Studies on the Pathophysiology, Risk Factors and Management of Diverticular Disease

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery, The University of Auckland, 2020.

ABSTRACT

INTRODUCTION Diverticular disease is a common gastrointestinal condition with significant associated morbidity. The objectives of this thesis are to improve understanding of the role of colonic pressure as a pathophysiological mechanism, predict more severe outcomes in acute diverticulitis and examine the need for antibiotics in uncomplicated acute diverticulitis.

METHODS A literature review consolidated information on the terminology and pathophysiology of diverticular disease, and recent changes to the management of uncomplicated acute diverticulitis. A systematic review examined the role of colonic pressure in diverticular disease and an *in vivo* high resolution manometry study was performed. A survey of Australasian surgeons assessed local diverticular disease management and two retrospective cohort studies identified risk factors for complicated acute diverticulitis and severe clinical course in uncomplicated disease. An international, double-blinded, placebo-controlled, randomised trial investigating the non-inferiority of placebo compared to antibiotic therapy was performed to investigate whether antibiotics are mandatory in this group of patients.

RESULTS The terminology and classification of diverticular disease is complex and not applied in a standardised manner. The manometry study found that participants with diverticulosis had fewer propagating contractions and lower intracolonic pressures when compared to controls. The clinician survey revealed a lack of consensus around the management of multiple aspects of diverticular disease, including more conservative and novel approaches. Independent risk factors for complicated acute diverticulitis included systemic inflammatory response syndrome, delayed presentation to hospital and raised C-reactive protein. Independent risk factors for severe course in uncomplicated disease included high self-reported pain score, fever, raised C-reactive protein and regular steroid/immunomodulator use. Non-inferiority between placebo versus antibiotic treatment was demonstrated by the clinical trial which compared length of hospital admission in participants with uncomplicated acute diverticulitis.

CONCLUSIONS Evidence supporting the role of motility and pressure in diverticula formation and diverticular disease is limited and not supported by high resolution manometry; risk prediction in acute diverticulitis may be a useful tool for research and clinical practice; and foregoing antibiotics is non-inferior to standard antibiotic therapy in the management of uncomplicated acute diverticulitis.

DEDICATION

To my grandparents Jaung Ki-Man and Bang Jung-Soon, and Woo Jong-Sun and Kim Jung-Sook.

ACKNOWLEDGEMENTS

I wish to thank my supervisor Professor **Ian Bissett** for his support, mentorship and encouragement. The integrity, enthusiasm and sincerity with which he approaches clinical research are among the greatest lessons I have learnt from him.

I am also grateful to my co-supervisor Dr **David Rowbotham** for his guidance and advice, and to A/Professor **Lindsay Plank** for so generously sharing his time and expertise.

The clinical trial in particular was only possible through the combined efforts of the study investigators and clinicians across all four study sites. Additionally, I would like to thank A/Professor **Greg O'Grady**, Professor **John McCall** and A/Professor **Roger Marshall** for their important input and direction as the Data Safety and Monitoring Committee.

I am indebted to my colleagues **Celia Keane**, **Tony Milne**, **Anthony Lin**, **Alistair Escott**, **Jason Robertson**, **Ryash Vather** and **Lois Blackwell** for their advice and camaraderie.

I am thankful to the **Auckland Medical Research Foundation** for the award of a Doctoral Scholarship and the **Colorectal Surgical Society of Australia and New Zealand** for a project grant for funding the clinical trial.

I am grateful for the love of my parents, **Hans** and **Yvonne Jaung**, and brother, **John**. I recognise the victims and survivors of **Japanese military sexual slavery** and the **Sewol Ferry Tragedy** for giving me a greater sense of purpose and perspective, and thank my friends of women of colour solidarity, **Korean New Zealanders for a Better Future** and in the public health world for their support.

Finally, I acknowledge all those participated in the studies contained in this thesis. I am eternally grateful for the time and effort which they selflessly contributed.

LIST OF PUBLICATIONS

Jaung, R., Robertson, J., Vather, R., Rowbotham, D. and Bissett, I.P. (2015), Changes in approach to acute diverticulitis. ANZ J Surg, 85: 715-719. doi:10.1111/ans.13233.

Jaung, R., Robertson, J., Rowbotham, D., & Bissett, I. (2016). Current management of acute diverticulitis: a survey of Australasian surgeons. NZ Med J, 129(1431), 23-9.

Jaung, R., Kularatna, M., Robertson, J., Vather, R., Rowbotham, D., MacCormick, A.D. and Bissett, I.P. World J Surg (2017) 41: 2258.

Jaung, R., Robertson, J., O'Grady, G., Milne, T., Rowbotham, D. and Bissett, I.P. (2017), Limited evidence of abnormal intra-colonic pressure profiles in diverticular disease–a systematic review. Colorectal Disease, 19(6), O168-O176.

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Nature of contribution by PhD candidate	Conception and design, literature review, analysis and interpretation of data, manuscript write-up
Extent of contribution by PhD candidate (%)	90

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. CHAPTER 5: SURVEY OF AUSTRALASIAN SURGEONS - CURRENT MANAGEMENT OF ACUTE DIVERTICULITIS Jaung, R., Robertson, J., Rowbotham, D., & Bissett, I. (2016). Current management of acute diverticulitis: a survey of Australasian surgeons. NZ Med J, 129(1431), 23-9.	
Nature of contribution by PhD candidate	Conception and design, survey design and construction data acquisition, analysis and interpretation of data, manuscript write-up
Extent of contribution by PhD candidate (%)	90

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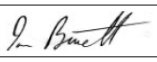
Ian Bissett		February 7 2020

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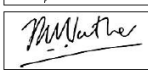
Ryash Vather		February 19 2020
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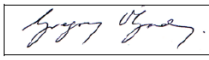
Greg O'Grady		February 10 2020
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Nature of contribution by PhD candidate	Conception and design, data acquisition, manuscript write-up
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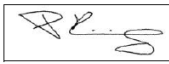
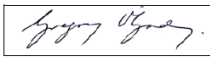
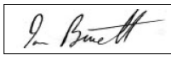
Phil Dinning		February 17 2020
Greg O'Grady		February 8 2020
Ian Bissett		February 7 2020

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Nature of contribution by PhD candidate	Conception and design, funding acquisition, project administration, data acquisition and curation, analysis and interpretation of data, manuscript write-up
Extent of contribution by PhD candidate (%)	75

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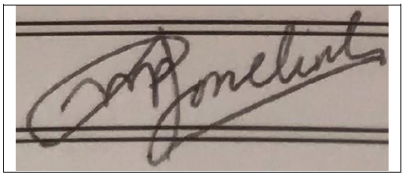
Martijn Pieter Gosselink		February 11 2020
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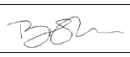
Bruce Su'a		February 18 2020
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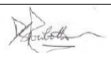
David Rowbotham		February 12 2020
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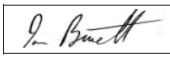
Ian Bissett		February 7 2020

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GLOSSARY

Symbols

%	Percent
℃	Degrees Celsius
β-HCG	Beta-Human Chorionic Gonadotropin
X^2	Chi-square

Numbers

5-ASA	5-Aminosalycilate Agent

A

Abx	Antibiotics
ACTRN	Australian Clinical Trials Registration Number
AD	Acute Diverticulitis
ADHB	Auckland District Health Board
ADU	Assessment and Diagnostic Unit
AE	Adverse Events
ANOVA	Analysis of variance
ANZCTR	Australian New Zealand Clinical Trials Registry
APACHE	Acute Physiology and Chronic Health Evaluation II
APU	Admission and Planning Unit
ASA	American Society of Anaesthesia
AUC	Area Under Curve

