Timing and type of surgical treatment of *Clostridium difficile*–associated disease: A practice management guideline from the Eastern Association for the Surgery of Trauma

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BACKGROUND: *Clostridium difficile* infection is the leading cause of nosocomial diarrhea in the United States; however, few patients will develop fulminant *C. difficile*–associated disease (CDAD), necessitating an urgent operative intervention. Mortality for patients who require operative intervention is very high, up to 80% in some series. Since there is no consensus in the literature regarding the best operative treatment for this disease, we sought to answer the following:
PICO [population, intervention, comparison, and outcome] Question 1: In adult patients with CDAD, does early surgery compared with late surgery, as defined by the need for vasopressors, decrease mortality?
PICO Question 2: In adult patients with CDAD, does total abdominal colectomy (TAC) compared with other types of surgical intervention decrease mortality?

METHODS: A subcommittee of the Practice Management Guideline Committee of the Eastern Association for the Surgery of Trauma conducted a systematic review and meta-analysis for the selected questions. RevMan software was used to generate forest plots. Grading of Recommendations, Assessment, Development and Evaluations methodology was used to rate the quality of the evidence, using GRADEpro software to create evidence tables.

RESULTS: Reduction in mortality was significantly associated with early surgery, with a risk ratio (RR) of 0.5 (95% confidence interval [CI], 0.35–0.72). The quality of evidence was rated "moderate." Considering only the first procedure performed, mortality seemed to trend higher for TAC, with an RR of 1.11 (95% CI, 0.69–1.80). Considering only the actual procedure performed, the point estimate switched sides, showing a trend toward decreased mortality with TAC (RR, 0.86; 95% CI, 0.56–1.31). The quality of evidence was rated "very low."

CONCLUSION: We strongly recommend that adult patients with CDAD undergo early surgery, before the development of shock and need for vasopressors. We conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery) when the diagnosis of The Centers for Disease Control and Prevention is known. (*J Trauma Acute Care Surg*. 2014;76: 1484–1494. Copyright © 2014 by Lippincott Williams & Wilkins)

KEY WORDS: Fulminant CDAD and surgery; surgery and *Clostridium-difficile* associated disease; *Clostridium-difficile* outcomes; *Clostridium-difficile mortality*; guidelines and GRADE methodology.

Discovered in 1935 and recognized to be associated with antibiotic use by the late 1970s, *Clostridium difficile* infection (CDI) is the leading cause of nosocomial diarrhea in the United States.[1] CDI severity is increasing, as 1% to 5% of affected patients require intensive care unit (ICU) admission and their disease leads to colectomy or death.[2] Fulminant *C. difficile*–associated disease (CDAD) is defined as severe CDI resulting in clinical deterioration, such as multiorgan system failure, peritonitis, and/or sepsis.[3] The mortality rate of patients with CDAD remains high even after surgical intervention.[4,5]

In the last decade, several changes in the treatment paradigm of CDAD have been elucidated, particularly with the introduction of new antibiotics such as fidaxomicin[6] and the emerging role of fecal transplants to reduce recurrence.[7] All of these tools are extremely useful for treating patients with such high mortality rates and disease burden. However, in patients with organ failure, surgical treatment remains a lifesaving option.[8–10]

Findings in the literature suggest that prompt surgical treatment of patients with fulminant CDAD is necessary to ensure patient survival.[9] However, controversy remains regarding the best surgical approach and timing. Recent efforts have been made in the creation of a scoring system to predict deterioration and improve patient care. New surgical approaches such as ileostomy and washout have shown promising results, but more rigorous data and longer follow-up, especially with regard to disease recurrence after ileostomy reversal, are needed to evaluate the true value of these techniques regarding mortality.[11]

The objective of this article, which was sponsored by the Eastern Association for the Surgery of Trauma (EAST), was to provide evidence-based recommendations that may be used to direct the decision-making processes related to the care of patients with severe CDAD that may require surgical intervention. This guideline has been developed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework that was recently adopted by EAST.[12,13]

The GRADE framework, now adopted by more than 70 international societies and organizations worldwide, provides a systematic and transparent framework for clarifying questions, determining the outcomes of interest, summarizing the evidence for such questions, and moving from evidence to a recommendation or decision. Importantly, within the GRADE framework, the evidence is rated not according to each individual study but across studies for specific patient-important clinical outcomes. Recommendation strength and direction are based not only on evidence quality but also on the balance between desirable and undesirable outcomes and patient values and preference.[14]

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OBJECTIVES

The objective of this guideline was to evaluate whether surgical timing (early vs. late) and type (total abdominal colectomy [TAC] vs. other surgical options) are associated with better outcomes in patients with severe CDAD.

The population (P), intervention (I), comparator (C), and outcome (O) questions are defined as follows:

PICO Question 1: In adult patients with CDAD, does early surgery compared with late surgery (as defined by the need for vasopressors) decrease mortality rates?

PICO Question 2: In adult patients with CDAD, does the use of TAC compared with other types of surgical interventions decrease mortality rates?

