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SYSTEMATIC REVIEW: CLOSTRIDIUM DIFFICILE & INFLAMMATORY BOWEL DISEASE

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**SYSTEMATIC REVIEW: CLOSTRIDIUM DIFFICILE &
INFLAMMATORY BOWEL DISEASE**

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17 Prof JM Rhodes,
18 APT

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21 23/11/2010

22
23 **Re: 'SYSTEMATIC REVIEW: CLOSTRIDIUM DIFFICILE IN INFLAMMATORY BOWEL DISEASE'**

24
25 Dear Jon,

26
27 Please find enclosed our revised manuscript and responses to the reviewer's comments. For
28 convenience and ease of reading we include here the reviewer's comments first (and in bold text)
29 and then our point by point response (in regular text).
30
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EDITOR'S COMMENTS TO AUTHOR:

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33 **Please address the comments of reviewer 2.**

34 See below.
35

REVIEWERS' COMMENTS TO AUTHOR:**Reviewer: 2****Comments for Transmission to the Authors**

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38 **The work is interesting but in many parts the text is confusing and should be rewritten and
39 references and numbers should be checked. The alignment of the tables has to be revised.**

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41
42 **Page 4 line 41: 'Recent epidemiological data report more cases of CDI in IBD than controls
43 and a worse outcome in patients with IBD' need to quote the reference**

44 We have referenced the latest 3 review articles on this subject.
45

46
47 **Page 6 line 18: should specify that "At the end, 42 records were included in qualitative
48 synthesis".**

49 We have amended this to "overall 42 records were included in the qualitative synthesis".
50

Page 8:

51
52 **1. line 14: It might be better to refer to diarrhoeal relapse or remission**

53 We have changed this text as requested.
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55
56 **2. line 17: The text is confusing. The number of studies reporting the incidence of CDI in
57 IBD is 36 but one study was excluded therefore 35 studies were evaluated and of this 35
58 studies the 40% only (14/35) included patients exclusively in relapse? In this order the**
59
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text is clearer.

The number of studies that report the incidence of CDI in IBD is 35 (33 of which are summarised in tables 1-3 (14 in relapse - table 1; 15 with mixed disease activity in table 2 and the 4 using the US database studies in table 3). We have inserted these references into the introductory section P8 L7-12, in order to make this clearer.

The Clayton et al study is not included in the tables (but is now referenced too), because it is the only study including patients exclusively in remission. Sonnenberg's analysis of US insurance databases is also excluded from table 3 as it is not possible to deduce overall incidence rates from the original paper.

Having read and re-read ours and the reviewer's versions of this sentence we would prefer to retain our own. The other 2 reviewers did not seem to find our version difficult to understand.

3. line 25: no significant differences in the weighted mean [weighted 95% CI] incidence of CDI in adult patients with UC or Crohn's disease by either culture (UC 6.7% [5.6-11.4], Crohn's disease 8.8% [2.5-15.1]) or toxin assay (UC 3.1% [0.1-6.2], Crohn's disease 7.0%(1.8-12.2) please quote the p value. A comment should be made on the fact that these studies has not the adequate power to detect a difference between CDI incidence in UC and CD.

We do not think that p-values would be helpful since the overlapping confidence limits in each case indicate that they are not different.

We have not changed our comments about sample size and hence power, as it is already stated on L39-41. We have changed the emphasis from "conceivable" to "possible".

Page 9:

1. It might be better to refer to disease activity instead to relapse or remission

Done

2. The text is confusing. Fifteen studies do not mention about the disease activity; among these studies , 4 are pediatric studies, 11 are studies in adults. One out of 11 studies in adults was excluded therefore 10 studies were analyzed. In this order the text is clearer.

Having read and re-read ours and the reviewer's versions of this sentence we would prefer to retain our own. The other 2 reviewers did not seem to find our version difficult to understand.

The 15 studies included did not specify diarrhoeal relapse or remission as specific inclusion criteria and hence were not stratified for disease activity. Of these 3 were conducted in children, and 11 in adults. 1 of the adult studies reported the denominator using the number of stools tested and not the number of patients included and so was excluded from the quantitative analysis (but was included in the tables for completeness).

3. ?Only 4/10 19, 28, 34, 35 of the studies that reported the relationship between CDI and disease activity found a positive association? It is not clear if all the 14 studies reported the relationship between CDI and disease activity. If so, this should be explained in the text at the beginning of the section (b).

Having read and re-read ours and the reviewer's versions of this sentence we would prefer to retain our own. The other 2 reviewers did not seem to find our version difficult to

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3 understand.

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6 **4. line 40: It is not clear why the US nationwide diagnostic coding-based case-controlled studies are reported at the end of section (b) . It is confusing.**

7 We have clarified why we chose to deal with these studies separately in the introductory
8 paragraph to section 3 of the results P8 L7-12 as well as in the methods as already stated.
9 Reviewer 3 appears to endorse the arrangement of the text.
10
11

12 **Page 10:**

13 **1. line 1: the lack of CD NAP1/027 strain in those identified in this selected population of IBD pts in clinical remission should be discussed**

14 We don't feel that this negative point needs discussion. It is probable that patients with IBD
15 will have acquired this strain but because of the limited ribotyping testing in IBD it simply
16 has not yet been reported. We have removed reference to this strain from this sentence.
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21 **2. line 10: immunosuppressive therapy should not be reported in the comment of section (c) because the study reported excluded patients on immunosuppressive therapy.**

22 We agree with this point and have removed the reference to immunosuppressive therapy.
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26 **3. line 27: Among the reasons explaining the differences in reported rates of CDI in IBD patients between the large-scale epidemiological studies and the single centre studies, should be stressed that CDI under reporting could be explained in administrative database studies by reimbursement reasons and that the results form single centre studies are very heterogeneous and often based on very small populations.**

27 We don't understand the reviewer's first point here. Reimbursement biases would tend to
28 lead to over-diagnosis (and as in our discussion of 'diagnostic creep' to explain why
29 incidence rates may be increasing) as opposed to under-reporting. We accept the point
30 regarding sample size and heterogeneity of the small studies and have added this to the
31 section dealing with publication bias.
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38 **Page 11:**

39 **1. ?However, the average age of CDI in IBD cohorts is much lower than in the general population controls, suggesting that patients with IBD have different risk profiles (Table 3)? Please check. In table 3 the age is reported only in 2 studies and within these studies, not for all populations of patients. In one study the average age of the mixed population was 47, in the other study in the CDI population with no IBD the average age was 73.**

40 We have checked this and made no changes.
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47 **Page 12:**

48 **1. ?Based on those studies adequately powered to detect a difference 33, 39-41, 43 and accepting their limitations as outlined above (Sections 3d and 4), patients with UC seem to be more at risk than patients with small bowel if not colonic Crohn's disease 41?**

49 **Administrative Database studies do not report the disease localisation if in the ileum or colon. Only the large cohort study by Issa33 report that CDI was detected in 42 colonic disease out of 46 total CDI.**

50 This was a composite summary sentence. We have now moved the references round in the
51 sentence so that the studies tally better with what is stated.
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58 **2. line 11: it should be specified that only a single study among those adequately powered reported disease extension.**

59 Done.
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3. line 18-19 check the quote. Reference 52 seems to be about antibiotics.

