The role of surgery in *Clostridium difficile* colitis

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*Clostridium difficile* infection was cited in one of every 250 death certificates completed in the United Kingdom in 2005,1 and it has become the leading cause of death from healthcare associated infections in much of the industrialised world.2 More than 50 000 cases of *C difficile* infection were reported in England in 2007—a 50-fold increase since 1990.1 Pseudomembranous colitis was first described in 1935, but it took another 40 years for *C difficile* to be identified as the causative organism.3 4 *C difficile* associated disease accounts for 15-25% of antibiotic associated diarrhoea,5 and its incidence is rising. The overall prevalence in patients admitted to hospital is around 1%; it can be as high as 20% in those who stay for more than one week and 50% in those who stay for at least four weeks.6 7

This review aims to draw attention to the symptoms of *C difficile* infection and to summarise evidence on the indications and optimum timing of surgical intervention for *C difficile* associated colitis. The quality of evidence for the treatment of *C difficile* associated disease is poor, and the recommendations in this review are based mainly on non-randomised observational studies (level III evidence).

How does *C difficile* disease present?

*C difficile* causes a wide spectrum of disease, ranging from asymptomatic colonisation of the gastrointestinal tract to diarrhoea and colitis, which can progress to acute severe disease with sepsis, haemodynamic instability, and toxic dilation of the colon, with risk of subsequent perforation. A review of observational data reported that 3% of patients with *C difficile* associated disease will progress to fulminant colitis, with a documented mortality of up to 80%.5 7 The pathogenicity of *C difficile* is related to the production of at least two toxins—toxin A, an enterotoxin; and toxin B, a cytotoxin.

*C difficile* associated disease increasingly presents to primary care doctors, especially in Europe, where up to 30% of *C difficile* infections are community acquired8 9; in the United States *Clostridium difficile* may be endemic in the nursing home population, with an prevalence as high as 33%.1

Part of the increase in incidence and mortality relates to the emergence in 2003 of a hypervirulent strain, known as ribotype 027,10 which was first seen in North America, but has since been isolated throughout Europe. Ribotype 027 is associated with a more severe disease profile, higher therapeutic failure rates, greater relapse rates, higher colectomy rates, and higher mortality.11 With the emergence of hypervirulent strains, the time from development of symptoms to septic shock may be reduced, making proactive and aggressive treatment regimens necessary.

How is *C difficile* disease diagnosed?

Detection of *C difficile* toxin in the stool of a patient with diarrhoea is the most widely accepted method of diagnosis. The sensitivity of toxin assays is not ideal (63-99%), thus stool culture is being advocated as a more sensitive (89-100%) but less specific test.12 Endoscopy may reveal a pseudomembrane coating the colonic wall, and this finding has a diagnostic sensitivity of 51%.12 Radiology may be useful in the diagnosis and surveillance of patients with acute severe colitis. Plain radiography of the chest and abdomen may show thickening of the colonic wall, thickening or loss of haustrations, toxic dilatation, or perforation.13 Abdominal computed tomography may show the “accordion” sign, so called because of alternating oedematous haustral folds separated by transverse mucosal ridges. This sign is more often seen in *C difficile* colitis than in other forms of colitis because of the typical extensive wall thickening.14

Are the causes of hospital and community acquired disease the same?

The link between the use of antibiotics and *C difficile* infection in hospital—with further nosocomial spread

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**Sources and Selection Criteria**

We did a PubMed search for English language articles on *Clostridium difficile* colitis, fulminant colitis, and surgery. Further papers were identified from the reference lists of relevant major articles.
related to hand hygiene and contaminated items—was established by epidemiological studies in the 1990s. In hospital, exposure to antimicrobial agents, particularly clindamycin and β-lactam agents, is the predominant risk factor. In the community, however, emerging evidence suggests that exposure to antibiotics is not always a factor, and reliance on a history of recent hospital admission or antibiotic use may contribute to “missed” diagnoses in primary care. A recent case-control study that aimed to identify risk factors for community acquired C difficile associated disease found that a third of cases had no history of hospital admission or antibiotic use. A large case matched study that assessed 836 cases of community acquired C difficile infection confirmed this finding and found significant links to the use of proton pump inhibitors, coexisting inflammatory bowel disease or irritable bowel syndrome, and contact with young children.