B

BP	Blood Pressure

C

CI	Confidence Interval

Cm	Centimetres
CMP	Cyclic Motor Patterns
CRP	C-reactive Protein
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CSSANZ	Colorectal Surgical Society of Australia and New Zealand
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events

D

DVT	Deep Vein Thrombosis
DMC	Data Monitoring Committee

E

ECG	Electrocardiogram
ED	Emergency Department

F

Fgb	Fibre Bragg Grating

G

g	Grams

H

H	Hour/s
HR	Heart Rate
HRM	High Resolution Manometry

I

ICC	Interstitial Cells of Cajal
ICD	International Classification of Diseases

ICU	Intensive Care Unit
IQR	Inter-Quartile Range
IV	Intravenous

K

kcal	Kilocalorie

M

mg	milligrams
mm	millimetres
MI	Motility Index
min	Minute/s
mmHg	Millimetres of Mercury
MSU	Mid-stream Urine

N

NBM	Nil By Mouth
NOS	Newcastle-Ottawa Scale for Case Control Studies
NHI	National Health Index
N/R	Not Reported
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs

O

OR	Odds Ratio

P

$PaCO_2$	Partial Pressure of Carbon Dioxide
PC	Personal Computer
PO	Oral
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRN	As Required

Q

Q1H	Every Hour
Q12H	Every Twelve Hours
Q5MIN	Every Five Minutes
Q6H	Every Six Hours
Q8H	Every Eight Hours
QID	Four Times a Day

R

RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic

S

SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SIRS	Systemic Inflammatory Response Syndrome
SpO_2	Peripheral Capillary Oxygen Saturation
STAND	Selective Treatment with Antibiotics for Non-complicated Diverticulitis
SSU	Sterile Services Unit SSU

T

TDS	Three Times a Day

U

UTI	Urinary Tract Infection

V

vs	Versus

W

WDM	Wavelength Division Multiplexing
WCC	White Cell Count

Chapter 1. Introduction

Although colonic diverticulosis had been described as early as 1700, diverticular disease of the sigmoid colon has only been widely recognised and studied over the last century (1-3). It is now one of the most commonly diagnosed non-communicable gastrointestinal conditions in the global north (4-6), resulting in significant health impacts for both individuals and healthcare systems. However, the term diverticular disease encompasses a spectrum of clinical manifestations associated with sigmoid diverticulosis and efforts to classify the different clinical entities in a uniform manner have been continually evolving in step with improving diagnostic tools and management techniques. This variable classification system has created difficulties for those investigating the pathologic basis of each sub-type of diverticular disease and subsequent identification and uptake of effective management strategies.

This chapter provides an overview of the most recent and widely accepted classification of diverticular disease with a focus on terminology, clinical manifestations and pathophysiology, followed by discussion around current approaches to the management of uncomplicated acute diverticulitis and concluding with an overview of the health significance of diverticular disease.

1.1. The Terminology of Diverticular Disease

1.1.1 **Diverticulosis**

Diverticulosis of the sigmoid colon refers to the acquired anatomical deformity in which the mucosal and submucosal layers of the bowel wall herniate through the muscular layers, usually at the sites where the vasa recta are penetrating (7). This is considered to be a separate pathology from similar deformities elsewhere in the gastrointestinal tract including the ascending colon and small intestine (8). Furthermore, sigmoid diverticula are considered 'pseudo-diverticula', as opposed to true diverticula which describe the herniation of all three layers of the bowel wall through a defect, are largely congenital and much rarer than sigmoid diverticula (4, 9).

1.1.2 **Diverticular Disease**

Diverticular disease is the term used to describe any symptoms arising as a consequence of having sigmoid diverticulosis. Diverticular disease can manifest as symptomatic uncomplicated diverticular disease but also encompasses acute, recurrent and chronic diverticulitis, diverticular bleeding, and sigmoid colitis associated with diverticular disease (9, 10).

1.1.3 **Acute Diverticulitis**

Acute diverticulitis arises when there is inflammation within a diverticulum and is the most commonly described manifestation of diverticular disease, an estimated 10-25% of those effected (11). Traditionally, the severity of acute diverticulitis was classified according to the Hinchey Classification for colonic perforation associated with diverticular disease (12, 13) (Table 1-1). This approach was initially based on intra-operative findings and more recently adapted for radiological findings, namely computed tomography (CT), which is currently the most commonly used imaging modality in the management of acute diverticulitis (14).

A number of variations of this have been proposed subsequently, however they are not widely used in current clinical practice. More recent literature proposes that acute diverticulitis should be divided into uncomplicated or complicated disease using a combination of clinical and radiological features (15, 16). This approach acknowledges the utility of CT for assessing severity of an episode as well as diagnostic purposes (17, 18). The way in which this new paradigm relates to the Hinchey Classification is outlined in Table 1-1. This classification

describes the initial stages of an episode of acute diverticulitis and does not encompass recurrent or refractory subtypes of acute diverticulitis, or segmental colitis associated with diverticular disease.

<table>
<tr><th>Hinchey classification</th><th>Proposed new classification</th></tr>
<tr><td>Ia Confined pericolic inflammation or phlegmon</td><td rowspan="5"><u>Uncomplicated AD</u>

Presentation: abdominal pain, fever, change in bowel habit (15)

Imaging findings: localised inflammation or small abscess in bowel wall

Treatment: can be managed as an outpatient (17, 19, 20), normal diet or bowel rest (21, 22), antibiotics at clinician’s discretion (23-27)</td></tr>
<tr><td>Ib localised abscess (para-colonic)</td></tr>
<tr><td>II Pelvic abscess</td></tr>
<tr><td>III Purulent peritonitis</td></tr>
<tr><td>IV Faeculent peritonitis</td></tr>
<tr><td></td><td><u>Complicated AD</u>

Presentation: fever, lower abdominal mass, ileus, generalised peritonitis (15) or a high risk patient (28)

Imaging findings: pelvic or distant abscess; fistula, intestinal obstruction (29)

Treatment: inpatient management, antibiotics given, may need percutaneous drainage or operation (14)</td></tr>
</table>

Table 1-1 Comparison of the modified Hinchey Classification (12, 13) and proposed potential new classification of acute diverticulitis (15-17). AD = acute diverticulitis

1.2. The Pathophysiology of Diverticulosis and Diverticular Disease

Diverticulosis an acquired condition. A combination of factors including genetic susceptibility (30), low dietary fibre (31-33), disordered colonic motility (34), and both congenital and acquired connective tissue abnormalities (35-38) have classically been proposed to play a role in the aetiology of diverticula formation.

As of yet, it is unclear why only a proportion of people with diverticulosis experience symptomatic disease such as symptomatic uncomplicated diverticular disease or acute diverticulitis. There is supporting evidence for the role of inflammation (39-42), differences in gut microbiome (43), and other environmental (44) and lifestyle factors (45, 46).

Although outside of the scope of this review, visceral hypersensitivity (47, 48) and psychological factors have also been found to be significantly associated with recurrent pain in patients with diverticulosis (49) and the possibility of epidemiologic overlap between chronic manifestations of diverticular disease and irritable bowel syndrome has been raised (50-52).

