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Increasing health burden associated with Clostridium difficile diarrhoea in patients with inflammatory bowel disease.

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3 **Increased health burden associated with hospital associated *Clostridium difficile***
4 **diarrhoea in patients admitted with inflammatory bowel disease.**
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Abstract**Background**

Clostridium difficile (*C. difficile*) infection in hospitals in developed countries continues to be a major public health hazard despite increased control measures including review of antibiotic policies and hygiene measures. Patients with colitis are thought to be particularly vulnerable to *C. difficile* associated diarrhoea (CDAD). Identifying the clinical burden among hospitalised patients admitted with inflammatory bowel disease (IBD) is an essential first step towards identifying and treating severe *C. difficile* infection in such individuals.

Aim

To determine excess morbidity and in-hospital mortality associated with hospital acquired *C. difficile* associated diarrhoea in patients with inflammatory bowel disease (IBD-CDAD-HAI) admitted to NHS hospitals in England compared with those admitted for IBD alone.

Methods

Time trends study of all admissions to NHS hospitals between 2002/03 and 2007/08. We developed case definitions for IBD-CDAD-HAI patients. The primary outcomes were in-hospital mortality and length of stay. The secondary outcome was gastrointestinal surgery.

Results

Patients in the IBD-CDAD-HAI group were more likely to die in hospital (adjusted OR 6.32), had 28.3 days longer in-patient stays and higher GI surgery rates (adjusted OR 1.87) than patients admitted for IBD alone.

Conclusions

Patients with IBD admitted to NHS hospitals in England with co-existent *C. difficile* infection are at risk of greater in-hospital mortality and morbidity than patients admitted for IBD alone.

Introduction

Clostridium difficile (*C. difficile*) associated diarrhoea (CDAD) has become a significant cause of hospital morbidity and mortality in recent years. The incidence of *C. difficile* infection in the general population has roughly doubled in the UK in the past 10 years^{1,2} and the problem has been compounded by the emergence of a new more virulent strain.³ Public concern about *C. difficile* infection in the UK has increased in the wake of recent high profile nosocomial outbreaks^{4,5} and has led to enhanced surveillance through mandatory reporting of all episodes of *C. difficile* infection in patients aged under 2 years to the UK Health Protection Agency (UK HPA). Health targets to reduce incidence have reportedly brought the problem under control since its peak in 2008 by improving hospital hygiene to reduce cross infection and focusing antibiotic policies to reduce the use of broad spectrum agents known to precipitate *C. difficile* infection.^{6,7} Yet these measures may not adequately address certain groups of patients who are at increased risk of infection.

Several high-risk groups for *C. difficile* infection include the elderly, immunocompromised patients, those with multiple co-morbidity and individuals needing prolonged hospitalisation.⁸ Inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease, is a chronic relapsing bowel condition often requiring hospital admission and treatment with immunosuppressive drugs. Retrospective reports from tertiary centres have suggested a disproportionate rise in the rate of *C. difficile* co-infection amongst this group of patients.⁹⁻¹¹ Epidemiological data from North America have supported these observations and have pointed towards a large increase in morbidity and mortality amongst this group.⁹⁻¹² Microbiological evidence suggests *C. difficile* carriage in IBD patients may be predominantly acquired in the community¹³ and CDAD may develop without antibiotic exposure.³ The UK HPA only reports microbiologically confirmed cases and may underestimate the clinical burden of disease. Since these patients often present with diarrhoea, in the absence of systematic surveillance of *C. difficile*, it is not possible to distinguish between active IBD and *C. difficile* infection. For this reason the incidence of *C. difficile* infection in IBD patients is unknown.

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5 Hospital Episodes Statistics (HES) is the hospital administrative dataset for England and
6 comprises data gathered locally through each hospital's Patient Administration System.¹⁴
7 It covers all in-patient activity delivered by NHS hospitals in England and as such is a
8 potentially excellent data source to explore the risk of *C. difficile* infection amongst IBD
9 patients. Using this national dataset we aimed to characterise demographic trends in the
10 occurrence of co-existent *C. difficile* infection and IBD and its impact on in-hospital
11 mortality and morbidity.
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18 19 **Methods**

20 *Data sources*

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22 The Hospital Episode Statistics (HES)¹⁴ contains data on all inpatient and day case
23 activity delivered by NHS hospitals including personal, administrative and clinical
24 information with more than 15 million records collected annually. It has been operational
25 since 1989 and has been used extensively for research.¹⁵ The dataset includes age, gender,
26 admission method (elective or emergency), primary diagnosis (the main reason for
27 admission) and up to thirteen secondary diagnosis fields, twelve procedural fields, length
28 of stay and method of discharge (including in-hospital death). The basic unit of the
29 dataset is the consultant episode, covering the continuous period of time during which a
30 patient was under the care of one consultant. Episodes of care were linked into
31 admissions and those ending in transfer to another hospital were linked together to avoid
32 multiple counting.
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44 *Definition of cohort groups and outcomes (Figure 1)*

