Challenges and Complexities in the Management of Acute Diverticulitis

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STATEMENT OF ORIGINALITY:

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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Nima Ahmadi

30/9/2022

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I designed the study, collected the majority of the data, analysed the data and wrote the draft

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I designed the study, supervised the analysis of the data and co-wrote the draft.

INTRODUCTION:

Colonic diverticulosis is a commonly encountered pathology, reported to have an incidence of up to 70% of the adult population by the age of 80 in western countries. This incidence is rising primarily due to a rising population (1, 2), however there are suggestions that the incidence in younger patients is also on the rise(3). Most of the patients with diverticular disease will remain asymptomatic with only 10-25% developing diverticulitis(4).

Pathophysiology:

The full aetiology of diverticular disease and the development of diverticulitis is not completely understood. The prevailing theory on the likely aetiology of diverticular disease has been that an increase in intra sigmoidal pressure (5) and segmentation result in localised compartments of high pressure. This then leads to pulsation forces(6), which coupled with possible altered composition of collagen and metalloproteinases, lead to weakening of the colonic wall(7) and herniation of mucosa at the weakest point of the colonic wall. This weak point is at the insertion of the vasa recta vessels through the muscularis layer(8). There are several risk factors associated with the development of diverticular disease with a low fibre diet the predominant environmental factor with large cohort studies demonstrating a significant risk reduction of 30-41% in patients who consume high fibre diets (9-11). Additional environmental factors include smoking(12, 13), use of steroids and immunosuppression (14, 15) or non-steroidal anti-inflammatory medications(13, 16, 17), and obesity(18). Genetics seem to play an important role in the development of diverticular diseases with sibling and twin studies demonstrating a genetic contribution of 40-53% to the development of diverticular disease(19, 20) although the exact mechanism is unknown. There are also suggestions that microbiome in patients with diverticulosis may be different to control patients. (21, 22) However, other studies have shown no difference in the microbiota of controls compared with patients with asymptomatic diverticulosis.(23, 24) Unfortunately, there is too much heterogeneity in the assessment techniques in the papers assessing the effects of the microbiota and a recent systematic review found that due to this, there is insufficient evidence for distinct microbiota signature in patients with diverticulosis(25).

The predominant site of diverticular disease in western countries is the left colon, however in Asia, up to 70% of the cases can occur in the right colon, at the caecum or ascending colon(26). The pathology of right sided diverticular disease is thought to be different, however, increased colonic pressure is also demonstrated to be a factor in the development of right sided diverticular disease(27).

The term diverticulitis describes a peri-diverticular inflammation of the bowel and surrounding tissue. The pathogenesis is unclear and is likely to be multifactorial. The prevailing theory to date has been that diverticulitis occurs due to a stasis or obstruction in the diverticulum which in turn leads to inflammation, bacterial overgrowth, oedema, local ischaemia and perforation(28). An alternate theory of the pathogenesis involves bacterial translocation due to a weaker barrier at the diverticulum(29). However with the new focus and interest in the role of colonic microbiome in the pathogenesis of colonic diseases including inflammatory bowel disease, there appears to be a role in the dysbiosis of the normal colonic microbiome that results in the development of diverticulitis. Multiple studies have examined the role of dysbiosis in the formation of peri-diverticular inflammation with eight studies examining the role of microbiota in the formation of diverticulitis.(24, 30-35). There is significant amount of heterogeneity between the studies including in different sampling , extraction, profiling and assessment methodology of the microbiota and therefore a meta-analysis is unable to be performed. However a recent systematic review demonstrated that there appears to be an abundance of butyrate-producing species that may be contributing to the pathogenesis of diverticulitis.(25) Butyrate which is a short chain fatty acid has been shown to be an anti-inflammatory effector on epithelial cells in the colon(36). Due to the heterogeneity of the studies, Cameron et al were not able to draw firmer conclusions about the definitive role of microbiome dysbiosis.(25) However better methodology and sequencing techniques may help understand the role of the microbiome in the development of diverticulitis in the future.

There is emerging evidence that uncomplicated diverticulitis may be an inflammatory process only without an infective component. Multiple randomised trials have demonstrated the safety and equivalent outcomes of patients with mild acute diverticulitis managed without antibiotics with those treated with antibiotics. (37-39) This has been confirmed with meta-analysis of the first two randomised trials.(40).

Presentation and diagnosis:

Diverticulitis causes a wide spectrum of presentations, from mild abdominal discomfort to peritonitis and sepsis. The most common presentation is with lower abdominal pain with localised tenderness and guarding to the left lower quadrant with a corresponding fever and leucocytosis(41, 42). Approximately 70% of patients will have abdominal pain, 50% will present with constipation, 25% with diarrhoea, 20-60% with nausea and vomiting, and 10% with urinary symptoms(42).

Uncomplicated diverticulitis is inflammation in a segment of bowel containing a diverticulum, with inflammation of the surrounding tissue but no signs of perforation or abscess formation. Complicated diverticulitis includes abscess formation, perforation with or without generalised peritonitis, fistulae formation or colonic obstruction due to stricturing. Majority of the patients admitted with a first episode of diverticulitis will have uncomplicated diverticulitis, while 15-25% of patients present with complicated diverticulitis(43-47).

Hinchey created a classification system for perforated diverticulitis in 1978 (48). Since its creation, the classification system has undergone many modifications which has unfortunately led to non-standardised and conflicting terminology in the literature. However, all these different systems aim to classify acute diverticulitis based on clinical, imaging or intra-operative findings. Computed tomography (CT) is now the gold standard for the diagnosis of diverticulitis with a sensitivity range of 94-97% (46, 49). The CT findings can also be used to stratify patients based on modified Hinchey classifications based on the presence of inflammation alone, abscess or purulent/faeculent peritonitis(45).

Management:

The management of acute diverticulitis is dependent on severity of the disease, comorbidity profile of the patient as well as the clinical condition on presentation with the literature supporting a stage based approach to the management of acute diverticulitis.

The vast majority of patients with uncomplicated diverticulitis can successfully be managed non-operatively and multiple studies have demonstrated safety and efficacy of this approach with success rates of 95-99%(50-52). As mentioned above, there is now evidence that in well patients with mild symptoms, patients can safely be managed without antibiotics. (37-40)

Diagnostic tools such as serial CT scans and inflammatory markers including the C-reactive protein (CRP) are useful in identifying patients that may fail non-operative treatment. Multiple studies have utilised the use of CRP as a predictive tool. These studies have either assessed CRP as a static marker(53-56) or in conjunction with other clinical factors to predict severity of disease(57). No studies had previously examined the role of a dynamic assessment of inflammatory marker in identifying response and predicting failure of treatment.

Patients with complicated diverticulitis (presence of abscess or peritonitis) are more likely to require intervention and this rate increases with higher Hinchey grades (51, 58). The use of percutaneous drainage under image guidance has emerged as the treatment of choice in patients with peri-colic and pelvic abscesses with multiple studies demonstrating success rates of 50-85%(44, 52, 58). This approach avoids the morbidity associated with emergency surgery in the majority of patients. Some patients fail this approach and require operative intervention, however in this cohort there is a higher rate of performing primary anastomosis with or without a covering ileostomy at the time of the surgery compared with Hartmann's procedure (Anterior resection and formation of end colostomy)(44, 59). This is important, as multiple studies have demonstrated that the rates of reversal of ileostomies are higher than colostomies (80-90% vs 40-50%)(60, 61) thus leading to higher stoma-free survival rates in patients.

Patients with purulent or faeculent peritonitis (Hinchey grade III or IV) are the most likely to undergo emergency surgery on admission. The Paradigm is shifting as to the most appropriate procedure in these patients. The previously held dogma of Hartmann's procedure for these patients has been challenged with more recent evidence suggesting that anterior resection with primary anastomosis with or without diverting ileostomy is safe with similar post-operative morbidity profile(61-66).

There remain many unanswered questions as to the optimal management of acute diverticulitis. These uncertainties include, but are not limited to, the optimal treatment of uncomplicated and complicated diverticulitis including risk stratification, when to opt for operative management, and if so, the best operation for the clinical condition of the patient. The aim of this thesis was to examine some of these questions and controversies and to focus on 3 specific aspects of the treatment of diverticulitis in our cohort of patients. The identification of patients at risk of failure of non-operative management, the optimal surgical operation for the management of complicated diverticulitis, and identifying if the treatment of a vulnerable subset of patients, namely the immunosuppressed patients, is and/or should be different than immunocompetent patients.

In chapter 1, The research question centred on the role of CRP trajectory on identifying patients at risk of failure of non-operative management. In chapter 2, the focus was on the role of primary anastomosis in the surgical management of acute diverticulitis. As mentioned above, the paradigm has slowly shifted as to the optimal surgical management of these patients. The aim of this paper was thus two fold; to compare the outcomes of patients undergoing Hartmann's procedure (HP) compared with anterior resection and primary anastomosis (PA) in our institution as well as assess if there was a temporal change in the rate of PA over the course of 13 years as new evidence emerged about the safety and efficacy of this approach. Chapter 3 focuses on immunosuppression, deemed most likely to require operative management and the aim of this study was to identify if the real life management of these patients differed compared to their immunocompetent counterparts. The secondary aim of this study was to assess if non-operative management was safe in this cohort.

CHAPTER 1:

C-reactive protein trajectory in the first 48 hours predicts the need for intervention in conservative management of acute diverticulitis

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Abstract

Background: C-reactive protein (CRP) is a useful marker for monitoring response to treatment in sepsis. The aim of this study was to examine the use of CRP trajectory in predicting the need for intervention in conservatively managed patients with acute diverticulitis (AD).