We have re-checked ref 52 (now reference 55, Dial et al 2008) and it discusses not only antibiotics but also PPIs.

4. line 34: cannot find reference 60 in the text e within the studies in the tables.

Page 13

The Sonnenberg analysis of the US database [Ref 60, now Ref 63] is dealt with on page 10 L54-59; it is not in the tables for reasons given above.

Page 13

1. line 50 comments: this is the personal opinion of the authors. I would suggest that antibiotics could be associate to iv corticosteroids, while awaiting the culture results , in patients with high risk of CDI infection.

We have added this.

Page 14:

1. line 22, colectomy rate and length of stay: the text is not clear and difficult to read and to understand , particularly the last sentence of the section. Missing the reference at line 34.

We chose to incorporate the length of stay and colectomy data in one paragraph to avoid repeating the comments to account for the differences, on the grounds of brevity and ease of reading.

We have added the Jodorkovsky reference.

Page 15:

1. line 6: 4.3% mortality?

We have changed the 5% to about 4% as suggested (the mean of all the mortality rates reported is 4.2%).

2. line 10: ? In contrast, taking all the deaths in each of the included cohort studies, only 0.6% (3/797) patients died 45, 48, a rate similar to the background mortality rate for IBD reported in the database studies?

Cannot understand from where these figures are from. Reference 45 and 48 refers to studies that are not included in Table 1-2. These should be clearly explained.

We have clarified this as suggested.

3. line 23-24: Why cases with IBD as secondary diagnosis were removed? The first diagnosis was CDI or other? Comorbidities? This should be clearly explained.

We have clarified this point as requested.

4. The higher rates of CDI infection in IBD patients than in control population reported in the administrative database studies should be stated at the beginning of the conclusions before the comments on the increasing incidence.

We have changed this text as requested.

Authors should revise the alignment of the Tables.

We will ensure that all the tables are aligned accorded to the house style during editing and typesetting.

In Table 2 are reported all the 15 studies, including the study excluded from analysis ,
instead in Table 1 are reported only the studies included in the analysis.

All studies that reported the incidence (using a population based denominator) are included
in each table. We chose to leave all the studies in each table to highlight the differences in
ways in which studies were reported. Reviewer 3 appears to condone this approach.

Reviewer: 3

Comments for Transmission to the Authors

I commend the authors for this excellent review which is presented in a structured, easy to
understand manner. The results have been presented very well in a coherent fashion. In
particular, care has been taken to avoid pooling of heterogeneous studies. I have no
additional comments or suggestions.

We hope that the changes we have made to the manuscript are acceptable.

Best wishes,

Yours sincerely,



David Rampton

Prof of Clinical Gastroenterology

d.rampton@gmul.ac.uk

Systematic Review: *Clostridium Difficile* & IBD

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4 **Title:** SYSTEMATIC REVIEW: CLOSTRIDIUM DIFFICILE & INFLAMMATORY BOWEL DISEASE
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7
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25 **Short title:** Systematic Review: Clostridium Difficile & IBD
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ABSTRACT

Background: There is increasing concern about the apparently rising incidence and worsening outcome of *Clostridium difficile* infection (CDI) associated with inflammatory bowel disease (IBD). We have systematically reviewed the literature to evaluate the incidence, risk factors, endoscopic features, treatment and outcome of CDI complicating IBD.

Methods: Structured searches of Pubmed up to September 2010 for original, cross-sectional, cohort and case-controlled studies were undertaken.

Results: Of 407 studies, 42 met the inclusion criteria: their heterogeneity precluded formal meta-analysis. CDI is commoner in active IBD, particularly ulcerative colitis, than in controls. Certainty about a temporal trend to its increasing incidence in IBD is compromised by possible detection bias and miscoding. Risk factors include immunosuppressants and antibiotics, the latter less commonly than in controls. Endoscopy rarely shows pseudomembranes and is unhelpful for diagnosing CDI in IBD. There are no controlled therapeutic trials of CDI in IBD. In large studies, outcome of CDI in hospitalised IBD patients appears worse than in controls.

Conclusions: The complication of IBD by CDI has received increasing attention in the past decade, but whether its incidence is really increasing or its outcome worsening remains unproven. Therapeutic trials of CDI in IBD are lacking and urgently needed.

BACKGROUND

Clostridium difficile is a gram positive spore-forming bacterium whose effects range from asymptomatic carriage through mild diarrhoeal disease to fulminant colitis. Although pseudomembranous colitis was first described in 1893, the microbiological characterisation of *C. difficile* did not occur until 1935^{1, 2}. Despite this, the causal association between the two was established only in the 1970s, when Tedesco *et al* reported *C.difficile*-induced diarrhoea in 21% patients given clindamycin, half of whom had pseudomembranes at endoscopy³. Since then nearly all broad spectrum antibiotics have been implicated in the acquisition of *C. difficile* infection (CDI), which is now the most common nosocomial infection in the UK⁴.

The changing face of *C. difficile* infection

Historically, *C. difficile* was considered an infrequent nuisance complicating necessary antibiotic usage in mostly elderly hospitalised patients. Even allowing for the change to mandatory case reporting in 2004, it seems remarkable now that in the UK in 1990 there were apparently only 1172 cases of CDI nationwide: in 2008 there were over 50,000⁵. In recent years, as well as a rising incidence, there has been a skew in the spectrum of illness towards a more severe disease course with more fatalities, in part explained by the emergence of the hypervirulent NAP1/027 strain exemplified by the outbreak in Quebec in 2002⁶ and now reported across North America and Northern Europe⁷.

C. difficile and inflammatory bowel disease

The characteristics of diarrhoeal relapse in IBD are often indistinguishable from those of enteric infections, including *C. difficile*. The marked differences in therapeutic approach, that is, specific antibiotic therapy versus escalation of immunosuppression to treat CDI and active IBD relapse respectively, emphasise the importance of promptly identifying superimposed infection. Recent epidemiological data report more cases of CDI in IBD than controls and a worse outcome in patients with IBD⁸⁻¹⁰.

We have now sought to review systematically the literature, using PRISMA guidelines¹¹, in order to evaluate not only temporal trends in incidence and associated mortality rates, but also disease-specific risk factors, diagnosis and treatment of *C. difficile* infection in patients with established IBD.