1.2.1 **Genetic Susceptibility**

The heritability of any type of diverticular disease has been demonstrated through twin/sibling studies (30, 53), and distinctive immunoregulatory ribonucleic acid (RNA) sequences (54) and haplotypes (55) have been characterised in patients with diverticular disease. One genome-wide study performed in Icelandic and Danish populations has also identified loci which are significantly associated with diverticular disease (56). However, as with many studies of genetic causality, these results only reflect a small proportion of those with diverticulosis and diverticular disease. Furthermore, these studies do not consistently differentiate between the different manifestations of diverticular disease, a step which is vital for the translation of these findings to the clinical context.

1.2.2 **Fibre Intake**

Low fibre intake is one of the classically proposed risk factors for developing diverticulosis and diverticular disease (32, 33) due to the role that fibre plays in regulating colonic motility (32) and more recently the gut microbiome (57). It was supported by epidemiological research which found that western diets with relatively low dietary fibre were associated with a higher incidence of diverticulosis when compared to African diets which were higher in fibre (58). Findings on benefit of dietary and supplemental fibre differ according to the type of diverticular

disease, study methodology and measured end point. A high fibre diet and frequency of bowel movements did not reduce the prevalence of diverticulosis (59) but high dietary fibre has been found to reduce hospital admission and death from diverticular disease (46). Based on existing evidence, international best practice guidelines have conflicting recommendations on the role of fibre in preventing and treating diverticular disease (60). However, the role of nuts, seeds and popcorn in causing acute diverticulitis has been disproven and this form of dietary advice is no longer recommended (61, 62).

1.2.3 **Disordered Colonic Motility**

Colonic dysmotility and high intracolonic pressures have long been proposed as the driving factor causing the prolapse of colonic mucosa through weak points in the muscular layer resulting in diverticular formation (32, 34). However, the evidence for this is conflicting and based a small number of studies with variable methodologies (63, 64). Changes to the enteric nervous system have also been found in patients with diverticulosis (65) and diverticular disease (66). There is a need for further clarification of the role of motility and pressure in diverticulosis and diverticular disease in order for clinically applicable findings to be derived. The existing body of evidence investigating the role of motility and pressure in diverticulosis and diverticular disease will be explored in Chapter 3 by means of a systematic review, and *in vivo* high resolution manometry (HRM) will be utilised as a novel method for gaining further insights into this aetiological pathway.

1.2.4 **Connective Tissue Abnormalities**

Acquired changes to the connective tissue composition of the colon including elastosis of the colon wall (36) and cross linking of colonic collagen (37) are processes which increase with age and have been found to be associated with diverticular disease requiring resection and diverticulosis respectively. Diverticular disease is also associated with congenital connective tissue disorders such as benign intra-abdominal cystic disease (67) and Ehlers-Danlos syndrome (68), although these conditions are much less common than diverticular disease.

One recent epidemiological study using national-level hospital administrative data identified statistically significant associations between diverticulosis/diverticular disease and a number of more common connective tissue disorders including rectal prolapse, female genital prolapse, non-aortic aneurysm, aortic aneurysm, inguinal hernia and dislocations of shoulder and other

joints (38). These findings raise the question of whether a common underlying connective tissue abnormality may increase the risk of disease across multiple organ systems.

1.2.5 **The Role of Inflammation**

Inflammation is a key feature of acute and chronic diverticulitis, segmental colitis associated with diverticular disease (39-42) and has also been noted in patients with symptomatic uncomplicated diverticular disease (60, 69). Historically the inflammation which occurs in acute diverticulitis was wholly attributed to infection and managed accordingly (10), in the last decade the theory that the pathophysiology of diverticular disease is analogous to that of a chronic inflammatory bowel disorder has also been postulated (70).

During an infectious or inflammatory process, pro-inflammatory cytokines are released, and these result in a greater and sustained inflammatory response. This inflammatory response itself can result in tissue damage and a systemic inflammatory response in addition to that caused by the primary pathology. Mesalazine is an anti-inflammatory agent which has been demonstrated to be of some benefit as an adjunct in the management of acute diverticulitis (71, 72). The evidence regarding the role of mesalazine in the management of diverticular disease will be discussed in the treatment section.

Faecal calprotectin is an intracellular antimicrobial compound found in granulocytes, monocytes, and macrophages (73). It is released by cell excitation and death and has been shown to be a sensitive marker of disease activity in ulcerative colitis (74, 75). Increased levels of faecal calprotectin were found in all forms of symptomatic diverticular disease (symptomatic uncomplicated diverticular disease and uncomplicated acute diverticulitis) but were found to be absent in patients with diverticulosis and irritable bowel syndrome (73). Decreased levels of faecal calprotectin were found in patients after treatment following acute diverticulitis with mesalazine and rifaximin, a regimen which combines an anti-inflammatory agent and an antibiotic (72). In another study of patients who had recovered from an episode of uncomplicated acute diverticulitis, faecal calprotectin was raised in all but one of those who had recurrence of acute diverticulitis (70).

Research which examines the role of inflammatory processes, particular in the pathophysiology of acute diverticulitis is promising in that it potentially adds credence to taking a selective approach to antibiotic therapy in the treatment of some patients with uncomplicated disease.

Further work which supports or negates this hypothesis will be vital for determining whether this burgeoning conservative approach to management will receive ongoing clinical support.

1.2.6 **The Gut Microbiome**

The gut microbiome is a symbiotic ecosystem of commensal microorganisms which plays an important role in the host's immune system and is a growing area of research in relation to many different gastrointestinal disorders (76-78). Small studies comparing the microbiome of participants with diverticular disease to controls or participants with other gastrointestinal conditions have identified differences in the distribution of different types of bacteria (43, 79-81) which may represent disruption of the homeostatic balance of the microbiome (dysbiosis) (52, 76, 82).

This is a growing field of research which complements investigations of the efficacy of probiotics, particularly in the management of chronic manifestations of diverticular disease, an area which is currently lacking in evidence-supported treatment options (52). The relationship between dietary fibre and the gut microbiome (57) also represents a potential mediating pathway between classical and novel understandings of the pathophysiology of this disease.

1.2.7 **Other Environmental and Lifestyle Factors**

Low vitamin D levels and low exposure to ultraviolet light have both been associated with an increased risk of acute diverticulitis (44, 83). Further studies are needed to confirm this association. Smoking and high red meat intake are lifestyle factors which have been associated with higher risk of diverticular disease and more severe outcomes in diverticular disease (45, 76). Obesity has been associated with acute diverticulitis, diverticular bleeding and increased rates of hospitalisation (84-86), while studies investigating associations between diverticular disease and physical activity have shown a reduction in disease incidence and complications (86, 87). Oral corticosteroids, opiate analgesics and non-steroidal anti-inflammatory drug (NSAID) use have also been associated with complicated acute diverticulitis (28), although clarification is needed regarding the level and duration of exposure which results in clinically significant increases in risk.

1.3. Clinical Manifestations of Diverticular Disease

1.3.1 **Acute Diverticulitis**

Acute diverticulitis is histologically defined by the presence of acute inflammation associated with one or more colonic diverticula (60). A number of theories have been proposed for the mechanism of acute diverticulitis, these encompass mechanical obstruction, microperforation and the role of gut flora, as well as the influence of environmental factors (44) and medications (88, 89). The most commonly described mechanism of disease starts with obstruction at the neck of the diverticulum, usually by faecal matter, resulting in damage to the mucosa followed by localised ischaemia and low-grade inflammation that can lead to intestinal flora breaching the lamina propria, resulting in further inflammation and eventually abscess formation (7, 88).

