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**Extended spectrum beta-lactamase producing bacteria and
Clostridium difficile in pouchitis patients**

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Keywords:	Pouchitis < Disease-based, Ulcerative colitis < Disease-based, Inflammatory bowel disease < Disease-based, Small intestine < Organ-based

EDITOR'S COMMENTS TO AUTHOR:

Both reviewers and myself agree that this is an interesting topic and original data. We also still think that the message would have been strengthened by the addition of adequate controls with the prevalence of ESBL+ among non pouch IBD.

Response:

We agree with the editor and reviewer's comments and hope in time to perform a follow-up study which reviews the prevalence of ESBL in pouch patients with and without a previous history of pouchitis.

REVIEWERS' COMMENTS TO AUTHOR:

Reviewer: 1

Comments for Transmission to the Authors

None

Reviewer: 2

Comments for Transmission to the Authors

Results:

1." Twenty patients had recurrent pouchitis and twenty eight (59%) patients had relapsing pouchitis. All patients with relapsing pouchitis were receiving treatment with maintenance antibiotic therapy... " relapsing pouchitis? it means refractory?

-Response:

-Thank you. We have corrected this typo.

2." ESBL producing organisms were identified in faecal samples from 16 (33%) patients, two of these patients were on two weekly alternating antibiotic treatment. 10 (55.6%) of 18 patients who were ESBL positive had symptoms of active pouchitis." It is not clear if the ESBL positive patients were 16 or 18. If 16: $10/16=62.5\%$

-Response:

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4 -This is a typo, the text should read; "10 (62.5%) of 16 patients who
5 were ESBL positive had symptoms of active pouchitis." We have
6 corrected this typo in the manuscript.
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9 3. " In an earlier open-label study reporting 10 patients with pouchitis
10 complicated by extensive pre-pouch ileitis treated with infliximab. Nine
11 achieved clinical remission (29). " , nine achieved clinical remission (29).
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13 -Response:
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16 -Unfortunately this reviewer's comment is not clear to us.
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For Peer Review

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4 **R2; Extended spectrum beta-lactamase producing bacteria and Clostridium**
5 **difficile in pouchitis patients**
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49 **Short running title**

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51 ESBL bacteria in pouchitis
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55 **Keywords:**

56 Restorative proctocolectomy, ileal pouch-anal anastomosis, Pouchitis, ulcerative colitis,
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58 inflammatory bowel disease, familial adenomatous polyposis, ESBL.
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Abstract

Background: Treatment with fluoroquinolones is associated with the development of *Clostridium difficile* and extended spectrum beta lactamase producing bacteria (ESBL). *Clostridium difficile* and ESBL are resistant to many antibiotics and each may cause pouchitis after restorative proctocolectomy (RPC) refractory to empirical antibiotic therapy.

Aim: To assess the prevalence and establish risk factors for the development of ESBL and CDT in RPC patients with recurrent or refractory pouchitis under follow-up at our institution over a one year period.

Method: An enzyme linked immunosorbent assay was used to detect *Clostridium difficile* toxins (CDT) and a culture technique was used to identify ESBL in faecal samples. All patients had previously received fluoroquinolone treatment.

Results: 48 patients (35 (74%) males; median age 42 years) underwent testing at a median interval from RPC of 8 (range 1-25) years. No patient had a positive CDT result but ESBL bacteria were identified in 16 (33%) samples. ESBL positivity was significantly related to pre-pouch ileitis ($p= 0.035$) and maintenance antibiotic therapy ($p= 0.039$).

Conclusions: ESBL but not CDT is a common finding in faecal samples from patients with recurrent or refractory pouchitis. Treatment with maintenance antibiotics and pre-pouch ileitis are risk factors for developing ESBL producing bacteria.

Background:

Restorative proctocolectomy with ileal pouch-anal anastomosis (RPC) is the surgical procedure of choice for patients with ulcerative colitis (UC) and selected patients with familial adenomatous polyposis (FAP) who require surgery (1).