METHODS

1. Search criteria

Structured searches of Pubmed were conducted using the medical subject heading terms (MeSH) "inflammatory bowel disease" and "clostridium difficile"; the search was repeated using "Crohn's disease" and "ulcerative colitis" in place of "inflammatory bowel disease". This search was last performed on 13th September 2010. Eligible studies as well as relevant review articles were hand searched to identify any

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4 additional studies omitted by the database searches. Non-English language articles were included and
5 translated when required.
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8 **2. Eligibility criteria**

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10 Published studies of incidence of CDI, its association with relapse of IBD, temporal trends, disease-specific risk
11 factors, diagnosis and endoscopic features, treatments and outcomes, including recurrence of CDI in IBD were
12 eligible. Titles and abstracts were screened for their relevance, and all eligible articles were assessed in full.
13 Adult and paediatric cross-sectional, case-control and cohort studies, but not case reports or reviews were
14 included. *In vitro* and animal studies were excluded. We have not attempted to review studies focussing on the
15 pathogenesis of CDI in IBD. JRG and WA independently reviewed all identified citations to determine eligibility
16 for inclusion. Discrepancies were resolved by consensus of the study team.
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22 **3. Data Abstraction**

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24 Using a standardized abstraction tool, the following data points were collected for each included study:
25 location and design, sampling time frame, number of patients included with ulcerative colitis (UC) or Crohn's
26 disease, age, method of diagnosis, incidence of CDI by conventional culture and the presence of its toxins, risk
27 factors for acquisition, treatment and outcome (length of stay, colectomy, recurrence, mortality rates).
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32 **4. Case ascertainment**

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34 **Case definition:** Most authors now agree that laboratory tests should be limited to diarrhoeal stool samples,
35 defining a case of CDI by a positive toxin assay from a stool that takes the form of its container¹².
36 Unfortunately, no universal definition of a case of CDI associated with IBD has been adopted by researchers
37 publishing on this topic. Therefore, we have grouped the studies according to whether the populations
38 reported included patients exclusively in diarrhoeal relapse (true CDI) (Table 1), patients with quiescent as well
39 as active IBD (Table 2) or quiescent disease only. In order to avoid bias by including duplicate positive samples
40 from a single individual, wherever possible we have presented the number of patients infected and not the
41 number of positive stool samples tested: studies that reported only proportions of positive stool samples were
42 excluded from the summative analyses.
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50 **Diagnostic testing:** Stool culture that allows antibiotic sensitivity testing and strain typing is widely available
51 and, until recent advances in polymerase chain reaction (PCR), has been considered the most sensitive method
52 of *C. difficile* detection. Importantly in view of the above definition of CDI, it cannot detect toxin production.
53 Cell cytotoxicity assays are both sensitive and specific but are labour intensive, expensive and require 2 days to
54 complete: despite being able to detect toxin at much lower levels, they have been largely superseded by
55 immunological assays. We have reported separately the proportions of patients with culture and toxin-positive
56 infections, outlining the method of diagnosis used in each instance. For patients with toxin-positive infections,
57 we have reported, where available, the proportions with colonic disease, exposure to preceding antibiotics,
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Systematic Review: *Clostridium Difficile* & IBD

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5 and with suspected or proven nosocomial acquisition. We have considered separately more recent studies that
6 have relied on diagnostic coding to identify CDI cases from nationwide insurance databases (Table 3).
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Quantitative analysis

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11 The marked heterogeneity in study designs and definitions of CDI used, as well as diagnostic techniques
12 employed, limited the overall quantitative summaries to mean (95% confidence intervals [CI]) proportions
13 weighted according to the sample size ¹³; more complex analysis of the data was considered futile.
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For Peer Review

RESULTS STUDIES

In the interests of brevity and convenience for the reader, we have followed each of the main results sections (3-8 below) with relevant comments, rather than combining them in the Discussion.

1. Search results

A total of 407 studies were returned using the Pubmed search criteria described above; an additional 2 studies were identified by searching the other papers' reference lists (Figure 1). 195 studies were excluded on the basis of the title and abstract as shown in Figure 1. 54¹⁴⁻⁶⁷ studies were assessed in full for eligibility, of which 12^{54-57, 59-62, 64-67} were excluded for the reasons shown in Figure 1: **overall 42 records were included in the qualitative synthesis.**

2. Overview of included studies

The majority of the studies included were single-centred (81% [34/42]), and conducted in North America (48% [20/42]) or Europe (45% [19/42]). Patients were recruited to these studies between 1979 and 2008. Overall, 55% [23/42] were prospective cohort studies. The remainder were retrospective observational studies.

The primary aim in 86% [36/42] studies was to report the incidence of CDI in IBD. The remainder were designed to define risk factors for acquisition and/or to report outcomes following infection.

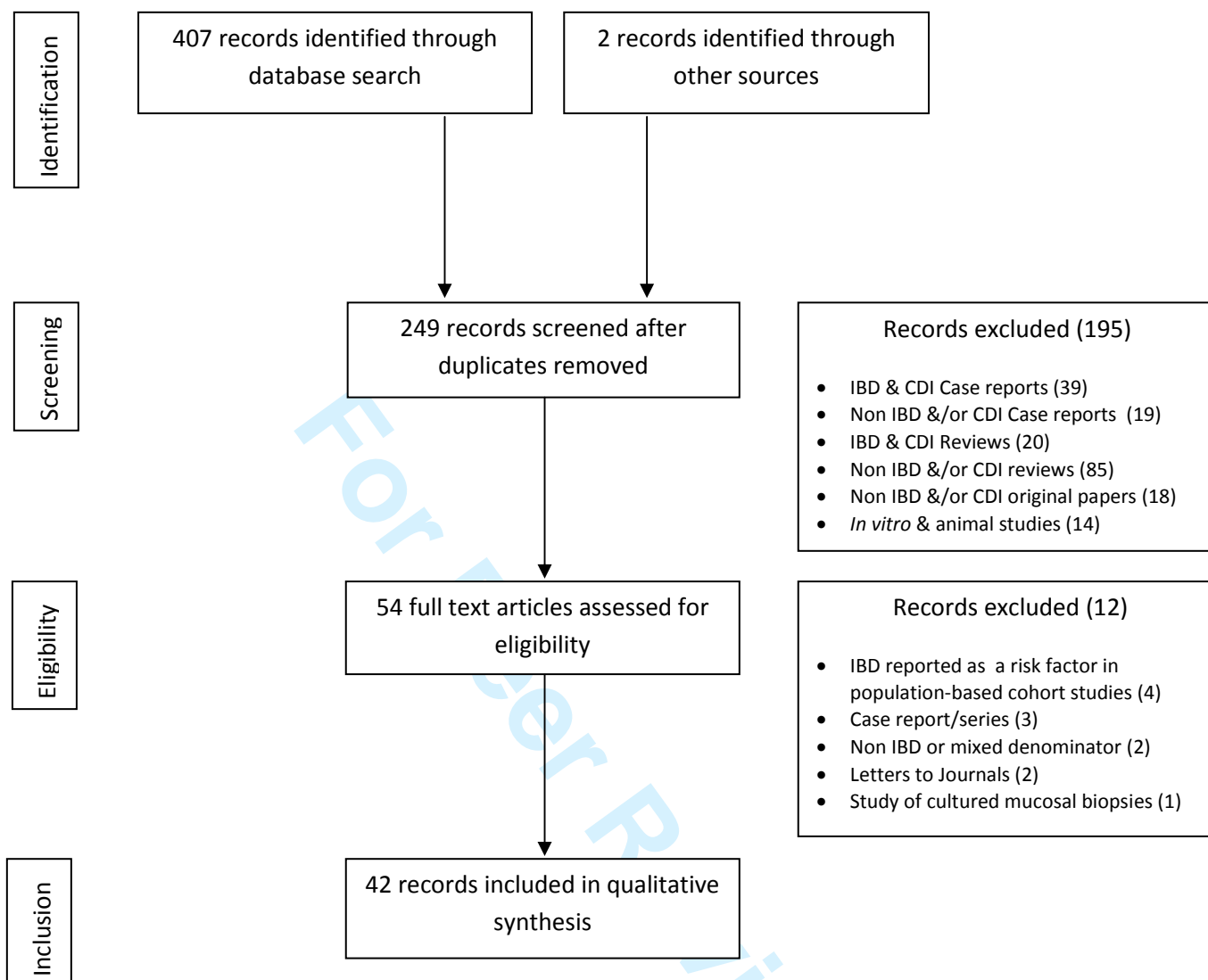
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Figure 1: PRISMA¹¹ flow diagram describing the identification, screening, eligibility and inclusion of studies.

