The first reported case of pseudomembranous enterocolitis was reported by J. M. Finney in association with William Osler in 1893. They described a 22-year-old woman who underwent resection of gastric tumour and developed postoperative diarrhoea. She died on the 15th postoperative day, and at autopsy, the small bowel revealed diphtheritic membranes.

During the dawn of the antibiotic era, PMC became a common complication of antibiotics use. Staphylococcus aureus, the principal nosocomial pathogen at that time, was implicated as the agent responsible for this condition due to its identification by Gram stains and cultures of stools. Thus, vancomycin became the standard treatment.

Because vancomycin therapy worked, the causative agent was not questioned until the middle to late 1970s. The use of clindamycin had become widespread during this period.(1)

In the 1970s, important clinical observations of clindamycin-associated pseudomembranous colitis and the demonstration of the potent cytopathic effects of Clostridium difficile-derived toxin in animal models established the cause and pathogenesis of this condition.(2)

Antibiotic-associated diarrhoea is defined as the diarrhoea that occurs in association with the administration of antibiotics. The frequency of this complication varies among antibacterial agents. The aetiology of antibiotic-associated diarrhoea (AAD) varies. The disruption of the normal enteric flora caused by antibiotics may lead to overgrowth of pathogens and functional disturbances of the intestinal carbohydrate and bile acid metabolism, resulting in osmotic diarrhoea. Allergic, toxic and pharmacological effects of antibiotics may also affect the intestinal mucosa and motility. Cytotoxin-producing Clostridium difficile is held to be the causative agent of approximately 20% of AAD and of nearly all cases of pseudomembranous colitis, the most severe manifestation of AAD. In hospitals, Clostridium difficile is an increasing problem, especially among the elderly patients with serious underlying diseases. AAD has been associated with increases in mortality, length of hospitalization and cost of medical care.
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In hospitals, Clostridium difficile is an increasing problem, especially among the elderly patients with serious underlying diseases.(5) AAD has been associated with increases in mortality, length of stay and cost of medical care. Other infectious agents with less convincing correlations with AAD include Klebsiella spp., Staphylococcus aureus, Salmonella spp., Shigella spp., Campylobacter coli/jejuni, Yersinia enterocolitica). The rigorous selection of the stool samples processed for C. difficile has an important role in obtaining an increased percentage of positive samples forCDAD. The low percentage identified for comunitary enteric pathogens emphasizes the importance of the CDAD diagnosis.(17)

With the recent emergence of hypervirulent strains, the incidence of C. difficile-associated diarrhea and intestinal inflammatory disease has increased significantly in both North America and Europe, causing lengthy hospitalization, substantial morbidity and mortality. Of further concern is the recent emergence of hypervirulent strains that are resistant to antibiotics. (18) The epidemic strain is resistant to fluoroquinolones in vitro, a characteristic which was an infrequent observation in Clostridium difficile strains prior to 2001. The epidemic strain produces a binary toxin, an additional toxin that is not present in other Clostridium difficile strains. Binary toxin is related to the iota-toxin found in Clostridium perfringens, and its role in CDAD pathogenesis is not fully understood. The epidemic strain produces substantially larger quantities of toxins A and B in vitro than other Clostridium difficile strains. The epidemic strain is toxinootype III; most other Clostridium difficile strains are toxinootype 0. Toxinoyping is based on analysis of the pathogenic locus (PaLoc) of the Clostridium difficile genome, the region that includes the genes for toxin A (tcdA), toxin B (tcdB), and neighbouring regulatory genes. The epidemic strain has a partial deletion of tcdC, a gene in PaLoc that is responsible for down-regulation of toxin production.

Outbreaks of CDAD due to the new, highly-virulent strain of Clostridium difficile have been recognized throughout European health care facilities, including 75 hospitals in England, 16 hospitals in the Netherlands, 13 healthcare facilities in Belgium, and nine healthcare facilities in France. In Germany, the first cases of the highly-virulent Clostridium difficile strain, reported in 2007 and characterized as PCR ribotype 027, were associated with high mortality. Larger outbreaks of Clostridium difficile have been reported in northern France in particular. These outbreaks are very difficult to control, and preliminary results from case-control studies indicate a correlation with the administration of fluoroquinolones and cephalosporins.

In Dublin, Ireland, Clostridium difficile is a major cause of infectious diarrhea in hospitalized patients. Between August 2003 and January 2004, there was an appreciable increase in the incidence of CDAD, peaking at 21 cases per 1000 patient admissions. Of the Clostridium difficile isolates recovered, 85 (95%) were identical toxin A-negative and toxin B-positive strains, corresponding to toxinootype VIII and PCR ribotype 017. All clonal isolates were resistant to multiple antibiotics, including ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin and gatifloxacin [minimum inhibitory concentrations (MICs) > 32 μg/mL] and erythromycin, clarithromycin and clindamycin (MICs > 256 μg/mL). Recurrent CDAD occurred in 26 (36%) of the patients.

Reported mortality rates from CDAD in the United States increased from 5.7 per million population in 1999 to 23.7 per million in 2004. These increased rates also may be caused by the emergence of a highly virulent strain of Clostridium difficile.(19) CDAD is now responsible for approximately 3 million cases of diarrhea and colitis annually in the United States, and has a mortality rate of 1%-2.5% (20). Zilberberg et
al have reviewed a sample of more than 36 million annual discharges from non-governmental US hospitals, and have concluded that 2.3% of the cases of CDAD were fatal, amounting for roughly 5500 deaths. That was nearly double the percentage that resulted in death in 2000.(21)

Due to the lack of a national diagnostic protocol for CDAD and that only a few laboratory diagnosis this infection, at the moment the incidence of this infection in our country is underestimated and cannot be compared to the multitude of existing data at European level and worldwide.

Unfounded use of antibiotics has led to a significant increase in microorganism's drug resistance. This led to the necessity of using some broad spectrum antimicrobial agents more often, thus maintaining a vicious circle. A major side effect of the unfounded antibiotherapy is a significant increase in the incidence of antibiotic induced diarrhoea, but its aetiology is not sufficiently studied in our country, yet.(22)

REFERENCES

10. Supensehinie HR, McDonald LC. Clostridium difficile-associated disease: New challenges from an established pathogen. Cleveland Clinic Journal Of Medicine 2006;73(2).
18. Xingmin Sun, Tor Savidge, Haming Feng. The Enterotoxicity of Clostridium difficile Toxins. Toxins. 2010;2;1848-1880.