Pouchitis is the most common cause of morbidity following RPC. The incidence increases with length of follow-up (1) rising to about 50% at five years with a prevalence of clinically significant recurrent or chronic refractory pouchitis in 5-10% of patients.

In addition about 13% of patients with pouchitis will have pre-pouch ileitis, this is a histological entity distinct from Crohn's disease and can be defined as inflammation proximal to the pouch in a patient with pouchitis and characteristic histological features (2). The histological features of the pre-pouch ileum in pre-pouch ileitis are the same as those seen in pouchitis and include colonic phenotypic change (3).

Empirical antibiotic treatment with ciprofloxacin (a fluoroquinolone) or metronidazole or in combination with other antibiotics is effective in chronic pouchitis and pre-pouch ileitis (4-6). Long-term follow up studies have shown that pouchitis is responsible for 10% of all pouch failures (7). The causes for this are not understood but the development of antibiotic resistance is likely to be important. Where patients are exposed to repeated antibiotic treatment, antibiotic resistance or

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3 Clostridium *difficile* infection may develop. Clostridium *difficile* is an important cause of treatment
4 failure in patients presenting with symptoms of pouchitis (8;9) and should be excluded in those with
5 pouchitis (1;10).
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8 Extended spectrum beta-lactamases (ESBL) are bacterial enzymes which are capable of hydrolysing
9 penicillins, broad-spectrum cephalosporins and monobactams. ESBL producing bacteria are
10 inherently resistant to many classes of antibiotic because other determinants of resistance are often
11 linked on the same plasmid (11). Fluoroquinolone resistance in particular is associated with ESBL
12 producing bacteria (12;13) and exposure to antibiotics including ciprofloxacin and metronidazole is
13 associated with an increased risk of developing ESBL producing bacteria (14).
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17 Faecal carriage of ESBL producing bacteria is uncommon in the general UK community. One group
18 report that during the period 2004-05 only 1% of 1253 community faecal samples taken from
19 patients with diarrhoea contained ESBL-producing bacteria (15). Certain patient groups have been
20 shown to have increased faecal carriage of ESBL producing bacteria, but to the best of our
21 knowledge this has not previously been studied in IBD or pouchitis patients. One recent UK study
22 identified ESBL-producing *E. coli* in 40% of asymptomatic nursing home residents (15). In countries
23 where antibiotics are available without prescription high levels of ESBL carriage in asymptomatic
24 individuals have been reported. In one study from Saudi Arabia ESBL-producing organisms were
25 isolated from 13.1% of asymptomatic outpatients (16), a study from Israel reported a prevalence of
26 8% in patients being admitted to hospital (17). These studies suggest that asymptomatic carriage of
27 ESBL producing bacteria is common in patients exposed to frequent antibiotic treatment.
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32 Recently we have shown that ESBL producing bacteria may in some cases be associated with
33 antibiotic refractory pouchitis (18). This may be particularly seen in recurrent or refractory pouchitis
34 which may require frequent courses of antibiotics or continuous maintenance treatment. In practice,
35 development of resistance to the usually prescribed antibiotics may limit the treatment options to
36 nitrofurantoin or colistin. Clostridium *difficile* toxin (CDT) has recently been reported to be present
37 in 18% of stool samples from RPC patients (19) but the prevalence of ESBL producing bacteria is
38 unknown. It is likely that ESBL producing bacteria in stool may predispose to an increased risk of
39 resistant pouchitis and pouch failure in the long-term due to failure of medical therapy.
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43 44 45 46 **Aim**

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48 To assess the prevalence and establish risk factors for the development of ESBL and CDT in RPC
49 patients with recurrent or refractory pouchitis under follow-up at our institution over a one year
50 period.
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52 53 54 55 **Method**

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57 Ethical permission was granted by the Brent and Harrow Research Ethics Committee to collect
58 prospective and retrospective data on RPC patients entered into the St Mark's Hospital Pouch
59 Registry. Consecutive patients with recurrent or refractory pouchitis defined as three or more
60 episodes of pouchitis per year or persistent pouchitis requiring continuous antibiotic treatment (4)
attending the outpatient clinic were identified over a one year period. Demographic details including