3. Incidence of CDI in IBD

The studies analysed in sections a-c below reported the incidence of CDI, measured by culture and/or toxin assay, in cohorts of patients with IBD which was active^{14-16, 19-21, 23-26, 28-30, 32} (Table 1), of mixed activity^{17, 18, 22, 27, 31, 33-41, 45, 68} (Table 2) or quiescent⁵⁰. In section d the results of United States (US) nationwide diagnostic coding-based case-controlled studies (Table 3), **that did not require laboratory based confirmation of CDI are described**^{42, 43, 46, 63, 69}.

a. Studies of patients in diarrhoeal relapse

Of the 35 studies reporting the incidence of CDI in IBD (Tables 1-3), only 40% [14/35] included patients exclusively in relapse and therefore satisfied the criteria for CDI. They included 640 patients with UC, 480 with Crohn's disease, and 40 with colitis of uncertain type or aetiology (CUTE) (Table 1). The median [range] number of IBD patients in each study was 60 [18-284]. One study was excluded from the following analysis because the authors reported the incidence of CDI using the number of positive stool samples tested²⁸. There were no significant differences in the weighted mean [weighted 95% CI] incidence of CDI in adult patients with UC or Crohn's disease by either culture (UC 6.7% [5.6-11.4], Crohn's disease 8.8% [2.5-15.1]) or toxin assay (UC 3.1% [0.1-6.2], Crohn's disease 7.0% [1.8-12.2]).

Two studies^{19, 25} reported incidence rates of CDI in IBD in children. The weighted mean incidence of CDI in IBD by toxin was higher than in adult patients 26.1% [16.1-36.1]. Only one of these studies reported the incidence in UC and Crohn's disease separately, so no further comparative analysis was made.

Comments: The observation that CDI seems to be as common in active UC as in active Crohn's is surprising given *C. difficile's* predilection for the colon⁷⁰, and the fact that about half of adults with Crohn's have terminal ileal disease with little or no colonic involvement⁷¹. It is **possible** that because of the relatively small sample sizes of each study, differences in the incidence rates between UC and Crohn's may have been missed. It is also possible that the apparent incidence of CDI in Crohn's disease was boosted by the preferential testing for CDI of patients with Crohn's colitis by clinicians believing the infection to be unlikely in patients with small bowel disease. Further elucidation of this explanation is impossible because too few studies reported Crohn's disease phenotypes.

The significantly higher rates of CDI complicating IBD in paediatric studies compared with those in adults could be due to several factors. Firstly, faeco-oral ingestion of spores may be more common in children^{45, 58} than in adults. Secondly, and in relation to IBD, children are more likely than adults to have colonic Crohn's disease and to have extensive UC⁷²⁻⁷⁴: not only the site of the underlying disease but also the immunosuppression and antibiotics used to treat it may be a risk factor for acquisition (see section 5 below).

b. Studies of patients with mixed disease activity.

Systematic Review: *Clostridium Difficile* & IBD

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Fifteen further studies, three of which were retrospective, reported the incidence of CDI in patients who were not stratified for disease activity (Table 2). They included 1810 patients with UC and 3311 with Crohn's disease as well as a group of 28 patients with undefined IBD. The median [range] number of IBD patients in each study was 54 [10-3397]. Based on sample size, two outlying studies were identified, Issa *et al*³⁶ (n=999) and Rodemann *et al*³⁹ (n=3397). 1¹⁸/11 studies in adults reported the proportions of positive stool samples tested and were excluded from the following analysis. There were no significant differences in the weighted mean incidence of CDI in adult patients with UC or Crohn's disease of mixed activity by either culture (UC 4.1% [-1.4-9.6], Crohn's disease 10.1% [3.3-16.9]) or toxin assay (UC 5.7% [2.9-8.5], Crohn's disease 2.4% [0.5-4.3]).

The weighted mean incidence in three studies that included only children with IBD of mixed disease activity reported the incidence of CDI by toxin assay in UC at 36.5% [-0.8-73.6] and in Crohn's at 31.9% [1.1-62.8], again suggesting a trend towards higher incidence in children than in adults.

Only 4/10^{19, 28, 34, 35} studies that reported the relationship between cdi and disease activity found a positive association.

Comments: As with the studies of patients in relapse there was no significance difference in the incidence of CDI in UC and Crohn's in the studies of patients with mixed disease activity: the reasons for this are likely to be similar to those above (see comments 3a). The larger cohort studies by Issa³⁶ and Rodemann³⁹ contained enough cases of CDI to allow identification of risk factors including disease type. They reported that the incidence of CDI in UC (6% and 4% respectively) was approximately double that in Crohn's disease (4% and 2% respectively). However, care has to be taken when interpreting these studies: both were retrospective and may have been subject to bias because of under-testing for *C. difficile* and missing data.

Because patients with both active and inactive disease were included, it is unclear from the studies shown in Table 3 whether or not there is an association between CDI and IBD activity. Indeed, this heterogeneous group of studies may have been under-powered to detect one. Alternatively, in the absence of criteria specifying diarrhoea at inclusion, the lack of association between CDI and IBD activity may be explained by *C. difficile* being a frequent commensal in IBD, a conclusion supported by a study of *C. difficile* colonisation in patients with inactive IBD⁵⁰ (see Section c below).

c. Studies of patients in remission

One prospective study has compared the colonization rate of adults with quiescent IBD with that of healthy controls⁵⁰ using polymerase chain reaction (PCR) and pulsed field gel electrophoresis to detect and type *C. difficile*. To eliminate confounding influences and study the effect of IBD alone, patients hospitalised and/or treated with antibiotics or immunosuppressants within 6 months of recruitment were excluded. Adults with IBD were more frequently colonised with toxigenic strains of *C. difficile* than healthy controls (UC 9% [6/64], Crohn's 7% [4/58], controls 1% [1/99]). The marked heterogeneity of strains identified and the strict inclusion

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criteria of this study, indicates acquisition in the community rather than from a limited number of healthcare sources⁵⁰.

