Clinical Manifestations and Outcome of Pseudomembranous Colitis in an Elderly Population in Israel

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Abstract

Background: Pseudomembranous colitis is a well-recognized cause of diarrhea in patients receiving antibiotics and has significant consequences in terms of morbidity, mortality and cost. *Clostridium difficile* infection is the single most important infectious cause of PMC. PMC is frequently nosocomial, with an increased risk of spread among institutionalized patients, both in hospitals and nursing homes.

Objective: To investigate the demographic, clinical and laboratory characteristics of PMC patients in an Israeli elderly population.

Methods: We studied 72 hospitalized patients with endoscopically proven PMC. The medical records of all patients including clinical history and laboratory data were reviewed, such as: age, pre-hospitalization status (dependency or not, in the community as compared to the nursing home), background medical history, presenting symptoms, antibiotic history, physical examination on admission, hematologic and biochemical parameters, treatment, duration of hospitalization, complications, mortality, and recurrence of disease.

Results: Of the 72 patients (34 males and 38 females, mean age 77 years) 47% were nursing home residents. Pre-hospitalization antibiotic treatment was given to 91.4% for infections of the upper respiratory tract (45%) and urinary tract (45%). The most common antibiotics were cephalosporin (64%), penicillins (42%) and quinolones (28%). Sixty-four percent of the patients were treated with more than one antibiotic, 26% of patients received anti-acid therapy and 36% had been fed with a nasogastric tube. On admission, leukocytosis was found in 79% of patients, $>20{,}000/mm^3$ in half of them; 60% were anemic, 60% had elevated erythrocyte sedimentation rate, and 78% had hypoalbuminemia. Treatment consisted of metronidazole (41%) or a combination of metronidazole and vancomycin (56%). Overall, 31% of patients recovered without complications, 29% died within 30 days of hospitalization, and 24% were re-hospitalized due to recurrence of PMC.

Conclusion: The most common antibiotics implicated in PMC are cephalosporin, penicillins and quinolones. The disease is associated with high mortality and recurrence rates.

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Clostridium difficile-associated diarrhea is a common nosocomial infection, with up to 21% of hospitalized patients becoming colonized with the bacterium. Of these, approximately one develops symptomatic infection [1]. The infection usually arises following antibiotic therapy, which profoundly alters the colonic microecology and results in loss of the normal microfloral barrier against pathogens [2]. The spectrum of illnesses associated with *Clostridium difficile* infection ranges from uncomplicated diarrhea with some abdominal cramping to colitis (20–30%) and pseudomembranous colitis (1–5%) [3].

PMC is frequently nosocomial with an increased risk of spread among institutionalized patients, either in hospitals or in nursing homes, but it may also be acquired in the community. The most common antibiotics implicated in PMC are cephalosporins, penicillins and clindamycin. Antibiotics that are less likely to cause PMC include aminoglycosides, quinolones, ureidopenicillins and trimethoprim [4]. Several risk factors for the development of PMC have been described, such as increasing age, severity of underlying diseases, use of a nasogastric tube, acid-reduction treatment, prolonged hospitalization, and prolonged and repeated antibiotic treatment courses [5]. The incidence has reportedly increased fivefold in recent years [6], but the factors responsible for the rise in incidence have not been reliably identified. Increasing use of cephalosporins, growing numbers of elderly patients in hospitals, and increased length of hospitalization has each been considered responsible [7]. The mortality rate of PMC is high, reaching 20–30%, and recurrence of the disease occurs in 14–30% of patients following antibiotic treatment [8].

In light of the significant increase in PMC prevalence and the changing profile of the antibiotics that cause it, we investigated the demographic and clinical characteristics, antibiotic utilization and outcome of PMC in an Israeli population with special reference to the elderly.

Patients and Methods

We studied patients with endoscopically proven PMC hospitalized at Laniado Hospital, a 210-bed tertiary care center located in Netanya, a coastal city in Israel with numerous nursing homes. The hospital serves a population of 200,000 persons.