Acute diverticulitis manifests as abdominal pain and tenderness, fever, and raised inflammatory markers; localised peritonism, constipation or diarrhoea, and systemic signs of sepsis may also be present. Acute diverticulitis can be further categorised as uncomplicated or complicated disease, which result in significantly divergent clinical pathways. It is difficult to differentiate between patients with uncomplicated versus complicated acute diverticulitis based solely on clinical presentations. However, there are patient factors, clinical and laboratory findings which are associated with the severity of the episode (90) (Table 1-1). A greatly elevated C-reactive protein level (91) as well as any elevation in white cell count (15) have been found to be discriminative for complicated acute diverticulitis.

Acute complications of diverticulitis include perforation, localised abscess formation, bowel obstruction, peritonitis and resultant sepsis. Chronic complications, usually following multiple or refractory bouts of acute diverticulitis, include colonic fistula and stricture. The first episode is usually associated with the highest incidence of complications (90).

1.3.2 **Symptomatic Uncomplicated Diverticular Disease**

Symptomatic uncomplicated diverticular disease is a relatively recently described manifestation of diverticular disease in which patients experience sustained abdominal symptoms in the absence of macroscopic evidence of colitis or diverticulitis (52, 60, 69). There is some discussion about the possibility of overlap between the pathophysiology of this manifestation of diverticular disease and irritable bowel syndrome (92), with evidence supporting the presence of visceral hypersensitivity (47, 48, 93), low-grade inflammation (94)

and changes to the intestinal microbiome in symptomatic uncomplicated diverticular disease (72, 92).

Symptoms that are commonly associated with symptomatic uncomplicated diverticular disease include recurrent bouts of lower abdominal pain, bloating, constipation and alteration in stool calibre (95).

1.3.3 **Segmental Colitis Associated with Diverticular Disease**

Segmental colitis associated with diverticular disease is the term used to describe the finding of inflammatory bowel disease-like lesions (focal erythema, friability, submucosal ecchymosis, erosions and ulcers) related to areas of bowel wall associated with diverticulosis on endoscopy. It is considered a separate entity to Crohn's disease, ulcerative colitis and acute diverticulitis (40, 96). It is estimated that 0.3-1.3% of patients with diverticulosis on colonoscopy also have endoscopic and clinical evidence (most commonly rectal bleeding) (39) of segmental colitis associated with diverticular disease (97, 98). Its aetiology is not yet clearly described, but it is proposed that, as in inflammatory bowel disease, immune dysregulation in response to gut flora plays a significant role, possibly exacerbated by changes to gut flora and shear force on the mucosa due to diverticulosis (39). Although it is a relatively uncommon form of diverticular disease, the recognition of segmental colitis associated with diverticular disease as a unique clinical entity has given weight to the theory that diverticular disease has a significant chronic component, highlighting an area where new interventions may be targeted.

1.4. Management of Uncomplicated Acute Diverticulitis

The management of acute diverticulitis varies with severity, with uncomplicated acute diverticulitis traditionally being treated with antibiotics, bowel rest and supportive therapy (14). Recent developments, however, have brought these management options into question. The following section will outline the key tenets of uncomplicated acute diverticulitis management, with a focus on emerging trends and recent changes in approach.

1.4.1 **Antibiotics**

Antibiotics have long been a cornerstone in the management of acute diverticulitis, as empiric treatment for the localised peritonitis that occurs as a result of diverticular perforation (99). The understanding has been that any localised inflammation results in microperforation of a diverticulum, with resultant contamination of the peritoneum, either from translocation of colonic bacteria or due to faecal spillage. Studies of the microbiology of acute diverticulitis have focused on those with peritonitis requiring procedural intervention (100), and other types of complex intra-abdominal infection have been used as a point of reference when considering appropriate treatment. To date, no studies have evaluated the microbiology of uncomplicated acute diverticulitis.

The advent of anti-microbial resistance and the risk of adverse effects related to antibiotic therapy have prompted discussions regarding more selective use of antibiotics. The practice of routine antibiotic therapy in the treatment of uncomplicated acute diverticulitis is based on low level evidence (14) and has been challenged by a number of recent studies (including two randomised control trials) that have indicated that antibiotics do not improve outcomes in such patients (23, 24, 101-104). The patient group that has been studied in this respect are those with uncomplicated acute diverticulitis and have been defined slightly differently by existing studies. The following criteria have been used to classify uncomplicated acute diverticulitis where antibiotic use has been investigated:

1. “An episode with a short history and with clinical signs of diverticulitis, without sepsis, with an increased body temperature and inflammatory parameters, verified by computed tomography (CT), and without any sign of complications such as abscess, free air or fistula.” (23)

2. “Diverticulitis without complications such as abscesses, perforation, colonic obstruction, or fistula found during computed tomography (CT) of the abdomen and pelvis.” (26)

3. “Acute mild (105) or Hinchey 1a diverticulitis (12) of the sigmoid colon.” (24)

4. Patients with CT-proven acute diverticulitis, excluding those with perforation on CT or those who required immediate surgery for severe disease (104).

There have also been changes to approach within the scope of antibiotic therapy regimens, the use of oral rather than intravenous (26), less broad spectrum antibiotic regimens (106) and short, rather than long-course intravenous therapy have been trialled without an increase in adverse events for select patient groups (107). Although this is by no means universally accepted, there is an increasing shift towards selective antibiotic treatment rather than treating every patient with acute diverticulitis with intravenous antibiotics on admission to hospital which is reflected in international best practice guidelines and expert consensus documents (21, 62, 108).

1.4.2 **Bowel Rest and Dietary Modification**

Although recommendations vary with regards to dietary modifications in acute diverticulitis, there is no evidential base to support dietary restriction in uncomplicated acute diverticulitis (21). One retrospective study found that clinicians put in place dietary restrictions independent of disease severity (as determined by Hinchey classification) and that clear fluid and nil by mouth regimens were associated with a longer hospital admission, suggesting that these regimens could result in delays in discharge (22). In cases associated with an inability to tolerate oral intake or systemic illness in the form of systemic inflammatory response syndrome (109), intravenous fluid therapy corrects the fluid and electrolyte deficits that result from reduced oral intake and increased losses from active inflammation (19). If bowel rest and intravenous fluid therapy are required, a normal diet is gradually reinstituted within the next 2-4 days with resolution of symptoms (7).

1.4.3 **Inpatient Admission**

With diagnostic imaging becoming more accessible and the knowledge that uncomplicated acute diverticulitis is usually self-limiting, the proportions of patients with acute diverticulitis who can be managed on an outpatient basis have increased. It is generally accepted that stable

patients who are able to tolerate oral intake, are without significant comorbidities and have a favourable home situation can be managed at home with oral antibiotics and a clear fluid diet, with plans for follow up (110). Studies evaluating this approach have found it is effective in over 90% of patients, and 'treatment failure' (defined as subsequent hospital admission or emergency room visit) did not lead to adverse outcomes for patients (110, 111).

A systematic approach to acute diverticulitis which maximises the number of patients who are treated on an outpatient basis could produce significant gains in terms of reducing unnecessary hospital admissions and the costs associated with them. Proposed models for promoting outpatient management include the adoption of institutional uncomplicated acute diverticulitis protocols which call for CT-confirmation of acute diverticulitis severity in the emergency department for patients with suspected uncomplicated disease (112), and include checklists of the characteristics of patients for whom outpatient management is likely to be appropriate (17).