INCLUSION CRITERIA FOR THIS REVIEW

Study Types

For the purpose of making recommendations, studies included randomized controlled trials, prospective observational or retrospective studies, and case control studies. Meta-analyses, case reports, letters, and reviews containing no original data or comments were excluded.

Participant Types

We included studies of adult patients without restricting sex, ethnicity, or degree of comorbidity. Only studies pertaining to the treatment of hospitalized patients with CDAD were included. CDAD was defined as severe CDI resulting in clinical deterioration, such as multiorgan system failure, peritonitis, and/or sepsis as a consequence of the disease.

Intervention Type

We included studies in which TAC or subtotal colectomy (each defined as removal of most of the colon excluding the rectum) was performed compared with other procedures such as segmental colectomy, exploratory laparotomy without colectomy, or ostomy formation.

Outcome Measure Types

Outcomes were chosen by the team and rated in importance from 1 to 9, with scores of 7 to 9 representing critical outcomes. The following outcomes were considered by the committee members: length of stay, ICU length of stay, cost, ventilator-free days, renal failure, and respiratory failure. However, all of these criteria were deemed noncritical for the decision-making process within the GRADE framework. In addition, the available literature did not provide sufficient or consistent measurements across the studies, specifically if the onset of related conditions such as renal or respiratory failure occurred before or after surgical intervention. Only a reduction in mortality was deemed a critical outcome for the decision-making process, and this was chosen as the primary outcome measure.

REVIEW METHODS

Search Strategy

With the assistance of an information specialist, we conducted a systematic search of the PubMed, EMBASE, and Cochrane Library databases for studies published from 1992 to January 2014. The search used the following MeSH terms alone or in combination: *Clostridium difficile*, *colitis*, *colectomy*, *surgery*, and *mortality*. We used the "Related Articles" function to broaden the search and scan all citations for relevance. We used only articles available in English. In addition to the electronic search, we manually searched the bibliographies of recent reviews and articles.

Study Selection

After completing the literature search, two independent reviewers screened the titles and abstracts; any disagreement on inclusion was resolved through consensus. We excluded case reports and narrative review articles. The resulting studies were subjected to full-text review by two independent reviewers.

Data Extraction and Management

Using a form developed by the team, two independent reviewers extracted data from the individual studies into Microsoft Excel, using double data entry for accuracy. We then entered these data into Review Manager X.6 (Review Manager [RevMan] [Computer program], Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), including information on the authors, study number, country of origin, study methodology, population, intervention, and relevant outcome measures.

Methodological Quality Assessment

The articles were evaluated using the GRADE framework,[12,14–29] which describes four levels of quality of evidence: high, moderate, low, and very low. Quality of evidence is reflected as the extent to which one can be confident that an estimate of effect is correct and includes an explicit consideration of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[21–26] The data were entered into GRADEpro for the generation of evidence tables.

Recommendations are based on the overall quality of evidence with implicit consideration of the risk-benefit ratio and patients' values and preferences. Strong recommendations are prefaced by the statement "we strongly recommend," while weak recommendations are prefaced by the statement "we suggest" or "we conditionally recommend" as per the GRADE methodology.

Measures of Treatment Effect

We reported the dichotomous outcome of mortality as a risk ratio (RR) with associated 95% confidence intervals (CIs) and p values since the baseline incidence of the primary outcome was thought to be relatively high in this population (>20%). The unit of analysis was individual patients.

Assessment of Heterogeneity

Potential heterogeneity exists because of population differences, different types of surgery performed, and how patients are defined. We examined these differences across studies to assess the clinical and methodological heterogeneity. For the meta-analysis, we used RevMan to calculate the Q statistic, and then the I^2 statistic (%) was used to determine the proportion of variation between studies attributable to heterogeneity and categorized as "low" (25–49%), "moderate" (50–74%), or "high" (74–100%). We also used the χ^2 test for heterogeneity and examined the CIs for overlap, with decreasing overlap representing increasing heterogeneity.

