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Clostridium Difficile Associated Diarrhoea and the Relationship to Antibiotic Prescription Practices and Proton Pump Inhibitor Use in Elderly Wards

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Abstract

Background: *Clostridium difficile*-associated diarrhoea (CDAD) is associated with an increased morbidity and mortality rate in elderly population. As in one of the north London hospitals, an increase in the cases of CDAD was observed in the Elderly Ward during a three-month period, the use of antibiotics and proton pump inhibitors (PPIs) was investigated for any relationship aiming to educate population and improve clinical practice during outbreaks.

Methods: In the first step (Group A) undertaken from July 2005 to September 2005, administration of antibiotics was checked in patients that developed CDAD in the Geriatric Ward. In the second evaluation (Group B) after years from January 2007 to October 2007, antibiotic prescription was rechecked identically. Similarly, the assessment was conducted when PPIs were used in patients that developed CDAD. All patients were positive for *C. difficile* toxin in their stools.

Results: No single group of antibiotics was associated with CDAD, but in both groups, many patients who developed CDAD were on multiple drug regimes. In the second group, a proton pump inhibitor was used by one third of patients during hospitalization. Except in one case it was not discontinued when CDAD was confirmed.

Conclusion: Restrictive policies in antibiotic consumption may help to lower the incidence of CDAD in hospitalized elderly patients.

Keywords: *Clostridium Difficile;* Diarrhoea; Antibiotic; Proton pump inhibitor; Elderly

Introduction

Clostridium difficile is a gram-positive spore-forming rod bacterium that is found in 3% of the general adult population[1] and is one of the most common bacterial causes of nosocomial diarrhoea and is a well recognized cause of outbreaks in elderly wards. The high incidence of *C. difficile* has been associated with the use of broad-spectrum antibiotics, PPIs, and insufficient infection control measures.[1,2] Broad-spectrum antibiotics may result in a decrease in normal gut bacteria, allowing the overgrowth of *C. difficile* spores. *C. difficile* was reported as the leading cause of antibiotic-associated diarrhoea. *C. difficile*-associated diarrhoea (CDAD) was shown as the cause of increased morbidity and mortality especially in the elderly population.[3-7]

Proton pump inhibitors (PPIs) were implicated as a risk factor for the development of CDAD as the reduction in gastric acidity disrupts the flora of the gastrointestinal tract.[8-10] Gastric acid plays an integral role in host defence against gastrointestinal infections. The vegetative form of *C. difficile* is rapidly destructed in the normal gastric pH, but survives in the gastric pH of patients taking PPIs. Additionally,

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PPIs were shown to make less effective the first line of treatment with metronidazole.[9]

In this study, the relationship between antibiotic consumption and its association with occurrence of CDAD in elderly population was evaluated.

Materials and Methods

The study was undertaken in a hospital located in a multi-ethnic borough in the north of London with 500 beds. There were four elderly care wards in the hospital, each with 29 patients. The admitted patients were older than 60 years old. Patients passing abnormal stool were tested for presence of *Clostridium difficile* toxin A/B in the stool samples. Patients with a positive bacterial toxin of A/B in their stool samples for the index period were enrolled. All specimens were tested based on the laboratory and infection control protocol of the hospital. Patients with diarrhoea but without the toxin were excluded from the study. All patients were admitted in the elderly wards. Their records were checked for any consumption of antibiotics and the person who prescribed. The type of antibiotic administered in CDAD was determined and the microbiology cultures were recorded.

In the first evaluation (Group A) undertaken from July 2005 to September 2005, administration of antibiotics was checked in 25 patients (12 females, 13 males; mean age=78 years; range=68-96 years) that developed CDAD in Geriatric Ward. Ten patients suffered from respiratory tract infection, 14 from urinary tract infection (UTI), and one from a falling injury. Diarrhoea was not the presenting complaint in any of the patients.

In the second evaluation (Group B) after years from January 2007 to October 2007, antibiotic prescription was rechecked identically in 32 patients (18 females, 14 males; mean age=82 years). Similarly, the assessment was conducted when PPIs were used in patients that developed CDAD. Two patients had diarrhoea when admitted. The rest of 30 patients developed diarrhoea during the index admission.