1.4.4 **Elective Surgery**

Depending on the methodology used and the population being described, the rate of disease recurrence following an episode of acute diverticulitis ranges from 13-47% of patients (113). Previously, elective sigmoid resection was offered to patients following two episodes of acute diverticulitis (14, 114), however multiple studies have demonstrated that recurrent acute diverticulitis is not associated with a higher risk of complicated acute diverticulitis (115-117). Current practice guidelines recommend discussion of factors such as impact on quality of life and risks of surgery for each individual patient in order to reach a decision (21, 108).

1.4.5 **Medical Management for Recurrent Acute Diverticulitis**

Mesalazine is a 5-aminosalycilate agent (5-ASA) that is a main-stay in the management of ulcerative colitis, both for inducing and maintaining remission. 5-ASA compounds have multiple anti-inflammatory and immunosuppressive effects including suppression of leukotrienes and prostaglandin synthesis and inhibiting the synthesis of pro-inflammatory cytokines (118). The efficacy of mesalazine (alone and in combination with rifaximin or probiotics) in the management of different manifestations of diverticular disease has been evaluated in a number of studies (118-125).

Treatment with mesalazine following an episode of acute diverticulitis has been shown to result in lower prevalence of persisting endoscopic and histological evidence of inflammation when

compared with rifaximin, a broad-spectrum, non-absorbable antibiotic (126). Mesalazine has already been used to effectively treat segmental colitis associated with diverticular disease and maintain remission (39, 40), although steroid dependent cases and requirement for biologic agents have been reported (127).

Mesalazine has been reported to have reduced symptoms of diverticular disease (119, 124). There have also been open-label studies which found that mesalazine prevented recurrence of uncomplicated acute diverticulitis without significant adverse effect (125, 126), although these data are conflicted at the level of systematic review (121, 123), and unsupported at the level of randomised control trials (71, 122). The use of mesalazine in diverticular disease, including in the management of recurrent acute diverticulitis is not currently supported by clinical guidelines (21, 62, 108, 128).

The inflammatory process which occurs during uncomplicated acute diverticulitis could potentially be targeted with anti-inflammatory agents such as mesalazine to reduce inflammation, possibly resulting in milder and earlier resolution of symptoms and reduction in indicators of inflammation. Although the evidence base is currently conflicted, strategies which target the inflammatory process, in conjunction with an increasing focus on outpatient management and more selective use of antibiotics for cases of uncomplicated acute diverticulitis, warrants further evaluation.

The efficacy of rifaximin (72, 129), and probiotics (130) in managing recurrent acute diverticulitis have also been investigated, but are not recommended for use based on the currently available evidence (108, 128).

1.5. Health Significance

1.5.1 **Epidemiology**

Diverticulosis is the most commonly found abnormality on colonoscopy (131), however, the true prevalence is difficult to ascertain as the vast majority of those affected are asymptomatic and may never undergo an investigation which leads to this incidental diagnosis

The prevalence of diverticular disease has been reported to be increasing across a number of different populations (88, 132, 133), including those that are predominantly non-European (134, 135). Current estimates are that less than 10% of people under 40 years old and 50-60% of people over 85 have diverticulosis (7). Ten to twenty-five percent of those with diverticulosis will experience symptomatic disease and 15-20% of those with symptomatic disease are diagnosed with acute diverticulitis (11, 136).

A number of studies have highlighted differences in disease distribution associated with gender and age (137-142), and in particular have investigated the significantly higher incidence of severe and complicated acute diverticulitis in younger patients (139-141) and more specifically, younger men (137, 142). The causes for this difference are yet to be elucidated.

1.5.2 **Impact for Patients**

Diverticular disease is known to have a significant impact on quality of life, particular for those affected by symptomatic uncomplicated diverticulitis and recurrent acute diverticulitis (52, 143), and for these patients, community and self-management are important parts of disease management.

Several aspects of uncomplicated acute diverticulitis management have been questioned in the past decade, in particular, the need to manage patients in hospital (110, 111, 144, 145) and the mandatory use of antibiotics (23, 24, 101). Currently, there is a lack of consensus among experts about the best way to translate this evidence into clinical practice (146) and as a result, these conservative management approaches are being implemented inconsistently. Consequently, the use of these approaches requires a more nuanced discussion of risk versus benefit with patients compared to more traditional approaches. It is unclear whether health information that is available to patients takes these recent advances into account.

Limited health literacy has been demonstrated to be a significant issue in several cohorts of surgical patients (147) and raises the question of whether the patients effected currently have access to accurate and appropriate health information. Given the importance of health literacy in accessing appropriate health services, chronic disease management and reducing unnecessary hospital admission, efforts in this domain should occur in parallel to our expanding knowledge of the pathophysiology and management of diverticular disease.

1.5.3 **Healthcare Systems**

American data rank diverticular disease as the eighth most frequent outpatient gastrointestinal diagnosis (114) and an estimated 2.4 billion dollars are expended annually on the treatment of diverticular disease (148), making it the fifth most costly gastrointestinal disease to manage (149). Data from New Zealand also show an increasing trend in the number of acute admissions for diverticular disease, from 1443 admissions in 2001 to 2701 admissions in 2011 (150).

Data from North America also indicate that hospital admissions due to acute diverticulitis are increasing, although rates of admission for perforation from acute diverticulitis have remained stable (151, 152). This indicates that the bulk of admissions are for uncomplicated acute diverticulitis and exploring ways in which the optimal treatment for this mild form of acute diverticulitis can be achieved would be a worthwhile task for healthcare decision-makers. Evaluating whether admission and antibiotics are required and minimising potentially unnecessary interventions are steps which could be taken towards meeting important healthcare goals such as increasing the number of healthy days spent at home and ensuring the efficient use of limited health resources.

One approach which reduces the risk of iatrogenic harm, is to reassess the role that antibiotics play in the management of uncomplicated acute diverticulitis. The adoption of selective antibiotic use in this patient group is an area in which prescribing practices could change based on new evidence (153) and Chapter 8 of this thesis describes the outcome of the first placebo-controlled randomised trial to investigate the non-inferiority of foregoing antibiotics in this clinical situation.

This potential shift in clinical practice holds great significance in the context of antibiotic resistance (154). A recent New Zealand-based study which compared antibiotic prescription rates between controls, those who had an acute manifestation of diverticular disease, and those who had been linked to a diagnosis of chronic diverticular disease found that antibiotic

prescription rates were increased in all diverticular disease groups, both before and after the index event which led to the diagnosis (155). This study highlights the limited body of research available on community-based management of acute diverticulitis. The lack of data regarding community antibiotic prescribing patterns and the paucity of knowledge around what safe selective antibiotic use would entail in this context are significant barriers to selective antibiotic use having a major impact on antibiotic prescribing patterns for patients with uncomplicated acute diverticulitis.

1.6. Summary

The aetiology of diverticulosis and the pathophysiology of diverticular disease are both areas of ongoing scientific inquiry, aided by the development of new tools including studies of the gut microbiome, genetic susceptibility and colonic motility. However, the findings of this research becomes more difficult to interpret due to the interchangeable use of terminology for describing different manifestations of diverticular disease. Ongoing research, guided by a common use of terminology is needed in order to meaningfully link the multi-factorial processes involved in the formation of diverticula, and the development and symptoms of diverticular disease.