TABLE 1. Study Characteristics

Author	Country	Type	Total	Surgery, n	Initial Operation			Data Early vs. Late	Overall Surgical Mortality, %
					TAC	Limited rsxn or Stoma	No resection		
Al-Abed[31] 2010	United Kingdom	Retrospective	528	20	17	3	—	—	40
Ali 2008	United States	Retrospective	36	36	28	8	—	X	47
Ananthakrishan[32] 2011	United States	Retrospective	13,713	574	574	—	—	—	non recorded
Byrn[33] 2008	United States	Retrospective	5,718	73	63	10	—	—	34
Chan[34] 2009	United Kingdom	Retrospective	15	15	12	3	—	—	67
Dallal 2002	United States	Retrospective	2,334	44	36	5	3	—	57
Dudukgian[35] 2010	United States	Retrospective	398	14	11	2	1	—	36
Gash[36] 2010	United Kingdom	Retrospective	1,398	17	16	1	—	—	53
Grundfest[37] 1996	United States	Retrospective	59	12	5	5	2	—	42
Halabi[57] 2013	United States	Retrospective	562,247	3,900	3,900	—	—	X	32
Hall[38] 2008	United States	Retrospective	3,237	36	34	2	—	X	36
Hermsen[39] 2008	United States	Retrospective	7,588	13	13	—	—	X	46
Issa[40] 2007	United States	Retrospective	60	12	12	—	—	—	NR
Jobe[41] 1995	United States	Retrospective	201	10	6	1	3	—	30
Kenneally[42] 2007	United States	Retrospective	278	6	—	—	—	—	33
Klipfel[43] 2000	United States	Retrospective	223	10	1	3	6	—	80
Koss[44] 2006	United Kingdom	Retrospective	3,472	14	9	5	—	X	36
Kurian[45] 2011	United States	Retrospective	14	14	14	—	—	—	28
Lipsett[46] 1994	United States	Retrospective	3,300	13	7	6	—	—	38
Longo[47] 2004	United States	Retrospective	67	67	53	14	—	—	48
Markelov[48] 2011	United States	Retrospective	13	13	12	1	—	X	46
Medich[49] 1992	United States	Retrospective	12	12	5	3	4	—	33
Morris[50] 2002	United States	Retrospective	157	12	12	—	—	—	25
Muto[51] 2005	United States	Retrospective	419	26	—	—	—	—	NR
Neal[11] 2011	United States	Prospective	42	42	—	42	—	—	19
Pepin[52] 2009	Canada	Retrospective	130	130	124	6	—	—	37
Perera[10] 2010	United States	Retrospective	35	35	32	3	—	X	46
Rubin[53] 1995	United States	Retrospective	710	4	2	2	—	—	50
Sailhamer[9] 2009	United States	Retrospective	4,796	78	69	6	3	X	35
Seder[54] 2009	United States	Retrospective	6,841	69	68	1	—	X	42
Synnott[55] 1998	Ireland	Retrospective	138	5	5	—	—	—	80
Trudel[56] 1995	Canada	Prospective	350	7	7	—	—	—	64

Data Synthesis (Meta-analysis)

We performed a meta-analysis of the outcome of mortality rate for each PICO question by using the RevMan software. We used the DerSimonian and Laird random-effects model method[30] because our studies did not share a common effect size and unknown influential factors could vary across studies (unknown confounders). This allowed us to incorporate both the intrastudy and interstudy variability along a distribution of the "true" effects, which weighs larger and smaller studies more evenly. Potential heterogeneity across studies was assessed using the Q statistic, I^2 statistic (%), and χ^2 test for heterogeneity. If heterogeneity was "moderate" to "high," we did not consider pooling the data; rather, we performed a qualitative narrative summary of the results only.

Sensitivity Analysis

We conducted a sensitivity analysis for PICO Question 2 to investigate the implications of the ultimate surgery type performed compared with the first surgery since some patients underwent more than one procedure. A further analysis was performed to examine only those studies that reported their conversion rates from other procedures to TAC.

RESULTS

The original search yielded 62 studies; after the elimination of studies that did not contain the original data, only 38 were deemed appropriate for full-text review. We further excluded six studies: one excluded study included a pediatric population, another was descriptive in nature, and four did not address the specific questions outlined in our review. We ultimately included 32 studies in this guideline for recommendations.[3–5,9–11,31–56] Of these articles, there were no randomized trials; two were prospective studies,[4,5,11,31–37,56] while the remaining were retrospective (Table 1). Note that in this table, some studies included the total number of patients with CDI as well as those patients who had CDAD that required intervention, while others included only patients with CDAD. As outlined in the PRISMA diagram in Figure 1, we included all 32 studies in

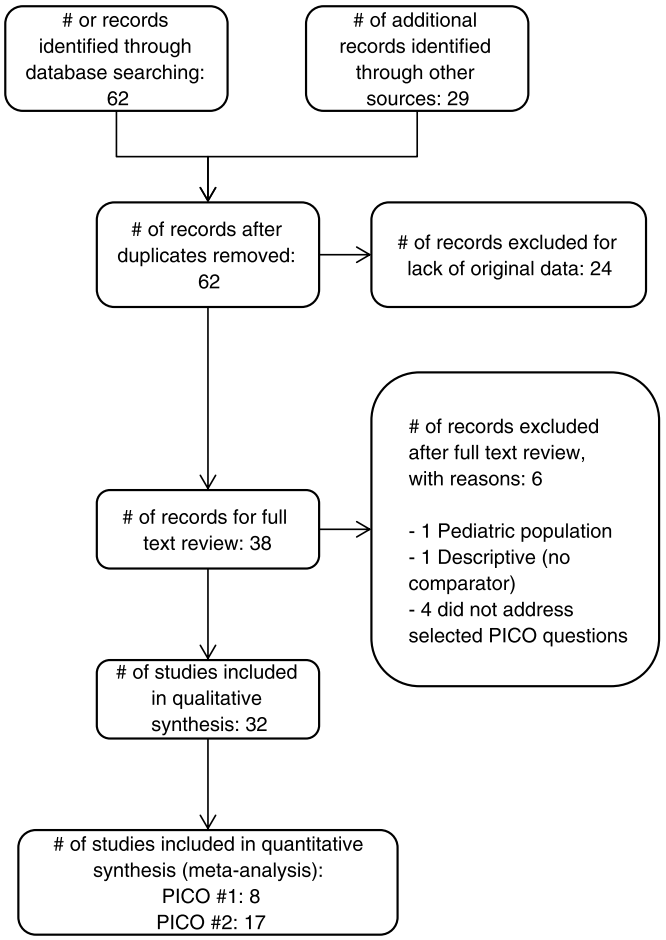

Figure 1. PRISMA flow diagram for study selection.