Results

In the first group among the 24 patients, infection was confirmed in 16 (67%) by culture. In 33% of patients either the culture was negative or the culture was not performed for them.

In 76% of the patients, an antibiotic had been prescribed during the index hospital admission. In 16% of the patients, the antibiotic had been administered during a penultimate hospital admission and the course of consumption was not completed before readmission. Only for 8% of patients, antibiotics were prescribed in an outpatient setting by a general practitioner (GP).

Forty percent of the patients received two types of antibiotics. Thirty two percent of the subjects received three or more types of antibiotics (Figure 1).

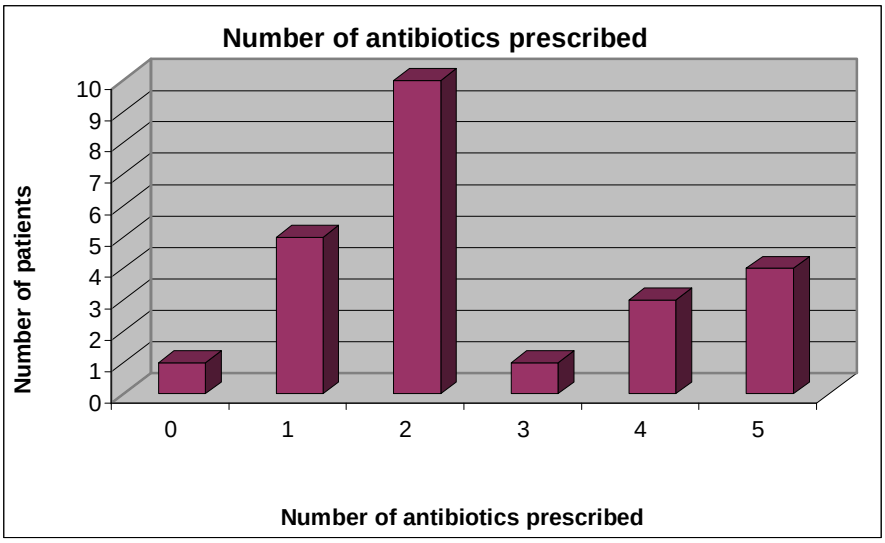

Fig. 1: Number of antibiotics prescribed during index admission (Group A).

The most prescribed antibiotic was amoxicillin/clavulanate (Co-Amoxyclav), which was administered for 64% of the patients. Sixty percent of the patients were on ciprofloxacin, mostly for suspected urinary tract infections when admitted in the hospital. This was followed by erythromycin and the cephalosporins, being prescribed to 33 and 24% of patients, respectively. Figure 2 demonstrates the frequency of administered antibiotics.

As the administered antibiotics in 2 of the patients were not recorded in their files; therefore, they were excluded from the study. Of 30 patients in group B, 97% were on antibiotic therapy during the index admission or two weeks prior (Figure 3). Forty-four percent of patients received three or more types of antibiotics. One patient received 8 antibiotics during the index admission prior to the onset of CDAD symptoms. One patient was not on any antibiotic therapy (Figure 3).

Figure 4 demonstrates the frequency of administered antibiotics in Group B. The most used antibiotic was amoxicillin/clavulanate administered in 63% of patients followed by administration of penicillins and