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46 We developed a cohort of IBD admitted cases by including all patients in whom the
47 primary diagnosis (the main reason for admission) or secondary diagnosis (any additional
48 reason for admission) was inflammatory bowel disease (ICD 10 code: K50, Crohn's
49 disease (CD) and K51, ulcerative colitis (UC) as cases of IBD. We excluded all day cases
50 patients undergoing endoscopic procedures) but included both elective and emergency
51 admissions.
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3 We ascribed the presence or absence of *C. difficile* associated diarrhoea (CDAD)
4 according to the presence of an ICD-10 coded diagnosis for *C. difficile* infection (A047)
5 in any of the admission record. Patients were recorded as having *C. difficile* in 2 ways: 1)
6 the primary diagnosis (main reason for admission) was *C. difficile* infection or 2) the
7 primary diagnosis or main reason for admission was IBD but they had a secondary
8 diagnosis of *C. difficile* infection
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16 For patients in whom the primary diagnosis (the main reason for admission) was *C.*
17 *difficile* infection, we ascribed the infection to be hospital or community acquired based
18 on evidence of prior exposure, i.e. whether they had had a previous hospital admission
19 (but not necessary an IBD admission), using a 90-day cut-off point. To do this we
20 ascribed the *C. difficile* infection as being hospital acquired if there was either a prior
21 admission for any reason within the past 90 days (not necessarily due to IBD) or at least
22 72 hours of exposure during the index admission.
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30 Similarly, we considered that patients admitted with a primary diagnosis for any
31 condition other than *C. difficile* but with a secondary diagnosis of *C. difficile* should have
32 had at least 72 hours' exposure in hospital to attribute the likely exposure/acquisition to
33 the hospital (probable hospital acquired *C. difficile* infections About 1% of patients in our
34 cohort fell into both these categories, but we have only counted them once. We defined
35 our prior exposure period based on consensus from clinicians supplemented with a
36 sensitivity analysis of HES data from the financial year 2007/08 showing that the
37 majority of prior admissions occurred within 90 days. We have clarified this method in
38 more detail in the draft.
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47 Our outcome measures were in-hospital mortality, total length of stay, emergency
48 readmission within 28 days of discharge from prior admission and gastrointestinal (GI)
49 surgery (with OPCS4 codes: G694, G713-G715, G721-G725, G729, H041 H043, H049,
50 H051-H053, H06-H07, H081-H085, H089, H091-H095, H098-H099, H10, H111-H115,
51 H119, H131-H135, H151-H153, H159, H161, H169, H291-H294, H31, G73-G75, G782,
52 G784, G785) that includes a sub-group of codes for colectomy.
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Statistical analysis

We used HES data for financial years 2002/03 to 2007/08. Our outcome measures were death in hospital, having GI surgery, emergency readmission within 28 days of discharge and length of stay. We compared IBD inpatients with co-existing *C. difficile* infection with inpatients that had IBD alone. We adjusted the odds ratios for age (18-19, 20-24, 25-29, five-year bands up to 90+), sex, area-level socio-economic deprivation (Carstairs index¹⁶ of deprivation in population-weighted quintiles), year (NHS financial year of discharge: from April 1st to March 31st) and co-morbidity (using the Charlson index,¹⁷ ranging from 0 to 6+). A previous study showed that models using HES data can have good discrimination (as assessed by the receiver operating curve c statistic) and calibration (using standardised residuals measuring goodness-of-fit).¹⁸

Secondly, we compared the relative risk of death and of having GI surgery for patients with and without healthcare associated *C. difficile*, adjusting for the same case-mix variables as mentioned above. This time we separated the two main clinical subgroups of patients with IBD: Crohn's disease (IBD-CD) and ulcerative colitis (IBD-UC).

Patients admitted to the same hospital will all be subject to similar hospital-level influences and will therefore have more similarity in their outcomes than similar patients admitted to another hospital. Also, some patients are admitted more than once. We used multilevel logistic and multilevel multiple regression¹⁹ to account for this 'clustering' within hospitals using the MLwiN program (version 2.10) and MCMC estimation procedures.²⁰

Results

During the six-year study period from 2002/03 to 2007/08, there were a total of 241,478 IBD admissions (Figure 1), of which there were 239,076 admissions of IBD alone and 2,402 admissions of IBD with *C. difficile* associated diarrhoea complications (IBD-CDAD). Of the latter, there were 2,185 admissions (91% of the total) where the *C. difficile* infection was likely to have been acquired from hospital (IBD-CDAD-HAI). A