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3 age and sex were recorded. Clinical details were also obtained including the presence of
4 symptomatic pouchitis at the time of testing, the interval from RPC, and a previous history of pre-
5 pouch ileitis. Information on whether mucosal healing was achieved after four weeks of antibiotic
6 treatment and whether the patient was taking maintenance antibiotic therapy was also obtained.
7 Fresh faecal samples were collected by patients themselves during their hospital attendance and
8 these were transported to the hospital laboratory and analysed without delay. An enzyme linked
9 immunosorbent assay was used to detect *Clostridium difficile* toxins A and B (Meridian Bioscience,
10 Cincinnati, Ohio, USA). To identify ESBL producing bacteria in the faecal samples a standard culture
11 technique as per British Society for Antimicrobial Chemotherapy and HPA guidelines was used
12 (20). This technique utilises Iso-sensitest agar (Oxoid, Cambridge, UK) which is a non selective media
13 used for sensitivity testing of gram negative and gram positive organisms. Faecal samples were
14 inoculated onto Iso-sensitest agar using a sterile swab and a rotary spreader. Antibiotic discs
15 containing ciprofloxacin, trimethoprim, cephalixin, co-amoxiclav, nitrofurantoin, cefpodoxime,
16 cefuroxime, and cefixime were added. We incubated plates at 37°C for 18 to 24 hours and recorded
17 the sensitivity patterns. ESBL status was defined as a zone size to cefpodoxime of ≥ 25 mm, as per
18 British Society for Antimicrobial Chemotherapy guidance (20).
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24 Statistical analysis

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26 SPSS version 15 (SPSS inc. Chicago, Illinois, USA) was used for all statistical analysis. For the
27 description of data, the median and range were calculated. The Mann-Whitney U test (two tailed)
28 was used to compare continuous data and a chi-squared test used to compare categorical variables
29 between the ESBL negative and ESBL positive groups. A two-tailed P-value less than 0.05 was
30 considered statistically significant. A multivariate analysis using a backwards stepwise regression
31 technique with a cut-off value of p less than 0.05 was also performed.
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39 Results

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41 48 patients of median age 42 years (range 20-69) and male gender in 35 (71%) were studied. Two
42 patients had familial adenomatous polyposis (FAP), three indeterminate colitis (IC) and the
43 remainder had UC. No patient had received regular treatment with a non-steroidal anti-
44 inflammatory drug (NSAID) in the preceding 6 months. The median interval from RPC to the present
45 assessment was 8 years (range 1-25). Twenty patients had recurrent pouchitis and twenty eight
46 (59%) patients had refractory pouchitis. All patients with refractory pouchitis were receiving
47 treatment with maintenance antibiotic therapy and 10 (20%) of these patients had
48 symptomatic pouchitis at the time of faecal testing. Of the patients treated with antibiotic
49 maintenance therapy, the antibiotics used were ciprofloxacin (18) co-amoxiclav (7), colistin (2),
50 nitrofurantoin (2), cefixime (1), trimethoprim (2). Three patients were on two weekly alternating
51 antibiotic combination therapy.
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59 ESBL producing organisms were identified in faecal samples from 16 (33%) patients, two of these
60 patients were on two weekly alternating antibiotic treatment. 10 (62.5%) of 16 patients who were
ESBL positive had symptoms of active pouchitis. Clinical and statistical data for the ESBL positive and

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3 ESBL negative groups are shown in Table 1. It can be seen that the presence of ESBL producing
4 bacteria was not associated with age, sex or the number of years from RPC. Univariate analysis
5 however identified an association with a history of pre-pouch ileitis complicating pouchitis and of
6 maintenance antibiotic therapy. Multivariate analysis demonstrated that only pre-pouch ileitis
7 predicated the development of ESBL-producing bacteria.
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11 CDT was not identified in any patient sample.
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Table 1.