The medical records of all patients, including their clinical history and laboratory data, were reviewed in detail. These data included: age, pre-hospitalization functional and living status, background medical history, presenting symptoms, antibiotic history, physical examination on admission, hematologic and biochemical parameters, treatment, duration of hospitalization, complications and mortality as well as recurrence of disease.

PMC was diagnosed in all patients by sigmoidoscopy. PMC was defined as yellow-white plaques loosely adherent to the inflamed

PMC = pseudomembranous colitis

mucosa, which was found in 87% of patients with fulminant disease, and within the reach of flexible sigmoidoscopy in 90% [9].

Results

During the period between January 1993 and December 1999 we identified 85 patients with PMC. Of these, 72 charts were available for review. Thirty-four of the patients were males (47.2%) and 38 females (52.8%). The mean age was 77 years, range 32–96 years. Thirty-eight patients (52.8%) lived in their homes and 34 (47.2%) were nursing home residents.

The demographic, clinical and functional parameters of the patients are shown in Table 1. Details concerning the pre-hospitalization antibiotic treatment are shown in Table 2. The most common antibiotics were cephalosporins (64%), penicillins (42%) and quinolones (28%). Altogether, 64% of the patients were treated with more than one antibiotic drug. Table 3 summarizes the clinical, biochemical and hematologic characteristics at presentation. The most common presenting symptoms and signs on admission were: diarrhea (88.9%), fever (58%), abdominal pain (29.2%), followed by general deterioration (20.8%), vomiting (12.5%) and abdominal distension (11.1%). Leukocytosis was found in 79% of patients, >20,000/ mm^3 in half of them; 60% were anemic, 60% had elevated erythrocyte sedimentation rate, and 78% patients had hypoalbuminemia.

Table 1 Clinical characteristics of the patients

Characteristics	No. of patients (%)
Place of residence	
Nursing home	34 (47.2)
Home	38 (52.8)
Functional status	
Bedridden	39 (57)
Partial dependency	23 (33)
Independent	7 (10)
Sphincter continence	
Incontinent	37 (57.8)
Continent	27 (42.2)
Background illness	
Hypertension	36 (50)
Coronary heart disease	33 (45.8)
Neurologic diseases (excluding stroke)	25 (34.7)
Stroke	24 (33.3)
Renal failure	13 (18.05)
Chronic lung disease	12 (16.7)
Pressure sores	11(15.2)
Malignancy	9 (12.5)
No. of background chronic diseases	
0	3 (4.2)
1	5 (6.9)
2	17 (23.6)
3	25 (34.7)
4	17 (23.6)
>4	5 (6.9)
Anti-acid treatment	19 (26.4)
Nasogastric tube	
Yes	26 (36.1)
No	41 (56)
Gastrostomy	4 (6.3)
Gastrointestinal procedures	
(within 2 months prior to hospitalization)	
Colonoscopy	3
Gastroscopy	3
PEG (percutaneous endoscopic gastrostomy) insertion	1

Table 2. Pre-hospitalization antibiotic treatment

Parameter	No. of patients (%)
Indication for antibiotic treatment	
Urinary tract infection (UTI)	25 (39)
Respiratory tract infection (RTI)	25 (39)
UTI + RTI	4 (6)
Other	10 (15.6)
Type of antibioics	
Cephalosporins	41 (64.1)
Penicillins	27 (42.2)
Quinolones	18 (28.1)
Macrolides	8 (12.5)
Aminoglycosides	7 (10.9)
Ureidopenicillins	6 (9.3)
Imipenem/aztreoname	7 (10.9)
Clindamycins	2 (3.1)
Other	5 (7.7)
No. of antibiotics	
1	23 (35.9)
2	16 (39)
3	15 (20.5)
4	5 (6.8)
>4	5 (6.8)

Table 3. Clinical, biochemical and hematologic characteristics at presentation

Parameter	No. of patients (%)
Symptoms and physical signs	
Diarrhea	65 (89)
Fever	28 (39)
Abdominal pain	21 (29.2)
General deterioration	15 (20.8)
Nausea and/or vomiting	12 (12.5)
Abdominal distension	8 (11)
Rectal bleeding	6 (8.3)
Ascites	1 (1.4)
Laboratory results	
Hemoglobin g/dl (mean)	12.3
White blood cells (per mm^3)	
5–10.9	10 (20.8)
11–9.9	20 (41.7)
> 20	18 (37.5)
Albumin (g/dl)	
<1.9	1 (1.4)
2.0–2.4	16 (22.5)
2.5–2.9	24 (33.8)
3.0–3.4	14 (19.7)
>3.5	16 (22.5)

