Is checking for antibiotic associated diarrhoea due to *Clostridium difficile* relevant to Sri Lankan hospitals?

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ABSTRACT

Background: *Clostridium difficile* associated diarrhoea has been increasing in most of the countries including United States, United Kingdom, India, other Western and South East Asian countries over the past two decades. No studies have been done in Sri Lanka to determine the proportions of *Clostridium difficile* associated diarrhoea. *Clostridium difficile* associated diarrhoea is not routinely diagnosed in Sri Lanka. Therefore the extent of its prevalence, epidemiological pattern and complications are not known.

Objectives: To determine the proportions, rates, source of infection and antibiotics that precipitate *Clostridium difficile* associated diarrhoea in three tertiary care hospitals in Sri Lanka.

Methods: Faecal toxin detection for both *Clostridium difficile* toxin A and B was performed using an Enzyme Linked Immuno Sorbant Assay, on 110 specimens collected from patients who presented with diarrhoea to three tertiary care hospitals, who were treated with antibiotics beforehand, from 1st October 2007 through 28th February 2009. Patient demographic and clinical data were collected using an interviewer-administered questionnaire. Total patient discharges were obtained in each hospital for the study period. Data were analyzed using Epi-info (version 6) software.

Results: Four out of 110 specimens were positive for the toxin A or B. Proportion of *Clostridium difficile* toxin positivity was 3.6%. Rates of *Clostridium difficile* associated diarrhoea were 0.01/1000 discharges, 0.008/1000 discharges and 0.004/1000 discharges at Teaching Hospital Karapitiya, Colombo South Teaching Hospital and National Hospital of Sri Lanka, respectively. Male to female ratio was equal for the toxin positivity.

Conclusions: In conclusion, this study shows that hospital acquired *Clostridium difficile* associated diarrhoea is seen in our country even though the proportions and rates remain very low in the three selected hospitals when compared to the other countries.

Keywords: Antibiotic associated diarrhoea, *Clostridium difficile*, faecal toxin detection.

Introduction

Clostridium difficile associated diarrhoea (CDAD) is the most common cause of infectious diarrhoea in hospitalized patients, with associated morbidity, increased length of stay and increased medical costs. More than \$ 1.1 billion in health care costs each year in the United States are due to CDAD (1).

Clostridium difficile infection ranges from mild to severe diarrhoea to, more unusually, severe inflammation of the bowel. Seven percent of community dwelling adults and 13% of hospitalized adults are asymptotically colonized with *Clostridium difficile* (2). In a proportion of colonized individuals, *Clostridium difficile* produces toxins that cause diarrhoea (2).

The pathogenesis of CDAD involves disruption of the normal bowel flora, usually after receiving broad-spectrum antibiotics, and growth of *Clostridium difficile* with production of its toxins (3). Common risk factors for CDAD include antibiotic consumption, increasing age, presence of co-morbid conditions and long hospital stay (4). In a review done by Ayyagari et al, *Clostridium difficile* continues to be the most common identifiable pathogen of antibiotic associated diarrhoea (AAD) and is responsible for 15% to 25% of AAD and nearly all cases of pseudo membranous colitis. Because of the frequent use of broad-spectrum antibiotics, the incidence of CDAD has risen dramatically in recent decades (5).

Symptoms of AAD generally start during antibiotic therapy but can be delayed by several weeks to months. *Clostridium difficile* produces two important toxins: toxin A, an enterotoxin, and toxin B, which is primarily a cytotoxin (6). CDAD often is perceived to be an occasional and easily treated side effect of antibiotic therapy. However 3% of patients develop severe CDAD and the mortality rate in them, ranges from 30-85% (5). Early diagnosis and prompt aggressive treatment are critical in managing CDAD.

In studies done in India, the prevalence of *Clostridium difficile* among acute diarrhoeal patients was 7.3% to 18% (7,8). In another study done in India, the incidence of CDAD was 15% (9).

As patients with diarrhoea are not routinely screened for *Clostridium difficile* in Sri Lanka, many aspects related to CDAD are not known. As CDAD remains undiagnosed, no preventive measures are taken to curtail the infection spreading in hospitals among patients. Therefore this research to determine the proportions, rates, source and precipitating antibiotics of patients with CDAD in three tertiary care hospitals of Sri Lanka, would offer an estimate of the extent of the problem thus assisting in making decisions regarding the management of CDAD and control of the spread of disease in health care institutions.

