

# Impact of Operative Delay on Sepsis and Mortality in Patients with Acute Diverticulitis

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## Abstract

**Background:** Ideal operative timing for non-emergent, acute diverticulitis (AD) remains unclear. Medical management is initially attempted to convert a high risk urgent surgery to a less morbid elective surgery, or to avoid surgery altogether. A large proportion of patients will fail medical treatment and require colectomy.

**Objectives:** To evaluate the effect of operative delay on sepsis and mortality in patients with AD.

**Methods:** Patients from the American college of surgeons national surgical quality improvement program (ACS-NSQIP) database who underwent colectomy with a primary diagnosis of diverticulitis between 2005 and 2014 were included. Multiple patient variables were analyzed to see their combined effect on death and sepsis. Patients undergoing surgical intervention on hospital day 0, emergent cases and those with preoperative sepsis were excluded. The impact of operative delay on mortality and sepsis was evaluated using day from admission as the predictor of the primary outcomes. Secondary outcomes included urinary tract infection (UTI), pneumonia (PNA), need for blood transfusion, septic shock, return to the operating room, length of stay (LOS), readmission, wound dehiscence, and surgical site infections (SSI). Frequency of patient variables was recorded and a multiple variable logistic regression analysis was performed to control for possible confounders. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for primary and secondary outcomes.

**Results:** 32,399 patients underwent colectomy for AD on hospital day 1-20. Adjusted for other factors, days to operation was found to be a significant predictor for death (OR = 1.038, 95% CI 1.020 - 1.057; P < 0.0001) and sepsis (OR = 1.051, 95% CI, 1.035 - 1.067; P < 0.0001). Each day in which surgical intervention was delayed was associated with a 3.8% increased risk of mortality and 5.1% increased risk of sepsis. Delay of surgery was also associated with an increased risk of blood transfusion, return to the operating room and increase LOS.

**Conclusions:** Delaying operation for patients with AD has a significant impact on sepsis and mortality. While non-operative approaches may be attempted, with each additional day operative therapy is delayed there is a significant increase in the risk of morbidity and mortality. This data suggests that surgeons should pursue operative therapy earlier in the hospital course to improve patient outcomes.

**Keywords:** Acute Diverticulitis, Operative Timing, Medical Management, Surgical Management

## 1. Background

Diverticulitis is a significant clinical problem accounting for over 130,000 hospital admissions per year in the United States and is the third most common gastrointestinal pathology requiring hospitalization (1-3). The diagnosis of AD encompasses a broad spectrum of disease states from uncomplicated disease, to pelvic abscess, to feculent peritonitis (4-6).

The American college of colon and rectal surgeons recommends non-operative management with oral or intravenous antibiotic therapy and diet modification for patients with uncomplicated diverticulitis (7). Diverticulitis

complicated by pericolic or pelvic abscess may be treated with intravenous antibiotics and possible image guided drain placement (6). Patients with peritonitis require emergent surgical resection (6, 8).

Some patients will require surgical intervention after an initial trial of non-operative management. The optimal length of non-operative management prior to surgical resection is unclear. Operating too soon may result in unnecessary surgical resections. Delaying operative intervention too long may result in increased morbidity and mortality.

## 2. Objectives

We aimed to determine the optimal timing of operative intervention in patients with AD that fail an initial course of non-operative management.

## 3. Methods

### 3.1. Patients

Patients requiring surgery for AD following an initial course of non-operative management were identified using the ACS-NSQIP. We searched the 2005 - 2014 data from the ACS-NSQIP database for all patients undergoing partial or total colectomy (Table 1). Both laparoscopic and open approaches were included. This group was then screened to include only patients with AD using ICD-9 codes 562.11 and 562.13, diverticulitis without mention of hemorrhage.

**Table 1.** CPT Codes Used for Patient Selection

CPT	Laparoscopic
44204	Laparoscopy, surgical; colectomy, partial, with anastomosis
44188	Laparoscopy, surgical, colostomy or skin level cecostomy
44206	Laparoscopy, surgical; colectomy, partial, with end colostomy and closure of distal segment (Hartmann-type procedure)
44207	Laparoscopy, surgical; colectomy, partial, with anastomosis, with coloproctostomy (low pelvic anastomosis)
44208	Laparoscopy, surgical; colectomy, partial, with anastomosis, with coloproctostomy (low pelvic anastomosis) with colostomy
<b>Open</b>	
44140	Colectomy, partial; with anastomosis
44141	Colectomy, partial; with skin level cecostomy or colostomy
44143	Colectomy, partial; with end colostomy and closure of distal segment (Hartmann-type procedure)
44144	Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucus fistula
44145	Colectomy, partial; with coloproctostomy (low pelvic anastomosis)
44146	Colectomy, partial; with coloproctostomy (low pelvic anastomosis), with colostomy

Patients were excluded if their surgical intervention was coded as “emergent” or had a pre-operative diagnosis of sepsis. These patients were excluded since they likely had indications for surgery on admission. Patients that underwent surgery on hospital day 0 were excluded as these patients were likely elective cases. Patients were excluded who underwent colectomy after hospital day 20. This resulted in a group of patients that underwent surgical resection after 1 - 20 days of non-operative management.

