



Research Article

CLOSTRIDIUM DIFFICILE, AN EMERGING INFECTION IN CHRONIC HEMODIALYSIS PATIENTS

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ABSTRACT

Background: Patients of the chronic renal disease require repeated hemodialysis and are hospitalized frequently. They are prone to nosocomial infections of which- the Clostridium difficile is common. It can be very lethal if diagnosed lately or have resistant strain as a causative organism.

Objective: To document the frequency of C. difficile infection among patients of chronic hemodialysis and its associated outcomes.

Study design: Retrospective study.

Settings: Department of Nephrology, Dubai Hospital, Dubai.

Material and methods: Data of a total of 18 cases of hemodialysis having diagnosed as C. difficile infection, both genders, age 45-85 years were extracted from medical records of SALAMA system and laboratory tests registry. All data were collected and recorded in Performa. Statistical Program for Social Sciences (SPSS) version 19 was used to analyze the data.

Results: Mean \pm SD age was 70.94 ± 11.51 years (Range 48-84). The majority (83.3%) were females. One-third of patients were of age >81 years. Hypertension and diabetes mellitus were common comorbidities. Patients presented with Gastroenteritis (22.2%), Chest infection with CO₂ retention (16.7%). One-third of patients were treated with Metronidazole while 61% needed vancomycin in addition. Total 02 patients (5.55%) could not survive both of which were females and were age 72 & 73 years respectively, however, their direct cause of death were unlikely related to CDI.

Conclusion: C.difficile continues to affect the old age, female and chronically ill patients. Their healthcare providers, as well as the patients, need to be educated for the prevention of unnecessary and overuse of antimicrobials.

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INTRODUCTION

With the increasing burden of chronic diseases like Hypertension and Diabetes Mellitus, there is a proportional surge in chronic renal disease-end stage renal disease (ESRD) worldwide and in UAE also. These patients either require renal transplantation or to a minimum, they need regular sessions of haemodialysis to survive. On an average one hospital admission and at least 14 days' stay per year has been documented for these patients during which they are routinely exposed to invasive devices for vascular access and other procedures. Frequent admission in the hospital, longer duration of stay, invasive procedures and immunocompromised state (due to uraemia and numerous comorbid conditions) during the chronic haemodialysis makes them prone to an exaggerated risk of nosocomial infections. ^{1,2} Among these Hospital-acquired infections, Clostridium difficile- a Gram-positive, spore-forming, toxin-producing, obligate anaerobe- is relatively common and of critical value.

Clinically; C. difficile may colonize asymptotically or otherwise may cause fulminant pseudomembranous colitis, septic shock, and death specifically in immunocompromised patients. ³ Diagnosis of C difficile is made by testing stool culture for a toxin. ⁴ This infection caused much havoc in the United Kingdom by the end of the 20th century and caused 16% ward closures. ⁵ Reasons for such an alarming situation are extensive use of broad-spectrum antibiotics. Other risk factors for Clostridium difficile infection (CDI) include older age, gastric acid suppression therapy and prolonged hospitalizations. ⁶ Also, the increase in the number of patients with compromised immunity bursts into C. difficile infection outbreaks in such patients' population/ hospitals. Thus; it has been identified as one of commonest nosocomial infections leading to severe morbidity and increased mortality rates in already chronically ill patients. ⁷ This raises the need for exclusive prevention measures to prevent the spread of CDI by prompt isolation followed by treatment of symptomatic patients and execution of strict antibiotic policies. ⁸

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Chronic dialysis patients are at manifold risk of C. difficile infection than any other group because of these known risk

factors and therefore represent a vulnerable group.⁹ Despite the raised prevalence of dialysis patients who are at increased risk for CDI outbreaks within outpatient haemodialysis facilities- there is very much lack of data on this issue. Only a few studies are conducted but these studies have conflicting results.^{7, 10, 11} With this need and motivation the current study was conducted with broader aim to evaluate the rate of *Clostridium difficile* infection (CDI) in patients undergoing long-term dialysis in our dialysis centre and its associated morbidity factors and mortality.

MATERIAL AND METHODS

This case series study was conducted at nephrology ward, Dubai hospital, Dubai from Jan 2015 – Dec 2017. Retrospective analysis of all nephrology admissions (total 2099) for hemodialysis during the study period was made. Out of this, 359 were dialysis candidates in which a sample of 18 patients with ESRD (on Chronic Hemodialysis) - who were diagnosed to have *Clostridium difficile* infection were included in the study. Selection criteria were being dialysis patients of both male or female gender and age range from 14-85 years. Data were retrieved from the medical records (as per coding system), dialysis patient's records, SALAMA system and laboratory tests registry. Presenting complaints and all related complications among patients were documented. A number of hospital admissions, length of hospital stay and related mortality noted. Ethical approval was obtained from Dubai scientific research ethics committee and confidentiality of patients was maintained by not exposing the identity and registering cases as per codes. All data were collected and recorded in Performa. Statistical Program for Social Sciences (SPSS) version 19 was used to analyze the data. Results were expressed in mean ± SD for continuous variables while frequencies and proportions for categorical variables.