**Initial management of C difficile associated diarrhoea**

The initial treatment for C difficile associated disease includes stopping antibiotics and offering supportive treatment. The Department of Health steering group report on managing such disease recommends administering specific antibiotics, with metronidazole and oral vancomycin being the principal first line agents. Unproved treatments (including intravenous immunoglobulin, probiotics, and cholestyramine) have been advocated by some, but recent Cochrane reviews report on managing such disease recommends administering specific antibiotics, with metronidazole and oral vancomycin being the principal first line agents. The guidance recommends different treatment regimens for each category, but few data indicate that prognosis varies between the five categories. In addition, some of the clinical entities, such as partial ileus, would be difficult to define in routine clinical practice. There is also little evidence that the efficacy of different antibiotic regimens differs.

**What are the risk factors for fulminant disease?**

Box 2 summarises the independent risk factors for developing fulminant disease, derived mainly from a retrospective case matched study that compared the characteristics of patients with C difficile infection who progressed to fulminant colitis with those who did not.

Increasing leucocytosis has also been identified as an indicator of progression towards fulminant disease by other workers, and leucocytosis is an independent risk factor of mortality at 30 days. A retrospective case series reported previous immunosuppression in 44% of cases of fulminant colitis. The presence of immunosuppression is also an independent predictor of 30 day mortality. In these studies the definition of “immunosuppressed” was broad—it included patients receiving corticosteroids for inflammatory conditions and post-transplant agents,

**Guidelines for categorising severity in C difficile infection**

The current report from the UK Department of Health on C difficile infection classifies the disease into mild, moderate, severe, complicated, and life threatening, and it provides treatment recommendations according to severity (table). The guidance recommends different treatment regimens for each category, but few data indicate that prognosis varies between the five categories. In addition, some of the clinical entities, such as partial ileus, would be difficult to define in routine clinical practice. There is also little evidence that the efficacy of different antibiotic regimens differs.

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**Classification and treatment of Clostridium difficile associated disease**

<table>
<thead>
<tr>
<th>Severity of disease</th>
<th>Definition</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Mild</td>
<td>≤3 stools (Bristol chart types 5-7) a day and a normal white blood cell count</td>
<td>Oral metronidazole</td>
</tr>
<tr>
<td>Moderate</td>
<td>3-5 stools a day (types 5-7) and raised white blood cell count (≥20x10⁹/l)</td>
<td>Oral metronidazole</td>
</tr>
<tr>
<td>Severe</td>
<td>White blood cell count ≥20x10⁹/l; temperature &gt;38.5°C, acute rising creatinine, or abdominal or radiological signs of acute colitis</td>
<td>Oral vancomycin</td>
</tr>
<tr>
<td>Complicated</td>
<td>Hypotension, partial ileus, or evidence of severe disease on computed tomography</td>
<td>Oral vancomycin + intravenous metronidazole</td>
</tr>
<tr>
<td>Life threatening</td>
<td>Complete ileus or toxic megacolon</td>
<td>Oral vancomycin + intravenous metronidazole; consider colectomy</td>
</tr>
</tbody>
</table>

**Box 2 Risk factors for developing complicated disease**

- Presence of leucocytosis ≥16x10⁹ cells/l at the start of treatment
- Presence of inflammatory bowel disease
- Patient immunosuppressed
- Recent surgery (within 30 days)
- Within 30 days of intravenous immunoglobulin therapy
- Patient infected with ribotype 027
patients with carcinoma (with or without chemotherapy), and people who were HIV positive. A case matched study linked pre-existing inflammatory bowel disease to the development of fulminant colitis. However, this may have been because 83% of patients with inflammatory bowel disease were immunosuppressed compared with 24% of those without bowel disease.