Forty-one percent of the patients were treated with metronidazole, while 56% received a combination of metronidazole and vancomycin. Thirty-one percent of the patients recovered without complications, 29% died within 30 days of hospitalization, and 24% were re-hospitalized due to recurrence of PMC.

Discussion

The spectrum of illnesses associated with *Clostridium difficile* infection ranges from mild diarrhea without systemic signs to fulminant colitis. The cases presented in our study represent an extreme manifestation of *C. difficile* infection, namely pseudomembranous colitis. Since the diagnosis was based on endoscopic appearance of PMC, it is possible that right-sided colitis, which may be responsible for up to 20% of the cases, asymptomatic as well as mild cases, were not diagnosed. During the 6 years of the study, 85 new cases of PMC were diagnosed, representing a prevalence rate of 14 new cases per year. Similar results were described by Anand et al. [10] in a 300-bed hospital in the United States.

Our study recognized a series of predisposing factors for PMC. The mean age of the patients in the study was 77 $\pm$ 13.1 years. This confirms that PMC is common in the older population, most probably due to the fact that older people are more likely to be treated with antibiotics and are thereby at increased risk for *C. difficile* infection [11]. However, 10% of the patients were under the age of 60, including a 33 year old retarded man.

About half of the patients were nursing home residents. Residence in a nursing home is considered a risk factor for PMC due to higher exposure *to C. difficile* from the staff and other residents [12], as well as high exposure to antibiotics.

Several studies have stressed the number and severity of background diseases as risk factors for PMC [12–14]. We found that two-thirds of the patients had more than three chronic diseases. Two of them had ulcerative colitis, which has been described in association with PMC. PMC in such circumstances may be missed and confused as an exacerbation of ulcerative colitis.

The most important risk factor for PMC is antibiotic treatment, as observed in 91.4% of our patients. Similar data were reported by Marts et al. [15] and by Benjaminov et al. in Israel [16]. The most common antibiotics in the present study were cephalosporins (64%) followed by penicillins and quinolones. This most likely reflects their extended use as well as their individual potential to cause PMC. In recent years, cephalosporins were reported to be the largest antibiotic group causing PMC [13,14,17]. Within this group, the most common drugs include: cefotaxim, ceftriaxone, ceftazidime and cefuroxime. Clindamycin, considered in the past to be the main etiologic factor for PMC, was given to only two patients, which probably represents the decline in its use but not the potential for causing PMC. All but three patients were treated intravenously. This may also reflect a hospitalized patient group with more severe infection but may by itself be a factor in PMC due to its higher suppressive effect on the normal intestinal flora. About two-thirds of our patients were treated with more than two antibiotics. Several studies identified this to be a risk factor for PMC [14,18]. We did not find that the number of antibiotics had any effect on the time interval until the onset of symptoms or on the prognosis.

Similar to other clinical series, the most common symptom was diarrhea (88.9%), followed by vomiting and consequent symptoms such as signs of dehydration and general deterioration. About 10% of the patients did not have diarrhea. In 8% of patients the diarrhea was bloody.

Peripheral leukocytosis is considered typical for PMC and was identified as a predictive factor for PMC in suspected patients with diarrhea [19,20]. In our series significant leukocytosis was noted in 79.2% of patients with half of them having more than 20,000/mm^3. This rate is slightly higher than in other toxin-based diagnosed series, where a rate of 50–60% of patients had leukocytosis [10,19], and may reflect the more severe disease in our endoscopy-based patient group. In another recent study from Israel, which was based also on endoscopic characteristics of PMC, Benjaminov et al. [16] reported significant leukocytosis in 85% of their patients.