RESULTS

The mean ± SD age of patients was 70.94 ± 11.51 years with a range of 48-84 years. (Table #1) Majority of patients (83.3%) were females. It was noted that about one-third of all patients were of age >81 years (Figure #1). All had at one or other comorbidity. All were hypertensive while other common comorbidities were Diabetes Mellitus (88.9%), Rheumatoid Arthritis (33.3%), Obstructive sleep apnea (16.7%), Hypothyroidism & Old TB each were 11.1%. Ischemic Heart Disease, Peripheral Vascular disease, Breast cancer, Multiple Myeloma, Lymphoma, Anoxic Brain Injury, HCV and PEG feeding were other less common comorbidities. (Table 2)

These patients were on chronic dialysis treatment for 2 months (minimum) to 06 years (maximum) with a mean SD ± duration of 2.09 ± 1.72 years. (Table #1) Majority of patients presented with Gastroenteritis (22.2%), Chest infection with CO2 retention (16.7%) and Wound infection, Sepsis & Septic shock - 11.1% each. Other reasons were Diarrhea, Febrile neutropenia and pneumonia & lower limb cellulitis. (Table #3). All patients had a history of using antibiotic within the last three months, and the most commonly used of these were Tazocin, Levofloxacin, Ciprofloxacin, Ceftriaxone, Ertapenem and others. Each were taken for 2 to 14 days with a mean SD ± duration of 6.78 ± 2.69 days. The risk factor of low albumin was present among 9 (50%) patients.

In the current series, it was noted that about 39% of patients were treated with Metronidazole only for the treatment of C.

difficile infection while 61% needed vancomycin along with Metronidazole. Eleven patients (61.11%) had relapsed and among them, 6 (54.54%) had three relapses at maximum. Total 02 patients (5.55%) could not survive both of which were females and were age 72 & 73 years respectively, though their direct cause of death was not related to CDI, as one patient had sepsis secondary to MRSA pneumonia (concomitant with CDI infection) while the other one died of hepatic encephalopathy and cardiac arrhythmias.

Table 1 Descriptive statistics of patients who were treated for percutaneous trigger finger release (n = 18)

n = 18	Minimum	Maximum	Mean	Standard Deviation
Age of Patient	48	84	70.94	11.51
Duration on Dialysis treatment in years	0.2	6	2.09	1.72
Duration of antibiotic use in days	2	14	6.78	2.69
Number of relapses	0	3	1.22	1.35

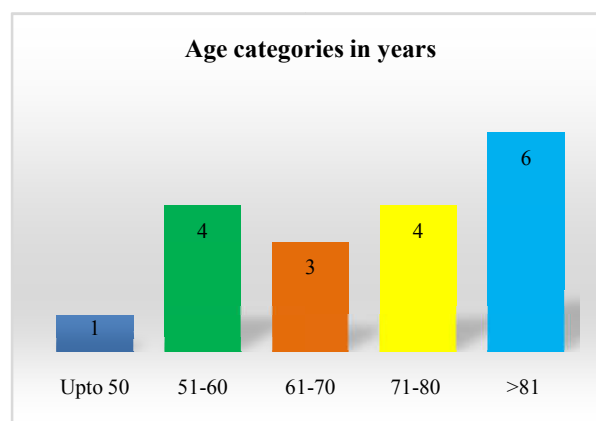


Figure 1 Age categories in years

Table 2 Frequency of comorbid conditions among patients

Comorbid	Frequency	Percentage
Diabetes Mellitus	16	88.9
Ischemic Heart Disease	1	5.6
Peripheral Vascular disease	1	5.6
Rheumatoid Arthritis	6	33.3
Breast cancer	1	5.6
Obstructive sleep apnea	3	16.7
Multiple Myeloma	1	5.6
Lymphoma	1	5.6
Anoxic Brain Injury	3	16.7
Hypothyroidism	2	11.1
Old TB	2	11.1
HCV	1	5.6
Peg feeding	1	5.6

Table 3 Frequency of reasons for the hospital admission

Comorbid	Frequency	Percentage
Diarrhea	1	5.6
Sepsis	2	11.1
Chest infection	1	5.6
Gastroenteritis	4	22.2
Chest infection with CO2 retention	3	16.7
Febrile neutropenia and pneumonia	1	5.6
Wound infection	2	11.1
Septic shock	2	11.1
chest infection	1	5.6
Lower limb cellulitis	1	5.6

DISCUSSION

First known to medical literature in 1935, the *C. difficile* was not identified as the causative pathogen of antibiotic-associated diarrhea and colitis until 1978. However; in recent years it has emerged as one of the most important causes of healthcare-associated infections especially in hospital admitted patients with chronic illness.¹² Patients receiving regular sessions of hemodialysis are very feeble, immunocompromised and prone to many complications – of which *C. difficile* infection is one which needs focused attention.