Methods: A retrospective review of patients with AD who were managed conservatively was performed. They were divided into four groups based on CRP relative to the median at day 0 and 2: ‘Low rise’ (levels below median at day 0 and 2), ‘High rise’ (levels above median at day 0 and 2), ‘Rapid rise’ (levels below median at day 0 but above median at day 2) and ‘Decline’ (levels above median at day 0 but below median at day 2).

Results: Intervention was required in 64 of 456 (14%) with 30 (48%) of these performed after day 2 of admission. There were 150 patients (54%) in the 'Low rise', 76 (27%) in the 'Decline', 26 patients (9%) in the 'Rapid rise' and 25 patients (9%) in the 'High rise' groups. Within these groups 5%, 8%, 19% and 32% of patients required intervention (P = 0.001). On multivariate analysis, patients with a pelvic abscess were more likely to need intervention (odds ratio 19.1 (confidence interval 6.2–59.4), P < 0.0001).

Conclusion: The CRP trajectory during the initial 48 h of admission can predict the need for intervention in AD patients being managed conservatively. Patients with a 'Rapid rise' or 'High rise' in CRP from day 0 to 2 are more likely to need intervention.

Introduction

Acute diverticulitis (AD) is a common acute surgical presentation to the hospital which is associated with a significant burden on the patients and the health system.[1,2] The majority of patients can be successfully managed conservatively and multiple studies have demonstrated the safety and efficacy of this approach.[3–5] However, a subgroup of patients will fail this approach and require intervention including the radiological insertion of drains or operative management. Multiple studies have explored the possible factors leading to the failure of this approach.[6,7] C-reactive protein (CRP) has been found to be a factor in predicting the risk of failure of conservative management as well as a predictor for severity.[8–10] Many of the studies in relation to CRP and diverticulitis have focused on a single CRP value at either the admission or on day 2 of admission.[8–11] However, due to CRP first-order kinetics, relative changes can be more informative than static measurements. This has been demonstrated in multiple studies looking at CRP in sepsis

in both the adult and paediatric population.[12,13] They have demonstrated that patterns of change in CRP can predict differences in severity and outcome. The aim of this study was to assess if the pattern or trajectory of CRP can predict failure of conservative management with antibiotics alone during admission with AD.

Methods

Ethics committee approval was obtained from our institution's ethics committee and the study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients with acute presentation of diverticulitis to Royal Prince Alfred Hospital, Sydney, Australia, between 1 January 2012 and 31 August 2016, were identified and their data were collected retrospectively using the electronic and paper records. Patients were identified using the hospital administrative health data set. All patients coded with the broad ICD codes K57 (diverticular disease of the intestine) were identified. The electronic records patients were reviewed to identify patients with acute presentation of diverticulitis. Patients who had operative management or interventional drain insertions prior to day 2 of admission were excluded (Fig. 1). Of the remaining group, demographic data including age, gender as well as co-morbidities, using the Charlson comorbidity index, were collected. CRP results during admission were collected. Patients with computed tomography (CT) scans on admission had the reports reviewed and were coded as per the Wasvary modification of the Hinchey classification and CT findings by Kaiser.[14,15] Complicated diverticulitis was classified as modified Hinchey classification 1a–4. Operation reports were reviewed for the type of operation, as well as the surgeon operating were recorded and operative findings were also coded as per the abovementioned modified Hinchey classifications. Details of hospital stay including the type of intervention as well as morbidity and mortality were recorded. The specific antibiotics used were not recorded and patients were discharged when they had minimal pain with no evidence of focal peritonism, afebrile for 24 h and tolerating solid diet. Statistical analysis was performed using SPSS v24 statistical package (Chicago, IL, USA). Receiver operating characteristics (ROC) was used for analysing the diagnostic value of CRP. Only markers with an area under the curve of >0.7 were eligible for selection for further analysis. Variables were analysed as appropriate using an independent- samples t-test, Mann–Whitney U test, Pearson's chi-squared test, Mantel–Haenszel test or Kruskal-Wallis H test. Correlation analysis was performed using Spearman correlation coefficient and binary logistic regression was performed on correlated factors including all factors with a P-value of <0.2.

Results

During the study period, there were 456 hospital admissions with an episode of AD in 412 patients. All patients were treated with intravenous antibiotics. A total of 64 (14.0%) patients required an intervention. Thirty-four (53%) of these patients had an intervention prior to day 2 and were therefore excluded from the remainder of the analysis (Fig. 1). Of the remaining 422 patients, 17 (4.0%) patients had surgery on the median day of stay (DOS) of six (inter-quartile range (IQR) 4–17) and 13 (3.0%) patients had a drain inserted by interventional radiology on median DOS of 5 days (IQR 3–8.5). Four (31%) patients who had a drain inserted under radiological guidance proceeded to have elective surgery on median DOS of 11 (IQR 9–34). The CRP data on both day 0 and 2 were available for 277 patients (66%) (Fig. 1). The CRP data were not available for three patients (10%) that required intervention after day 2.

The mean age of the total cohort of patients was 57 (standard deviation (SD) 14.0) years old. There were 196 (46%) males, and 84% of patients had a Charlson comorbidity index of 0–1. Table 1 demonstrates the demographic data including the admission CT- modified Hinchey classification. The median day of intervention was on day 5 (IQR 3–10) of admission. The median length of stay for the group needing intervention was 16.5 compared with 3.5 for the group not needing intervention ($P < 0.0001$).

Age and gender were not associated with a need for intervention. The mean age for the group needing intervention was 58 compared with 57 for the no intervention group ($P = 0.70$) and 12 (6%) of males had an intervention compared with 18 (8%) of females ($P = 0.57$). Similarly, a higher Charlson comorbidity index was not associated with an increased risk of needing intervention. Seven patients (10%) in the group with a Charlson index of 2+ needed intervention compared with 22 (6%) in the Charlson 0–1 group ($P = 0.185$).

Hinchey classification on admission was a predictor of failing conservative management with 14 (50%) patients with Hinchey 2 needing intervention compared with 2 (12%) and 12 (3%) of patients with Hinchey 1b and Hinchey 0–1a, respectively ($P < 0.0001$). The median CRP values on days 0 and 2 were avail- able for 277 for the group and are displayed in Table 2. The median CRP values for different modified Hinchey classification are demonstrated in Table 3. The median CRP on admission (day 0) was statistically significant between the groups, however, there was no statistical difference in the median CRP on day 2 between the groups.

There was a statistically significant result of CRP on day 2 only, between the group that required intervention and the group that did not (Table 2). The result of ROC analysis showed the area under the curve for values of CRP on day 0 and 2 were 0.614 and 0.686, respectively, and therefore had poor diagnostic value.

The CRP difference between day 2 and 0 was calculated and there was no statistically significant difference in the median values between the groups that required intervention and the group that did not (median 28.3 (−30.45 to 128.10) versus 4.25 (−35.65 to 59.580), P = 0.204 Mann–Whitney U test).

The mean CRP values for patients that required intervention were calculated to be 87.3 and 193.2 for days 0 and 2. To allow for easy implementation in the bedside clinical setting, whole number cut-offs, namely 80 and 200 mg/L on days 0 and 2, respectively, were used. These specific whole number values were used as they had the best sensitivity and specificity (52% sensitivity and 69% specificity for day 0, 51% sensitivity and 85% specificity for day 2). These values were then used to categorize patients into 4 groups dependent on the pattern of change of their CRP over the first 2 days of admission (Fig. 2). There were 150 (54%) patients in the 'Low rise' group who had a CRP level below 80 mg/L at day 0 and 200 mg/L at day 2; 76 (27%) patients in the 'Decline' group who had a CRP level above 80 mg/L at day 0 but below 200 mg/L at day 2; 26 (9%) patients in the 'Rapid rise' group who had a CRP level below 80 mg/L at day 0 but above 200 mg/L at day 2; and 25 (9%) patients in the 'High rise' group who had a CRP level above 80 mg/L at day 0 and 200 mg/L at day 2. There was a significant difference in the rate of patients requiring intervention between the 4 groups. The risk of requiring intervention in the 'Low rise', 'Decline', 'Rapid rise' and 'High rise' groups were 5%, 8%, 19% and 32%, respectively (P < 0.001 Mantel–Haenszel test).

A subgroup analysis of 28 patients with Hinchey 2 on admission was performed (22 out of 28 had data available). The 'High rise' (n = 9) and 'Rapid rise' (n = 6) groups were more likely to require intervention compared with the 'Low rise' (n = 1) and 'Decline' (n =6) groups (100%, 100%, 44% and 33%, respectively, P = 0.02).

Correlation analysis was performed between the modified Hinchey classification and the CRP pattern of change groups they were noted to be significantly correlated (Spearman correlation coefficients of 0.139, P = 0.02). A binary logistic regression was therefore performed to ascertain the effect of modified Hinchey classification and CRP pattern of change grouping with Charlson comorbidity index included (Table 4). The logistic regression model was statistically significant ($\chi^2 = 55.244$, df = 8, $P < 0.0001$) and the model explained 39% (Nagelkerke R^2) of variance in need for intervention and correctly classified 92% of cases. Patients with a modified Hinchey classification of 2 were 29.52 (confidence interval (CI) 9.38–92.91) times more likely to require intervention compared to patients with modified Hinchey classification 0 ($P < 0.0001$), patients in the 'High rise' and 'Rapid rise' groups were 5.55 (CI 1.29–23.91, P = 0.021) and 6.70 (1.74–25.85, P = 0.006) times more likely to require intervention compared with the 'Low rise' group. The remaining factors were not significantly associated with an increased risk of requiring intervention.