Diverticular disease is a common disease which results in a high number of hospital admissions as well as significant morbidity in the community. Acute diverticulitis is the most common reason for hospitalisation with diverticular disease, and appears to exist as two distinct sub-types, uncomplicated and complicated. There is a developing understanding that inflammation, rather than infection, is a significant part of the pathophysiology of uncomplicated acute diverticulitis and the clinical course and appropriate management for these two sub-types differ significantly.

This shifting understanding about the clinical course of uncomplicated acute diverticulitis has had a major impact on clinical management, with a trend towards gradually reducing the use of unnecessary broad spectrum antibiotics and increasing the number of patients who are self-managing episodes of uncomplicated acute diverticulitis as outpatients with input from clinicians. This requires the sharing of the still evolving knowledge around the causes and management of acute diverticulitis and the process of sharing information is likely to be an important target for intervention as this conservative approach to management becomes more widely accepted.

Chapter 2. Thesis Objectives and Overview

Chapter 1 has summarised shifting perspectives on the pathophysiology of diverticulosis and diverticular disease, and how acute diverticulitis is classified and managed. The research embodied in this thesis aims to improve understanding of the pathophysiology of diverticular disease and improve clinical management of acute diverticulitis by answering the following specific questions:

1. What is the role of colonic dysmotility in diverticular disease?
2. How is acute diverticulitis currently managed in Australasia?
3. Which clinical factors predict a more severe clinical course in acute diverticulitis?
4. Are antibiotics necessary in the management of uncomplicated acute diverticulitis?

Answers to these questions were sought by systematically reviewing current literature, carrying out an international randomised control trial of a therapeutic intervention, surveying clinicians, analysing retrospective clinical information to construct a risk prediction score, and characterising colonic motility in participants with diverticulosis.

Chapter 3 summarises existing research on the role of colonic motility in diverticular disease. This was achieved through a systematic review of *in vivo* manometry studies performed on comparable patients with diverticulosis and diverticular disease. The findings of this study were used to describe the abnormal colonic profiles associated with these conditions and identify gaps in current knowledge.

Chapter 4 sought to build on the findings of Chapter 3 through an *in vivo* manometry study comparing participants with diverticulosis with control participants. High-resolution colonic manometry was used to record descending and sigmoid colon activity pre and post- meal in participants with established, asymptomatic diverticulosis and in healthy controls. Antegrade and retrograde propagating contractions, distance of propagation, and mean pressures in the descending and sigmoid colon were compared for all propagating contractions and cyclic motor patterns independently. This study was unique in that a fibre-optic high resolution manometer was used to observe colonic motility during pre-and post-prandial periods.

Chapter 5 used survey methodology to describe current clinical practices and perspective on diverticular disease among Australasian surgeons. The results of this survey were compared to practice guidelines and informed local positions on the equipoise for the randomised control trial.

Chapters 6 and 7 are both retrospective cohort studies investigating two different clinical questions. Both studies resulted in the construction of risk prediction scores which, following validation, could be used in order to inform prospective treatment decisions for patients with acute diverticulitis.

Chapter 6 is retrospective cohort study of patients who were admitted to Auckland City and Middlemore Hospitals with acute diverticulitis over a period of eighteen months. This study aimed to identify risk factors for complicated acute diverticulitis in patients managed by a tertiary hospital surgical unit.

Chapter 7 is retrospective cohort study of patients who were admitted to Auckland City and Middlemore Hospitals with uncomplicated acute diverticulitis only over a period of eighteen months. This study aimed to identify risk factors for severe clinical course in patients with uncomplicated acute diverticulitis and severe clinical course was measured by two end points, the need for procedural intervention, and admission $\geq$7 days.

Chapter 8 is an interventional trial which aimed to demonstrate the non-inferiority of placebo versus antibiotic treatment for the management of uncomplicated acute diverticulitis. This international (New Zealand and Australia), multi-centre, placebo-controlled and double-blinded randomised control trial recruited participants with computed tomography scan-proven Hinchey 1a uncomplicated acute diverticulitis to receive antibiotics or placebo. The primary endpoint was length of hospital admission and the main secondary endpoints were occurrence of adverse events and readmission within one week and 30 days.

Chapter 3. Systematic Review - Limited Evidence of Abnormal Intra-Colonic Pressure Profiles in Diverticular Disease

3.1. Background

Despite its high prevalence and impact, there are still significant gaps in our understanding of the aetiology and pathogenesis of diverticular disease (52, 93). It is commonly assumed that high intra-colonic pressures are the cause of diverticula particularly in the context of a low-fibre diet, but it is largely unknown why some individuals are predisposed. It is unclear why some individuals appear predisposed to develop diverticular disease and why only a proportion of people experience symptoms. It has been suggested that there may be an interaction between abnormal intraluminal pressure, inflammation connective tissue abnormalities and visceral hypersensitivity (36, 48, 93, 156, 157).

Detailed characterisation of colonic pressure activity in patients with diverticulosis, would provide evidence to support the role of abnormal colonic pressure in the aetiology and symptomatology of diverticular disease. A number of studies describing this activity have been published but this body of literature has not been previously reviewed.

3.2. Study Objectives

The aim of this systematic review was to collate studies comparing colonic pressure profiles in diverticulosis and diverticular disease to controls, in order to define current evidence for the role of colonic motility in the pathophysiology of diverticula formation and diverticular disease.

3.3. Study Methods

3.3.1 **Literature Search**

A review protocol was formulated prior to the commencement of the literature search. A systematic literature search of the Ovid MEDLINE, EMBASE and SCOPUS databases was performed with no earliest time restriction and including those published to the end of 2014. Searches were restricted to 'Humans' with no language limits applied. The following 'search strategy' was applied to identify all published evidence.

[Diverti.mp] OR [diverticulitis/or diverticulosis/ OR colon disease/ or colon diverticulosis/]*

AND

[Manometry/ OR intestine pressure/ or pressure transducer/ or pressure measurement/ or anorectal pressure/ OR intestine motility/ or gastrointestinal motility/] OR [motil.mp] OR [manome*mp.]*

*NOT [Esophagus/] NOT [Esoph*mp.]*

3.3.2 **Search Strategy**

Searches were concomitantly performed by two authors (Rebekah Jaung and Jason Robertson) with all results screened to identify those reporting on manometric studies of diverticulosis or diverticular disease. Full text papers of selected studies were then further evaluated independently by the authors to identify those eligible for inclusion. Final decisions regarding eligibility were determined by group consensus with any conflicts being adjudicated by the senior author (Ian Bissett). Citations within all eligible articles were also hand searched for potentially relevant studies not identified on the initial literature search.

3.3.3 **Inclusion and Exclusion Criteria**

Studies using manometry to record intraluminal pressure in the sigmoid colon of patients with diverticulosis or diverticular disease were included. Exclusion criteria were studies focused on the treatment of diverticular disease, studies of diverticula outside of the sigmoid colon, case reports, conference abstracts, reviews, and letters, histopathological studies and studies of patients following bowel resection. Studies that dealt exclusively with patients with right-sided diverticular disease were also excluded.

3.3.4 **Outcomes of Interest and Definitions**

We included any studies which described pressure profiles of the sigmoid colon in patients with diverticulosis or diverticular disease. Individual outcomes were not specified due to the diverse methodologies and definitions within the published literature.