Patient demographics including age, race, and gender were recorded as well as comorbidities including history

of diabetes, COPD, MI, smoking history, alcohol use, functional status, ASA classification. We also recorded operative approach (open vs laparoscopic) and operative time.

The primary outcomes were 30-day mortality and sepsis. Secondary outcomes included, shock, UTI, PNA, need for blood transfusion, return to the operating room, LOS, readmission, postoperative wound dehiscence, superficial, deep and organ space surgical site infection.

This study did not require approval by the cooper university health system institutional review board as approval was granted through an agreement with the ACS-NSQIP.

### 3.2. Statistical Analysis

Frequency of categorical patient variables and means with standard deviation for continuous patient variables were summarized. Single and multiple variable logistic regression analysis were used to identify predictors of the primary and secondary outcomes. Potential confounders were included in the multiple variable model to control for patient characteristics. The multiple variable logistic regression analysis estimated odds ratios and 95% confidence intervals for days from admission for each outcome adjusted for confounders. The solution to the regression equation was used to predict the average probability of each outcome for each day following admission (1-20). Average predicted values for each day were plotted to show the trend over 1 - 20 days. A P value of < 0.05 was used for statistical significance in all analyses. Data was analyzed using SAS v9.4 (9).

## 4. Results

We identified 148,203 patients that underwent a non-emergent colectomy for AD from 2005 - 2014. 115,060 underwent intervention on hospital day 0 and were excluded due to the presumed elective or emergent nature of the case. An additional 694 patients were excluded for having a resection after hospital day 20. 50 patients could not be accounted for as their information was incomplete in the database. This left 32,399 patients that met our inclusion criteria.

### 4.1. Patient Variables

Frequency of patient variables can be found in Table 2. Univariate analysis demonstrated an increased mortality in patients with increased age, male sex, COPD, impaired functional status, increased ASA class, and open operative approach (Table 3). African American race, COPD, impaired functional status, increased ASA class, longer operative time, and open operative approach significantly increased the risk of sepsis. (Table 4).

**Table 2.** Patient Characteristics of Those Undergoing Operative Intervention Between Hospital Days 1 - 20

Patient Characteristic	Included Patients (n = 32,399)
Age (mean ± SD)	65.41 ± 16.03 years
BMI (mean ± SD)	27.69 ± 7.18
Days to operation (mean ± SD)	4.44 ± 3.74 days
Operative length (mean ± SD)	157.79 ± 89.45 minutes
Male	46.97%
African American	12.33%
Current smoker	20.37%
Diabetic	18.19%
Functional status 0	85.38%
Functional status 1	11.04%
Functional status 2	3.58%
ASA class 1	1.30%
ASA class 2	27.50%
ASA class 3	57.74%
ASA class 4	13.26%
ASA class 5	0.19%
Open surgery	72.49%

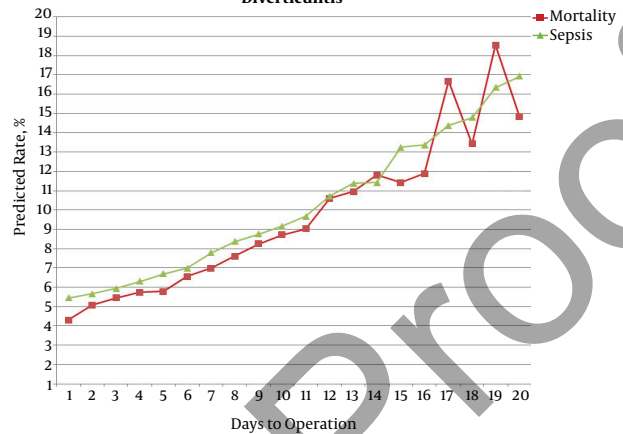
#### 4.2. Primary Outcomes

The overall rate of mortality for these patients was 4.9%. After controlling for differences in patient variables using multiple variable logistic regression analysis, a significant increase in the risk of mortality occurred with each hospital day (Figure 1). Patient mortality increased 3.8% per day [OR=1.038 (95% CI 1.020 - 1.057);  $P < 0.0001$ ].