Inpatient surgical treatment during the month before the onset of *C. difficile* infection is a significant risk factor for progression to fulminant colitis. This is probably the result of a combination of strain factors, with previous inpatient hospital stay increasing infection with nosocomial—rather than community acquired—strains, and the immunosuppression associated with the surgical stress response. Risk is also related to the strain of clostridium involved. Since 1999 a more virulent strain, known as the pulse field type 1 (NAP1) or ribotype 027, has been implicated in disease epidemics. Initial reports were from North America, with the first UK outbreak being reported in Stoke Mandeville hospital in 2003. Since then the incidence has spread rapidly in NHS hospitals throughout the UK and other institutions in northern Europe. *C. difficile* produces two toxins (A and B) that stimulate cytokine release. Ribotype 027 produces up to 23 times more of these toxins than is produced by the older strains. In addition, this new strain can be resistant to fluoroquinolones, is increasing in incidence, and is associated with higher morbidity and mortality.

**What is the role of surgery in the management of *C. difficile* associated disease?**

Patients with acute severe disease should be identified early, so that disease progression can be rapidly identified and treatment optimised. Although more patients could be referred for colectomy and at an earlier stage than is currently the case, overall mortality may remain high because of the general physiological state and underlying disease conditions of many patients with severe *C. difficile* colitis.

Surgery may be life saving for patients with acute severe colitis. However, patients with severe comorbidities have a poor prognosis after major surgery, which is worsened by the emergency nature and physiological disturbances encountered with acute severe colitis. Careful evaluation of patients will ensure that surgery is offered to those most likely to benefit. Considerations are:

- Which patient?
- When to operate?
- Which operation?

**Who should be selected for surgery?**

The criteria for surgical intervention are not clear. The best data came from a large (165 cases) retrospective observational study, which showed that patients with fulminant colitis and a leucocytosis of 20–49 × 10⁹/l fared better after colectomy than those given medical treatment alone (mortality 21% v 55%). Once leucocytosis exceeded 49 × 10⁹/l or serum lactate was greater than 5.0 mmol/l, mortality increased to 63% after surgical treatment and 95% with medical management. Leucocytosis, immunosuppression, and the presence of shock were predictors of mortality. The authors concluded that colectomy had the greatest survival benefit in patients who were over 65 years, immunocompetent, and had a white cell count of more than 20 × 10⁹/l or a lactate concentration between 2.2 mmol/l and 4.9 mmol/l. Other authors have found that shock, the need for treatment with a vasopressor, and high leucocytosis correlates with increased mortality after colectomy. In addition, organ dysfunction or failure is associated with increased mortality after salvage colectomy. This evidence suggests that patients with *C. difficile* colitis and increasing leucocytosis should undergo treatment review and have a surgical team involved in the management process.

If the patient has radiological or endoscopic evidence of fulminant disease, particularly with a white cell count of more than 20 × 10⁹/l or a lactate concentration between 2 mmol/l and 5 mmol/l, colectomy may confer a survival benefit as high as 24% compared with medical treatment alone. Because a rapidly rising white cell count often precedes haemodynamic changes, we believe that surgical review should be sought in all patients with marked or increasing
leucocytosis to avoid missing a window of opportunity for surgery.