Clinical and statistical data for ESBL positive and ESBL negative groups

	ESBL Negative	ESBL Positive	P value	Odds-ratio (95% confidence interval)
Number of patients (%)	32 (67%)	16 (33%)		
Median age (range) years	42 (21-58)	45 (20-69)	0.991	
Male	22 (67%)	13 (81%)	0.363	2.321 (0.449-12.0)
No. of years from RPC median(range)	8.5 (1-25)	6.5 (2-25)	0.539	0.956 (0.858-1.064)
History of pre-pouch ileitis (%)	8 (50%)	9 (69%)	0.033	3.020 (0.764-11.938)
Maintenance antibiotic therapy (%)	16 (48.5%)	13 (81.3%)	0.037	3.823 (0.801-18.238)
Mucosal healing following antibiotic treatment	14 (44%)	9 (56%)	0.419	

Discussion

In the light of a recent report indicating that ESBL producing bacteria may in some cases be the cause of antibiotic refractory pouchitis (18), we reviewed the prevalence of ESBL in our RPC patients with recurrent or refractory pouchitis. The study has shown that ESBL producing bacteria occur in 33% of such patients and that maintenance antibiotic therapy and pre-pouch ileitis are associated with a significantly increased risk of ESBL producing bacteria.

None of the patients studied had detectable CDT. This is in contrast with a recent finding by Shen *et al* who studied 115 RPC patients undergoing routine pouchoscopy for surveillance or investigation of pouch dysfunction. These authors reported a prevalence of 18% of which 5% of patients were symptomatic. In their univariate analysis, male gender and a previous history of left sided colitis were associated with an increased risk of CDT after RPC. Surprisingly the previous use of antibiotics