Comments: The reason why patients with IBD are more frequently colonised than controls has not yet been elucidated.

d. Association of *C. difficile* with IBD in studies using diagnostic coding

Utilising data from the US Healthcare Cost and Utilisation Project (HCUP) Nationwide Inpatient Sample (NIS), 4 studies using International Classification of Disease (ICD) diagnostic coding to identify cases have employed a retrospective nested case-controlled design to compare CDI rates and outcomes in hospitalised IBD patients and controls (Table 3). In these studies, the co-incident hospitalisation rate of CDI and UC is about 3%, and of CDI and Crohn's disease 1%, both higher than in the control population (0.5%), but lower than in most of the single centre studies described above (Tables 1 and 2).

Comments: The differences in reported rates of CDI in IBD patients between these large-scale epidemiological studies of hospitalised patients and the single centre studies outlined in Tables 1 & 2 may have several explanations. Firstly, the large database studies because of their retrospective design may have underestimated the incidence of *C. difficile* as a result of miscoding, missed diagnoses and under-testing for the organism. The accuracy of ICD coding for CDI has been assessed and although it is 99% specific when compared to microbiological data, its sensitivity was only 82%⁷⁵. Secondly, these studies may conceivably have overestimated the denominator (IBD) in these calculations as the cause of the relevant hospital admission: this could be a consequence of the coding phenomenon labelled diagnostic creep⁷⁶. Thirdly, the studies shown in Tables 1 and 2 included a mix of in- and out-patients, and it is possible that these two patient groups have different CDI rates. Fourthly, including only patients who are insured will tend to exclude patients of lower socio-economic status, a factor which although unproven might lead to underestimation of CDI rates. Finally, publication bias in the **heterogeneous and mostly small cohort studies** may account for a relatively higher rate in incidence reported by the single centre studies, since small cohort studies showing low CDI rates may not have been accepted or even submitted for publication; in contrast, studies reporting higher incidence rates, for example following a significant single centre outbreak, are more likely to have been considered favourably by journal editors. Differences in study design may also explain why the database studies, unlike those listed in Tables 1 and 2, have shown a higher rate of CDI in UC than in Crohn's disease.

Sonnenberg's analysis of data from the HCUP NIS database⁶³ suggests a north-south divide in the USA, with states in the north-east having a higher prevalence of CDI and associated mortality than those in the south. It is not clear whether there is an environmental risk factor predisposing IBD patients to CDI in the north, or if *C. difficile* is shaping the geographic patterns of IBD admission.

4. Temporal changes in the incidence of CDI in IBD

In view of recent data from the general population showing that the incidence of *C. difficile* is increasing over time^{5,77}, we examined the literature for temporal changes of the incidence of CDI complicating IBD.

There was no temporal trend over the years 1980-2010 in the published incidence rates for CDI in the fourteen studies (Table 1) that reported it in patients in relapse of either UC or Crohn's disease. In contrast, the data from the two large studies of Issa *et al*³⁶ and Rodemann *et al*³⁹ that confirmed toxin-positive disease, and from those relying on diagnostic coding (Table 3), all suggest a steady increase in incidence in the last 10 years, particularly in UC and colonic Crohn's disease.

Comments: Why is there an apparent steady increase in the incidence of CDI complicating IBD in the very large studies but not in the smaller ones? It is difficult to determine from the former the extent to which the observed trend is due to increased clinical awareness of and therefore testing for CDI in patients presenting with active IBD, or to diagnostic creep⁷⁶. Conversely, given the different populations studied and diagnostic methods used, it is not possible to amalgamate data from all the studies to evaluate temporal trends in CDI incidence.

5. Risk factors for acquisition of *C. difficile* in IBD

One of the major advantages of the database (Table 3) and other large studies^{36, 39} is that their large sample sizes allows identification of risk factors associated with, if not causal for, acquisition and associated mortality of CDI in IBD. Against the usefulness of the database studies in this respect is that only a limited number of potential risk factors are entered onto the HCUP database: perhaps most importantly it is not possible to determine IBD activity from these studies.

a. Age & co-morbidity

Nguyen *et al*⁴³ reported in adults that, like in the general population, increasing age and co-morbidity increase the risk of acquisition of CDI in IBD. However, the average age of CDI in IBD cohorts is much lower than in the general population controls, suggesting that patients with IBD have different risk profiles (Table 3).

b. Community versus nosocomial infection

C. difficile is the most common nosocomial infection in the UK. However, community-acquisition is recognised in the general population and is estimated at running between 10.7%⁷⁸ and 20.3%⁷⁹. Patterns of acquisition in IBD appear to differ from those of the general population. In keeping with the data from Clayton *et al*⁵⁰ suggesting multiple community sources rather than acquisition of *C difficile* by patients with IBD from a limited number of healthcare sources, nosocomial acquisition, where reported, was suspected in only 26% (5/19) of patients with relapse (Table 1) and in 12% (13/109) of those with mixed disease activity (Table 2).

c. IBD Phenotype

Based on those studies adequately powered to detect a difference and accepting their limitations as outlined above (Sections 3d and 4), patients with UC seem to be more at risk^{36, 42-44, 46} than patients with small bowel if not colonic Crohn's disease⁴⁴. Furthermore, in UC, patients with more extensive disease appeared to be at greater risk than those with distal disease alone, **in the one adequately-powered study that has reported it³⁶**.

d. Drug Usage

The main pharmacological risk factor for CDI in the general population is use of broad spectrum antibiotics⁸⁰. Patients taking immunosuppressants and proton pump inhibitors (PPIs) are also frequently affected^{54, 55}.

Antibiotic use in IBD, however, is less of a prerequisite for CDI than in the non-IBD population. Where reported, and taken together (Table 1), only 43% (23/54) toxin-positive relapse samples were associated with antibiotic use (up to 3 months before inclusion). Similarly, for those patients with mixed IBD activity (Table 2), only 52% (51/98) toxin-positive samples were associated with preceding antibiotic use.

Single centre cohort studies have infrequently reported immunosuppression as a risk factor, perhaps because most were conducted before the widespread use of immunosuppressants, and were therefore underpowered to detect small effect sizes. Issa *et al* reported that immunosuppression, defined as any of thiopurines, methotrexate and/or steroids, doubles the risk of CDI (OR 2.58 95%CI 1.28 - 5.12) in patients with IBD³⁶. The database studies^{42-44, 46, 63} do not include pharmacological data and so were unable to report on drug risk factors. Schneeweiss *et al*, by combining insurance healthcare records and a pharmacological database from admissions in British Columbia, found no association with infliximab or immunomodulator use and admission of IBD patients with *C. difficile* infection: corticosteroids, however, increased the risk three fold (OR 3.3 95%CI 1.53 - 4.57)⁵².

PPI use has been reported in only 2 studies in IBD^{38, 48} and the numbers of patients taking them were too small to detect significant effects.

6. CDI in specific IBD-related circumstances

Pouchitis and enteritis: In a study omitted from the above analyses because it restricted its inclusion to 115 patients with an ileo-anal pouch for UC, *C. difficile* was detected by ELISA in the stools in 18% (21/115) patients. There was a positive association with pouch disease activity scores and endoscopic inflammation, which improved with treatment with rifamixin or tinidazole⁵³. On multivariate analysis, risk factors associated with CDI included male gender (OR 5.1 [95% CI, 1.4-20.5) and distal disease preoperatively (OR 8.4 [95%CI1.3-56.4]. *C. difficile* infection has been reported to cause an acute enteritis in IBD patients with ileostomies in several case studies (for review⁸¹) and colitis in the rectal stump of a patient with ileostomy and sub-total colectomy for UC⁸².