The current study is a premier study in this region to investigate this very critical health aspect of chronic hemodialysis patients- the nosocomial infection with *C. difficile*. There were a total of 2099 admissions in the nephrology ward of Dubai hospital during the study period. Out of these, 359 hemodialysis patients were admitted while 18 of these developed *C. difficile* infection. This makes a *C. difficile* infection rate of 5.01% among them. In a study, See I, *et al.*, investigated hemodialysis outpatients and found that CDI incidence was 13.51%.⁸ This quite alarming situation and needs to be dealt preemptively by building capacity for diagnosis, surveillance and prompt/ exclusive treatment.

In the current series, most of the patients had a previously identified risk profile of old age, comorbidity, and recent antibiotic use superimposed on chronic hemodialysis making them vulnerable to nosocomial infection. One-third of all patients were of age >80 years while a quarter of patients were below 60 years- as young as one patient was of 48 years. The reason for the younger age may be the immunocompromised state however; most of the times chronic dialysis patients are of elder age. Other studies like Keddis MT, *et al.* have noted that most of their patients (64.4%) receiving dialysis were 65 years of age or older.⁷

All patients had one or other comorbidity in addition to being hypertensive while diabetes mellitus was also present in >80% patients. Both or these disease producing a synergistic effect, lead to quick kidney damage and ESRD. Studies reported that > two-thirds of all patients who were undergoing long-term dialysis had comorbidities like hypertension and diabetes mellitus and were twice more likely to develop CDI than in non-ESRD patients and 1.33 times more likely than ESRD patients not undergoing dialysis (P-value <0.001).⁷

Different studies from North America and Europe have caught attention about the emergence of a very lethal fluoroquinolone-resistant strain of *C. difficile*.^{13,14} It was noted in the current study too that fluoroquinolone antimicrobials like Levofloxacin, Ciprofloxacin, as well as other antimicrobials; Tazocin, Ceftriaxone were being repeatedly used by these patients in the last few weeks. Some of the patients had used antimicrobials for as much as 2 weeks with a mean duration of one week. Todd B has reported that CDI was detected even in patients who had no history of taking antimicrobials- however, there was no further evidence was reported.¹⁵ Female patients of chronic dialysis were more affected by *C. difficile*. However; other studies have found no major gender difference in this regard. Longer hospital stay is a major risk factor for CDI. In the US it was reported that with a >2 days' hospital stay; the rate of CDI in the hospital which colonize the infection- elevates up to 10%.¹⁶

The increasing incidence and severity of *C. difficile* in the last few decades have spread outside healthcare settings as well. A well-known reason for this is frequent antibiotic use and the emergence of a hypervirulent *C. difficile* strain.¹⁷ Previously; it was thought that *C. difficile* is invariably affected hospital admitted patients who are either chronically ill or have used too much of antimicrobials, however; the studies have now found that CDI is affecting the outpatients also who might develop severe conditions with high morbidity and mortality.^{8,18} Vulnerable groups outside the hospital include specific populations that were previously at low risks, such as children and pregnant women.^{19,20} Therefore, CDI should be considered when diagnosing any patient with persistent diarrhea.²¹ Gastroenteritis, diarrhea, chest infection and sepsis are commoner presenting symptoms of CDI.

It is commonly found that the most effective antibiotics for treating *C. difficile* infection are oral metronidazole and vancomycin. The current study also noted that one-third of patients were treated with oral metronidazole while the remaining required additional vancomycin. These are effective and up to mark treatment options available. Kim SC, *et al* found that there is among the patients who had used vancomycin even before the CDI had a very little response to metronidazole and in them, the in-hospital mortality rate was 11.5%.²² In the current series, it was noted that 2 (5.55%) patients could not survive, however, their direct cause of death were unlikely related to CDI. A study from Europe documented that at follow up, 101 (22%) of 455 patients had died, and *C. difficile* infection played a part in 40 (40%) of deaths.²³ Keddis MT, *et al.* had found in-hospital mortality up to 10% among patients admitted for dialysis who had CDI.⁷ However; prevention of emergence of *C. difficile* by controlling the irrational use and controlling the antimicrobials exposure to chronically ill patients is the mainstay of safety from this extremely lethal infection.^{24,25} Confirmed, as well as doubtful cases of CDI, may be isolated and contact safety through gown and gloves be practices strictly. Alcohol does not kill spores therefore; soap and hypochlorous solutions are mainstays of disinfection.

World over; there is a great difference in *C. difficile* investigation criteria and diagnosis methods between laboratories of different countries. Non-presence of one standard diagnostic guideline may reflect into the difference of incidence rates throughout the healthcare setting of the world.²⁶

CONCLUSION

The current study has highlighted a critical issue of hemodialysis care. Such patients are very prone to lethal infections which have very limited options of antimicrobials. Their healthcare providers, as well as the patients, need to be educated for the prevention of unnecessary and overuse of antimicrobials. If not given importance with specific preventive measures may it turn into major adverse incidence.

Conflict of interest: None.

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