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3 further 217 admissions (9% of the total) had *C. difficile* associated diarrhoea that was
4 likely to have been acquired from the community (they had either no prior admissions,
5 their prior admission was more than 90 days before the index admission or their
6 admission lasted less than three days) and were excluded from our cohort.
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12 The two groups consisted of 239,076 admissions with IBD alone and 2,185 admissions
13 with IBD and CDAD complication likely acquired from hospital (IBD-CDAD-HAI).
14 Descriptive characteristics of both groups are in Table 1. During the study period, the
15 numbers of IBD as well as IBD-CDAD-HAI both rose with increasing proportion of
16 IBD-CDAD-HAI compared with IBD alone. The IBD-CDAD-HAI group had a higher
17 proportion of older patients versus IBD alone but had similar in sex and deprivation
18 profiles. Patients in the IBD-CDAD-HAI were more likely to have one or more comorbid
19 condition compared with those who had IBD alone (adjusted OR 7.75 for the peak
20 Charlson co-morbidity score of 4). The proportion of IBD-CDAD-HAI versus IBD was
21 nearly 4 times higher for patients who were been admitted as emergency than for those
22 admitted electively.
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33 Main and secondary outcomes including in-hospital mortality (overall and within 30
34 days), mortality (within 30 days and one year), having bowel surgery, emergency
35 readmission within 28 days of discharge and length of stay for both groups are
36 summarized in Table 2. We found a higher proportion of all outcomes in the IBD-CDAD-
37 HAI group than the IBD alone group, particularly for mortality.
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44 The estimated relative risk of three main outcome measures (in-hospital mortality, having
45 GI surgery, having emergency readmission within 28 days of discharge from prior
46 admission) for the IBD-CDAD-HAI group compared with the baseline group of IBD
47 alone via multilevel modeling are listed in Table 3. A significantly higher risk of dying in
48 hospital was found for inpatients in the IBD-CDAD-HAI group compared with those
49 admitted to hospital for IBD alone (adjusted OR = 6.32, CI 5.67 to 7.04). Overall,
50 patients with IBD-CDAD-HAI were 1.87 times (CI 0.06 to 5.85) more likely than IBD
51 inpatients to have GI surgery but we found no significant difference of emergency
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3 readmissions rate within 28 days between the two groups. Patients in the IBD-CDAD-
4 HAI group had hospital length of stays that were 27.9 days longer than those with IBD
5 alone (CI 27.1 to 28.7 days). During the study period (in Figure 2), the IBD-CDAD-HAI
6 group had a 5 to 7 times higher risk of dying in hospital and a 1.2 to 3 times higher risk of
7 having GI surgery than the IBD group. In contrast, there was a mixed pattern for
8 emergency readmissions.
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16 Table 4 gives the unadjusted and case-mixed adjusted relative risks of dying, of having
17 GI surgery rates and length of stay for the IBD with and without hospital acquired *C.*
18 *difficile* infection groups, with IBD divided into UC and Crohn's disease. There was a
19 significantly higher risk of death in hospital and of having GI surgery for inpatients in the
20 IBD-CDAD-HAI-CD group than in the IBD-CD group. There was a longer hospital stay
21 by 27 days for both IBD-CDAD-HAI-CD and IBD-CDAD-HAI-UC groups than IBD-
22 CD and IBD-UC respectively.
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30 To examine if the higher surgery rates for IBD_CDAD_HAI patients was a consistent
31 pattern in sub groups of elective and emergency procedures, we compared patients
32 undergoing any GI surgery or colectomy for elective and emergency admissions between
33 patients with IBD and patients with IBD and *C.difficile* infection (Table 5). There was
34 approximately a 2 fold increase in all emergency GI surgery and colectomy rates in IBD
35 patients with *C.difficile*. In contrast elective surgery rates were substantially reduced in
36 this group.
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44 Discussion

47 Main findings

49 This national study using hospital admissions data obtained in England confirms a rising
50 trend in co-existent *C. difficile* infection amongst patient admitted to hospital with IBD
51 over the period 2002-2008 and amongst these co-infected patients there is an increased
52 in-hospital mortality and morbidity. IBD patients co-infected with *C. difficile* were
53 approximately six times more likely to die in hospital than patients admitted for IBD
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3 alone. IBD patients with co-existent *C. difficile* also had a substantially increased length
4 of stay with a median length of stay 26 days compared with 5 days for patient admitted
5 with IBD alone and were twice as likely to have GI surgery or undergo emergency
6 colectomy. Encouragingly time trends suggest a recent improvement in in-hospital
7 mortality and rates of surgery during this period.
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12 13 14 **Strengths and weaknesses**