7. Endoscopic features of CDI in IBD

While there have been no studies comparing different microbiological methods of diagnosis CDI in patients with IBD, flexible endoscopy has been assessed as a diagnostic method in this setting. Pseudomembranes, comprised of neutrophil degradation products, fibrin, and bacterial remnants filling the intestinal crypt, are characteristic of *C. difficile* infection and at endoscopy are seen in approximately 50% of patients without IBD⁸³. However, in 7 studies in patients with IBD^{31, 32, 35-37, 47, 49} only 9% (13/150) patients were found to have pseudomembranes at sigmoidoscopy or colonoscopy. In one study, fever at onset predicted pseudomembranes at subsequent endoscopy⁴⁷.

Comments: Why pseudomembranes are infrequently seen in IBD is unclear, but flexible endoscopy cannot be recommended for diagnosis of CDI in patients with IBD.

8. Treatment and outcome of CDI in IBD

There is very little data, and in particular there are no controlled trials of the efficacy of antibiotics or other treatments for CDI in IBD.

Medical treatment: Where reported in the studies shown in Tables 1 & 2, 88% (300/340) patients were treated with metronidazole, vancomycin or both. In most cases (88% [258/292 patients]), this treatment was apparently successful.

Since the symptoms of active IBD are usually indistinguishable from those of CDI, CDI in patients with IBD is frequently treated with both antibiotics and immunosuppression, particularly corticosteroids. In a retrospective cohort study from centres across Europe⁴⁸, 12% [11/104] patients given antibiotics together with immunomodulators reached a composite endpoint of death or colectomy within 3 months of admission or in-hospital megacolon, bowel perforation, haemodynamic shock or respiratory failure, compared with none of 51 given antibiotics alone. This difference did not appear to be explained by the patients given combined therapy being sicker at the outset than those given antibiotics alone. Use of more than one immunomodulator increased the risk of having an adverse outcome independently of disease severity at presentation (OR 17 95%CI 3.2-91).

Comments: In the absence of prospective randomised controlled data, antibiotic therapy alone for CDI occurring in patients with acute severe IBD cannot yet be recommended. In sick inpatients, it remains entirely reasonable to start patients on intravenous corticosteroids **and metronidazole or vancomycin** while awaiting the results of *C. difficile* assay. Conversely in less unwell outpatients, decision making can often await the result of stool testing.

Recurrence of CDI in IBD: We could find no relevant studies in adults. One retrospective nested case control study in children defined recurrence as a separate episode of CDI within 60 days of the index infection, with microbiological evidence of CDI clearance between the two infections. 34% [38/111] children with IBD

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5 experienced a recurrence, significantly more than in the non-IBD controls (7.5%). No difference in recurrence
6 rates were seen according to the use of acid suppression or immunosuppressants, or to whether
7 metronidazole or vancomycin was used to treat CDI⁵⁸. Wultanska *et al* in their prospective cohort of Polish
8 children reported that 17% of their 58 patients experienced a recurrence, but did not insist on microbiological
9 evidence of CDI clearance between the first and subsequent infection. Indeed, when strains were genotyped
10 using PCR ribotyping, similar proportions of patients had acquired a new strain (re-infection) as had persistent
11 carriage of the original one⁴⁵.

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16 **Comments:** Although this data is limited, the former by being retrospective and subject to bias in relation to
17 how controls were identified⁵⁸, and the latter by the imprecise definition of recurrence⁴⁵, it suggests that, at
18 least in children with IBD, there is an increased risk of recurrence of CDI.

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22 **Colectomy rates and length of stay:** Contradictory data are reported concerning length of hospital stay (LOS).
23 In the studies using NIS HCUP data, the LOS was significantly longer (up to 3 days longer) in the IBD patients
24 than in controls (Table 3). In contrast, reports from most single centre cohorts suggest that the LOS of IBD
25 patients with CDI is similar to or shorter than that of CDI controls^{36,51}.

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29 Variable rates of colectomy have been reported in IBD complicated by CDI (Tables 1 - 3). Analysis of the NIS
30 HCUP for colectomy rates is unhelpful, since IBD patients' admissions are frequently for elective surgery, a fact
31 likely to make a substantial contribution to the 6 fold increase reported over the colectomy rate for patients
32 with CDI unrelated to IBD (Table 3). Jodorkovsky *et al*⁵¹, describing the long term outcome of 46 UC patients
33 with superimposed CDI treated with appropriate antibiotics, reported that over the following year 44% of the
34 UC – CDI patients had come to colectomy compared with only 25% in the non-infected UC control group; these
35 figures are similar to the colectomy rates reported by Issa *et al* in their IBD cohort in 2004 (45%) and 2005
36 (25%)³⁶. These US colectomy rates are much higher than the immediate rates reported from Europe by
37 Bossuyt *et al*⁴⁹ [5% (1/15)], and Ben-Horin *et al*⁴⁸ [6% (9/152)]. Indeed colectomy was reported in only 1 of 49
38 patients in whom outcome was detailed in the single centre studies shown in Table 1.

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46 **Comments:** The conflicting rates in LOS and colectomy in the above studies could conceivably be accounted for
47 by differences in the interests and experience of the primary caring physician as well as in the threshold for
48 surgery. The single centre cohort experiences were reported by gastroenterologists with interests not only in
49 IBD but also *C. difficile*. It is likely that the index of suspicion for diagnosis of, rates of testing for, and use of
50 empiric treatment of CDI would be higher in these specialist centres than those associated with the practice of
51 less specialist physicians sampled in the NIS HCUP databases. Furthermore, although specific ribotypes were
52 not reported by Jodorkovsky or Issa *et al*, the hypervirulent strain NAP1/027 was endemic in the USA during
53 their sampling time frames and might have contributed to the higher colectomy rates occurring in the USA
54 than Europe

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5 **Mortality:** Similar discrepancies exist for data regarding mortality. The NIS HCUP database studies suggest
6 that about 4% patients with CDI complicating IBD will die on that admission, the risk factors for mortality being
7 increasing age, co-morbidity, treatment in a teaching hospital, intestinal surgery and lack of an insurance
8 policy. In contrast, taking all the deaths in each of the included cohort studies (Tables 1&2 and references^{48,}
9 ⁵¹), only 0.6% (3/797) patients died, a rate similar to the background mortality rate for IBD reported in the
10 database studies.
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14 **Comments:** Possible explanations for these contrasting mortality rates include the facts that in the database
15 studies all of the patients were in hospital and therefore presumably more unwell than many of those in the
16 cohort studies reporting on both out- and in-patients, and that their average age was higher. The database
17 studies are restricted to all-cause mortality on that admission whereas the deaths reported in the single centre
18 cohorts were more likely to be *C. difficile*-related. Furthermore, at least in the Anathankrishnan dataset⁴²,
19 when the mortality rates were re-analysed by primary (IBD) versus secondary diagnosis (other co-morbidity),
20 after removal of the cases where IBD was listed as a secondary diagnosis, the association between mortality
21 and IBD was no longer statistically significant⁴².
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CONCLUSIONS