Discussion

AD is a common surgical presentation and can have a significant burden on the patients as well as the health-care system as a whole.[1,2] While the majority of the literature focus on the management of AD in the severe spectrum of the disease, conservative management of diverticulitis has been demonstrated to be safe and efficacious in the selected group of patients with no evidence of florid sepsis.[3–5] However, there is a subgroup of patients will fail this approach and require radiological or surgical intervention which has been reported to be as high as 12–15%.[6,7] In our cohort, the risk of intervention was 16% overall, and 7% beyond day 2 of admission.

Multiple studies have defined factors associated with a higher likelihood of failure of conservative management. Juang et al. identified systemic inflammatory response syndrome, high-pain scores, first episode, immunomodulatory use and CRP of >200 mg/L as factors associated with severe outcomes in patients managed conservatively.[8] They showed that patients with a CRP of >200 mg/L were four times more likely to experience severe course as defined by need for intervention, prolonged stay or readmission. It is important to note that the authors did not examine the role of the modified Hinchey classification on the computed tomography scan as a risk factor. There have also been multiple other retrospective studies examining the role of CRP alone in predicting the severity of the disease.[10,11,16,17] These studies have all looked at a CRP level measured at a specific time point, either on admission or a delayed measure. CRP was first dis- covered in early 1930[18] and is an acute phase reactant produced by hepatocytes with a strong correlation between the intensity and duration of the inciting stimulus. This results in a higher peak and a protracted increase when the inciting stimulus is stronger and longer.[19] Multiple studies have demonstrated the utility of dynamic CRP measurements as a predictor of response to therapy in patients with sepsis.[12,13,20,21] Our study aimed to utilize this dynamic measurement of CRP as a predictor of the need for intervention in the subgroup of patients with AD that were managed conservatively. Given the relatively short period to intervention, with median DOS of 5 (IQR 3–10) we were unable to utilize the patterns described in these studies as they require up to 14 days of CRP measurements. We therefore have used pragmatic, easy to use CRP cut-offs of which were selected by rounding the median CRP of the intervention group to the nearest whole numbers with acceptable sensitivity and specificity as identified by ROC analysis. These were 80 and 200 mg/L on day 0 and 2. This allowed the cohort to be stratified into four groups depending on the pattern of change in the CRP (Fig. 2). Our results demonstrated that patients with a rapid increase in CRP ('Rapid rise' group) and patients with persisting high CRP ('High rise' group) in the first 48 h of antibiotic treatment had a risk of 19% and 32% of needing an intervention during the hospital stay.

A higher modified Hinchey classification has been associated with an increased need for intervention especially in patients with Hinchey 2 or above.[15,22] Multiple studies have also demonstrated that CRP on admission can be used as a predictive tool for higher modified Hinchey grades.[16,17] Within our cohort, we also demonstrated a relationship between the day 0 CRP and the modified Hinchey classification on CT, with higher classifications having significantly higher median CRP (Table 3). This effect, however, was not present on the day 2 CRP which suggests that the modified Hinchey classification is a confounder of CRP, presumably due to higher inflammatory stimuli with higher modified Hinchey classification. However, these results suggest that response to therapy is likely to have a larger effect on the CRP levels on day 2 in keeping with control of the inflammatory insult after the commencement of therapy. Within our cohort, the only other significant predictor of failure of conservative management on multivariate analysis was the presence of pelvic abscess (modified Hinchey classification) with these patients being 29.5 times (CI 9.4–92.9, $P < 0.0001$) more likely to need intervention.

The main limitation of the study was the retrospective nature of the study; however, using regression analysis, the risk of bias has been minimized. We utilized somewhat arbitrary whole number cut-offs for the CRP values derived from the cohort's median CRP values. This was to allow for the creation of a rapid, easy bedside prognostication tool that can be used by the junior medical staff to escalate appropriate investigation earlier as well as allow for better communication of likely outcome with the patient. External validation of this method as well as cut-offs are currently under way; however, a prospective analysis would be helpful in further assessing the usefulness of the CRP trajectory as a predictive tool in AD patients managed conservatively.

Conflicts of interest: None declared.

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Tables and Figures:

Table 1: Demographic data for patients with acute diverticulitis, initially managed conservatively

		Intervention required		
Patient characteristics	All patients (n = 422)	Yes (n=30)	No (n=392)	p-value
Age, Mean, (SD)	57 (13.8)	58 (14)	57 (13.8)	0.70
Gender male, n (%)	196 (46)	12 (40)	184 (94)	0.58
Charlson comorbidity score n (%)				MH 0.18
0-1	356 (85)	22 (76)	334 (85)	
2+	65 (15)	7 (24)	58 (16)	
Modified Hinchey classification on admission n%				MH < 0.0001 *
0	353 (85)	12 (43)	341 (88)	
1a	18 (4)	-	18 (5)	
1b	17 (4)	2 (7)	15 (4)	
2	28 (7)	14 (50)	14 (4)	
3	1 (0.2)	-	1 (0.3)	
4	-	-	-	

SD: standard deviation, MH: Mantel–Haenszel test
* p < 0.05

Table 2: Median C-reactive protein based on need for intervention.

Intervention required	C-reactive protein *median (IQR)*	n	p-value
Day 0			
No	58.6 (23.3 – 108.1)	250	0.115
Yes	87.3 (27.5 – 188.2)	27	
Day 2			
No	68.2 (32.5 – 138.3)	250	0.001 *
Yes	193.2 (63.9 – 258.9)	27	

IQR, interquartile range
* p < 0.05

Table 3: Median C-reactive protein based on modified Hinchey classification on day 0 and 2.

Modified Hinchey	C-reactive protein *median (IQR)*	n	p-value
Day 0			
0	55.8 (81.6)	338	
1a	73.6 (96.3)	18	
1b	93.8 (155.4)	15	
2	102.8 (193.8)	27	KW 0.005 *
Day 2			
0	65.9 (110.4)	234	
1a	103.2 (115.9)	14	
1b	107.6 (100.9)	15	
2	121.7 (170.5)	23	KW 0.115

IQR, interquartile range; KW, Kruskal-Wallis test
* $p < 0.05$

Table 4: Results of binary logistic regression analysis

Variables	OR	95% CI	p value
CRP pattern			
'Low rise'	reference		
'Decline'	1.29	0.36 – 4.60	0.70
'Rapid rise'	5.55	1.29 – 23.91	0.02 *
'High rise'	6.70	1.73 – 25.85	0.006 *
Modified Hinchey			
0	reference		
1a	-		
1b	4.26	0.76 – 23.94	0.10
2	29.51	9.38 – 92.91	< 0.001 *
3	-		
Charlson comorbidity score			
0-1	reference		
2 +	2.26	0.71 – 7.21	0.17

OR, Odds ratio, CI, confidence interval $p < 0.05$*

Figure 1: Flow diagram of patients included in the study.

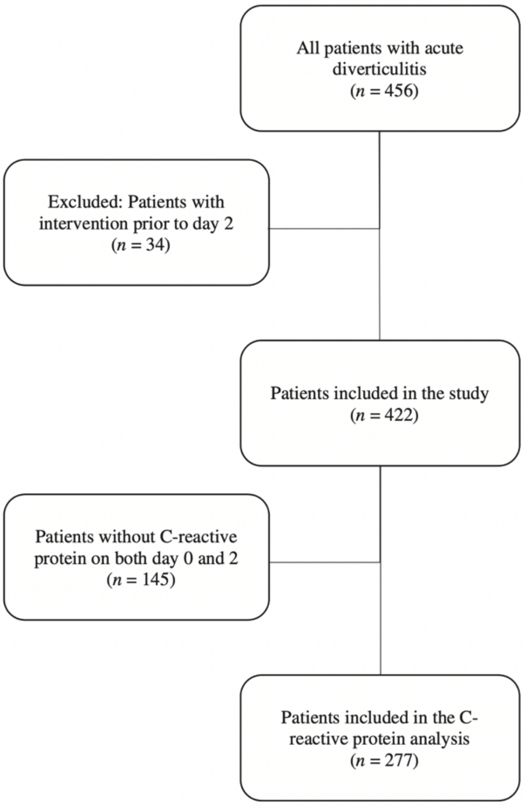
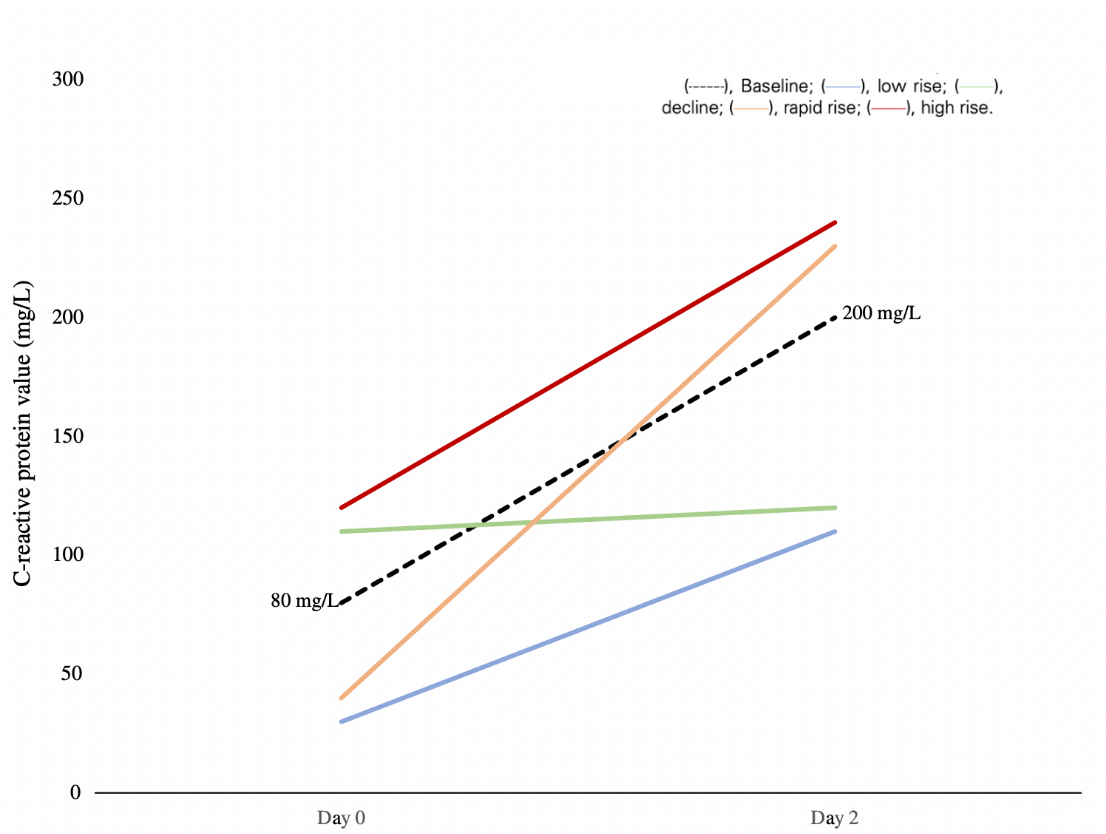