15 To our knowledge this is the first nationwide study of *C. difficile* infection in IBD
16 patients in the UK and avoids the potential biases of previous single tertiary centre
17 studies.⁹⁻¹¹ Previous nationwide studies performed in North America may not necessarily
18 reflect the picture in the UK because health care provision and prescribing practice
19 differ.^{12, 21}
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26 Our study has a number of important limitations. HES data do not contain information on
27 disease severity, how *C. difficile* diagnosis was reached or antibiotic and
28 immunomodulator prescribing, all of which are potential confounders. Recently North
29 American workers in the field have attempted to develop a risk score for Crohn's
30 disease using an administrative database and this is worth further evaluation in the future
31 using the HES database.²²
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39 A recent systematic review highlighted the low positive predictive value of kits used to
40 detect *C. difficile* toxin potentially making epidemiological data sets like HES less
41 reliable since *C. difficile* infection is most frequently based on the detection of the toxin
42 by an ELISA kit. The study revealed these kits may give variable false positive and false
43 negative results thus the accuracy of diagnosis is called into question.²³ The diagnosis of
44 *C. difficile* infection is made in the presence of clinical symptoms and signs with
45 laboratory confirmation. In HES data, the A047 coded diagnosis of *C. difficile* infection
46 is entered by clinical coders in hospital who examine doctors' clinical discharge
47 summaries for clinical information about diagnosis, positive laboratory assay results and
48 culture. These summaries are not cross-referenced routinely with laboratory reports.
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3 However, in most hospitals the diagnosis is based on toxin identification variably backed
4 up by a cytotoxin assay.
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9 Although the quality of HES data can be challenged, it has been shown that the overall
10 percentage of admissions with missing or invalid data on age, sex, admission method, or
11 dates of admission or discharge was only 2.4% in 2003. For the remaining admissions,
12 47.9% in 1996 and 41.6% in 2003 had no secondary diagnosis recorded (41.9% and
13 37.1%, respectively, if day cases are excluded).²⁴
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19 The diagnosis fields within HES rely on the quality of coding locally in NHS hospitals
20 and can be subject to misclassification. HES is known to have previously under-record *C.*
21 *difficile* cases. The numbers of *C. difficile* cases from a selection of acute NHS trusts
22 which participated in the Health protection Agency's (HPA) mandatory surveillance for
23 the financial years 2004 and 2005 were compared between HPA and HES datasets.²⁵
24 HES was found to code only a third of HPA's laboratory records with a consistent level
25 of under-recording from 2004 to 2005. However, the numbers coded in HES have
26 increased slightly over time from 53.2% to 54.8% and 55.5% of the HPA's laboratory
27 total records for the years 2007, 2008 and 2009 respectively. More importantly, it has
28 also been found that between 15 and 30% the samples in HPA's dataset were repeat
29 records.²⁶
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41 The accuracy of coding for IBD and *C. difficile* in the HES database is unknown since all
42 identifiable data is removed to maintain patient anonymity and thus validation through
43 cross-referencing with patient notes and hospital pathology records is not normally
44 possible. Linking HES data with local records can exceptionally be achieved through
45 personal identifiers that are normally suppressed and require specific ethical approval that
46 is beyond the scope of this study. However, in a previous study Aylin et al. demonstrated
47 the potential of using HES administrative data by comparing with three national clinical
48 databases of colorectal excision for cancer, coronary artery bypass graft and abdominal
49 aortic aneurysm procedures.²⁷ The results suggested that the administrative data to predict
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3 risk of death are comparable with that obtained from clinical databases and the numbers
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5 of admissions coded in administrative data is higher than clinical databases.
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9 The advantages and disadvantages of administrative databases have recently been well
10 described.²⁸ In summary, databases like HES are well suited to the study of IBD
11 particularly in evaluating uncommon outcomes like surgery where singles centre studies
12 cannot provide sufficient numbers of patients for meaningful analysis. However since
13 these databases have not primarily been constructed for research purposes studies using
14 them need to be interpreted with a degree of caution.²⁹ We acknowledge, therefore, the
15 main limitation of this study is that case ascertainment using the HES administrative
16 dataset is not confirmed through medical records or laboratory data. Despite the fact that
17 HES may not capture all cases of *C. difficile* we would not anticipate a differential
18 misclassification in respect to other variables and hence it is unlikely to invalidate the
19 observed associations.³⁰
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30 Findings in relation to other studies