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30 *C. difficile* infection has become a major public health problem. Although the US administrative database
31 studies suggest that the incidence of CDI in IBD, as in the general population, is increasing, their design makes
32 it hard to distinguish the extent to which this reflects growing awareness of CDI in IBD, with consequent
33 detection bias. Infection without prior healthcare contact or antibiotic exposure is common in IBD patients.
34 IBD appears to be an independent risk factor for commensal carriage compared with the general population,
35 and the difference in risk profile between IBD patients and the general population warrants further
36 investigation. Endoscopy is rarely helpful in diagnosing CDI in patients with IBD. Unfortunately, there have
37 been no prospective studies of treatment of CDI specifically in patients with IBD but these are urgently needed
38 given the apparently adverse outcome associated with the use of combined antibiotic and
39 immunosuppressant therapy compared with antibiotics alone. Therapeutic decision-making would be easier
40 with the development of more rapid, for example PCR-based, methods of detection of *C difficile*. For the
41 moment, however, a high index of suspicion for CDI in all patients presenting with active colonic IBD is
42 essential.
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Systematic Review: *Clostridium Difficile* & IBD

Reference & study location	Design & Setting	Sampling time frame	Patients		<i>C. difficile</i> % (n/n)			Risk Factors for toxin positive CDI % (n/n)			Outcome % (n/n)	
			Disease (n)	Average age (yrs) [range]	Diagnosis method	Culture	Toxin	Preceding antibiotics	Colonic disease	Nosocomial acquisition	Treated	Surgery or Death
Bolton <i>et al</i> 1980, UK ¹⁴	Prospective inpatients	n/r	17 UC 7 CD	n/r	Culture CCA	24% (4/17) 14% (1/7)	24% (4/17) 14% (1/7)	0/5 (3 months)	5/5	n/r	4/5	0/5
Lishman <i>et al</i> 1981, UK ²⁴	Prospective out/inpatients	n/r	26 UC 8 CD	n/r	Culture CCA	0% (0/26) 0% (0/8)	0% (0/26) 0% (0/8)	n/a	n/a	n/a	n/a	n/a
Keighley <i>et al</i> 1982, UK ²³	Retrospective inpatients	1978-1980	21 UC 48 CD	42 [21-91]	Culture CCA	19% (4/21) 19% (9/48)	0% (0/21) 4% (3/48)	3/3	n/r	3/3	3/3	0/3
Gurian <i>et al</i> 1983, USA ²⁰	Prospective Inpatients	1980-1981	21 UC 11 CD	36 n/r	Culture CCA	5% (1/21) 0% (0/11)	0% (0/21) 0% (0/11)	n/a	n/a	n/a	n/a	n/a
Rolny <i>et al</i> 1983, Sweden ³⁰	Prospective out/inpatients	1980-1981	40 UC 13 CD	48 [18-82] 29 [16-65]	Culture CCA	n/a n/a	5% (2/40) 8% (1/13)	0/3	2/3	n/r	0/3	1/3 ^c

Systematic Review: *Clostridium Difficile* & IBD

Burke & Axon 1987, UK ¹⁶	Prospective Outpatients	1984- 1986	62 UC	43 [19-75]	Culture CCA	5% (3/62)	2% (1/62)	0/1 (2 months)	n/r	n/r	n/r	n/r
Gryboski J.D. 1991, USA ¹⁹	Prospective out/inpatients	1986- 1990	28 UC 37 CD	8 [1.5-17]	CCA	n/r n/r	18% (5/28) 14% (5/37)	3/10 (3 weeks)	n/r	1/10	10/10	0/10
Brown <i>et al</i> 1992, UK ¹⁵	Prospective inpatients	n/r	94 UC	n/r	CCA	n/a n/a	0% (0/94)	Exclusion criteria	n/a	n/a	n/a	n/a
Weber <i>et al</i> 1992, Germany ³²	Prospective out/inpatients	1991- 1992	15 UC 49 CD	29 [19-49] 31 [17-62]	Culture (biopsies) CCA	0% (0/15) 2% (1/49)	7% (1/15) 8% (4/49)	0/5	5/5	0/5	0/5	0/5
Markowitz <i>et al</i> 2001, USA ²⁵	Retrospective out/inpatients	1996- 1999	85 UC 179 CD 20 CUTE	13 [0.4-22]	EIA ^{a&b}	n/a	29% (81/284)	n/r	n/r	n/r	n/r	n/r
Meyer <i>et al</i> 2004 USA ²⁶	Retrospective out/inpatients	2000- 2001	20 UC 14 CD 14 CUTE	Median 49 [18-89]	OIA ^a or EIA ^{a&b}	n/a n/a	15% (3/20) 36% (5/14) 7% (1/14)	9/9 (1 month)	n/r	n/r	9/9	0/9
Mylonaki <i>et al</i> 2004 UK ²⁸	Retrospective out/inpatients	1997- 2001	146 UC 65 CD 2 CUTE	n/r [16-81]	ELISA ^{a&b} ≈	n/a n/a	6% (13/237)	7/13 (Current)	n/r	n/r	13/13	0/13
Gursoy <i>et al</i> 2007 Turkey ²¹	Prospective Inpatients	n/r	16 UC 2 CD	n/r [20-65]	EIA ^a		0% (0/16) 0% (0/2)	n/a	n/a	n/a	n/a	n/a
Navarro-Llavet	Prospective	2002-	49 UC	36		n/r	2% (1/49)	1/1	1/1	1/1	1/1	0/1

Systematic Review: Clostridium Difficile & IBD

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et al 2009 Spain 29	Inpatients	2004	47 CD 4 CUTE	n/r	OIA ^a		0% (0/47) 0% (0/4)					
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Table 1: Studies reporting the incidence of *C. difficile* infection in association with relapse of IBD; n/r, not reported; UC, ulcerative colitis; CD, Crohn’s disease; CUTE, colitis of uncertain aetiology; CCA, cell cytotoxicity assay; n/a, not applicable; ^c, colectomy; EIA, Enzyme immunoassay; ^a, toxin A; ^b, toxin B; OIA, optical immunoassay; ELISA, enzyme-linked immunosorbant assay; ≈ incidence reported per stool sample tested.