the qualitative synthesis. We then identified eight studies that were appropriate for quantitative synthesis (meta-analysis) for PICO Question 1, and 17 studies for PICO Question 2.

RESULTS OBTAINED FOR PICO QUESTION 1

In adult patients with CDAD (P), does early surgery (I) compared with late surgery (C) (as defined by the need for vasopressors) decrease mortality rates (O)?

Qualitative Synthesis

Overall surgical mortality was 19% to 80% in the included studies (Table 1). Seder et al.[54] described 6,841 patients with CDAD and showed a decreased mortality associated with surgery before the development of the vasopressor requirement. The experience of Hall et al.[38] with 3,237 consecutive cases of CDAD showed an increased mortality rate when surgical exploration was performed after intubation or the development of respiratory failure and the use of vasopressors.

Longo et al.[47] found that peritonitis and bowel perforation indicative of delayed surgical therapy were associated with increased mortality rates. Delaying surgery until after the development of respiratory failure, defined as unplanned intubation, was found to result in increased mortality rates in six articles,[4,9,38,44,54,57] while similar findings were noted in four studies when surgical intervention followed renal failure.[38,44,54,57] Finally, in 10 studies, delaying surgery until the patient became hemodynamically unstable and required vasopressors was associated with increased mortality rates.[4,9,10,32,38,39,44,48,52,54,57] Overall, these studies suggested that early surgery before the development of shock or organ failure was associated with lower mortality rates in patients with CDAD.

While most studies do not address a specific period in which surgery should be considered, a few studies suggest that the window for optimal surgical management is relatively short. In the study of Ali et al.,[32] survivors had surgery at a mean of 3.2 days, compared with nonsurvivors at 5.4 days. Sailhamer et al.[9] similarly showed that of patients admitted to the ICU for CDAD, mean time to the operating room for survivors was 1.9 days compared with a mean time of 3.9 days for nonsurvivors. The most recent article addressing the association with mortality and specific timing of surgery in patients with CDAD was published in November 2013.[57] Halabi et al.[57] retrospectively reviewed the Nationwide Inpatient Sample from 2001 to 2010 for colectomy in patients with *C.*

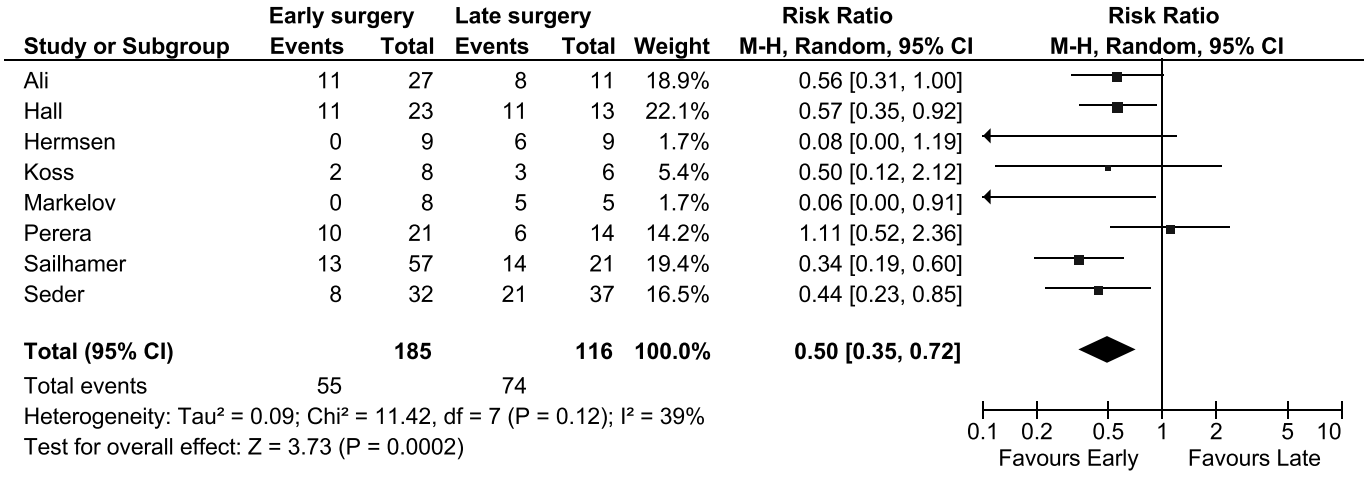

Figure 2. Early versus late surgery defined as need for vasopressors, meta-analysis.

