Is colectomy for fulminant *Clostridium difficile* colitis life saving? A systematic review

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Abstract

**Aim** It is unclear whether colectomy for fulminant *Clostridium difficile* colitis (FCDC) leads to an improvement in survival compared with continued medical therapy for this moribund population.

**Method** Selected studies from 1994–2010 were identified through a comprehensive search theme applied to MEDLINE (OvidSP and PubMed), EMBASE and by hand searching. Data regarding mortality rates between medically and surgically treated patients were extracted. Risk of bias was assessed using a Newcastle–Ottawa Scale score. A meta-analysis of the odds ratios for mortality between surgical and medical treatment for FCDC was conducted using the Mantel–Haenszel method and fixed-effects modelling.

**Results** Five hundred and ten patients with FCDC were identified in six studies. The pooled adjusted odds ratio of mortality comparing surgery with medical therapy was 0.70 (0.49–0.99), suggesting that surgery provided a survival benefit.

**Conclusion** Emergent colectomy for patients with FCDC provides a survival advantage compared with continuing antibiotics. Though there is selection bias of patients having surgery, the results of this systematic review suggest that colectomy has a therapeutic role in treating severe forms of *C. difficile* colitis.

**Keywords** *Clostridium difficile*, colitis, fulminant, mortality, colectomy

Introduction

Although *Clostridium difficile* colitis (CDC) was once an infectious disease notably present among patients with haematological malignancy and other severely immunocompromised states [1–3], an abrupt and dramatic epidemiological shift [4,5] has recently developed. CDC may now routinely affect patients with none of the usual risk factors [6,7] previously associated with this infection, which affects 16 of every 1000 hospitalized patients [8]. The broadened group of at-risk patients has transformed CDC from a medical ailment isolated to immunosuppressed patients to an infection which can occur in any patient. The extent to which aggressive care is undertaken now includes even the option of an emergent total colectomy [9,10] with an end ileostomy for the 3–8% of patients whose disease progresses to a fulminant state with severe sepsis despite maximal medical therapy [11].

The few previous reports which have reported the outcome of colectomy for CDC patients largely include a heterogeneous group of case series of narrative type [12,13]. This has presented a challenge in defining, on the basis of empirical study, at what point in a patient’s medical therapy nonsurgical treatment should be declared a failure, and thus at what point colectomy should be considered as the only remaining viable treatment. An even more fundamental question relates to whether colectomy under such extenuating circumstances actually reduces patient mortality at all, or whether it does more harm in such severely ill patients.

A systematic review of the existing literature was performed to assess the effect on mortality by colectomy for the treatment of fulminant CDC (FCDC).

**Method**

**Definitions**

Fulminant CDC was defined as disease of such severity as to require any one of the following: (i) admission to...
the intensive care unit, (ii) consideration for surgery, or (iii) death due to CDC. One of the authors (DS) initially evaluated all studies retrieved through a database query for inclusion criteria. A second author (MW) performed a separate review of all the identified studies to assess their eligibility for inclusion in the present analysis, which included a full text review of those articles that either met the eligibility criteria or those with unclear eligibility. The data extracted from each study included study design, data on treatment modalities and overall mortality.

Literature search strategy
A comprehensive literature search was performed to identify those peer-reviewed publications reporting on mortality following colectomy for CDC. Searches were conducted while restricting the language to English, and the search included all available published data from 1994–2010 in MEDLINE (using both OvidSP and PubMed) and EMBASE. Searches were performed using subject heading terms and a keyword (‘Clostridium difficile’) to identify matches within any field in the article: ['colectomy' OR 'mortality' OR 'death' OR 'postoperative' OR 'surgery' OR 'outcomes']. Search terms were applied as medical subject headings as well as free text. For all studies which met the inclusion criteria, the reference list for each publication was subjected to a manual cross-reference search in order to identify articles for a full text evaluation. A separate literature search for other systematic reviews and prospective studies was also performed, though none were identified.

