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A prospective study of community-associated *Clostridium difficile* infections: The role of antibiotics and co-infections

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Summary *Objectives:* This prospective study was performed to determine the incidence, risk factors, severity and outcomes of community-associated *Clostridium difficile* infection (CA-CDI) in the SE of Scotland.
Methods: All patients (335) diagnosed with laboratory confirmed CDI in the city of Edinburgh, East Lothian and Midlothian regions of Scotland between August 2010 and July 2011 were followed up for one year after diagnosis. Clinical details and laboratory markers were recorded. Stool samples were tested for *C. difficile*, other bacterial pathogens and norovirus. Molecular epidemiology of *C. difficile* isolates was studied by PCR-ribotyping.
Results: Of the total 335 confirmed CDI cases, PCR-ribotype 001 was the commonest (14.1%), followed by PCR-ribotypes 078 (12.9%) and 015 (11.7%), respectively. CA-CDI represented 12.5% of the cases. In these, PCR-ribotype 078 was the commonest (19.0%), followed by PCR-ribotypes 014/020 (16.7%), PCR-ribotype 015 (14.3% and PCR-ribotype 001 (11.9%). A lower Charlson co-morbidity index and a lower age was observed in the CA-CDI group as was total number of different antibiotic classes whereas age >75 was more common in the HA-CDI group. On multivariable analysis presence of PCR-ribotype 078 was significantly associated with community acquisition ($p = 0.006$) whereas a greater proportion of immunosuppressed patients and those on antibiotics 8 weeks preceding diagnosis ($p = 0.035$ and $p = 0.005$ respectively) were found among HA-CDI cases. Charlson co-morbidity index, number of

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different antibiotics given in the eight weeks preceding onset, severity of infection and rural residence were not significantly different between the two groups.
Conclusion: This study demonstrates that patients with CA-CDI may also present with severe infection, are less likely to receive antibiotics prior to CDI, more likely to be younger in age and have a greater proportion of PCR-ribotype 078 compared with CDI acquired in a hospital setting. Hence a high level of vigilance must be maintained to detect CDI cases which present in the community without the traditional predisposing factors.

Introduction

Human acquisition of *Clostridium difficile* infection (CDI) in the community has been known since the 1980s.[1,2] Although there are a number of studies on CDI acquired in a health care setting, those analysing CA-CDI are limited, which may be due to difficulty in collecting dispersed community-based data. In addition, most existing studies are retrospective using previously recorded electronic databases. Recent surveillance reports have suggested an increasing incidence of CA-CDI,[3] which may be due to heightened awareness, increase in organism fitness or antibiotic pressure. Spread via community sources such as contact with pets or ingestion of contaminated food products is also possible.[4,5] Some studies have found a high incidence of ribotype 078 among farm animals and have suggested the association of this ribotype with acquisition in the community.[6–9]

This prospective study was performed to establish the incidence, risk factors, severity and outcomes of CA-CDI in a major region of SE Scotland and to compare differences with hospital-associated acquisitions.

Materials, patients and methods

Patients and clinical definitions

The Royal Infirmary of Edinburgh microbiology laboratory serves the city of Edinburgh, East Lothian and Midlothian regions of SE Scotland including all hospitals, long-term care facilities and approximately 127 GP practices. This study was conducted from August 2010 to July 2012. All patients whose stool samples were submitted to the microbiology laboratory for investigation from Aug 2010 to July 2011 (inclusion period) and which tested positive for *C. difficile* by a two-step algorithm were included in the study and prospectively followed up for one year after inclusion. All liquid stool samples (Bristol stool chart grade 5–7) from inpatients more than two years of age were tested for CDI. As per department of health guidelines, stool samples were not re-tested if there was a previous positive result in the past 28 days. Samples from GP practices and outpatients were tested if requested by the physician, or when antibiotics were mentioned in the history or as per the microbiologists' discretion based on history provided which included previous CDI positivity and recent hospital admission. CDI tests were performed daily including weekends and results were informed to the attending clinicians in order to start treatment as soon as possible.

The tests comprising the two-step algorithm were toxin A and/or B by EIA (Tox A/BII, Techlab) and glutamate dehydrogenase: GDH (C.DIFFCHEK-60, Techlab). Appropriate ethical approval from the local human investigations committee was obtained for access to their demographic and clinical data.

An episode of CDI was defined as diarrhoea where the stool takes the shape of the container (grade 5–7 as per Bristol stool chart) with stool positive for *C. difficile* toxin A and/or B without other known aetiology or endoscopic evidence of pseudomembranous colitis.[10] A recurrence was defined as another episode of CDI, which occurred after cessation of treatment of the initial episode, that occurs within 8 weeks following the onset of a previous episode. A positive stool test was not required for a recurrent episode if diagnosed by the attending physician. Since each patient was followed up for one year after initial diagnosis, all episodes which occurred within the follow up period have been recorded and analysed. Mortality was recorded at 30 d and 1 year.

CDI was considered severe if any of these markers were present; white cell count $>15 \times 10^9$/L, creatinine >50% increase above baseline, temperature of >38.5 °C, evidence of severe colitis (abdominal or radiological signs) partial or complete ileus, toxic megacolon, pseudomembranous colitis,[11] or evidence of severe disease on CT or MRI scans.

Hospital acquired CDI (HA-CDI) was defined as CDI, which developed after 48 h of admission into a healthcare-facility (HCF). CA-CDI was defined as CDI, which developed in a patient with no history of healthcare contact in the 12 weeks prior to diagnosis. Contact with hospital was defined as admission to an acute-care hospital or long-term care facility that provided skilled nursing care to the patient for ≥1 overnight stay, or had an invasive surgical procedure in a day surgical unit. Healthcare-associated (HCA) CDI was defined as CDI within four weeks after contact/discharge with a HCF.[2] For the purpose of analysis HCA-CDI was included in the HA-CDI category. Those cases that had contact with a hospital 4–12 weeks before CDI (indeterminate origin) were excluded from the principle analysis but a separate analysis has been provided in which they are included in the CA-CDI category. Patients admitted to long-term care institutions with facilities similar to a hospital like environment were included in the HA-CDI group. Patients with CDI living in institutions where the environment was similar to elderly residential home without acute-care facilities (and without admission to a hospital in the past 12 weeks) were designated NH-CDI and have been excluded from the principle analysis. However, a separate analysis including them in the CA-CDI category is provided in the Supplementary Tables.