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3 was not (19). The reasons for the difference in the prevalence of CDT in the present study and that
4 of Shen *et al* are unclear but could be related to differences in antibiotic use and the prevalence of
5 *Clostridium difficile* in the local hospital and community population. There were limitations to our
6 study. The number of patients was small but this reflects the fact that recurrent or refractory
7 pouchitis is uncommon in the general RPC population, affecting only about 5% of patients (1).
8 Patients requiring antibiotic maintenance therapy at our institution are treated with ciprofloxacin
9 according to our own and others previously published guidelines (1;22). In those where this becomes
10 ineffective faecal coliform sensitivity testing is performed and an appropriate antibiotic prescribed
11 according to the sensitivity patterns identified. Therefore all patients treated with maintenance
12 therapy will have received ciprofloxacin; consequently we were unable to reliably establish whether
13 different antibiotics are associated with an increased risk of developing ESBL-producing bacteria.
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19 On univariate analysis pre-pouch ileitis and long term antibiotic treatment were both associated
20 with an increased risk of developing ESBL producing bacteria. Of these, pre-pouch ileitis was shown
21 to be the more important on multivariate analysis. It is known that exposure to antibiotics is
22 associated with an increased risk of developing ESBL producing bacteria (14) therefore the finding in
23 the present study is not surprising. Why ESBL producing bacteria are more common in patients with
24 pouchitis complicated by pre-pouch ileitis than in patients with pouchitis only is less clear. Pre-pouch
25 ileitis may be due to reflux of pouch contents into the pre-pouch ileum (2). It can be treated with
26 combination antibiotic therapy (23), suggesting that bacteria are important in its aetiology. The
27 present study has also shown that patients with pre-pouch ileitis or those treated with maintenance
28 antibiotic therapy are at increased risk of developing ESBL producing bacteria. It is possible that
29 pouchitis complicated by pre-pouch ileitis may be associated with a higher bacterial load
30 predisposing to the development of bacterial resistance (24).
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35 The majority of patients with ESBL producing bacteria in this study were asymptomatic. It is possible,
36 however, that over time symptomatic pouchitis secondary to ESBL-producing bacteria (ESBL
37 pouchitis) may occur. Treatment of ESBL pouchitis with nitrofurantoin or colistin is effective in most
38 but not all cases (18) and it is likely that resistance to these antibiotics may develop over time. Thus
39 it is possible that the carriage of ESBL producing coliforms may be associated with an increased risk
40 of pouch failure.
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44 Strategies to reduce antibiotic use and therefore to reduce the risk of developing EBSL producing
45 bacteria and *Clostridium difficile* should be considered. We have now adopted the practice that all
46 patients with symptoms of pouchitis undergo endoscopy to confirm the diagnosis before initiating
47 antibiotic treatment and we have been careful not to treat patients before the diagnosis is certain.
48 In patients where a flexible pouchoscopy cannot be arranged promptly, measurement of faecal
49 calprotectin to confirm a clinical diagnosis of pouchitis is a reasonable alternative (25). Non-
50 antibiotic treatment would clearly reduce the risk but few effective treatments have been reported.
51 Oral budesonide was suggested to be useful in patients with refractory pouchitis who did not
52 respond to single antibiotic therapy (open label study) (26), but unfortunately a randomised double
53 blind study of budesonide enemas found it no more effective than metronidazole (27). Infliximab
54 has recently been reported to be efficacious in chronic refractory pouchitis. 10 patients received
55 Infliximab, and of these seven maintained a clinical response at a median follow up of 8.5 months
56 (28). In an earlier open-label study reporting 10 patients with pouchitis complicated by extensive
57 pre-pouch ileitis treated with infliximab. Nine achieved clinical remission (29). Adalimumab has been
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3 reported to be effective in RPC patients with Crohn's disease but has not yet been studied in
4 patients with UC (30). Sulphasalazine has been reported to be an effective treatment for pouchitis.
5 In an open-label study of 11 patients 63% of patients were in remission after 8 weeks treatment
6 (31). The probiotic VSL#3 has been shown to be effective in patients with mild to moderate pouchitis
7 (defined as a PDAI between 7 and 12). In an open-label study Gionchetti *et al* studied 23 patients
8 who were treated with VSL#3 (900 billion bacteria) twice daily for four weeks. Sixteen (69%) entered
9 remission. Following this, maintenance treatment was continued with 1800 billion bacteria per day,
10 and all 16 patients maintained remission for 6 months (32). It is possible that VSL#3 may be an
11 alternative to antibiotic agents in the treatment of mild to moderate pouchitis.
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16 Maintenance therapy with an antibiotic or VSL#3 is recommended in patients with chronic antibiotic
17 dependent pouchitis (21). Treatment with VSL#3 rather than ciprofloxacin maintenance therapy may
18 reduce the risk of developing ESBL producing bacteria or *Clostridium difficile*, but evidence of
19 efficacy is limited to patients with complete (33) or near-complete mucosal (34) healing. This may
20 partly explain the disappointing results reported in an open-label clinical study (35). Surprisingly
21 there is no evidence that immunomodulators are useful in pouchitis. Although there are no
22 controlled studies, two groups have reported the occurrence of pouchitis in patients treated with
23 azathioprine for primary sclerosing cholangitis (36;37) suggesting that this may not be effective.
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28 In conclusion we found no evidence of *Clostridium difficile*, but ESBL producing bacteria occurred in
29 33% of our patients with recurrent or refractory pouchitis. Further research is required to establish
30 whether ESBL are common in all RPC patients or as is more likely, occur only in those who have
31 received antibiotics. Because ESBL pouchitis is difficult to treat, longitudinal studies are warranted to
32 establish whether the presence of ESBL producing bacteria predisposes to pouch failure. Although
33 the present study supports the policy that antibiotics for pouchitis should be limited wherever
34 possible it is, however, unlikely that they can be avoided in most patients with recurrent or
35 refractory pouchitis.
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42
43 Simon McLaughlin is supported by the St. Mark's Hospital Foundation and the the Broad Medical
44 Research Program of The Broad Foundation.
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47 **Statement of interests**

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49 All authors declare that they have no conflicts of interest.
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