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Systematic Review: *Clostridium Difficile* & IBD

Reference & study location	Design & Setting	Sampling time frame	Patients		<i>C. difficile</i> % (n/n)			Risk Factors for toxin positive CDI % (n/n)			Outcome % (n/n)	
			Disease (n)	Average Age (yrs) [range]	Diagnosis method	Culture	Toxin	Preceding antibiotics	Colonic disease	Nosocomial acquisition	Treated	Surgery or Death
*Trnka & Lamont 1981, USA ³¹	Prospective out/inpatients	1979-1980	35 UC 24 CD	34 [9-72] 43 [21-68]	CCA	n/r	11% (4/35) 29% (7/24)	3/11 (2 months)	8/11	n/r	8/11	n/r
Meyers <i>et al</i> 1981, USA ²⁷	Prospective out/inpatients	n/r	18 UC 26 CD	34 [11-77] 39 [14-62]	CCA	n/r	17% (3/18) 4% (1/26)	4/4 (2 months)	4/4	n/r	n/r	n/r
Willumsen 1982, Denmark ³³	Prospective out/inpatients	n/r	UC 39 CD 8	n/r n/r	Culture CCA	0% (0/39) 0% (0/8)	0% (0/39) 0% (0/8)	n/a	n/a	n/a	n/a	n/a
Dorman <i>et al</i> 1982, USA ¹⁷	Prospective out/inpatients	1980-1981	50 CD	35 [15-74]	Culture CCA	8% (4/50)	0% (0/50)	n/a	n/a	n/a	n/a	n/a
Greenfield <i>et al</i> 1983, UK ¹⁸	Prospective out/inpatients	1980-1981	67 UC 42 CD	n/r n/r	Culture≈ CCA≈	12% (14/219) 13%	7% (16/219) 5% (6/114)	n/r +ve asscn	n/r	n/r +ve asscn	n/r	n/r

Systematic Review: *Clostridium Difficile* & IBD

						(15/114)						
*Jonard <i>et al</i> 1983, Belgium ²²	Prospective out/inpatients	n/r	9 UC 31 CD	36 - 31 -	Culture CCA	0% (0/9) 17% (5/31)	0% (0/9) 6% (2/31)	1/2	1/2	n/r	n/r	n/r
Wright <i>et al</i> 1984, Canada ⁴¹	Prospective out/inpatients	n/r	10 CD	36 [21-46]	CCA	n/a	0% (0/10)	n/a	n/a	n/a	n/a	n/a
*Hyams & McLaughlin 1985, USA ³⁵	Prospective out/inpatients	1982- 1983	12 UC 32 CD	10 [4-16] 14 [5-19]	IVCA	n/a n/a	0% (0/12) 9% (3/32)	0/3 (4mont hs)	n/r	0/3	0/3	0/3
*Kochhar <i>et al</i> 1993, India ³⁷	Prospective out/inpatients	n/r	50 UC	37-	Culture IEP	8% (4/50)	14% (7/50)	Exclusi on criteria	7/7	Exclusion criteria	7/7	0/7
Vaishnavi <i>et al</i> 2003, India ⁴⁰	Prospective out/inpatients	n/r	94 UC	n/r [17-72]	LA ^{A&B}	n/r	13% (12/94)	8/12	12/12	n/r	n/r	n/r
Issa <i>et al</i> 2007, USA ³⁶	Retrospective out/inpatients	2004- 2005	262 UC 737 CD	41 n/r	ELISA ^{A&B}	n/r	6% (16/262) 4% (30/737)	28/46	42/46	11/46	46/46	12/46 ^C
Rodeman <i>et al</i> 2007, USA ³⁹	Retrospective inpatient	1998- 2004	1066 UC 2331 CD	48 [15-92] 45 [10-99]	CCA ⁽²⁰⁰²⁾ EIA ^{A&B}	n/r	4% (42/1066) 2%(37/2331)	n/r	n/r	n/r	n/r	n/r
Balamurugan <i>et al</i> 2008, India ³⁴	Prospective out/inpatients	2004- 2005	37 UC 36 HC	41 [22-67]	ELISA ^{A&B}	n/r	22% (8/37)	Exclusi on	37/37	n/r	n/r	n/r

Systematic Review: *Clostridium Difficile* & IBD

								criteria				
*Pascarella <i>et al</i> 2009 Italy ³⁸	Retrospective out/inpatients	2005- 2007	61 UC 19 CD	8 [1.6-17]	Immuno- card ^{A&B}	n/r	21% (13/61) 35% (7/19)	7/20	20/20	2/20	n/r	n/r
*Wultanska <i>et al</i> 2010 Poland ⁴⁵	Prospective out/inpatients	2005- 2007	37 UC 21 CD	[3-18] [3-18]	Immuno- card ^{A&B}	n/r	73% (27/37) 62% (13/21)	n/r	n/r	0/40	n/r	n/r

Table 2: Studies reporting the incidence of *C. difficile* infection in populations with mixed disease activity. n/r, not reported; UC, ulcerative colitis; CD, Crohn's disease; CUTE, colitis of uncertain aetiology; CCA, cell cytotoxicity assay; n/a, not applicable; ^c, colectomy; EIA, Enzyme immunoassay; ^a, toxin A; ^b, toxin B; OIA, optical immunoassay; ELISA, enzyme-linked immunosorbant assay; LA, latex agglutination; ≈ incidence reported per stool sample tested.

Systematic Review: *Clostridium Difficile* & IBD

Reference & study location	Sampling time frame	Time point reported	Patients		Outcome (%)				
			Disease (n)	Average age (yrs) [range]	Incidence (% of admissions)	In-hospital mortality	Intestinal surgery	Average LOS (Days)	
Anathankrishnan <i>et al</i> 2008, USA ⁴²	1998-2004	2004	1843 UC & CDI	IBD - 54	3.9	5%	10.4%	7	
			961 CD & CDI		1.2	3%	8.0%	6	
			44,400 CDI		73	n/a	3.7%	1.4%	5
			77,366 IBD		42	n/a	0.5%	16.9%	4
Nguyen <i>et al</i> 2008, USA ⁴³	1998-2004	1998-2004	1628 UC & CDI	n/r	3.73	4.1%	n/r	9.9	
			797 CD & CDI	n/r	1.09	1.1%	n/r	9.5	
			527,187 MIP	47	0.45	n/r	n/r	n/r	
			42,017 UC	n/r	n/a	0.9%	n/r	6.7	
			72,400 CD	n/r	n/a	0.4%	n/r	5.7	
Ricciardi <i>et al</i> 2009, USA ⁴⁴	1993-2003	1993-2003	3688 UC & CDI	n/r	2..3	7.7%	n/r	n/r	
			2298 CD & CDI	n/r	1.04	2.4%	n/r	n/r	
			299,453 CDI	n/r	0.38	8.8%	0.27%	n/r	
			350,822 IBD	n/r	n/a	1.4%	12.6%	n/r	
Anathankrishnan <i>et al</i> 2010, USA ⁴⁶	1998 -2007	2007	4632 UC & CDI	n/r	5.3	9.3%	6.3%	n/r	
			2276 CD & CDI	n/r	1.5	1.9%	0.8%	n/r	
			Non-IBD CDI	n/r		9.4%	n/r		

Systematic Review: *Clostridium Difficile* & IBD

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Systematic Review: *Clostridium Difficile* & IBD

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5 **Table 3: Studies that used diagnostic coding to report the association of *C. difficile* infection in hospitalised patients with IBD.** All studies involved retrospective nested
6 case control analysis of nationwide hospital discharge databases. UC, ulcerative colitis; CD, Crohn's disease; MIP, mixed inpatient population; n/r, not reported; n/a, not
7 applicable.
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For Peer Review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3/4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3/4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 & 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4,
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8 - 15
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 & 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	21 - 28
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 - 15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	21 - 28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 - 15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 - 15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8 - 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8 - 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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