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Background

Clostridium difficile (CD) is implicated in 20 to 30% of patients with antibiotic-associated diarrhoea, in 50 to 70% of those with antibiotic-associated colitis and in more than 90% of those with antibiotic-associated pseudomembranous colitis[1-4]. The incidence of CD associated diarrhoea ranges from 1 in 100 to 1 in 1,000 hospital discharges depending on the antibiotic prescribing habits of the hospital[5-7].

The consequences of CD can be severe. At one academic medical center over a three-year period, 21 of 710 cases (3%) of CD colitis required intensive care unit admission or died as a result of their infection[8]. These deaths were associated with co-morbid conditions such as malignancy, chronic obstructive pulmonary disease or renal failure and therapies such as immunosuppressive drugs, anti-peristaltic medications or the prior administration of clindamycin[9]. At another university hospital the morbidity of the infection was higher and 24 of 157 patients (15.3%) with CD colitis died from their infection[10]. The new variant of CD - which is capable of secreting much higher amounts of toxin A & B and is more resistance to standard antibiotic therapy - results in greater incidence in hospitalized patients[11], a greater need for urgent colectomy for toxic colitis and a significantly higher mortality rate[12]. The economic consequences of CD infection can also be severe, with one report finding a mean cost of $10,970 (US$) per patient for the treatment of the infection and its complications[13].

Due to the high incidence of CD infection on a 24-bedded ward in a busy district general hospital in Merseyside - UK, all microbiologically confirmed infections over a period of one month were identified and studied for predictors of mortality and morbidity.

Aims

The primary objective of our study was to determine the baseline characteristics of in-patients with hospital acquired Clostridium difficile and to ascertain their eventual outcomes, and thus evaluate the effectiveness of disease severity in predicting mortality, morbidity at discharge and discharge destination.
Secondary aims included an analysis of the epidemiology of the infected population and if antibiotic-related infection varied in prognosis to sporadic (antibiotic-unrelated) infection.

Methods

All patients with diarrhoea admitted to a 24-bedded (cohort) ward in at Whiston Hospital, Merseyside – UK over a four week period (May 2008) were prospectively identified and their case-notes were retrospectively reviewed. The study was approved by the Clinical Governance Department of the hospital.

Case definitions and measures

Clostridium difficile (CD) infection: A patient admitted to the cohort wart during the period of the study with symptoms and microbiological confirmation of Clostridium difficile infection.

Antibiotic-related infection: A case of confirmed Clostridium difficile infection with documented receipt of oral or parenteral antibiotic therapy as an in-patient or in the community within 6 weeks prior to the onset of symptoms.

Measures of morbidity: Karnofsky[14] and Zubrod (also called ECOG [Eastern Cooperative Oncology Group]) [15] scoring systems were employed in determining the morbidity of the infected population at diagnosis and at the eventual outcome. A Karnofsky score of </= 40 (40 being the requirement of special care and assistance [disabled], and 0 being death) and a Zubrod score of >/=3 (3 being limited self care with confinement to a bed/chair for >50% of waking hours, and 5 being death) signified increased morbidity.

Measure of disease severity: Severity of infection was determined using the Clostridium difficile Severity Assessment Scoring System of the UK's Department of Health (2008). A score of >/=3 was identified as 'severe disease' and a score of <3 as 'non-severe disease'.

Outcome measures: Outcome measures were death (resulting directly from the infection), morbidity scores at discharge and discharge destination.

All results were expressed as mean or percentages. Fisher's T test was employed to explore statistical significance.

Results

16 patients with confirmed CD infection were identified during the period of the study. The mean age of the infected population was 80 years (age range: 59-89 years, median: 82 years).

Pre-admission morbidity state:

The average pre-admission Karnofsky and Zubrod scores of the studied population were 50 and 2.57 respectively, suggestive of some disability even before the onset of the infection. The average number of pre-existing co-morbidities was 5.