Figure 2: Patterns of change of C-reactive protein relative to cut-offs at day 0 and 2.



CHAPTER 2:

Increasing primary anastomosis rate over time for the operative management of acute diverticulitis

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Abstract

Background: Over the past two decades, there has been mounting evidence that primary anastomosis (PA) is a safe alternative to Hartmann's procedure (HP) in acute diverticulitis. In addition, specialized colorectal surgeons are more likely to perform PA. This study aimed to analyse if this evidence has led to an increase in the rate of PA in a major tertiary institution over time.

Methods: A retrospective observational study of patients requiring operative management of acute diverticulitis from 1 January 2001 to 31 December 2015 at a tertiary teaching hospital.

Results: One hundred and eighteen patients underwent surgery for acute diverticulitis. Patients who failed initial conservative management were more likely to have PA (43% versus 21%, P = 0.044). There was no difference in medical or surgical complications, readmission rate or mortality between patients who had a PA compared with HP. Patients were more likely to have a PA if a colorectal surgeon was operating compared with a

colorectal surgery fellow or general surgeon (36% versus 19% versus 10%, P = 0.039). In patients with modified Hinchey 0–2, there was an increased PA rate within the study period, 21%, 43%, 63% to 57% from the first to the fourth quartile of patients (P = 0.038).

Conclusions: The mounting evidence for the safety of performing PA has led to an increase in the PA rates for acute diverticulitis. Patients who were operated by a colorectal surgeon were more likely to have a PA. The morbidity and mortality were similar in patients who had PA compared with HP.

Introduction

Acute diverticulitis is a common acute surgical presentation to the hospital and can lead to a significant burden on the patient as well as the health system.[1,2] The vast majority of patients with uncomplicated diverticulitis can be successfully managed non-operatively, and multiple studies have demonstrated the safety and efficacy of this approach with failure rates of 1–5%.[3–5] Patients with complicated diverticulitis, however, are most likely to undergo an emergency procedure. The surgical procedure of choice for these patients is changing. The previously held dogma of Hartmann's procedure (HP) has been challenged particularly for patients needing surgery with less severe diverticulitis. Recent retrospective and randomized data have pointed to the safety of primary anastomosis (PA) with or without a diverting ileostomy with similar morbidity and mortality.[6–8] However, a major advantage in performing PA with a diverting ileostomy is the higher rate of reversal for patients (80–90% versus 40–50%).[8,9]

Over the past two decades, there has been a reduction in the number of patients being managed operatively for complicated diverticulitis. In the patients requiring emergency surgery, there has been mounting evidence that PA with or without ileostomy is a safe alternative to HP in patients without florid sepsis.[6,7,10,11] The rates of PA have been increasing as this evidence is accumulated.[12] There is also evidence that the sub-specialization of surgeons increases the rate of PA.[13,14]

The aim of this study was to analyse if this increasingly strong evidence has led to a temporal change in the rate of PA in patients undergoing operative management of their acute diverticulitis in our unit, which is a major tertiary institution in Sydney, Australia.

Methods

Ethics committee approval was obtained from our institution's ethics committee and the study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients with acute presentation of diverticulitis to the Royal Prince Alfred Hospital, Sydney, Australia, between 1 January 2001 to 1 January 2016, were identified and their data were collected retrospectively using the electronic and paper records. All patients coded with the broad ICD codes K57 (Diverticular disease of the intestine) were identified and their electronic records were reviewed to identify patients with acute presentation of diverticulitis. Within this cohort, the data for patients who underwent an operation during their admission was collected. Computed tomography (CT) reports were reviewed and were coded as per the Wasvary modification of the Hinchey classification and CT findings by Kaiser.[15,16] Demo- graphic data including age, gender and co-morbidities, using the Charlson comorbidity index (CCI), were collected. Operation reports were reviewed and type of operation, the surgeon operating and operative findings were recorded. Details of hospital stay including the type of intervention as well as morbidity and mortality were recorded. Statistical analysis was performed using SPSS v24 statistical package (Chicago, IL, USA).

Results

Demographic data

Of the total cohort of 1027 patients presenting with acute diverticulitis, 133 patients underwent an operation. Of these 13 were taken to the operating theatre for a clinical diagnosis of appendicitis and it was noted intraoperatively that the patients had right-sided diverticulitis. There were an additional two patients who had a right hemicolectomy for complicated right-sided diverticulitis. These patients were excluded. Of the remaining 118 patients, 39 were initially managed conservatively but failed this treatment approach during their hospital stay. The remaining 75 patients were taken to the operating theatre on admission, of these, 19 did not have a CT prior to the operation. Table 1 outlines the demographic data of this group.

Within the whole group, one patients had a laparoscopic wash- out, four patients had a subtotal/total colectomy and one patient had a de-functioning stoma as there was concern regarding malignancy at the time of the operation. These patients were not included in the final analysis of patients undergoing HP versus PA.

Morbidity and mortality

Overall, there were six deaths (5%) in the cohort. Patients who died were more likely to have higher CCI (median CCI 3 versus 1, P = 0.01). Sixty-eight patients (58%) experienced complications which included 52 cases (44%) of medical complications and 30 (26%) with surgical complications (Table 2). One patient (3%) had an anastomotic leak which required a return to theatre for lavage and formation of ileostomy. Twenty-five patients (21%) had a Clavien-Dindo 1–3, and 37 (32%) had Clavien-Dindo 4.

Patients with higher CCI scores had a higher rate of morbidity and a higher grade (46 patients (53%) with CCI 0–1 and eight patients (21%) with CCI 2+ had no morbidity and there was one (1%) death in patients with CCI 0–1 versus 4 (11%) in patients with CCI 2+, P < 0.001). Patients who experienced complications were older than the patients that did not (mean age 64 (SD 14) versus 52 (SD 16), P = 0.004). Patients with a higher CCI were also older (mean age 68 (SD 12) for patients with CCI 2+ versus 58 (SD 16) for patients with CCI of 0–1, P = 0.001). There was no temporal change in the rate and grade of morbidity during the study period. Higher modified Hinchey classification did not lead to significantly higher morbidity. Patients with modified Hinchey classification of 0, 1–2 and 3–4 had 33%, 61% and 64% rates of Clavien-Dindo 4 morbidity, respectively (P = 0.432).

There was no difference in the rate of death and readmission between the group of patients who had a HP or PA (Table 2). Patients who had a PA were less likely to have medical complications compared with patients who had a HP (28% versus 50%, P = 0.038). There was no difference in the rate of surgical complication (Table 2). There was no statistically significant difference between the two groups when comparing patients with modified Hinchey classification 0–2 only. This group of patients were significantly younger than patients with Hinchey 3–4 (mean age 58 (SD 16) versus 64 (SD 14), P = 0.048).

Operative data

Thirty-nine patients were initially managed non-operatively but required operative intervention. Eleven percent of these patients had a peri-colic abscess, and 43% had pelvic abscesses. Eleven patients (28%) had a percutaneous drain inserted. Patients who had a percutaneous drain were taken to OR later than patients who did not have percutaneous drainage (median 12 (interquartile range 14) versus 4 (interquartile range 4), P = 0.006).

Twenty-three of the patients had a CT finding of normal or mild diverticulitis. Nine of these patients had immediate surgery due to significant free air noted in CT or clinical signs of sepsis. Within this group of patients, two had mild diverticulitis on operative modified Hinchey classification, two had a phlegmon, one had a pelvic abscess and four had purulent peritonitis. The other 14 patients with mild diverticulitis on CT, had an operation after a median period of 4days due to worsening clinical condition despite antibiotic therapy.

Of the total 112 patients who included in the analysis, 80 (71%) had a HP and 32 (29%) had a PA with 21 (66%) having a covering ileostomy. There was no difference in the PA rate based on co- morbidity or gender. Patients who had HP were significantly older with the mean age of 64 versus 54 years (P = 0.005). Patients who had a higher modified Hinchey grade were less likely to have a PA (Table 3). Patients who were initially managed conservatively but failed this approach had a higher rate of PA (45% versus 20%, P = 0.009).