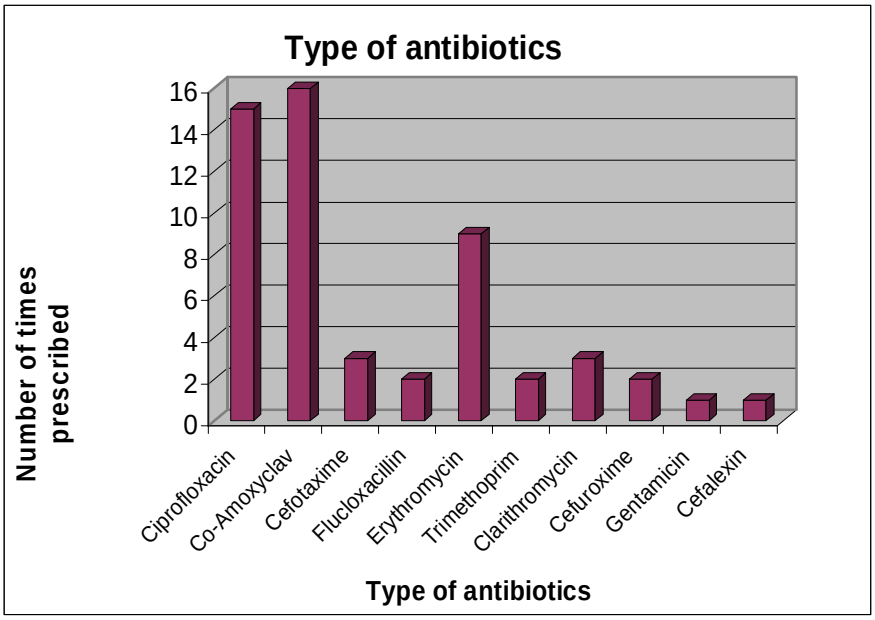

Fig. 2: Frequency and types of antibiotics prescribed (Group A)

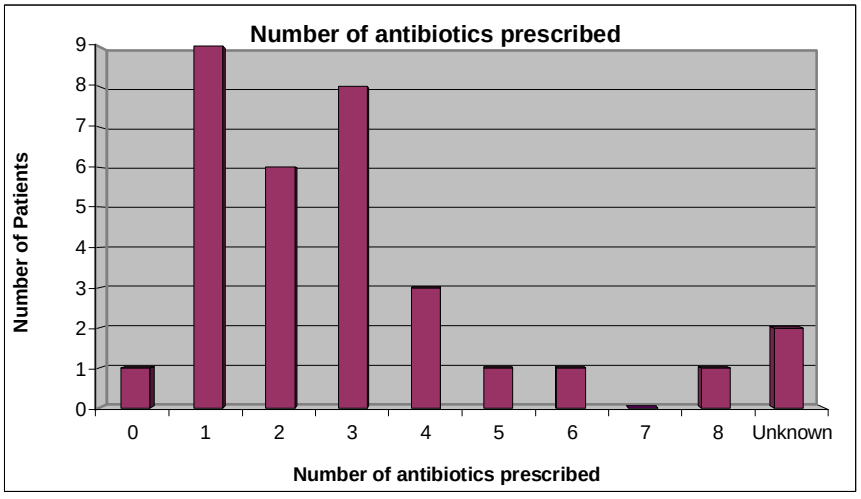

Fig. 3: Number of antibiotics prescribed during index admission (Group B)

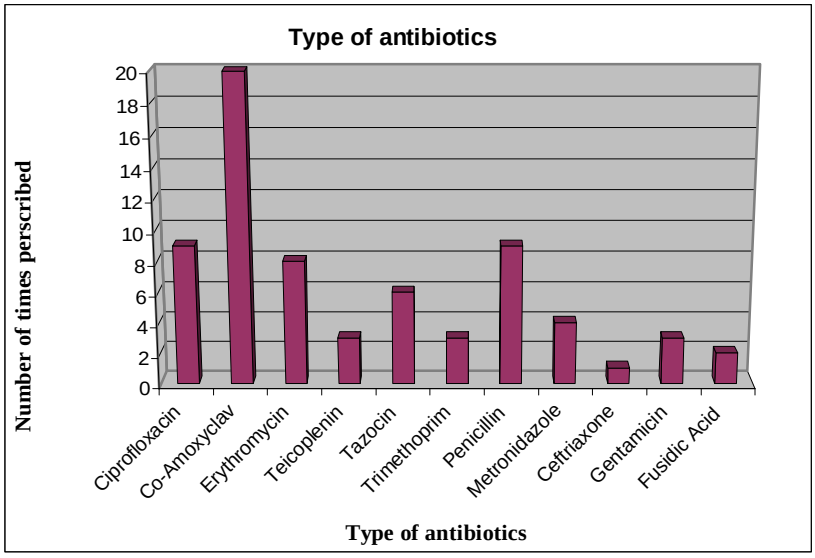

Fig. 4: Frequency and types of antibiotics prescribed (Group B)

quinolons, both being prescribed to 28% of patients and then macrolides.