Question: Should Early surgery versus late surgery be used for C. difficile Colitis?

Bibliography: . [Intervention A] versus [intervention B] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Early surgery versus late surgery		Risk with Control	Risk difference with Early surgery versus late surgery (95% CI)
Reduction in Mortality (CRITICAL OUTCOME)											
301 (8 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	74/116 (63.8%)	55/185 (29.7%)	**RR 0.5** (0.35 to 0.72)	**638 per 1000**	**319 fewer per 1000** (from 179 fewer to 415 fewer)

[1] Reduction of 50% is quite large

Figure 3. Early versus late surgery defined as need for vasopressors, evidence profile.

difficile colitis and the association with mortality. The overall mortality associated with colectomy was 30.7%. Surgical intervention delayed for more than 3 days after admission in patients with CDAD was associated with higher mortality rates (odds ratio, 1.09; 95% CI, 1.05–1.14; $p < 0.05$).

Quantitative Synthesis (Meta-analysis)

Before pooling study data, we assessed methodological and clinical heterogeneity across the studies and found variability in how the intervention and comparator were defined. The most commonly defined measure of early versus late surgery was progression to the need for vasopressors. With the use of this definition, eight studies were included in the meta-analysis. We found that early surgery was associated with reduced mortality rates with an RR of 0.50 (95% CI, 0.35–0.72; Fig. 2). Of note, the I^2 statistic was 39%, falling into the "low" heterogeneity category, indicating that the studies were comparable.

Grading the Evidence

With the use of the GRADE framework for assessing the outcome of reduced mortality rates, no serious risk of bias, inconsistency, indirectness, or publication bias was found. However, severe imprecision was noted since the studies were small and the CIs were large. Starting from observational studies (which are considered low quality), we then rated down for imprecision. Therefore, the overall quality of evidence was very low (see the GRADE profile shown in Fig. 3).

DISCUSSION

Early surgery for patients with fulminant CDAD is associated with reduced mortality rates. In the absence of validated prediction scores, determining which CDAD patients will progress to shock can be difficult to elucidate. However, the early signs of hemodynamic stability, such as low mean arterial pressures or decreasing urine output, can potentially serve as triggers for the need for surgical intervention (early surgery) before the development of multiorgan system failure or shock.

Using hemodynamic instability as the trigger for surgical intervention is associated with increased mortality, and patients should proceed to surgery before progression to shock. Although an exact time frame is unclear, the current data suggest that this is usually within 3 days to 5 days after diagnosis if patients are worsening or not clinically improving. While this is not a definite time frame, it may be helpful to guide clinicians in identifying patients prospectively who are at risk for proceeding to hemodynamic instability. We anticipate that this will be enhanced in the future as a physiologic scoring system is refined.[8]

RECOMMENDATION

Within the GRADE framework, once the overall quality of evidence across studies and outcomes is determined, the guideline panel will make a recommendation that considers the following: quality of the body of evidence, patients' values and preferences, and cost/resource use. Despite the overall quality of evidence being very low, the panel considered that most patients would place a high value on the potential 50% reduction in mortality and that the potential benefit outweighs any potential harm in performing surgery early. This allows for a strong recommendation. Within the GRADE framework, a strong recommendation implies that most individuals would want the recommended course of action and only a small proportion would not.[12–14]

RECOMMENDATION: In adult patients with CDAD, we strongly recommend that patients undergo surgery early, that is, before the development of shock or the need for vasopressors. This recommendation is based on very low quality evidence but considers that individual patients will place a high value on the overall benefit (reduced mortality rates).

RESULTS FOR PICO QUESTION 2

In adult patients with CDAD (P), does TAC (I) compared with other types of surgical intervention (C) decrease mortality rates (O)?

Qualitative Synthesis

In some studies,[4,5,31,32,37,38,41,43,47,48,52] total colectomy carried a higher mortality rate than partial colectomy, although this was not statistically significant. In these cases, it was not specified whether patients who underwent total colectomy were sicker or had extensive necrosis and tissue damage as an indication for total rather than partial colectomy. Several studies assigned mortality or survival to the initial procedure performed despite the fact that many patients were later