Study selection and data abstraction
Several criteria were applied in judging individual studies for inclusion. Studies were included if: (i) they were cohort or prospective studies of inpatients with CDC; (ii) the C. difficile infection under consideration was classified as fulminant or severe; (iii) the interventions in the study under consideration included both medical and surgical therapies, and sufficient data were reported to compute an odds ratio (OR) for mortality if an OR was not provided in the study; (iv) mortality rates were reported separately for patients treated surgically and medically; (v) studies were written in English. Alternatively, studies were excluded if: (i) they were review articles; (ii) there was no comparison between surgical and medical therapy; (iii) mortality was either not reported or was not reported separately for medical and surgical treatment groups; (iv) there was no designation of patients to indicate the severity of colitis; or (v) there were no operative data.

Data from the cohort studies were extracted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement [14].

Study outcome
The primary outcome for the present study was the pooled adjusted OR comparing mortality for patients undergoing surgical therapy with those continuing with medical therapy for FCDC. The definition of mortality reflected that used by each individual study, which was either in-hospital mortality or 30-day postoperative mortality.

Meta-analysis
The presence of heterogeneity was determined through calculation of the $I^2$ index. Since 0% heterogeneity was found, indicating immeasurably small variation among the studies due to heterogeneity rather than random events, and given that each of the included studies were conducted under similar conditions with similar subjects and study outcome, a fixed-effects model was utilized to estimate the overall pooled OR of mortality [15–18]. The Mantel–Haenszel model was used to estimate the pooled OR and the 95% confidence interval (CI) using data from all eligible cohort studies.

Statistical analysis
All statistical analyses were conducted using STATA version 11.2 (StataCorp LP, College Station, TX, USA). The quality of each individual study was assessed using the Newcastle–Ottawa Scale (Table 1). All included studies were judged to be of high quality and with a low risk of bias.

Results

Literature search
Figure 1 provides a flow diagram describing the pedigree of the articles identified through the comprehensive literature search. A total of 77 citations were initially identified. An initial screening of the article titles demonstrated 33 published works [9,10,12,19–48] which were subsequently reviewed in detail. Of these, 27 were excluded due to lack of comparison between medically treated and surgically treated groups ($n = 20$), lack of information regarding mortality for medically and surgically treated patients ($n = 8$), or failure to identify the severity of CDC ($n = 15$).
Characteristics of the included studies

The characteristics of the six studies [42–44,46–48] included in the final analysis are provided in Table 2. The $I^2$ for heterogeneity was 0.0% and the chi-square test suggested homogeneity across the studies ($P = 0.52$). Each of these studies was an analysis of a retrospective cohort, and all required a positive C. difficile stool test for confirmation of CDC, with no presumptive diagnosis of CDC included and with all patients having symptoms of colitis. Additionally, the characteristics of patients with FCDC were similar, including demographic characteristics such as age and gender, with this group of patients uniformly requiring critical care and with the ubiquitous presence of haemodynamic shock either requiring vasopressor therapy and/or manifesting evidence of organ failure.

Mortality – surgery vs medical therapy

The OR of mortality for patients undergoing emergent colectomy for FCDC, compared with ongoing medical therapy for FCDC, was calculated for each of the six studies (Table 1). Two demonstrated no difference in mortality between surgery and continued medical therapy, although they accounted for only 31 patients. When all six studies numbering 510 patients were analysed, the pooled adjusted OR of mortality comparing surgery with medical therapy, and weighted by the contribution of each study, was 0.70 (0.49–0.99), suggesting that surgery was protective in terms of mortality (Fig. 2).