3.3.5 **Data Extraction and Analysis**

Data were extracted by one researcher (Rebekah Jaung) into standardised data extraction tables and checked by a second researcher (Jason Robertson). Where possible, all reported figures for pressure measurements were converted to mmHg for consistency. When data were available, results of studies were pooled as weighted means. The Newcastle-Ottawa Scale for case control studies (NOS) (158) was used to assess the risk of bias in the included studies. Matching for age and gender were considered the most significant covariates that defined comparability.

A meta-analysis was planned for studies rated as 'fair' (≥5 out of 9) on the NOS (148). A formal meta-analysis was not performed in this study as only two studies reached this cut-off point but these did not have comparable results.

3.4. Results

3.4.1 **Results of Literature Search**

Details of the initial search results and refined inclusions are presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram in Figure 3-1. Of the 1849 articles identified based on the above search strategy 23 full text articles were reviewed. Of these 13 were excluded because of: a lack of control group (159-164) inclusion of diagnoses other than sigmoid diverticulosis (165, 166), insufficient details to extract or calculate the necessary data from the published results (167), retrospective study design (168), and, technique other than manometry used to study gut motility (169-171).

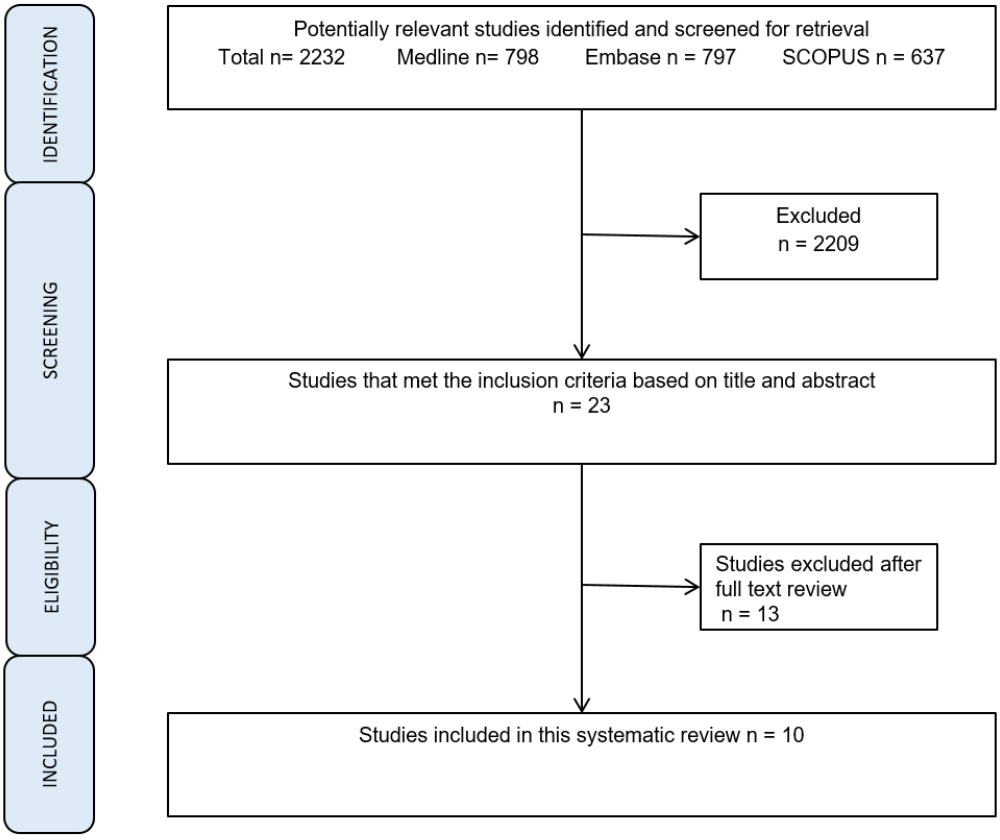


Figure 3-1 PRISMA diagram

The remaining 10 studies were included in the analysis (34, 51, 63, 157, 172-176). All of the studies that were included had a prospective case-control study design. The characteristics of these studies are outlined in Table 3-1. All studies compared large bowel manometry readings of normal controls with those taken from patients with diverticulosis identified on

colonoscopy or barium studies. Studies included both asymptomatic participants with diverticulosis and those with diverticular disease.

Reference	Year	Country	Inclusion criteria	Study size	Number of sensors	Distance between sensors	Distance from anal verge	Recording period
Arfwidsson *et al.*	1962	Sweden	Radiological evidence	40 (20 diverticulosis and 20 controls)	2	10cm	35cm	140min
Bassotti *et al. (1)*	2005	Italy	History of SUDD and radiological evidence	32 (12 SUDD and 20 controls)	8	12cm	To splenic flexure	24h
Bassotti *et al. (2)*	2001	Italy	History of SUDD and radiological evidence	26 (10 SUDD and 16 controls)	8	12cm	To splenic flexure	24h
Cortesini *et al.*	1991	Italy	Clinical diagnosis of AD/SUDD	90 (30 SUDD, 30 Asymptomatic, 30 controls)	2	15cm	65cm	6h
Katschinski *et al.*	1990	Germany	Symptoms of SUDD and	28 (15 SUDD, 13 controls)	1	N/A	25cm	130min

			radiological evidence					
Leandro *et al.*	1984	Brazil	Radiological evidence	25 (15 diverticulosis, 10 controls)	2	10cm	10-20cm	30min
Painter and Truelove	1964	England	Radiological evidence	60 (28 diverticulosis, 32 controls)	3	7.5cm	To sigmoid	60min
Parks and Connell	1969	Ireland	Radiological evidence	54 (36 DD, 18 controls)	3	7.5cm	25cm	60min
Shafik *et al.*	2004	Egypt	Radiological evidence and symptoms	58 (36 DD, 22 controls)	1	N/A	To sigmoid	Two 30min sessions
Trotman and Misiewicz	1988	England	Radiological evidence and symptoms	19 (6 DD, 13 controls)	4	10cm	55cm	60min

Table 3-1 Details of articles

SUDD = symptomatic uncomplicated diverticular disease, DD = diverticular disease, AD = acute diverticulitis, N/A = Not applicable, cm = centimetre, min = minute

3.4.2 **Details of Patients**

Patient details are summarised in Table 3-1. A total of 238 patients were assessed, of whom 37 patients had asymptomatic diverticulosis, 122 diverticular disease, and in the remaining n 79 patients the disease status was unclear. A total of 194 controls underwent large bowel manometric investigation. The patients with indeterminate disease status were excluded from further analysis. The study size ranged from 6 to 60 patients. Patient age ranged from 20-79 and control participants' age ranged from 25-80 years old. Criteria for inclusion were a combination of imaging and clinical assessment.

3.4.3 **Manometry Techniques**

Table 3-1 outlines the details of sensor position, recording time and other aspects of the methodology of pressure measurement.

3.4.4 **Intrasigmoid Pressure**

Manometric outcomes reported are collated on Table 3-2. Intrasigmoid pressure was reported in several different studies as mean maximal pressure (34, 157, 174, 176, 177). Fasting intrasigmoid pressure was reported as being higher in patients with diverticulosis/diverticular disease compared to controls in three of the five studies reporting this measure (34, 63, 176) and not significantly different in the remaining two studies (51, 174). Two of these studies reported statistically significant results using ANOVA (176, 177).