Patients were more likely to have a PA if a colorectal surgeon was operating compared with the colorectal surgery fellow or a general surgeon (37% versus 18% versus 8%, P = 0.015) (Fig. 1). There was no difference in medical or surgical complications, readmission or death between patients who had an operation by colorectal surgeons compared with general surgeons or colorectal fellows.

Of the 40 patients with intraoperative modified Hinchey scores of 3 or 4, only three (8%) had PA. Within the group of patients with intraoperative modified Hinchey scores of 0 to 2, operated by colorectal surgeons, there was a statistically significant temporal change in the PA rate within the study period (P = 0.038) (Fig. 2). There was no temporal change in the modified Hinchey classification of patients (rate of modified Hinchey 2 over the four quartiles were 63%, 23%, 50%, 62%, P = 0.09).

Of the 80 patients who had HP, data regarding the possible reversal of their stoma was available for 58 patients. Of these 44 (76%) had a reversal of HP. Of the 21 patients who had an ileostomy formation, 20 (95%) had their ileostomy closed in a subsequent procedure. This difference was not statistically significant (P = 0.269).

Discussion

Diverticulitis is a common pathology encountered in general surgery with a rising incidence in the ageing population. The majority of patients with diverticulitis are managed non-operatively with intravenous antibiotics. The optimal management of complicated diverticulitis has been changing, and some institutions have had a significant reduction in their operative rates with an increasing use of radiological intervention including percutaneous drainage.[17]

The optimal operative management of diverticulitis has also been a subject of debate recently with the previously held dogma of per- forming HP in complicated diverticulitis being challenged. Multiple systematic reviews of case series including the recent meta-analysis by Cirocchi et al., as well as randomized trials including the DIVERTI have demonstrated the safety and equivalence of PA compared with HP as well as likely improved morbidity and length of stay.[6,7,10,11,18,19] They have demonstrated comparable morbidity between the two groups and a higher stoma reversal rate with the patients undergoing HP. This paper focused on the rate or PA versus HP in the group of patients with Hinchey 0–2 as it was noted that only three (8%) patients had a PA in the context of intraoperative modified Hinchey classification of 3–4. This could partially be due to the fact that the group of patients with Hinchey 3–4 were older (mean age 64 versus 58, P = 0.048). Given these findings, the comparison of PA versus HP focused on the group of patients with intra-operative modified Hinchey classification 0–2. Within this group there was no statistically significant difference in morbidity in an echo of the current literature.

There has also been increasing evidence that sub-specialization has led to an increase in PA rate with cohort studies demonstrating a higher PA rate when colorectal surgeons are performing the operation.[13,14,20] This finding is also demonstrated in this study, with a significant difference in the PA rate between colorectal surgeons, colorectal surgery fellows and general surgeons (8% versus 18% versus 37%, P = 0.015). This is most likely related to the increased experience and comfort colorectal surgeons have in looking after patients following colonic resection and managing the associated complications including anastomotic leaks. Another reason may be that colorectal surgeons are more likely to alter their practice sooner with the increasing evidence emerging regarding the feasibility and safety of PA.

In addition to the above, there appears to be a trend that with the mounting evidence for the use of PA in the recent decade, there has been a shift in the management of complicated diverticulitis with fewer operations and higher PA rates if an operation is required.[12,17,21] This is again demonstrated in this study with an increasing PA rate of 21%, 43%, 63% and 57% from first to the last quartile of consecutive patients with intraoperative modified Hinchey classification of 0–2, operated by colorectal surgeons (P = 0.038). This is likely explained by the increasing evidence of the feasibility and safety of this surgical approach.

The major weakness of this study is that it is retrospective review of a single tertiary institution's experience with the operative management of patients with complicated diverticulitis. Nonetheless, this paper has demonstrated an increase in the PA rate with sub-specialization and demonstrated a significant increase in the PA rate during the study period when colorectal surgeons are performing the procedure. It has also shown that the morbidity and mortality were not different in patients undergoing HP compared with patients having a PA in the selected group of patients with intraoperative modified Hinchey of 0–2.

Conflicts of interest None declared.

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Tables and Figures:

Table 1: Demographic data

Patient characteristics	All patients managed operatively n = 118	patients initially managed non-operatively n = 39	patients initially managed operatively n = 79	
Age, Mean, (SD)	61 (15.8)	56 (15.2)	64 (15.5)	0.016*
Gender male, n (%)	60 (51)	19 (49)	41 (52)	0.845
Charlson comorbidity score n (%)				MH 0.681
0-1	79 (67)	25 (64)	54 (68)	
2+	39 (33)	14 (36)	25 (32)	
Modified Hinchey classification n (%)				MH < 0.0001 *
0	23 (24)	14 (38)	9 (15)	
1a	4 (4)	2 (5)	2 (3)	
1b	9 (10)	4 (11)	5 (9)	
2	27 (28)	16 (43)	11 (19)	
3	27 (28)	1 (3)	26 (44)	
4	6 (6)	0 (0)	6 (10)	
Known diverticular disease, n (%)	37 (32)	18 (46)	19 (24)	0.021 *
Number of previous attacks n (%)				MH 0.185
0	4 (14)	1 (7)	3 (21)	
1	15 (54)	7 (50)	8 (57)	
2	6 (21)	4 (29)	2 (14)	
3+	3 (11)	2 (14)	1 (7)	

MH, Mantel-Haenszel test
* p < 0.05

Table 2: Morbidity based on operations performed

Morbidity	Primary anastomosis (n = 320	Hartmann's procedure (n = 80)	p-value
Complications, n (%)	12 (38)	52 (65)	0.011*
Medical complication, n (%)	9 (28)	40 (50)	0.038*
Cardiac	*5(16)*	*12(15)*	
Respiratory	*0 (0)*	*11(14)*	
AKI	*0 (0)*	*2 (3)*	
Other	*5 (16)*	*17 (21)*	
Surgical complications, n (%)	5 (16)	23 (29)	0.156
Wound infection	*3 (9)*	*13 (16)*	
Prolonged Ileus	*2 (6)*	*5 (6)*	
Anastomotic leak	*1 (3)*	-	
Intra-abdominal collection	*1 (3)*	*5 (6)*	
Other	*1 (3)*	*4 (5)*	
Readmissions, n (%)	1 (3)	2 (3)	1.000
Death, n (%)	1 (4)	5 (6)	0.672

* $p < 0.05$. AKI, acute kidney injury

Table 3: Demographics of patients based on operation type

Patient characteristics	Primary anastomosis (n = 32)	Hartmann's procedure (n = 80)	p-value
Age, Mean, (SD)	55 (17.0)	64 (14.3)	0.005
Gender male, n (%)	19 (59)	39 (49)	0.403
Charlson comorbidity score (n%)			0.181
0-1	25 (78)	51 (64)	
2+	7 (22)	29 (36)	
Operative modified Hinchey classification (n%)			< 0.0001 *
0	3 (10)	2 (3)	
1a	10 (33)	6 (9)	
1b	1 (3)	8 (11)	
2	13 (43)	17 (24)	
3	2 (7)	22 (31)	
4	1 (3)	15 (21)	

MH, Mantel-Haenszel test, SD, Standard deviation
* $p < 0.05$.

Figure 1:Primary anastomosis rate based on surgeon performing operation.