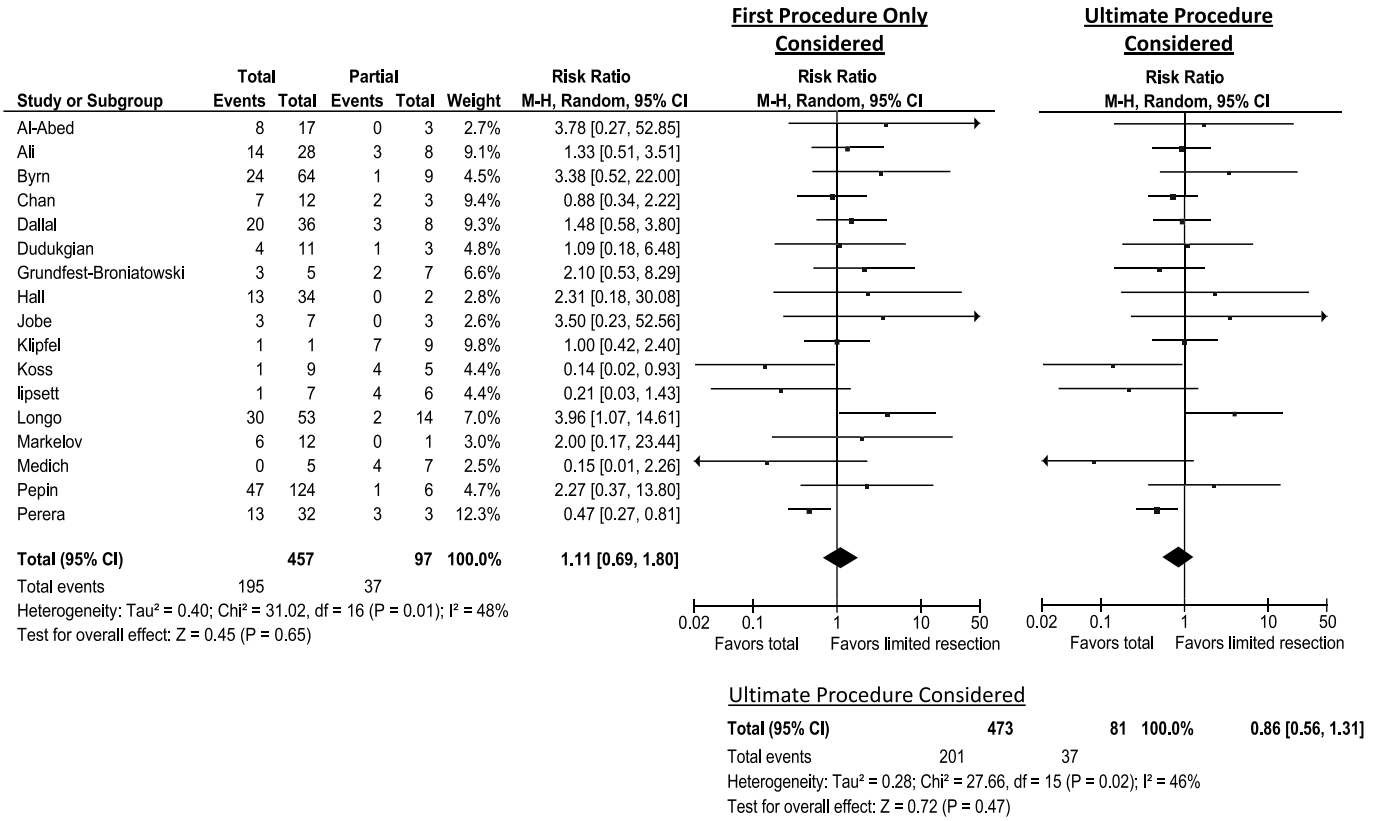

Figure 4. Total colectomy versus partial or no resection, meta-analysis.

converted to TAC (an intention-to-treat approach). These studies were likely confounded by timing, with later conversions to TAC representing a delay in appropriate treatment, thus assigning mortality inappropriately.

Klipfel et al.[43] showed that CDAD and an acute abdomen is a lethal combination that carries an 80% mortality rate regardless of the procedure performed; however, a major limitation of these findings was that these patients received prolonged antibiotic treatments and that the decision for surgical intervention was purely subjective. Recognizing that the diagnosis and treatment of CDAD have evolved during the past two decades, the 1994 study by Lipsett et al.[46] found that partial colectomy is uniformly fatal, with a mortality rate of 100% versus a mortality rate of 14% in patients undergoing total colectomy. In this series, a worse outcome was associated with the presence of peritonitis as shown in earlier studies.[46]

Quantitative Synthesis (Meta-analysis)

Although there was minimal methodological heterogeneity, there was some clinical heterogeneity because the comparator

