteritis -CDE), may be involved occasionally as it is the case of the ileum. It has been described in patients with an ileostomy time after colectomy for different diseases or other abdominal surgery. Patients with prior Inflammatory Bowel Disease (IBD) may be particularly prone to this complication [25–30]. CDE may also occur in non-colectomized patients after different types of abdominal surgery [31].

Main manifestations of CDE include watery diarrhea, abdominal pain, leukocytosis and fever and pseudomembranes may be present on the ileal mucosa [32,33]. Radiologically the presence of ascites with distended fluidfilled small bowel (>2.5 cm) and bowel wall thickening (>0.3 cm) suggests *C. difficile* enteritis.46 Endoscopy may facilitate differentiation between IBD enteritis, pouchitis, and *C. difficile* enteritis in patient post surgery.28.

The pathogenesis of CDE is unclear, animal models and authopsy