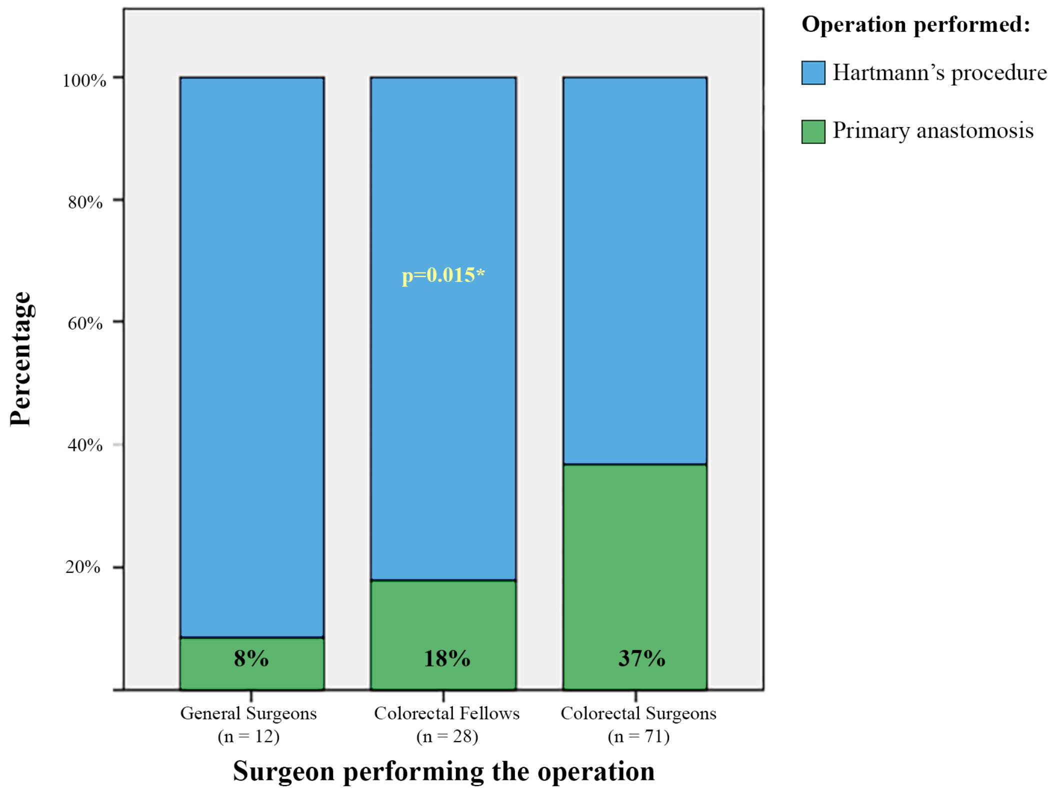

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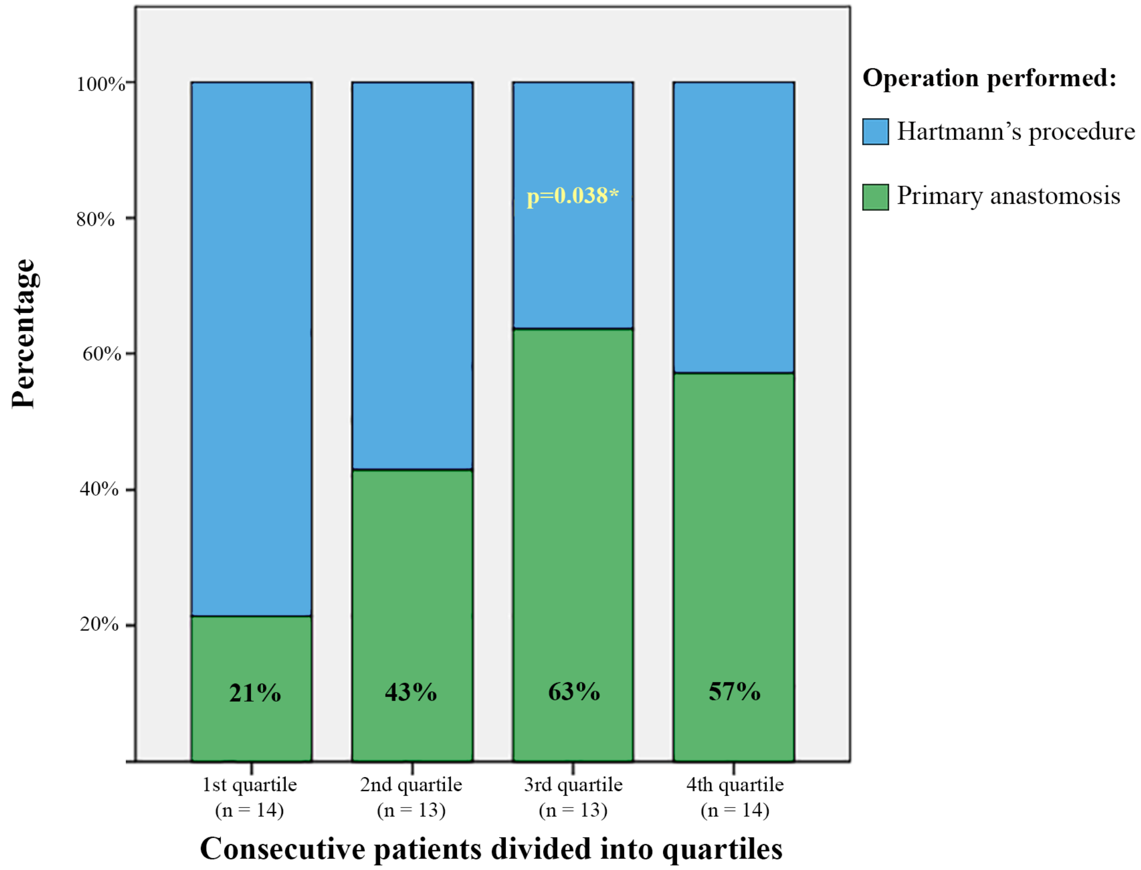
Figure 2: Change in primary anastomosis rate over the study period for patients with modified Hinchey 0–2, operated by colorectal surgeons..



CHAPTER 3:

Acute diverticulitis in immunosuppressed patients: a 12-year management experience.

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Citation

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Abstract

Background: Diverticular disease of the colon occurs commonly in developed countries. Immunosuppressed patients are thought to be more at risk of developing acute diverticulitis, worse disease, and higher complications secondary to therapy. This study aimed to assess outcomes for immunosuppressed patients with acute diverticulitis.

Method: A retrospective single-centre review was conducted of all patients presenting with acute diverticulitis at a major tertiary Australian hospital from 2006 to 2018.

Result: A total of 751 patients, comprising of 46 immunosuppressed patients, were included. Immunosuppressed patients were found to be older (62.25 versus 55.96, $p = 0.016$), have more comorbidities (median Charlson Index 3 versus 1, $P < 0.001$), and undergo more operative management (13.3% versus 5.1%, $P = 0.020$). Immunosuppressed patients with paracolic/pelvic abscesses (Modified Hinchey 1b/2) were more likely to undergo surgery (56% versus 24%, $P = 0.046$), while in patients with uncomplicated diverticulitis, there was

no difference in immunosuppressed patients undergoing surgery (6.1% versus 5.1% $P = 0.815$). Immunosuppressed patients were more likely to have Grade III-IV Clavien-Dindo complication ($P < 0.001$).
Conclusion: Immunosuppressed patients with uncomplicated diverticulitis can be treated safely with non-operative management. Immunosuppressed patients were more likely to have operative management for Hinchey 1b/II and more likely to have grade III/IV complications

Introduction

Colonic diverticular disease is a common condition in Western countries, with a steady increase in prevalence in the last few decades and estimated prevalence of over 50% in those older than 60 years.(67) With such high prevalence, diverticulitis has a lifetime incidence of 10%– 25% in patients with diverticular disease.(67, 68) Lifestyle factors have been associated with the development of diverticulitis, including Western diet (high fat, high protein, and low fibre). Obesity, and smoking have also been associated with increased risk of diverticulitis, while high fibre diet and physical activity are seen as protective.(67)

The severity of diverticulitis can vary from uncomplicated, such as thickening of the colonic wall, to complicated disease, with fistula, abscess, or perforation.(69) As such, the management of diverticulitis is tailored to patient acuity from conservative management with intravenous antibiotics to surgical resection.(67)

Immunosuppressed patients are widely considered to have a higher incidence of acute diverticulitis and are more likely to develop free perforation and faeculent peritonitis.(69, 70) Compared to immunocompetent patients, immunosuppressed patients are more likely to undergo emergency surgery at the first episode of diverticulitis, and also have worse mortality.(71) Previously, elective resection was identified as an important consideration in the immunocompromised patient, most notably by the American Society of Colonic and Rectum Surgeons (ASCRS) in 2014.(72) However, there is a movement for non-operative management which is reflected in the latest guidelines from ASCRS (2020) as well as European Society of Coloproctology (ESCP) (2020), which advocate non-operative management for uncomplicated diverticulitis in immunosuppressed patients.(73, 74)
The aim of this study was to compare outcomes for immuno- suppressed patients with acute diverticulitis treated in our centre over a 12-year period.

Method:

Ethics committee approval was obtained from our institution's ethics committee and the study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients with acute presentation of diverticulitis to Royal Prince Alfred Hospital, Sydney, Australia, between 2006 and 2018, were identified and their data were collected retrospectively using electronic and paper records. Patients were identified using the hospital administrative health data set. All patients coded with the broad ICD codes K57 (diverticular disease of the intestine) were identified. The electronic records of patients were reviewed to identify patients over the age of 18 with acute presentation of diverticulitis. Any patients with malignancy identified and/or with established colo-vesical or entero-cutaneous fistula or strictures were excluded. Demographic data including age, gender as well as co-morbidities, using the Charlson comorbidity index, were collected. Patients with computed tomography (CT) scans on admission had the reports reviewed and were coded as per the Wasvary modification of the Hinchey classification and CT findings by Kaiser. Immunosuppression use as well as the reason for immunosuppression was recorded Complicated diverticulitis was classified as modified Hinchey classification 1a–4. Operation reports were reviewed for the type of operation, as well as the surgeon operating were recorded, and operative findings were also coded as per the above-mentioned modified Hinchey classifications. Details of hospital stay including the type of intervention as well as morbidity and mortality were recorded. Deviation from initial treatment intention was considered as the primary outcome, with a specific look at the comparison of immunosuppressed and immunocompetent groups. Statistical analysis was performed using SPSS v24 statistical package (Chicago, IL, USA). Variables were analysed as appropriate using an independent samples t-test, Mann–Whitney U test, Pearson's chi- squared test, Mantel–Haenszel test or Kruskal–Wallis H test.

Results:

Seven hundred and fifty-one patients were included in our study with a mean age of 57.3 years (SD 14.4) and equal male to female ratio (male: 54.5%, female: 45.5%) and the average length of stay was 6.6 days (SD 7.9). At the time of presentation, 594 (89.9%) were treated conservatively, while 30 (4.5%) underwent percutaneous drainage by interventional radiology, and 37 (5.6%) underwent surgery. The median Charlson comorbidity index (CCI) was 1 (range 0–8), and the median CT Modified Hinchey score was 0 (IQR 0).

Forty-six of 751 (6.1%) patients were immunosuppressed at presentation. The reason for immunosuppression included solid organ transplantation (n = 10), active chemotherapy (n = 12), rheumatological on high-dose steroids (n = 12), Autoimmune disorders, including IBD on biologics at the time of diagnosis (n = 6), and HIV (n = 6). The demographic data is displayed in Table 1.

The patients that were immunosuppressed were more likely to be older (62.5 years versus 56.0 years, P = 0.016), and have more comorbidity (CCI 3 versus 1, P < 0.001). While immunosuppressed patients had worse CT Modified Hinchey, this was not statistically significant (P = 0.065).