Similar results were found for sepsis. The overall rate of sepsis for the group was 6.7%. After controlling for differences in these patient variables using multiple variable logistic regression analysis, a significant increase in the risk of sepsis occurred with each hospital day (Figure 1). The risk of sepsis increased 5.1% with each hospital day [OR = 1.051 (95% CI, 1.035 - 1.067);  $P < 0.0001$ ] respectively.

#### 4.3. Secondary Outcomes

Of the secondary outcomes, operative delay was found to increase the risk for blood transfusion [OR = 1.035 (95% CI 1.020 - 1.050);  $P < 0.0001$ ], return to the operating room [OR = 1.014 (95% CI 1.000 - 1.029);  $P = 0.0489$ ], and LOS [ $P < 0.0001$ ]. (Table 5) There was no significant effect in the rate of postoperative septic shock, PNA, UTI, wound dehiscence, readmission, superficial, deep or organ space SSI, with delay of surgery.

**Figure 1.** Average Predicted Rates of Sepsis and Mortality for Each Day Operative Therapy is Delayed in Patients with AD**Figure 1.** Average Predicted Rates of Sepsis and Mortality for Each Day Operative Therapy is Delayed in Patients with AD

## 5. Discussion

In this retrospective review of the ACS-NSQIP database, operative delay was found to be an independent predictor of mortality and sepsis in patients with non-emergent AD. Each day operative intervention was delayed there was a 3.8% [OR=1.038 (95% CI 1.020 - 1.057)] increased risk of mortality and a 5.1% [OR=1.051 (95% CI, 1.035 - 1.067);  $P < 0.0001$ ] increased risk of sepsis. Operative delay was also associated with increased risk of blood transfusion, return to the operating room and increased LOS. LOS includes both pre-operative and postoperative days which will increase with each day intervention is delayed. While we did not see a statistically significant increase in the other secondary outcomes that we measured, the rates of these outcomes increased with delay of surgery.

The timing of operative management of AD patients requiring admission to the hospital can be challenging. Uncertainty remains when it comes to managing patients who require hospitalization but not emergent intervention. Ideally, these patients would be operated on in an elective setting or avoid operative intervention altogether (10). Operative intervention during the acute inflammatory process is associated with higher rate of morbidity, mortality and ostomy creation when compared to operative intervention in the elective setting (11-14). However, for those patients who will not be able to avoid operative intervention during the admission for AD, delaying surgical intervention may result in delays in source control and may lead to untoward effects. Our data supports that for those patients who undergo operative treatment at the time of their admission for AD, delaying surgery may lead to infe-

**Table 3.** Patient Variables Effect on Mortality (Multiple Variable Analysis)

Variable	Odds Ratio	95% Confidence Limits	P Value
Age	1.033	1.026 - 1.040	< 0.0001
Male sex	1.589	1.59 - 1.859	< 0.0001
African American	0.728	0.567 - 0.935	0.0130
BMI	0.992	0.981 - 1.004	0.1845
Diabetic	1.068	0.889 - 1.283	0.4844
COPD	1.590	1.304 - 1.939	< 0.0001
MI	0.804	0.489 - 1.320	0.3879
Current smoker	1.211	0.977 - 1.501	0.0804
Alcohol use	0.886	0.560 - 1.401	0.6050
Functional status	1.991	1.782 - 2.224	< 0.0001
ASA class	2.332	2.039 - 2.667	< 0.0001
Operative length	0.999	0.998 - 1.000	0.0764
Open surgery	2.003	1.613 - 2.587	< 0.0001
Days to operation	1.038	1.020 - 1.057	< 0.0001

**Table 4.** Patient Variables Effect on Sepsis (Multiple Variable Analysis)

Variable	Odds Ratio	95% Confidence Limits	P Value
Age	0.998	0.994 - 1.003	0.4956
Male sex	1.031	0.906 - 1.174	0.6432
African American	1.280	1.065 - 1.538	0.0086
BMI	1.003	0.995 - 1.012	0.4783
Diabetic	0.999	0.847 - 1.178	0.9892
COPD	1.346	1.105 - 1.640	0.0032
MI	0.639	0.352 - 1.162	0.1424
Current smoker	1.006	0.853 - 1.186	0.9460
Alcohol use	1.009	0.717 - 1.420	0.9597
Functional status	1.317	1.178 - 1.471	< 0.0001
ASA class	1.260	1.129 - 1.406	< 0.0001
Operative length	1.002	1.002 - 1.003	< 0.0001
Open surgery	1.541	1.299 - 1.829	< 0.0001
Days to operation	1.051	1.035 - 1.067	< 0.0001

rior outcomes. In this study, each additional day in which operative intervention was delayed was associated with an increase in the rate of mortality and sepsis.