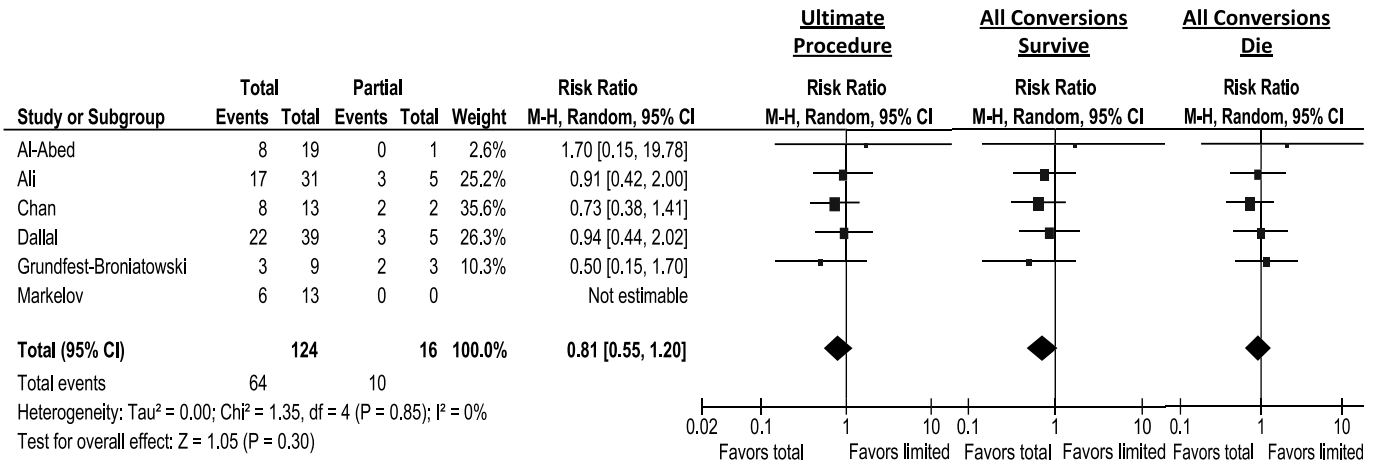

Figure 5. Subgroup analysis, total colectomy versus partial or no resection—conversion rate given; sensitivity analysis evaluating best- and worst-case scenario for conversion.

Question: Should Total vs Partial or No Resection- Ultimate Procedure be used for C. difficile Colitis?

Bibliography: . [Intervention A] versus [intervention B] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Partial or No Resection- Ultimate Procedure	With Total		Risk with Partial or No Resection- Ultimate Procedure	Risk difference with Total (95% CI)
Reduction in mortality (CRITICAL OUTCOME)											
554 (17 studies)	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	serious[2]	undetected	⊕◯◯◯ VERY LOW[1,2,3,4] due to imprecision	37/81 (45.7%)	201/473 (42.5%)	**RR 0.86** (0.56 to 1.31)	**457 per 1000**	**64 fewer per 1000** (from 201 fewer to 142 more)

[1] Minor clinical and methodologic heterogeneity, not directly related to outcome

[2] Confidence intervals wide and have potential for favorability in either direction

[3] Greater than 10% reduction in mortality

[4] Potential confounding by delay in TAC

Figure 6. Ultimate procedure, total colectomy versus partial or no resection, evidence profile.

to TAC was not consistent across all studies. Of note, however, the number of patients undergoing procedures other than TAC or partial colectomy was quite low. The I^2 statistic was "low" at 48%, although this is likely due to the wide CIs of each study rather than a true homogeneity between the studies.

Twenty studies compared total colectomy versus other procedures or no surgery as treatment for CDAD,[4,5,10,31,32,34,35,37,38,41,43,44,46–49,52–56] 17 of which had sufficient data for analysis. Because the ultimate procedure performed likely dictates prognosis, this was chosen for the comparison group.

When considering only the first procedure performed, mortality seemed to trend higher for TAC, with an RR of 1.11 (95% CI, 0.69–1.80). When taking into account that many patients were converted to TAC in a later operation, the point estimate actually switches sides, showing a slight change in results, with an RR of 0.86 (95% CI, 0.56–1.31). This is shown in Figure 4. Although neither reaches statistical significance (likely due to power), change in direction of the point estimate is compelling within the construct of evidence-based medicine.

A sensitivity analysis was performed on the subgroup of studies that reported conversion rates to investigate the potential confounding impact of the delay associated with first performing a procedure other than TAC. The ultimate procedure performed was compared with a best-case scenario where all patients who converted instead underwent TAC first and survived, compared with a worst-case scenario in which all patients who were converted underwent TAC first and died. In each case, the point estimate favored TAC, although the CIs crossed the null hypothesis (Fig. 5).

Grading the Evidence

With the use of the GRADE framework, no serious risk of bias, indirectness, or publication bias was detected; however, we rated down for inconsistency (which was apparent due to clinical heterogeneity and a borderline I^2 statistic) and imprecision (due to few events and wide CIs) (Fig. 6).

DISCUSSION

In the worst-case scenario with the given data, total colectomy does not increase mortality. In the best-case scenario with the given data, total colectomy may decrease mortality. Many of the patients who ultimately died after total colectomy had significant delay in this procedure, with many first undergoing a more limited procedure, thus blunting the effectiveness of the total colectomy and making our positive estimate likely too conservative. In addition, in each of the studies, the proportion of patients undergoing less than a total colectomy is quite small. This likely reflects selection bias. Most of the studies suggest that the patients were quite different, with the patients undergoing total colectomy being much sicker, with having more comorbidities, thus having a higher baseline mortality.