Eventual outcomes:

The average eventual morbidity scores of the population was Karnofsky 33.75 and Zubrod 3.32 with 68.8% (11 cases) having a score of </= 40 and >/=3 respectively, denoting a significant decline in their morbidity status. 31.25% (5 cases) died in hospital as a result of their infection. However, 54.5% (6 cases) of the 11 survivors were fully dependent and eventually required institutional care at discharge.

Disease severity as a predictor of eventual outcome:

The mean disease severity score of the identified population was 3.72. 9 patients (56.3%) had an infection severity score of >/=3 (signifying 'severe disease') while the remaining 7 had non-severe disease. Increased morbidity and mortality was noted in the population with severe disease. 7 (77.8%) of the 9 patients with severe disease had an eventual Karnofsky score of </=40 and an eventual Zubrod score of >/=3 (increased morbidity) while increased morbidity was noted in 4 (57.1%) of the 7 patients with non-severe disease [p=0.37]. Similarly, 44.4% (4 cases) of patients with severe disease died and another 44.4% (4 cases) required institutional care on discharge compared to 14.3% and 28.6% respectively in patients with non-severe disease [p values of 0.3 and 0.45 respectively]. This is demonstrated in Table 1.

Table 1: Disease severity as a predictor of outcome in CD infection

	Severity score >/=3 *N=9*	**Severity score <3** *N=7*	**Total** *N=16*	**P value**
Eventual K score </= 40	7 (77.8%)	4 (57.1%)	11 (68.8%)	0.3654
Eventual Z score >/= 3	7 (77.8%)	4 (57.1%)	11 (68.8%)	0.3654
Institutional care on discharge	4 (44.4%)	2 (28.6%)	6 (37.5%)	0.4510
Death	4 (44.4%)	1 (14.3%)	5 (31.3%)	0.3077

Prognostic difference between antibiotic-related and antibiotic-unrelated infection:

13 patients (81%) were confirmed to have antibiotic-related infection. Significantly increased morbidity and mortality was noted in the population with antibiotic un-related infection. 8 (61.5%) of the 13 patients with antibiotic-related disease had an eventual Karnofsky score of </=40 and an eventual Zubrod score of >/=3 in comparison to all 3 patients (100%) with antibiotic-unrelated infection [p=0.29]. And while 15.4% of patients with antibiotic-related disease died, the mortality rate in those with antibiotic-unrelated infection was 100%

[p=0.036]. Table 2 provides details of these findings.

Table 2: Outcome difference between antibiotic-related and antibiotic-unrelated disease

	Antibiotic-related infection *(N=13)*	**Antibiotic-unrelated infection** *(N=3)*	**Total** *N=16*	**P value**
Eventual K score </= 40	8 (61.5%)	3(100%)	11 (68.8%)	0.2946
Eventual Z score >/= 3	8 (61.5%)	3(100%)	11 (68.8%)	0.2946
Death	2 (15.4%)	3(100%)	5 (31.3%)	0.0179

Discussion

Our study confirms that CD is a disease that affects a predominantly elderly and frail population with multiple co-morbidities and poor performance status, and carries a large mortality and morbidity burden. This is in keeping with the findings of previous studies which have highlighted that pre-existing morbidity is a significant risk factor to acquiring the infection and that the overall prognosis of this patient group is generally poor[16, 17].

Disease severity scores seem to have a reasonably realistic predictory value of eventual outcome of the infection. In our study, those patients identified as having a severe disease course did have a higher rate of mortality than those with non-severe disease, and those who survived the infection were left with elevated morbidity and a poorer performance status, with most requiring institutional care on discharge.

Antibiotic use was the single most important contributing factor to developing the infection. Over three-quarters of our inpatients with confirmed CD infection were noted to have had oral or parenteral antibiotics in the preceding 6 weeks and this corroborates with the findings in existent medical literature[6]. However, a notable finding of our study is that prognosis and mortality rates are significantly worse in those with antibiotic-unrelated CD infection. This should be taken into consideration in the formulation of appropriate treatment strategies in order to combat the high levels of mortality and morbidity ensuing from antibiotic-unrelated Clostridium difficile infection.

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