The immunosuppressed group was more likely to have surgical management on admission (13.3% versus 5.1%; P = 0.020) and immunosuppressed patients had a higher percentage undergoing Hartmann's procedure as opposed to primary anastomosis with or without covering stoma compared to immunocompetent patients, however, this was not shown to be statistically significant (89% versus 58%, P = 0.078). In the cohort of patients that were treated surgically on admission, there was no difference in the rate of severe disease, based on modified Hinchey classification, between the immunosuppressed and immunocompetent groups (27% versus 20% complicated disease, P = 0.251). Figure 1 shows the intention to treat on admission.

In subgroup analysis, immunosuppressed patients with a para- colic or pelvic abscess (Modified Hinchey classification of 1b or 2) were more likely to undergo operative intervention compared to the immunocompetent group (56% versus 24%, P = 0.046). In patients with uncomplicated diverticulitis (Modified Hinchey classification of 0 or 1a), there was no difference in immunosuppressed patients undergoing surgery compared to immunocompetent patients (9% versus 5%, P = 0.315). Immunosuppressed patients underwent surgery on average at day 3, compared to immunocompetent patients, which received surgery on average on day 12 of admission, however, this was not statistically significant (P = 0.27).

Immunosuppressed patients were more likely to have grade III– IV Clavien–Dindo complications after surgery with 3/10 patients (30%) experiencing a significant complication compared with 4/57 (7%) patients in the immunocompetent group (P < 0.001). We had no mortality in our cohort. Immunosuppressed patients who experienced grade III–IV complications included, Wound infection requiring VAC dressing (n = 2) and haematoma (n

= 1), while immunocompetent patients with grade III–IV complications included, deep vein thrombosis (n = 1), wound infection requiring VAC dressing (n = 2) and bibasal collapse, acute kidney injury and septic shock (n = 1).

Within the total cohort of patients treated conservatively, there was no difference between immunocompromised patients and immunocompetent patients (8% versus 5%, P = 0.347) failing this conservative treatment and requiring percutaneous drainage or surgery. In patients with paracolic or pelvic abscesses (Modified Hinchey classification of 1b or 2) that were managed conservatively, there was no difference in failure of conservative treatment (need for percutaneous drainage or surgery) between the immuno- suppressed or immunocompetent groups (20% versus 13%, P = 0.538). Of the patients who were treated conservatively with Modified Hinchey classification of 1b or 2, 25 patients had percutaneous drainage, with only one immunocompromised patient. Eight of those patients failed conservative treatment and required surgery.

The immunocompromised patient was one of them. There was no difference in the rates of readmission within 30 days between the immunosuppressed and immunocompetent patients managed conservatively (5.7% versus 5.2%, P = 0.702).

Of the 11 patients with grade 3 or 4 Modified Hinchey classification, 10 had surgical management, of which three were immuno- compromised. One patient with Modified Hinchey 3 score who was immunocompetent was managed conservatively.

Discussion:

Management of acute diverticulitis can be challenging, particularly in immunosuppressed patients. In this cohort, healing can be impaired and systematic manifestations can be masked, secondary to immunosuppressive medications.(69) This understanding has led to surgeons having a lower threshold for operative management. The historical data that support this approach, suggesting patients are more likely to fail medical treatment and have a higher mortality rate, is based on small retrospective cohort studies.(71) This aggressive approach is mirrored in our experience in this study with a higher proportion of patients undergoing operative management on presentation despite no difference in the severity of the disease with 27% and 20% rates of complicated disease respectively. In subgroup analysis, 56% of immunosuppressed patients with paracolic or pelvic abscesses had surgical management on admission compared with 24% of immunocompetent patients. It is unclear if this was due to a worse clinical condition in the immunosuppressed group, as this data was not available, or due to surgical decision making based on the immunosuppression status and published guidelines.(73, 74)

More recent evidence suggests that conservative management of immunosuppressed patients is safe and feasible.(69, 75) In our cohort, the immunosuppressed patients that underwent conservative management had a similar rate of failure of conservative treatment as their immunocompetent counterparts (8% versus 5%). When comparing the subgroup of these patients with paracolic or pelvic abscesses, there was still no significant difference in failure of conservative management with 20% and 13% failure rates respectively.

A recent retrospective group by the Mayo clinic with 122 patients showed similar success with conservative management with 2% of immunosuppressed patients with uncomplicated diverticulitis and 5% of patients with abscesses failing conservative management(69). The authors did not compare the immunosuppressed group to an immunocompetent cohort.

Serrano Gonzalez et al. analysed the outcome of 40 immunosuppressed patients managed conservatively and found 20% failed this approach.(68) Unfortunately, they did not compare this group directly to a cohort of immunocompetent patients. Furthermore, in a recent meta-analysis, only six out of 11 studies reported non-operative outcomes, and those that reported the non-operative data, did so inconsistently and therefore a meta- analysis was not able to be performed for this cohort.(71)

In our cohort, there was a trend towards performing Hartmann's procedure in immunosuppressed patients that underwent emergency surgery with 89% compared with 58% of patients in the immunocompetent group. This was similar to a result in a recent meta-analysis where 72.9% of immunosuppressed patients compared with 37.8% of immunocompetent patients underwent a Hartmann's procedure.(71) We have previously reported a temporal change and increasing rates of resection and primary anastomosis, with or without covering stoma, in patients undergoing emergency surgery in our institution.(76) Unfortunately, due to the low number of immunosuppressed patients a similar analysis was not possible in this cohort to ascertain if this trend was also seen in this cohort.

Immunosuppressed patients undergoing surgical management were more likely to have significant morbidity (Clavien–Dindo grade III–IV) morbidity in our cohort (30% compared with 7%). The recent meta-analysis demonstrated no difference in morbidity in the immunosuppressed and immunocompetent patients that underwent emergency surgery, however, the rate of complication in the former group was similar to our cohort with 279/739 (37.7%) of the pooled patients experiencing morbidity.(71)

There is a shift in the paradigm of management of immuno- suppressed patients with acute diverticulitis. The European Society of Coloproctology (ESCP) guidelines from 2020 acknowledge that non-operative management of uncomplicated diverticulitis is safe, however, there is still doubt as to the safety of non-operative management of complicated diverticulitis.(74) The American Society of Colon and Rectal Surgeons (ASCRS) does advocates for per- forming sigmoid resection and primary anastomosis as opposed to Hartmann's procedure where appropriate and they do not deem immunosuppression a contraindication in this approach.(73) The current evidence in this area is limited to small retrospective cohort studies and due to the heterogeneity of the reported outcomes, meta-analysis may not be able to completely answer all the questions regarding the ideal approach to these patients. However, the current literature does support conservative management in immunosuppressed patients where appropriate, as well as the utilization of restoring bowel continuity in select cases if surgical intervention is required in immunosuppressed patients. Our study adds to this evidence base.

Our study has several limitations. This is a retrospective study from a single institution and our patient cohort is heterogenous and there are multiple differing reasons for immunosuppression and therefore differing levels of suppression of immune function in our patient cohort which may have impacted their clinical course. Furthermore, the number of immunosuppressed patients was not high enough to allow for multivariate analysis to better reflect factors affecting interventions. Also, we did not have complete data on recurrence rates of the diverticulitis as well as the need for elective surgery after discharge. This is in part due to the referral of these patients, especially transplant patients, to our unit from other geo- graphic areas of our state as we are a tertiary referral hospital, which results in loss of patients to follow up which occurs locally. The study was designed to assess the management of immuno- suppressed patients and to ascertain if this is different than in immunocompetent patients as well as quantify this cohort's out- comes in the different management strategies including conservative and surgical management. The risk of recurrence and the need for elective surgery was beyond the scope of this study.

Conclusions:

Immunosuppressed patients with acute diverticulitis are more likely to undergo operative management on admission despite no significant difference in the severity of their disease.

They are more likely to have a Hartmann's procedure compared with sigmoid resection and primary anastomosis with or without a covering ostomy. They are more likely to have significant post-operative morbidity compared with immunocompetent patients. Immunosuppressed patients with uncomplicated diverticulitis and immunosuppressed patients with paracolic or pelvic abscesses who were treated conservatively had similar rates of failure of conservative management compared with immunocompetent patients.

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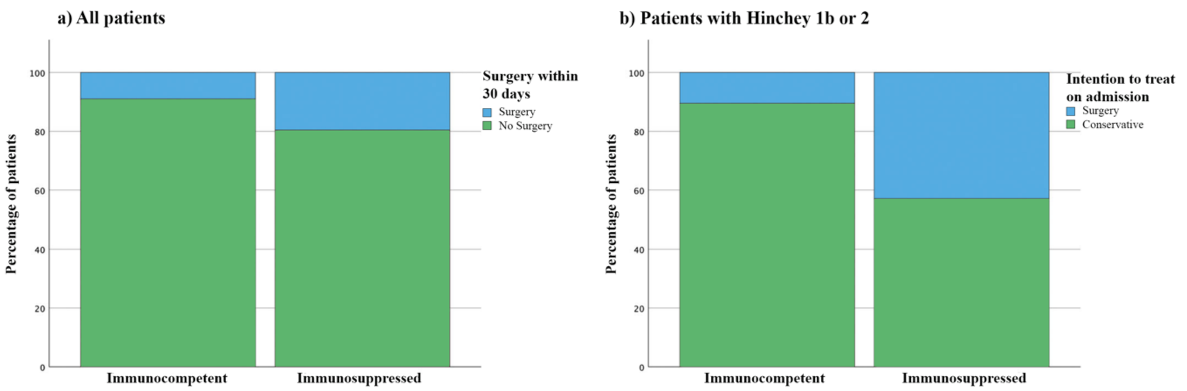
Tables and Figures:

Table 1: Demographic data

	Total Cohort n = 751	Immunosuppressed n = 46	Immunocompetent n = 612	P value
Gender	n (%)			
Male	302 (54.5%)	17 (37.0%)	283 (46.3%)	0.219
Age	57.34 (SD 14.42)	62.25 (SD 13.96)	55.96 (SD 14.43)	**0.016***
Charlson comorbidity index	1 (IQR 21)	3 (IQR 3)	1 (IQR 3)	**<0.001***
Diabetic	84 (13.1%)	9 (20.4%)	75 (12.6%)	0.293
CT Modified Hinchey				
0	515 (79.7%)	32 (71%)	483 (80.4%)	
1a	25 (3.9%)	1 (2%)	24 (4.0%)	
1b	31 (4.8%)	2 (4%)	29 (4.8%)	
2	64 (9.9%)	7 (16%)	57 (9.5%)	
3/4	11 (1.7%)	3 (7%)	8 (1.3%)	0.065 MH

* $p < 0.05$. MH, Mantel–Haenszel test.
Abbreviations: SD, Standard deviation. IQR, Interquartile range

Figure 1: intention to treat patients with either surgery or conservative management separated by status of immune system. (a) shows all patients and (b) shows patients with Hinchey 1b or 2.