31 Co-morbid illness has previously been recognised as a significant risk factor for *C.*
32 *difficile* associated disease.³¹⁻³³ We found that older IBD patients (aged 45 and above),
33 those with a higher Charlson index indicating more co-morbid conditions, and those
34 admitted as emergencies rather than as elective inpatients were more likely to have *C.*
35 *difficile* infection. The increase in length of stay observed in this study was much greater
36 than reported from national datasets in North America.^{12,21} The difference in length of
37 stay may reflect differences in the health care system, methods of data collection, case
38 ascertainment or antibiotic prescribing. Recent reports suggest most cases of *C. difficile*
39 in IBD are acquired in the community, suggesting that the increase in length of stay can
40 reasonably be attributed to infection.^{9,10,13}
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51 The incidence of co-existent *C. difficile* in patients admitted to hospital with IBD
52 increased nearly twofold during the study period between 2002 and 2008, tallying with
53 trends in the US between 1998 and 2004.^{12,21} Some of this rise may be accounted for by
54 improvements in diagnosis and reporting protocols. It is also likely the emergence of the
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3 more virulent NAP1/027 strain of *C. difficile* has contributed the rise.³ However, in the
4 last two years of this study the increase in *C. difficile* incidence amongst IBD patients
5 appears to have flattened out with admission of these patients as a proportion of all IBD
6 admission steady at 11.3 per 1000 admissions between 2007 and 2008 and this contrast
7 with temporal trends in North America.²² The aOR for in-hospital mortality was 0.67 in
8 2007/8 compared with in-hospital mortality in 2002/3. This finding may reflect a growing
9 clinical awareness of the higher risk of *C. difficile* infection in IBD patients and
10 improvements in management once diagnosis is made.
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19 In-hospital mortality, requirement for surgery and length of stay are higher in both
20 patients with UC and Crohn's disease co-infected with *C. difficile*. Our sub analysis
21 indicates that all coded GI surgery and the sub-group of colectomy was increased two
22 fold in IBD patients with *C. difficile* during emergency admissions. In contrast, elective
23 surgery rates were reduced in the group. Our findings contrast with those of previous
24 studies from North America who reported reduced rates of surgery in this group.¹² We
25 speculate that *C. difficile* infection may complicate the medical management of
26 emergency admission, for example hastening the onset of toxic megacolon, and thereby
27 precipitate emergency surgery. This explanation is consistent with other studies, which
28 have shown that emergency surgery is the major cause of mortality in IBD and is
29 reflected in our findings indicating increased mortality amongst IBD patient with *C.*
30 *difficile*.³⁴⁻³⁶
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42 In contrast with previous researchers we found no differences in morbidity and in-
43 hospital mortality between sub-groups of IBD. Ananthakrishnan et al. previously reported
44 a small increase in mortality and surgery rates among UC patients and Nguyen et al.
45 described a disproportionate rise in *C. difficile* co-infection in UC compared with Crohn's
46 patients.^{12,21} It is not clear why our findings differ in this respect but may suggest
47 problems of sub-type misclassification in HES data collection.
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54 Despite its limitations our study provides important information quantifying the increased
55 risk of morbidity and in-hospital mortality amongst IBD patient infected with *C. difficile*.
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3 Secular trends suggest the tide may be turning in the UK with a plateau in the rise of
4 infection and a reduction of in-hospital mortality in this cohort and this may reflect
5 recently instituted infection control measures in the UK. On a local level we have found a
6 package of measures including rigorous cleaning protocols and reduction in the use of
7 empirical broad spectrum antibiotics has resulted in 70% reduction in *C. difficile*
8 infection in a London teaching hospital however, these findings may not be applicable to
9 the IBD cohort since *C. difficile* in IBD patients seems to be largely community
10 acquired.³⁷⁻³⁹
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19 Further work is needed to better define the reasons for increased *C. difficile* infection in
20 IBD patients and the reasons for increased susceptibility in this group. Recent evidence
21 published in this journal indicates that IBD patients treated with corticosteroids in
22 combination with an immunomodulator, such as azathioprine, may have an increased risk
23 of *C. difficile* infection.⁴⁰ Given the high in-hospital mortality and morbidity associated
24 with *C. difficile* infection, our findings reinforce the clinical importance of testing for *C.*
25 *difficile* amongst IBD in-patients and we further recommend screening of all in-patients
26 with diarrhoea for *C. difficile* infection become part of mandatory surveillance.
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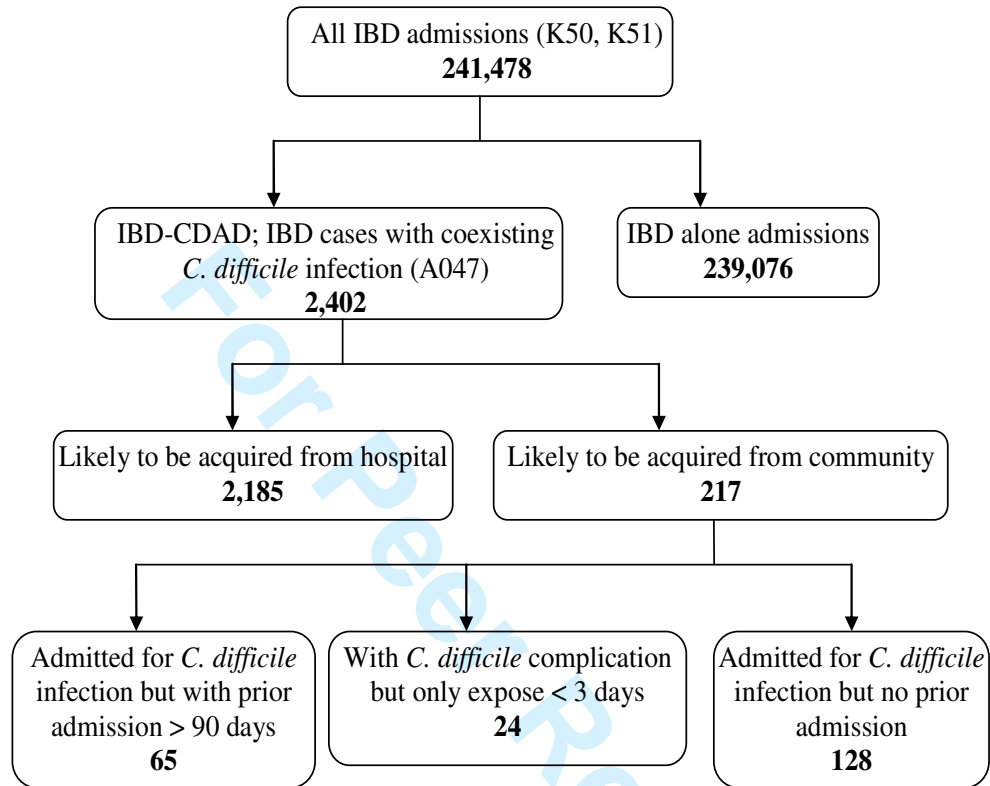
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Figure 1 Flow chart of case definitions and likely source of *C. difficile* infection in all IBD admissions in patients from 2002/03 to 2007/08