Various studies have evaluated the effect of non-operative measures on morbidity and mortality in patients with complicated diverticulitis. Non-operative management was found to have a 91% success rate when utilized

on a cohort of patients who were hemodynamically stable with an associated abscess or free air in the absence of free fluid on CT scan (15). Those who failed non-operative therapy had a broad range of disease severity; 28.6% had pericolic air without abscess, 14.3% had an abscess < 4 cm or < 2 cm collections of distant free air and 57.1% had an abscess > 4 cm or collections of distant free air > 2cm.

**Table 5.** Effect of Operative Delay on Secondary Outcomes

Secondary Outcomes	Odds Ratio	95% Confidence Limits	P Value
Blood transfusion	1.035	1.020 - 1.050	< 0.0001
Return to OR	1.014	1.000 - 1.029	0.049
UTI	1.009	0.990 - 1.028	0.348
PNA	1.006	0.988 - 1.025	0.506
Septic shock	1.009	0.990 - 1.029	0.341
Readmission	1.033	0.987 - 1.081	0.166
Wound dehiscence	1.000	0.972 - 1.028	0.992
Superficial SSI	0.991	0.976 - 1.007	0.265
Deep SSI	1.010	0.982 - 1.039	0.474
Organ space SSI	1.019	0.999 - 1.039	0.059
	<b>Parameter Estimate</b>	<b>Standard Error</b>	<b>P-value</b>
LOS	1.236	0.019	< 0.0001

Sallien et al. retrospectively reviewed 194 patients admitted with AD and CT scan findings of pericolic air, extraluminal distant free air or retroperitoneal air (16). They found that those with a small amount of distant intraperitoneal air without free fluid or peritonitis had a success rate of 86% when treated with non-operative management, while those with large amounts of free intraperitoneal air or retroperitoneal air without peritonitis has a success rate of 57% - 60%. They did not find any significant association between patient factors such as sex, age > 65 years, corticosteroid use, previous history of AD, clinical exam, temperature, white blood cell count or C-reactive protein, and failure of non-operative management.

Mozier et. al performed a retrospective ACS-NSQIP similar to our study focusing on strictly emergent cases of AD as defined by clinical deterioration related to sepsis (17). Operative delay beyond 24 hours was associated with an increase in morbidity but not mortality. This study highlights the importance of early intervention in the most critically ill patients with AD. In contrast, our study directs attention to a more difficult subset of patients in which illness severity is less extreme making management decisions more variable and challenging. With the additional increased risk of mortality seen with surgical delay in our patient population, timely intervention is critical. While non-operative management of acute complicated diverticulitis is a safe initial option, our data indicates that if the patient fails to progress, each additional day operative intervention is delayed increases the risk of sepsis and mortality independent of patient characteristics. It is an important that those patients managed medically be thoroughly reassessed on a daily basis to convert to surgical

management as soon the surgeon determines it is clinically indicated in efforts to avoid such morbidity and mortality.

This study has some limitations. We did not control for complexity of surgery. Those patients undergoing intervention later in their hospital course may have had a more difficult resection; therefore, it is not surprising that they had higher rates of sepsis, death, required more blood products, more return trips to the operating room and had a longer LOS.

A second limitation in this study is the retrospective design due to the nature of the NSQIP database and is subject to selection bias. Additionally, data may be misclassified and subject to data entry errors.

Another limitation is that patients admitted with AD who were successfully managed medically (no surgery during the admission), are not captured in NSQIP and could not be analyzed. The data is limited to those patients who for any reason had a delay prior to surgery. Surgical delay may be a proxy for poor operative candidacy and hesitancy for surgical intervention. Radiographic evidence of abscess formation, free fluid or air was not available to assess the severity of disease nor was there information available about previous episodes of diverticulitis, management or outcomes. While we know the hospital day in which patients went to the operating room, we do not know the duration or progression of symptoms.

### 5.1. Conclusions

For patients who undergo surgical management of AD, the risk of sepsis and mortality are increased for each day surgery is delayed. Earlier intervention may be favorable

for patients who will likely proceed to operative management. Daily assessment of the patient response to medical management is critical in initiating surgical intervention when appropriate. Earlier intervention in such patients may improve patient outcomes, particularly the risk of sepsis and mortality.

## Footnotes

**Authors' Contribution:** Study concept and design: Robin F. Irons, Michael E. Kwiatt, Michael J. Minarich, John P. Gaughan, Francis R. Spitz and Steven J. McClane; acquisition of data: John P. Gaughan; analysis and interpretation of data: Robin F. Irons, Michael E. Kwiatt, Michael J. Minarich, John P. Gaughan, Francis R. Spitz and Steven J. McClane; drafting of the manuscript: Robin F. Irons; critical revision of the manuscript for important intellectual content: John P. Gaughan, Michael E. Kwiatt, Francis R. Spitz, Steven J. McClane; statistical analysis: John P. Gaughan.

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