Proton pump inhibitors were prescribed in 12 out of 32 patients (38%) at the time of the diagnosis of CDAD. In one of the 12 patients, the PPI was discontinued when diagnosis was first established or when treatment with metronidazole was commenced.

Discussion

In group A, a significant increase was noticed in the number of cases of CDAD as compared to previous years. In order to establish tight infection control standards, the patients who were positive for *C. difficille* toxin were designated to a special ward, restricted to key medical personnel and implementation of strict hand washing procedures.

Our data suggest that CDAD does not attribute to a certain class of antibiotic, but to prescribing practices. In both groups, over one third of the patients received three or more types of antibiotics and most of these patients had taken the antibiotics during an in-patient setting. Several antibiotics were used before the patient developed CDAD. It is important that in this setting, vigilance is exercised when choosing antibiotics, especially for elderly patients.

To establish a definitive diagnosis prior to commencing antibiotics, culture and sensitivity tests, avoiding the use of multiple antibiotics, and periodical review and reassessment of patients' antibiotic regimes are recommended.

Although initial treatment should not be delayed, continued use of antibiotic should be supported by an antibiotic sensitivity test to eliminate the need of multiple broad-spectrum antibiotics for a prolonged period.

Some studies,[5,6] denoted to specific antibiotic for developing CDAD. Despite the fact that some antibiotics were more prescribed (ciprofloxacin, amoxicillin, cephalosporins), various group of antibiotics including metronidazole have been shown to CDAD. Metronidazole,[6] due to cost-effectiveness is used as the first line of treatment for CDAD in UK. So there is a necessity for implementation of restrictive policies in antibiotic administration. NHS Trusts have initiated restrictive policies to curtail antibiotic use in an effort to combat CDAD successfully.[7-9] Restrictive antibiotic policies were shown to lower the incidence of CDAD and to decrease the cost of therapy.[7,8] The Health Care Commission surveyed all NHS Trusts in 2005 and reported that 38% did not restrict administration of broad-spectrum antibiotic use.[10]

It was demonstrated that an association is present between proton pump inhibitors and development of CDAD.[2] Although the exact mechanism is unclear, it is known that gastric acid suppressants raise the pH of the stomach. This can disrupt the normal gut flora predisposing to enteric infections or possibly lead to decreased destruction of *C. difficile* spores.[2] The risk is substantially increased in those taking PPIs as

compared to H-2 receptor antagonists.[3] Cohort and case controlled studies of 1187 patients in Montreal found a statistically significant association with the use of PPIs and the development of CDAD, the adjusted odds ratios being 2.1 and 2.7, respectively.[2] Treatment outcomes with first line metronidazole in patients taking PPIs have demonstrated an increased non-responsiveness to therapy or greater chance of reoccurrence.[4] Therefore, it is important to evaluate the necessity of PPIs in elderly patients and those on multiple antibiotics therapy. Discontinuing PPIs may be beneficial when treating patients with known CDAD.

Our Geriatric wards have experienced a significant rise in the incidence of CDAD as compared to previous years. Although the studies were observational in nature and limited to a small sample size, they demonstrated an overuse of antibiotics. Further observational case-controlled studies can be conducted in future to establish relative risk of exposure to multiple antibiotics regimes and the development of CDAD in our institution. Additionally, the multiple antibiotic regimes could be further analyzed to determine if certain compositions posed a greater risk.

Rather than a certain class of antibiotics used, prescription practices and the number of antibiotics used appear to be causative factors in our groups. It is also important for providers to assess the need for PPIs in the elderly patients on multiple antibiotic regimes as they are at a higher risk for developing CDAD. Limiting the number of antibiotics and PPIs prescribed, as well as making restrictive policies can help to reduce the incidence of CDAD. For those who have developed CDAD, medications should be assessed and unnecessary antibiotics and PPIs should be discontinued. It is important for clinical staff to work with pharmacists and microbiologists in formulating antibiotic regimes. These can be potentially life-saving interventions as CDAD can have a significant mortality among the elderly.

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Conflict of interest: None declared.

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