Discussion

The results of this systematic review provide evidence that for the patient with FCDC, whose disease has progressed to the point of a life-threatening infection despite medical therapy, colectomy provides a mortality benefit compared with ongoing medical therapy. Though an extensive procedure with a mortality up to

<table>
<thead>
<tr>
<th>Author</th>
<th>Year(s)</th>
<th>Cohort design</th>
<th>Number of patients with fulminant colitis</th>
<th>Number of patients undergoing colectomy for CDC (%)</th>
<th>Mortality of colectomy patients (%)</th>
<th>Odds ratio for mortality in surgical cohort (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin et al. [43]</td>
<td>1989–1992</td>
<td>Cohort 21</td>
<td>44 (1.8)</td>
<td>2/2 (100)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
<tr>
<td>Dallal et al. [47]</td>
<td>1989–2000</td>
<td>Cohort 64</td>
<td>38 (23)</td>
<td>5/14 (35.7)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
<tr>
<td>Lamontagne et al. [48]</td>
<td>1996–2007</td>
<td>Cohort 165</td>
<td>75 (39)</td>
<td>13/38 (34)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
<tr>
<td>Sailhamer et al. [46]</td>
<td>1996–2007</td>
<td>Cohort 199</td>
<td>38 (28)</td>
<td>25/44 (57)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
<tr>
<td>Dudukgian et al. [44]</td>
<td>1999–2006</td>
<td>Cohort 50</td>
<td>14 (28)</td>
<td>24/75 (32)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
<tr>
<td>Kyne et al. [42]</td>
<td>2003–2005</td>
<td>Cohort 11</td>
<td>4 (36)</td>
<td>5/14 (35.7)</td>
<td>Not reported by authors</td>
<td>Not reported by authors</td>
</tr>
</tbody>
</table>

Table 1 | Details regarding studies included in the final meta-analysis.
80% [40], the present review provides evidence that among patients with FCDC, colectomy should be expected to provide a greater chance of survival than continuing medical therapy that has failed to halt the progression of severe sepsis. Thus for many patients, surgery should be regarded as worth the risk rather than being an invasive and expensive exercise in futility.

There are several limitations of the study. The literature investigating surgery for CDC is extremely narrow, with few publications comparing medical treatment with sufficient methodological rigour. Among the many publications which even broach the subject of colectomy for CDC, only six met the inclusion criteria. The small number of available studies was the main reason why the present review restricted itself to one outcome, since analysis of several endpoints would have had limited strength. Additionally, the retrospective studies included in the meta-analysis did not define explicitly the criteria for failed medical therapy and which patients therefore would require surgery, as would have been established in planning a prospective study. Similarly the studies did not consistently define criteria for determining which patients would not be considered a candidate for colectomy. This introduces a selection bias favouring colectomy. Another limitation of the present review was some lack of information on what constituted medical therapy including antibiotic dose and timing, which again would have been given in a prospective study. The method of diagnosis also differed or was not stated. The six studies demonstrated heterogeneity of the surgical subspecialties represented, which could potentially have introduced additional bias in terms of the decision for surgery. Although each study reported mortality in the surgery group, the official cause of death for all patients was not provided. Additionally, the outcome for the studies generally focused on a short-term (30 days) period.

These limitations are applicable to systematic reviews in general, but interpreting the results of the present review should be done with caution given the quality of data in the literature as a whole. The present study does not necessarily lead to the conclusion that surgery should be offered to every patient with FCDC regardless of age and co-morbidity. Surgery did not reduce mortality among medical therapy failures in every study, but when all were taken together it did so. Nor did the studies offer any information on the exact indication for surgery, and yet this is perhaps the most important consideration for physicians. The absence of this information will not remove the self-fulfilling prophecy that a patient offered surgery too early may appear to have been snatched from the brink of death by a timely colectomy, while those felt to be at too high a risk for surgery will die anyway, affirming a preconception against surgery.

It has recently been suggested that a diverting loop ileostomy with colonic lavage as an alternative to colectomy can be as effective and safer. Neal et al. [49] recently published the results for 42 patients with FCDC who underwent a diverting loop ileostomy, with polyethylene glycol and vancomycin introduced through the efferent limb. It was maintained that the mortality after this procedure was less than a historical control group of patients having colectomy. Though this study does not answer the question of when to operate, it may be the beginning of a paradigm shift on what form of surgery should be performed once the decision for intervention has been made. Despite its potential importance, the study has the limitations that diversion did not always avoid a colectomy. In addition the need to identify which type of C. difficile will respond to diversion and lavage and the rate of recurrent CDC following ileostomy closure are also important considerations. It is unclear whether diversion and lavage will reduce the need for a permanent ileostomy, even if the surgery to form the original ileostomy is better tolerated than colectomy. Nor is it clear whether less traumatic surgery will reduce mortality if performed late in the course of the disease when the surgeon is usually consulted.