Methods

The study was a hospital-based descriptive, cross-sectional study carried out in three tertiary care hospitals, namely, Colombo South Teaching

Hospital (CSTH), National Hospital of Sri Lanka (NHSL) and Teaching Hospital Karapitiya (THK), from 1st October 2007 through 28th February 2009. Toxin detection was done in the Department of Microbiology, Faculty of Medical Sciences (FMS), University of Sri Jayewardenepura (USJ).

Patients admitted to above hospitals, with diarrhoea who gave a history of treatment with antibiotics within the past two months were selected for the study. Further, patients who developed diarrhoea after admission to above hospitals but received antibiotics prior to the onset of diarrhoea were also included in the study population. Specimens from children less than two years were not tested.

Sample size was calculated according to the prevalence studies done in India and other South East Asian countries. Ethical clearance was obtained from ethics committees of the hospitals and the institutes involved in the study. Each patient was interviewed using a questionnaire. Total discharges were obtained in each hospital for the study period.

Diarrhoea was defined as three or more loose stools per day for at least two days. Data were analyzed using Epi-info (Version 6) software.

Faeces specimens were collected from patients admitted to medical wards, surgical wards, medical intensive care units and surgical intensive care units of CSTH, NHSL and Teaching Hospital Karapitiya.

Specimens were transported to the Department of Microbiology, FMS-USJ, immediately after the collection. When unable to transport specimens immediately, they were stored at 2-8°C and transported in a carrier with ice within 24 hours of collection.

As the numbers of specimens were not adequate to perform the test daily, all the specimens were stored at -70°C as instructed by the manufacturers of the test kit, until processing. Specimens were processed according to the manufacturer's instructions. A separate specimen from each suspected patient was taken for the isolation of other common diarrhoeal pathogens.

An Enzyme Linked Immunosorbant Assay (ELISA) [(DRG® *Clostridium* Toxin A+B (EIA - 4203) – DRG International, Inc, USA.] was used to detect the presence of *Clostridium difficile* toxins A and B in faeces specimens.

Results

During the 1-year and 8-month study period, 110 patients were tested for the presence of *Clostridium difficile* toxin A or B. Of these, 04 patients had positive test results, (3.6%) and 106 patients had negative results. (96.4%) Two out of the four patients were from a single centre and one each from the other two.

Proportions of CDAD positivity in individual hospitals were, 7.4% for CSTH, 3% for Teaching Hospital Karapitiya and 1.96% for National Hospital of Sri Lanka.

Rates of CDAD at each hospital during 2007 – 2008 were, 0.01/1000 discharges at CSTH in 2007 and 0.008/1000 discharges at CSTH in 2008, 0.01/1000 discharges at THK in 2008 and 0.004/1000 discharges at NHSL in 2008.

Offending antibiotic could not be withdrawn in the toxin positive group and 97 patients (91.5%) in the toxin negative group, due to the severe underlying illness.

Common bacterial pathogens causing diarrhoea were not isolated from any of the specimens.

Table 1: Demographic and clinical characteristics of 110 patients with suspected antibiotic associated diarrhoea, according to results of assay for *Clostridium difficile* toxins

Variable	Toxin positive patients (n = 4)	Toxin negative patients (n = 106)
Mean age (Range)	42.8 (14 - 55 years)	53 (2 - 85 years)
Male to female ratio	1:1	1:0.6
Location in the hospital		
ICU	4 (100%)	67 (59%)
Ward	0	39 (41%)
Mean duration of antibiotic intake at the time of toxin detection (range)	18.8 (12 - 27 days)	9.7 (1 - 38 days)
Mean duration of hospital stay at the time of toxin detection (range)	19.5 (13 - 28 days)	11.6 (1 - 47 days)
Mean duration for the development of diarrhoea from the date of admission (range)	17.5 (12 - 26 days)	8.2 (1 - 45 days)
Mean number of antibiotics taken (range)	6.75 (3 - 13)	3.5 (1 - 13)
Number (%) with fever	4 (100%)	67 (63.2%)
WBC count		
>13,000 cells / μ l	4 (100%)	57 (53.8%)
<13,000 cells / μ l	0	43 (40.6%)
Not performed	0	06 (6.3%)
Acquisition of the AAD		
Health care facility	4 (100%)	101 (95.2%)
Community	0	0
Community onset healthcare facility associated	0	5 (4.7%)
Treatment options		
Oral Metronidazole	3 (75%)	19 (19.8%)
Oral rehydration Solutions	1 (25%)	77 (80.2%)

Discussion

Literature survey did not reveal any studies done previously in Sri Lanka to determine the extent, antibiotics that contribute or the origin, whether hospital acquired or community acquired, of CDAD.