When should you operate?
The timing of surgical intervention is crucial. A case series of 36 patients showed that mortality after colectomy improved from 65% to 32% between the 1995-9 series and the 2000-6 series, and that this improvement was associated with a reduction in mean time before the surgical consultation and the operation. Indeed, timely surgical intervention before the onset of haemodynamic instability, multiple organ failure, leucocytosis, and high serum lactate has been advocated by several authors. A large retrospective medical record review of 5718 cases of C difficile associated disease found that non-survivors had a significantly longer duration of medical treatment before colectomy than did survivors. Postoperative mortality is significantly higher once signs of shock are evident or the patient is dependent on vasopressor support. In patients with antibiotic sensitive disease, a position paper on C difficile diarrhoea and colitis reported that most patients improve clinically within two days of starting medical treatment, with resolution of diarrhoea within four days. In addition, a change of antibiotics in non-responders may not be helpful and may delay surgical review. Vancomycin, the recommended antimicrobial in many treatment regimens for recurrent or severe C difficile associated disease has not been shown to be better than metronidazole in 027 ribotype disease. This evidence supports surgical intervention earlier than in most documented treatment regimens, which suggest changes in antimicrobial treatment and up to 10 days’ administration. Patients at high risk of developing fulminant colitis should be closely monitored, and institutions with documented cases of ribotype 027 as the infective agent should be particularly vigilant. Early surgery may significantly improve the outcome in these cases.

Which operation is most suitable?
Subtotal colectomy (removal of the colon leaving the rectum in situ) with end ileostomy is associated with lower morbidity and mortality than more conservative procedures. Some series have undertaken segmental resection in selective cases, but this approach should be used with caution. The external appearance of the colon is often unremarkable and not a reliable indicator of the extent of disease. Because these patients are often critically unwell, undergoing what is essentially a lifesaving operation, segmental resection that risks leaving diseased colon behind is not recommended.

Conclusion
C difficile colitis carries a high mortality, which may be reduced by emergency colectomy. Certain characteristics of the patient and strain of clostridium increase the risk of progression to fulminant disease. To reduce mortality from this increasingly common disease, high risk patients should be identified and monitored, with early surgical intervention in those who do not respond to medical treatment.

The quality of evidence for the treatment of the current epidemic of people with C difficile associated disease is poor, coming largely from non-randomised observational studies. Although it may be difficult—ethically and logistically—to randomise patients, evidence from randomised controlled trials is needed to guide treatment protocols. We also need validated scoring systems for prognosis and for determining

**SUMMARY POINTS**
The incidence of Clostridium difficile infection is increasing
A hypervirulent strain has recently emerged (ribotype 027)
Consider ribotyping in institutions where the incidence of complicated or fulminant colitis is increasing
Treatment should be proactive
Patients need a minimum twice daily review and deterioration should prompt action
Mortality is high but can be improved by timely intervention

**FUTURE RESEARCH**
Questions for further research
What factors are associated with outcome and deterioration?
What are the risk factors for and true incidence of community acquired Clostridium difficile colitis?
Areas for future research
Studies are needed to formally classify C difficile associated disease
Validated scoring systems for C difficile associated disease need to be developed

**ADDITIONAL EDUCATIONAL RESOURCES**

**Resources for healthcare professionals**
Publicationsandstatistics/Publications/
PublicationsPolicyAndGuidance/DH_093220

**Resources for patients**
NHS Direct (http://cks.library.nhs.uk/patient_information_leaflet/clostridium_difficile) —Patient information leaflet
Department of Health (www.dh.gov.uk/en/Publichealth/Healthprotection/Healthcareacquiredinfection/
Healthcareacquiredgeneralinformation/DH_4115800) —A simple guide to Clostridium difficile
which patients are suitable for surgical or other interventional treatments.

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We will give priority to a drug or device trial if it

- Has a main outcome measure that’s sufficiently clinically relevant and, if it’s a composite outcome, matters enough to patients
- Has important results: please note that we welcome “negative” trials as long as their research questions are important, new, and relevant to general readers, and their designs are appropriate and robust
- Is reported fully in line with the CONSORT statement or the relevant CONSORT extension statement and has sufficient internal and external validity
- Is submitted with the original study protocol, for use in confidence during peer review

with outbreaks of severe disease in North America and Europe.

- Is reported transparently, as explained in our detailed advice below on reporting industry sponsored trials
- Is a phase III, IIIb, or IV trial. Trials done for “label extension” may be useful to BMJ readers if they ask research questions that are sufficiently new and relevant to practice.

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