Hypoalbuminemia due to protein loss through the infected mucosa is a serious complication of PMC. Several studies have shown that hypoalbuminemia on admission followed by a continuous decrease of serum albumin level during hospitalization might predict a worse prognosis [21]. We found a low serum albumin level on admission in 77.5% of our patients, and severe hypoalbuminemia of less than 2.5 mg/dl in 24% [Table 3].

About half of the female patients and 90% of males had anemia, and 60% had a high sedimentation rate. These findings are nonspecific for PMC and may be attributed, in addition, to the background infection and other diseases.

In our series, 40.8% of patients were treated with metronidazole, 2.8% with vancomycin and 56.3% with both drugs. In the latter group vancomycin was usually added due to lack of response to metronidazole. The mean hospitalization time was shorter in the metronidazole group (8.1 days) than in the combination group (11.2 days), presumably reflecting the more severe illness in the latter.

Several studies support the theory that disturbing the gastrointestinal flora can predispose to the overgrowth or acquisition of *C. difficile*. The condition can result from antibiotics, gastrointestinal surgery, enemas, nasogastric drainage, enteral feeding or anti-acid treatment. In our study 26.4% of the patients were treated with anti-acid drugs, most of them with H_2 receptor blockers. Previous studies that examined the influence of this treatment on *C. difficile*-associated disease revealed contradictory findings. While several studies did not find H_2 blocker consumption to be a risk factor for PMC [14,18], others noted that these agents were a risk factor for *C. difficile* carriage [13,22]. The mechanism may be the reduction of the antimicrobial barrier of the stomach.

Several studies identified use of nasogastric tubes as a risk factor for *C. difficile*-associated morbidity and carriage [9, 12, 14, 20, 23], while others did not [13]. In the present study 36% of the patients had a nasogastric tube at the onset of PMC. There are several mechanisms by which a nasogastric tube might be responsible for the higher rate of *C. difficile* morbidity and carriage: a) such feeding usually requires involvement of nursing staff who might transfer the infection between patients; b) the feeding formulas may be contaminated; c) feeding formulas usually contain a low amount of fibers, which permits bacterial colonization; and d)

the nasogastric tube interferes with the acid barrier of the stomach. This is more prominent in patients with post-pyloric nasogastric tube, which bypasses the gastric barrier.

Several other gastrointestinal procedures such as endoscopies have been found to be risk factors for PMC [14,18]. Ten percent of the patients in the present study underwent gastrointestinal endoscopies (not including the endoscopies for diagnosing PMC).

The recurrence rate in our study was 24%, which is slightly higher than the rate published in the literature, 10–20% [21]. This may reflect the more severe cases in our series

Twenty-one patients (29%) died within 1 month of the diagnosed disease. This high mortality rate reflects the more severe pattern of PMC in our patient group. Another study reported a mortality rate of 30% in a similar patient group [24]. In a recent study from Israel, Tal and colleagues [25] reported an even higher mortality rate, 46.5%, in *C. difficile*-associated diarrhea in elderly patients. Several risk factors for mortality have been described, including: patient's age, living in nursing homes, low serum albumin (<2.5 mg/dl) at admission, rapid lowering of serum albumin (>1.1 mg/dl) during hospitalization, pre-treatment with three or more antibiotics, and the presence of *C. difficile* toxin in the stool 1 week after initiating treatment [18,19]. We observed a recurrence rate in 24% of the patients, while Tal and co-workers [25] reported an even higher recurrence rate of 53.1%. In their study, the diagnosis of both the initial and recurrent *C. difficile* infection was based on cytotoxins A and B assays, which might explain the difference in the recurrence rate between the two studies. They found that fecal incontinence, longer duration of fever, and H_2-antagonist treatment were all risk factors for recurrence.

In conclusion, PMC is an important complication of antibiotic therapy, which is responsible for an increasing incidence of disease in hospitals and long-term care facilities. It will probably continue to be a problem, given the increasingly elderly inpatient population and the widespread use of broad-spectrum antibiotics. The most common antibiotics implicated in PMC are cephalosporins, penicillins and quinolones. The disease is associated with significant recurrence and mortality rates, especially in old and debilitated persons.

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