It is likely that a substantial proportion of AAD cases are not due to CDAD in our study. That could be due to other infective causes of AAD, direct gut toxicity of antibiotics or other medical aetiologies. The proportion of CDAD in our study was 3.6%. It was less compared to the studies done in India, other South East Asian countries and Western countries (7,8,9).

The rates of CDAD in each hospital in our study were very low when compared to most of the studies done in other countries; i.e. 3.2/1000 admissions or discharges in a large teaching hospital in Singapore (10), 35.6/100,000 population in the region of Quebec in 1991 and 156.3/100,000 population in the same hospital in 2003 (11). Incidence of CDAD has increased with recent estimates of 22 cases per 1000 admissions or discharges, corresponding to the spread of a recently characterized hypervirulent strain of *Clostridium difficile* (12). In Oregon, the incidence has increased from 1.4 to 3.3 cases per 1000 hospital discharges from 1995 to 2002 (13).

Mean age of the CDAD patients in our study was 42.8 years whereas in other studies a higher mean age has been noticed (1,12,14,15,16). When compared with a study done in Boston and a study done in Netherlands, the length of hospital stay before the CDAD diagnosis was little more in our study for toxin positive group (14,16).

The mean duration of antibiotic use in the toxin positive group in our study was 18.8 days. This was little less when compared with a study done in Iowa (15). Mean number of antibiotics used in the toxin positive group was more than double in our study when compared with two studies done elsewhere (14,15).

All 4 patients had fever with neutrophil leukocytosis at the time of toxin detection which they have noticed in studies done elsewhere (11).

Even though the attending consultant could not withdraw the ongoing antibiotics, mainly because of the severity of the underlying illness, three of the toxin positive patients were empirically treated with oral metronidazole, which is the treatment of choice.

At the time of toxin detection, all patients were on either a second or third generation cephalosporin or broad spectrum penicillin; all except one had been treated with carbapenem; 2 had been treated with quinolone, of which one had been treated with a newer fluoroquinolone. All of the antibiotic groups which were used on the toxin positive patients in our study were found to be either belonging to high risk or moderate risk of antibiotics causing CDAD in the literature (15,17).

As the number of toxin positive cases was very low, we could not analyse risk factors for CDAD in our study group.

In absence of proper antibiotic policies in our healthcare system, several classes of broad spectrum antibiotics are been used unnecessarily on patients with much overlapping. As uncontrolled use of broad spectrum antibiotics is a known fact associated with CDAD, strict antibiotic policies are urgently needed to prevent the risk of facing large outbreaks of CDAD in the future.

Patient isolation is very important when we consider CDAD, as the causative agent is an anaerobic spore forming bacillus. Except one, all the other ICUs which were included in our study did not have isolation facilities. Isolation facilities were even poor in ward set-up. Hence the chances of the spread of infection among non infected patients were very high in our healthcare system.

Next important observation was the lack of dedicated staff for caring of the individual patients. When a single health care worker cares for several patients, the chance of cross contamination is higher. In ICU settings, ideally one to one ratio of nursing staff to patients should be maintained. But in the ward settings it is very difficult to maintain this. Therefore at least cohort isolation of the CDAD infected or suspected patients should be done in the ward setting. Furthermore, it is necessary to emphasize on contact precautions among ward staff in the absence of dedicated patient care.

Hand washing with soap and water is very important in the prevention of transmission of CDAD. Alcohol based hand rubs were proven to be ineffective against the *Clostridium difficile* spores [18]. Thus it is very important to educate the staff regarding the issue, because it may cause more harm than good if they use these alcohol based hand rubs before attending on new patients after caring for a known CDAD patient with false sense of security.

Limitations

Due to financial constraints, toxin detection could not be compared with the gold standard – vero cell cytotoxin assay or the toxigenic culture and further other infective causes of AAD were not looked for in this study. For the same reasons we could not type the strains of the *Clostridium difficile*.

Conclusions

This study showed that hospital acquired CDAD is seen in Sri Lanka, even though the incidence remains very low.

Diagnosis of CDAD is important as the rates might go up in future with increase uncontrolled use of broad spectrum antibiotics.

Awareness of CDAD and its management among clinicians and other staff was very poor. There is a need to increase the awareness of CDAD and its treatment for patients in ICUs as well as in wards and the infection control measures, because the mortality, morbidity and hospital costs are high with CDAD.

There are no proper antibiotic policies in our health care system. Thus it is necessary to implement proper antibiotic policies in hospitals in Sri Lanka.

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