ICD 10 codes for Inflammatory Bowel Disease (K50, K51), and *Clostridium difficile* associated diarrhoea (CDAD) A047

Table 1 Demographics of admissions in patients with inflammatory bowel disease (IBD) alone, or with Clostridium difficile infection and IBD (IBD-CDAD-HAI)

Characteristics	IBD (n=239,076)	IBD-CDAD- HAI (n=2,185)	IBD-CDAD-HAI / (IBD+ IBD-CDAD- HAI), %
Years			
2002/03	32126	235	0.73
2003/04	35412	243	0.68
2004/05	38043	303	0.79
2005/06	40767	357	0.87
2006/07	45406	512	1.12
2007/08	47322	535	1.12
Age groups (years)			
18-19	5100	27	0.53
20-29	36347	124	0.34
30-39	42289	168	0.40
40-49	38342	153	0.40
50-59	35663	229	0.64
60-69	31994	324	1.00
70-79	29948	544	1.78
80-89	17079	540	3.06
90+	2314	76	3.18
Sex			
Male	106947	955	0.89
Female	132129	1230	0.92
Charlson comorbidity index			
0	177305	1254	0.70
1	37496	500	1.32
2	14647	211	1.42
3	5024	118	2.29
4	1552	45	2.82
5	2183	36	1.62
>=6	869	21	2.36
Method of admission:			
Emergency	171431	1980	1.14
Elective	67645	205	0.30
Deprivation quintile			
1 (least deprived)	40251	348	0.86
2	47698	441	0.92
3	51291	483	0.93
4	51331	455	0.88
5 (most deprived)	48273	456	0.94
6 (unknown: invalid postcode)	232	2	0.85

Table 2 The proportion of outcome measures including in-hospital mortality, mortality, bowel surgery, emergency readmission within 28 days and length of stay in IBD alone admissions in patients (IBD) compared with admissions in patients who had coexisting likely hospital acquired *C. difficile* infection (IBD-CDAD-HAI)

Outcomes	IBD (%) (n=239,076)	IBD-CDAD-HAI (%) (n=2,185)
In-hospital mortality¹	7313(3.1)	555(3.9)
In-hospital mortality within 30 days²	6028(2.5)	315(14.4)
Total mortality within 30 days (2002-2005)³	7005(2.9)	329(15.1)
Total mortality within 365 days (2002-2004)⁴	15913(6.7)	725(33.1)
Bowel surgery	28455(11.9)	269(12.3)
Median length of stay (Q1-Q3⁵) in days	5 (2-10)	26 (12-51)
Emergency readmission within 28 days⁶	31194(13.0)	304(13.9)

¹ Patients who died in hospital before discharged from hospital;