THESIS DISCUSSION:

Acute diverticulitis is a common surgical presentation to the hospital with a significant burden on the patients and the healthcare system. The optimal management is tailored to each patient and depends on their comorbidities, clinical condition and the severity of the disease. There remain complexities and challenges associated with the management of patients with acute diverticulitis. These range from optimal patient selection for non-operative management to the ideal operative technique with the focus on reducing morbidity and improving quality of life.

The majority of patients with uncomplicated diverticulitis can be managed successfully with non-operative management with 94-99% success rates (50, 52). A select group of patients with complicated diverticulitis with no evidence of florid sepsis can also be successfully managed non-operatively (50-52). However the success rate in this group is lower with as many as 12-15% of patients failing this approach and requiring radiological or surgical intervention (64, 77). The challenge is to identify these patients at risk of failure to reduce morbidity. Multiple studies have attempted to identify factors associated with severity of disease as well as an attempt to predict patients at risk of failure. One factor identified that has been shown to predict severity of illness in several studies is the C-reactive protein (CRP) (53-57). These studies have assessed CRP as a static marker, however, the CRP is an acute phase reactant with correlation to duration and intensity of the stimulus(78). This lends the CRP to being a useful dynamic marker of response to sepsis with multiple studies demonstrating its utility in predicting response to treatment in the setting of sepsis(79-81). In Chapter 1, we explored the utility of dynamic measurement of CRP trajectory patterns in predicting the likelihood of failure of non-operative management. In this study, we devised a pragmatic, simple to use assessment of CRP using cut-offs of 80 and 200 at day 0 and 2 respectively to stratify the patient cohort into 4 groups based on change of CRP relative to these values. These CRP values were chosen as they were round numbers close to the mean CRP values on day 0 and 2 of admission. This was done to allow for the development of a simple to use tool. The 4 groups were;

1. “rapid rise”: Patients with a day 0 CRP lower than the mean but had a CRP higher than the mean on day 2,
2. “high rise”: Patients with higher CRP relative to the mean on day 0 and 2

3. “Decline”: Patients with higher CRP relative to the mean on day 0 but lower CRP relative to the mean on day 2
4. “low rise”: Patients with CRP lower than the mean on days 0 and 2.

The study demonstrated that patients in the “rapid rise” and “high rise’ groups, that is patients with higher rise in the trajectory of their inflammatory markers, in the first 48 hours of antibiotic treatment had an intervention risk of 19% and 32% respectively. The intervention rate was more significant in patients with a pelvic abscess (100% and 100% respectively). In addition to being useful to clinicians as part of the assessment of ongoing response to non-operative therapy, this simple tool could also be used to help patients understand their risk and manage expectations more easily.

The optimal surgical management of patients with perforated diverticulitis has been assessed in numerous studies. Patients with complicated diverticulitis with clinical indications to undergo emergency surgery, traditionally had a Hartmann’s procedure (HP) which involves an anterior resection and formation of an end colostomy. This dogma has been challenged over the past two decades with some surgeons advocating for laparoscopic washout and others advocating for primary anastomosis (PA) with or without diverting ileostomy. Multiple randomised trials(82-84) and meta-analyses(85) have demonstrated increased rates of reintervention in laparoscopic lavage groups, although long-term data have shown reduced ostomy rates and comparable overall complication rates. There is also increasing evidence for the safety of restoring colonic continuity with PA with or without diverting ileostomy at the initial surgery. Numerous retrospective and randomised data have demonstrated improved morbidity and mortality with this approach. Binda et al randomised 34 patients to PA and 56 patients to HP for diverticulitis with peritonitis. They found no difference in mortality (2.9% vs 10.7% p=0.24) or morbidity (35.3% vs 46.4% p=0.38) between the groups. The patients had a similar stoma reversal rates (64.7% vs 60%, p=0.65), however the patients in the HP group had higher morbidity associated with the stoma reversal (23.5% vs 4.5% p=0.05)(63). ColonPerfRCT and DIVERTI trials also reported similar findings with no difference in morbidity among their 62 patients and 102 patients respectively included in their randomisation(62, 65). ColonPerfCRCT was terminated early as the interim analysis demonstrated significantly more complications in the HP patients undergoing reversal compared with ileostomy reversal (20% vs 0%). The LADIES trial (DIVA arm) randomised 133 patients to HP or PA with or without defunctioning ileostomy. Patients with PA had a higher 12-month stoma-free survival (94.6% vs 71.7%) and there was no significant differences in mortality (3% vs 6%, p=0.44) or morbidity (44% vs 39%, p=0.60) between the two groups(64). A recent meta-analysis confirmed these findings with no difference in morbidity (RR, 0.88; 95% CI, 0.59–1.32) and mortality (RR, 0.84; 95% CI, 0.34–2.08) within the two groups. The patients in the PA group were more likely to be stoma-free at 12 months (RR, 1.34; 95% CI, 1.15–1.54) and had a reduced risk of morbidity in the subsequent stoma reversal operation (RR 0.23; 95% CI, 0.07–0.70)(86). The study in chapter 2 examined our institutional data over a 13 year period and echoed the literature with no differences noted in the morbidity and mortality of HP or PA patients. One interesting aspect of the study demonstrated a temporal change in the rates of PA performed in our institution from 21% in the first quartile to 57% in the last quartile of consecutive patients. This may reflect the cut-through of the increase in the evidence for safety of PA in the acute setting during the 13 year period of the study. Another interesting trend that was demonstrated was that the PA rates increased, the more subspecialised a surgeon was in colorectal surgery with colorectal surgeons more likely to perform PA compared to colorectal fellows or general surgeons. (37% vs 18% vs 8%, p=0.015). This could be related to the time of day these operations were performed, with more HPs performed after-hours. One of the limitations of our study was the lack of availability of this data point. Nonetheless, our unit now provides more supervision to our colorectal fellows, despite their seniority, and general surgeons no longer look after colorectal specific pathologies.

Patients who are immunosuppressed have a documented increase incidence and severity of diverticulitis(14, 15). Additionally, healing can be impaired and systemic manifestation of sepsis can be masked due to immunosuppressive medication. These factors have led to lower threshold for operative management in patients with diverticulitis in the setting of immunosuppression. In chapter 3 we examined management of 46 immunosuppressed patients in our institution which mirror the published literature and old American and European guidelines. They were more likely to undergo operative management compared to their immunocompetent counterparts despite no significant difference in the severity of their disease on imaging. In patients with paracolic or pelvic abscesses, a significant number of immunosuppressed patients compared with immunocompetent were managed operatively. More recent evidence in small retrospective studies suggest that non-operative management of these patients can be feasible and safe(15, 75, 87). Sugrue et al reported on 20 transplant recipients comparted with 134 immunocompetent patients treated non-operatively. There was no mortality associated with this approach and no difference in morbidity. On multivariate analysis, the sole predictor of complication was operative management(75). He et al demonstrated a success rate of 93% in 86 immunosuppressed patients with acute diverticulitis complicated diverticulitis. Of these 22 had complicated diverticulitis with abscesses and 95% were successfully managed non-operatively(15). They had no comparator group however, their result demonstrate safety and feasibility of non-operative management. A recent meta-analysis demonstrated emergency surgery in immunosuppressed patients was associated with a higher mortality rate (RR 1.91, 95%CI 1.24-2.95, $p < 0.01$) but not higher morbidity rates (RR 1.40, 95%CI 0.68-2.90, $p = 0.37$). There was a significant difference in the rate of HP performed with 72.9% of immunosuppressed patients compared with 37.8% of immunocompetent patients undergoing HP. The authors were unable to perform a meta-analysis of non-operative management in these patients due to inconsistent outcome reporting in the six papers included(87). The recent evidence on the treatment of immunosuppressed patients with acute diverticulitis has led to a paradigm shift the most recent European Society of Coloproctology (ESCP) guidelines acknowledge the safety of non-operative management of immunosuppressed patients(88) and the American Society of Colon and Rectal Surgeons (ASCRS) no longer recommends HP for immunosuppressed patients and advocates for PA where appropriate(89).

The treatment of acute diverticulitis is complex and dependent on a multitude of factors including the patient's comorbidities, severity of disease and clinical status. There remain numerous complexities and challenges in the optimal treatment of these patients and it is only through ongoing clinical research that we can improve the tailored approach to the treatment of these patients and ensure optimal management strategies.

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