A recent meta-analysis by Bhangu et al.[58] showed a point estimate for total colectomy that was unfavorable. Because the CIs cross the null hypothesis and indicate no difference, they could only accurately conclude that total colectomy is a reasonable option. Their ultimate conclusion (in opposition to their point estimate) that total colectomy is superior and thus

Question	Recommendation
PICO#1	In adult patients with Clostridium Difficile Associated Disease (CDAD), we strongly recommend that patients undergo early surgery, prior to the development of shock and need for vasopressors. **Strong recommendation** (very low quality of evidence, very large magnitude of effect)
PICO#2	In adult patients with Clostridium Difficile Associated Disease (CDAD) undergoing surgery, we conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery) when the diagnosis of Clostridium Difficile colitis is known. **Conditional recommendation** (very low quality of evidence).

Figure 7. Recommendations.

the procedure of choice was interestingly not supported by their meta-analysis.

In our meta-analysis, we considered that having multiple operations constituted a treatment failure at initial operation, such that the ultimate operation performed would have significant impact. When we explored this, we did indeed find that our effect estimate shifted to the other side, in favor of total colectomy. Although the null hypothesis is still included, the magnitude of the effect is a nearly 15% reduction in mortality, and that the effect changes direction is compelling. On subgroup analysis of the studies specifically reporting conversions from limited procedures to total colectomy, we find similar estimates, with sensitivity analysis considering best- and worst-case scenarios for mortality after conversion, maintaining a point estimate in favor of total colectomy.

RECOMMENDATION

While the overall body of evidence that informs this recommendation is very low, the authors took into account that potential confounding factors (i.e., delay in undergoing TAC as the procedure) could plausibly lead to an underestimated version of the true effect. In this case, that sicker patients (having failed the initial procedure) were converted to TAC but still seemed to fare better increases our confidence in the intervention.

In addition, the panel again considered patients' values and preferences, noting that most patients would favor definitive treatment at the time of initial surgical intervention and in weighing the desirable and undesirable outcomes, they would again place a high value on one definitive treatment that could reduce their mortality. Taking into account all these factors, the panel voted for a conditional recommendation in favor of TAC.

RECOMMENDATION: In adult patients with CDAD undergoing surgery, we conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery). This recommendation is based on very low-quality evidence but places a high value on patient preferences for a definitive surgical intervention that may more effectively reduce mortality rates.

Future Investigation

A multi-institutional randomized controlled trial (ClinicalTrials.gov identifier NCT01441271) entitled "Optimal surgical treatment of fulminant *Clostridium difficile* colitis"[59] was initiated to determine the best operative procedure for patients with CDAD. In this study, patients were intended to be randomized to ileostomy with colonic lavage versus total colectomy; however, the study was recently closed due to a lack of meaningful enrollment.

Neal et al.[11] described an innovative procedure in which an ileostomy is created to allow for colonic washing and direct topical treatment with vancomycin enemas. This article quoted a 19% mortality rate in these patients compared with a 50% mortality rate in historical controls who underwent total colectomy. The article showed encouraging results; however, the recurrence rate after ileostomy reversal and a longer follow-up period need to be reported in addition to reproducibility verification in other institutes before this procedure can be accepted as a standard of care. Additional studies evaluating this treatment and other novel surgical approaches are also needed. Finally, further investigation is required to evaluate scoring systems that can predict deterioration to better inform decision making with regard to surgery timing and type.

USING THESE GUIDELINES IN CLINICAL PRACTICE

These guidelines represent a very detailed summary of the literature regarding CDAD and surgical timing and type and are meant to inform the decision-making process, not replace clinical judgment. Patients with fulminant CDAD carry a very high mortality rate. The literature available for review thus far supports the course of earlier intervention when deterioration is present and total colectomy as the procedure of choice.

CONCLUSION

In summary, two important evidence-based recommendations can be provided by using the GRADE methodology (Fig. 7). First, we strongly recommend that adult patients with CDAD undergo early surgery before developing shock and the need for vasopressors. The literature suggests that this may be between 3 days and 5 days after diagnosis in patients who are worsening or not clinically improving. Second, in adult patients with CDAD undergoing surgery, we conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery) when the diagnosis of *C. difficile* colitis is known.

AUTHORSHIP

P.F., T.M.D., and E.R.H. conceived the study. P.F. created the PICO questions. P.F., C.G.V., E.R.H., A.P.-E., T.E., H.D., N.D.M., P.B., A.R., and T.M.D. voted regarding the outcomes of interest for these PICO questions. H.D. and N.D.M. evaluated the articles independently for other outcomes, specifically renal failure and respiratory failure. E.J. and P.F. performed the entire literature search, read all of the abstracts, and selected the articles for review. P.F., C.G.V., E.R.H., A.P.-E., T.E., H.D., N.D.M., P.B., A.R., and T.M.D. reviewed and summarized the selected articles. P.F. extracted the data from the selected articles. S.S. and P.F. entered the extracted data into the RevMan and GRADEpro programs and evaluated the results for recommendations. C.G.V. extracted the data and performed the same task independently. P.F. and C.G.V. wrote the manuscript. P.F. and C.G.V. contributed equally to this work and should be noted as co–first authors. S.S. reviewed the manuscript for methodological content and made critical revisions to the final draft. All authors participated in the critical review of all versions of this article.

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DISCLOSURE

The authors declare no conflicts of interest.

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