² Patients who died in hospital within 30 days after their admitted date and before discharged from hospital;

³ Patients who died within 30 days after admission to hospital; data only available from 2002 to 2005;

⁴ Patients who died within one year after admission to hospital; data only available from 2002 to 2004;

⁵ Q1: first quartile, Q3: third quartile;

⁶ Emergency admission within 28 days of discharge from previous admission

Table 3 Multilevel logistic regression analysis of in-hospital mortality, bowel surgery and emergency readmission within 28 days in IBD alone admissions in patients (IBD) compared with admissions in patients who had coexisting likely hospital acquired *C. difficile* infection (IBD-CDAD-HAI)

Predictors	In-hospital mortality: odds ratio (95% CI)	P value	Bowel surgery: odds ratio (95% CI)	P value	Emergency readmission <28days: odds ratio (95% CI)	P value
Unadjusted (IBD as base)	9.87 (8.98 - 10.84)	<0.001	1.02 (0.32 - 3.19)	0.29	1.07 (0.95 - 1.21)	0.27
Adjusted (IBD as base)	6.32 (5.67 - 7.04)	<0.001	1.87 (0.60 - 5.85)	<0.001	0.96 (0.85 - 1.09)	0.56
Factors adjusted for						
Years (2002/03 as base)	1.00	<0.001	1.00	<0.001	1.00	0.004
2003/04	0.93 (0.86 - 1.01)		0.97 (0.92 - 1.02)		1.01 (0.97 - 1.06)	
2004/05	0.89 (0.82 - 0.97)		0.91 (0.87 - 0.96)		1.07 (1.02 - 1.12)	
2005/06	0.78 (0.72 - 0.85)		0.85 (0.81 - 0.90)		1.13 (1.08 - 1.18)	
2006/07	0.77 (0.71 - 0.83)		0.84 (0.80 - 0.88)		1.11 (1.06 - 1.16)	
2007/08	0.67 (0.62 - 0.73)		0.83 (0.79 - 0.87)		1.11 (1.06 - 1.16)	
Sex (Male as base)	1.00	0.004	1.00	<0.001	1.00	<0.001
Female	1.07 (1.02 - 1.12)		0.83 (0.81 - 0.85)		0.90 (0.88 - 0.93)	
Deprivation quintile (1: least deprived as base)	1.00	0.03	1.00	0.004	1.00	0.006
2	1.09 (1.00 - 1.18)		0.99 (0.95 - 1.03)		1.04 (1.00 - 1.08)	
3	1.13 (1.04 - 1.22)		0.94 (0.90 - 0.98)		1.11 (1.06 - 1.15)	
4	1.22 (1.13 - 1.32)		0.93 (0.89 - 0.97)		1.15 (1.10 - 1.20)	
5 (most deprived)	1.09 (1.00 - 1.18)		0.90 (0.86 - 0.95)		1.24 (1.18 - 1.29)	
6 (unknown: invalid postcode)	1.07 (0.44 - 2.60)		0.91 (0.61 - 1.38)		0.56 (0.33 - 0.94)	
Method of admission (Emergency)	1.00	<0.001	1.00	<0.001	1.00	<0.001
Elective	0.19(0.17 - 0.20)		5.79 (5.63 - 5.96)		0.62 (0.60 - 0.64)	
Charlson comorbidity index (0 as base)	1.00	<0.001	1.00	0.001	1.00	0.001
1	2.18 (2.06 - 2.31)		0.68 (0.65 - 0.71)		1.19 (1.15 - 1.23)	
2	3.68 (3.44 - 3.94)		0.71 (0.67 - 0.76)		1.30 (1.23 - 1.36)	
3	6.15 (5.64 - 6.70)		0.50 (0.44 - 0.56)		1.42 (1.32 - 1.53)	
4	7.75 (6.79 - 8.84)		0.41 (0.32 - 0.53)		1.58 (1.39 - 1.80)	
5	9.14 (8.11 - 10.29)		1.15 (1.01 - 1.32)		1.55 (1.38 - 1.73)	
6+	14.22 (12.02 - 16.82)		0.87 (0.69 - 1.10)		1.10 (0.90 - 1.34)	
Age (18-44 as base)	1.00	<0.001	1.00	<0.001	1.00	<0.001
45+	12.45 (11.13 - 13.93)		0.67 (0.65 - 0.69)		0.95 (0.92 - 0.97)	

Figure 2 Time trends of odds ratio 2002/03 to 2007/08 of in-hospital mortality, bowel surgery and emergency readmissions within 28 days. Odds ratios are relative to IBD alone in 2002/3