### Table 2 Odds ratios (ORs) determined by meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>Newcastle–Ottawa Scale</th>
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<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>Selection</td>
</tr>
<tr>
<td>Rubin et al. [43]</td>
<td>1.727</td>
<td>0.212 14.048</td>
<td>****</td>
</tr>
<tr>
<td>Dudukgian et al. [44]</td>
<td>0.357</td>
<td>0.116 1.095</td>
<td>****</td>
</tr>
<tr>
<td>Dallal et al. [47]</td>
<td>0.568</td>
<td>0.258 1.253</td>
<td>****</td>
</tr>
<tr>
<td>Sailhamer et al. [46]</td>
<td>0.938</td>
<td>0.534 1.649</td>
<td>****</td>
</tr>
<tr>
<td>Lamontagne et al. [48]</td>
<td>0.587</td>
<td>0.294 1.173</td>
<td>****</td>
</tr>
<tr>
<td>Kyne et al. [35]</td>
<td>1.4</td>
<td>0.232 8.464</td>
<td>****</td>
</tr>
<tr>
<td>Mantel–Haenszel pooled OR</td>
<td>0.703</td>
<td>0.497 0.994</td>
<td></td>
</tr>
</tbody>
</table>

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While exact cut-off values for laboratory test results or vital sign measurements have not been validated in any study to indicate a ‘point of no return’ for continued medical treatment for CDC, when severe sepsis progresses despite intensive care, colectomy should be discussed. To achieve this goal, the surgeon should be notified when any patient with CDC is transferred to the intensive care unit. The present evidence indicates that surgery should take the form of colectomy, relegating the use of a diverting stoma to research until further data are available.

Emergency colectomy for FCDC provides a survival advantage compared with continuing antibiotics which no longer appear to be effective. Although the present evidence is subject to selection bias, it suggests that colectomy is associated with a lower mortality than continued medical treatment when the patient is no longer improving.

**Author contributions**

All authors contributed equally to study design, data acquisition, data interpretation and manuscript preparation.

**References**

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Colectomy for fulminant *Clostridium difficile* colitis


46 Sailhamer EA, Carson K, Chang Y *et al.* Fulminant *Clostridium difficile* colitis: patterns of care and predictors of
Editor’s choice
doi:10.1111/codi.12339

From a hospital, insurer and societal perspective, *Clostridium difficile* (*C. difficile*) infection poses a major financial strain on the health system. From the patient’s perspective, hospital-acquired *C. difficile* infection may run the gamut from diarrhoea causing minor discomfort to prolonged hospital stay and on to life-threatening enterocolitis associated with mortality rates exceeding 50%. Adult *C. difficile* fulminant colitis is on the rise and treatment standards, be they medical or surgical, have not been set. This is discussed in the present systematic review with a view to determine whether emergent colectomy has a role to play, or may even be preferable to medical management, in fulminant *C. difficile* colitis. The systematic review assessed six papers that compared the outcome of medical versus surgical treatment in just over 500 patients. The authors duly acknowledge the limitations of the review but conclude firmly that colectomy has its role in the management of fulminant *C. difficile* colitis refractory to medical management. The management of fulminant *C. difficile* is certainly not set in stone and is in need of further research. Awareness of the condition and early recognition of patients failing medical management, probably before patients go to the intensive care unit, is essential. This requires a multidisciplinary approach as with any patient with acute fulminant ulcerative colitis. The issues of exact timing of surgery and whether we should do a colectomy, loop ileostomy and colonic lavage or other procedures need clarification and this will no doubt spawn future research.

**Alexander Engel**
Editor, Colorectal Disease