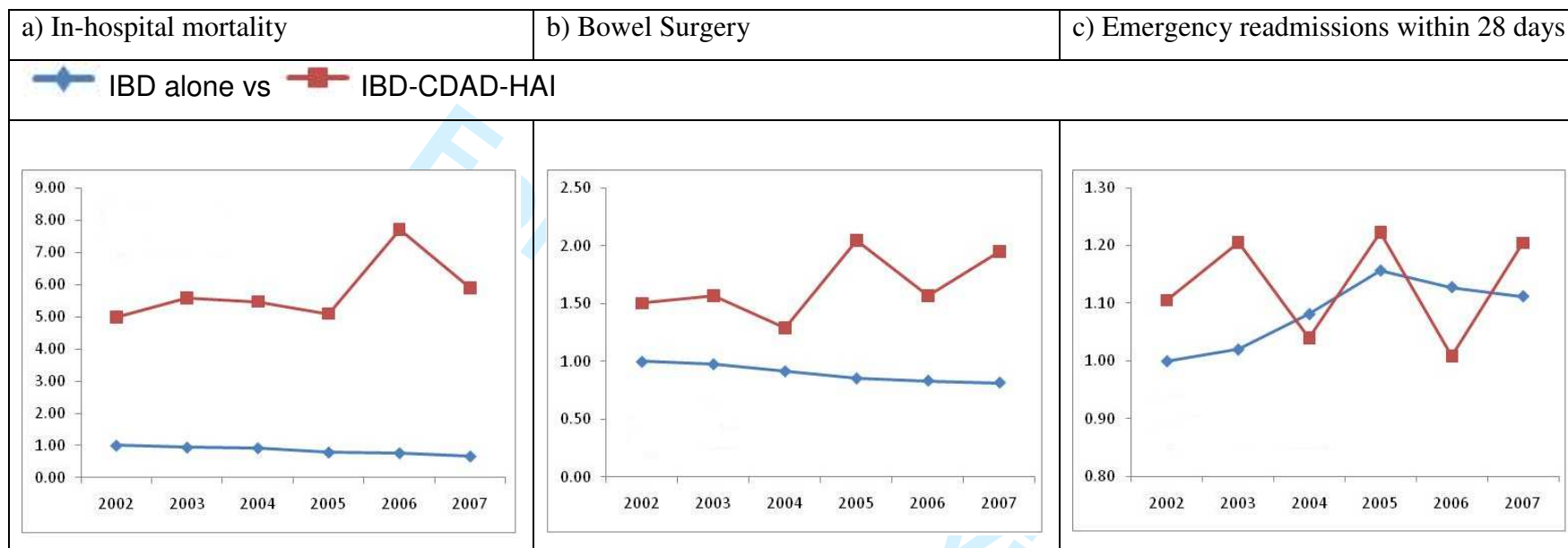


Table 4 Multilevel logistic regression analysis of in-hospital mortality, bowel surgery and length of stay in the IBD clinical subgroups of IBD-CD and IBD-UC admissions in patients compared with the admissions in patients with concomitant *C. difficile* infections

IBD subgroups	In-hospital mortality: odds ratio (95% CI)	<i>p</i> value	Bowel surgery: odds ratio (95% CI)	<i>p</i> value	Length of stay: days more than base group (95% CI)	<i>p</i> value
a) Crohn's disease (IBD-CD)						
Unadjusted (Crohn's disease alone as the base)	9.9 (8.6 – 11.4)	<0.001	1.3 (1.1 – 1.6)	0.008	29.2 (28.0 – 30.4)	0.057
Adjusted ⁷ (Crohn's disease alone as the base)	6.8 (5.7 – 8.0)	<0.001	1.6 (1.3 – 2.0)	<0.001	27.9 (26.7– 29.1)	<0.001
b) Ulcerative colitis (IBD-UC)						
Unadjusted (Ulcerative colitis alone as the base)	7.3 (6.6 – 8.2)	<0.001	0.9 (0.7 – 1.0)	<0.001	28.6 (27.6 – 29.7)	<0.001
Adjusted (Ulcerative colitis alone as the base)	5.5 (4.8– 6.2)	<0.001	1.7 (1.4 – 2.1)	<0.001	27.2 (26.1 – 28.2)	<0.001

⁷ Factors adjusted for are: year, sex, deprivation quintile, method of admission, Charlson comorbidity index and age.

Table 5 Comparison between admissions in patients with IBD alone and IBD with *C. difficile* infection undergoing GI surgery or colectomy for elective and emergency admission

Type of admissions	IBD alone (%)	IBD with <i>C. difficile</i> (%)
GI surgery		
all	22362	113
emergency	5130 (22.9)	49 (43.4)
elective	17232 (77.1)	64 (56.6)
Colectomy		
all	10902	67
emergency	3092 (28.4)	37 (55.2)
elective	7810 (71.6)	30 (44.8)

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