References	Mean intrasigmoid pressure (mmHg)	% duration of regular contractile activity	Motility index (MI)[1]	Standardised MI[2]	Effect of DD on MI[3]
Arfwidsson *et al.*	C: 10.77±3.3 DD[4]: 56.61±10.6*				↑
Bassotti *et al. (1)*	C: 25±9 DD: 29±11	C: 6.4 DD: 31*		C: 160 DD: 899	↑
Bassotti *et al. (2)*			C: 5,362 ± 1,259 DD: 11,485 ± 3,155*		↑
Cortesini *et al.*		C: 2.84 ± 0.47 A: 5.05 ±0.52* DD: 11.73±2.12*	C: 107.46 ± 8.77 A: 116.04± 6.67 DD: 263.10±3.28*		↑
Katschinski *et al.*			C: 379(224.5-636.5) DD: 282 (209.0-394.0)		
	C: 15.3±6.3	C:28.41 ±11.92	C:598.01±325.78	C: 434.67±1.54	

Leandro *et al.*	DD: 16.4±6.7	DD:28.91±5.63	DD: 651.74±297.74	DD: 474±1.06	
Painter & Truelove		C: 1.07 D: 0.87			
Parks &Connell	C: 3.8 DD: 6	C: 18.6 DD: 18	C: 159 DD: 224	C: 70.68 DD: 108	
Shafik *et al.*	C: 5.8±0.8 Advanced DD[5]: 11.6±1*				↑
Trotman & Misiewicz		C: 42.5±12.2 DD: 54.3±15.6*	C: 2743.5± 1542.5 DD: 6422.2 ± 4726.0		↓
Weighted mean	C: 12.1 DD: 12.6	C: 9.23 DD: 14.48		C: 183.8 DD: 345.8	

Table 3-2 Outcomes measured

*P-value < 0.05 vs controls, N/R = not reported, C = control, A = asymptomatic, DD = diverticular disease, MI = motility index, [1] Definitions of motility index are outlined in Table 3-3, [2] Standardised motility index = mean amplitude (mmHg) * % duration of regular contractile activity, [3] Net effect of diverticulosis/DD on pressure profile in studies reporting a statistically significant difference, [4]This study used cm^2 as the unit for measurement of pressure, [5]Advanced DD = the advanced group (20 patients) had an involved colonic segment that showed well-formed diverticula of variable sizes and shapes." (176)

3.4.5 **Percentage Duration of Regular Contractile Activity**

The percentage duration of regular contractile activity was reported in six studies (34, 51, 157, 172, 174), the weighted mean for this measure was higher in diverticulosis/diverticular disease than in controls (14.5% vs. 9.2%). The results for this measure varied greatly between studies, 1.07-42.5% for controls and 0.87-54.3% for diverticulosis/diverticular disease. This may be attributed partially to the varying numbers of sensors used by the different investigators (2-8 sensors).

3.4.6 **Motility Index**

The motility index was a frequently used measure of overall motility (34, 51, 63, 172, 174, 178) and its definition varied between different studies (Table 3-3). The most commonly used definition (mean amplitude in mmHg x % activity duration) could be calculated from three studies, and was also higher in diverticulosis/diverticular disease on pooled analysis (weighted mean 183.8 vs. 345.8). Quantitative meta-analysis was not conducted for this outcome due to the heterogeneous nature of the studies and limited data from which to derive mean and measures of variance.

Reference	**Definition**
Bassotti *et al.* (2)	Half the mean amplitude of pressure waves * sum of their duration
Cortesini *et al.*	Undefined
Katschinski *et al.*	Sum of contractile activity (mmHg * min)
Leandro *et al.*	mean amplitude * % duration of activity
Parks and Connell	mean amplitude* % duration of activity
Trotman and Misiewicz	median maximal amplitude * % duration of activity

Table 3-3. Definitions of motility index

3.4.7 **Meal Response**

The seven studies that examined meal response as part of their recordings all reported increased contractile activity in the post-prandial period in both control and

diverticulosis/diverticular disease groups (Table 3-4). One study observed an increased frequency of high amplitude waves in the post-prandial recordings of patients with diverticular disease (177). Two of the studies suggested that this post-prandial increase in activity was exaggerated in diverticulosis/diverticular disease (34, 172), however the opposite phenomenon was observed in two other studies (63, 157), making it difficult to draw any conclusions about post-prandial changes.

Reference	**Observed post-prandial response**		
Arfwidsson *et al.*	↑ pressure in both groups ↑ frequency of 'strong waves'[1] in DD*		
Bassotti *et al.* (1)	↑ contractile activity in controls only*		
Bassotti *et al.* (2)	At transverse and descending colon: ↑ MI in both groups* At sigmoid colon: ↑ MI in controls only*		
Cortesini *et al.*	↑ MI in both groups, greater in DD*		
Katchinski *et al.*	↑ MI in both groups, greater in controls but effect sustained for longer in DD		
Parks and Connell		Controls	DD
	Sigmoid colon	↑ 52%	↑153%
	Rectosigmoid	↑32%	↑46%
	Rectum	↑18%	↑100%
Trotman and Misiewicz	↑ pressure and MI in both groups*		

Table 3-4 Post-prandial changes to pressure activity.

DD = diverticular disease, *reported as statistically significant, MI = motility index, [1]Pressure wave > 30cm.

3.4.8 **Study Quality**

The NOS (158) was used to assess the risk of bias in the included studies (Table 3-5). The mean rating was 4.4 (SD 1.2). Most of the studies rated well in terms of selection and outcome but did not or failed to report on the measures taken to ensure than the diverticulosis/diverticular disease group and control group were comparable. In only three studies were controls and patients matched for age or gender (172, 176, 178) and only two studies (172, 176) met the cut-off point for being 'fair' quality (148) in terms of bias.

References	Selection	Comparability	Exposure
Arfwidsson *et al.*	♦♦		♦♦
Bassotti *et al. (1)*	♦♦♦		♦
Bassotti *et al. (2)*	♦♦♦		♦
Cortesini *et al.*	♦♦♦	♦♦	♦
Katschinski *et al.*	♦	♦♦	♦
Leandro *et al.*	♦♦		♦♦
Painter & Truelove	♦♦		♦♦
Parks &Connell	♦♦		♦♦
Shafik *et al.*	♦♦♦♦	♦♦	♦
Trotman & Misiewicz	♦♦		♦

Table 3-5 Newcastle-Ottawa Scale assessment of study quality.

The highlighted studies scored at or above the cut-off point for a fair study (≥5 out of 9)

3.5. Discussion

Altered colonic pressure profiles are commonly thought to play a significant role in the aetiology of diverticulosis and pathophysiology of diverticular disease. This review demonstrates that there is only a limited volume of literature investigating pressure in patients with diverticulosis, and results from these studies are too heterogeneous to allow for consistent conclusions. Pooled data from these existing studies showed no difference in intrasigmoid pressure (34, 157, 174, 176, 177) and duration of activity (51, 157, 172) when comparing patients with diverticulosis/diverticular disease and controls, suggesting that there is only weak evidence to support the role of characteristic patterns of pressure activity in this condition.

Increased intrasigmoid pressure is attributed with causing outward protrusion of the colonic mucosa at points of natural weakness (89), and a significant association has been found between abdominal pain and regular contractile activity in the sigmoid colon in patients with diverticular disease (157). These models are based on the assumption that colonic pressure activity is demonstrably different in patients with diverticulosis and diverticular disease when compared to controls.

Based on the findings of this review, it is clear that further research into this field is required. The existing studies varied substantially in their methodology; in the number and position of pressure sensors as well as important technical factors such as bowel preparation and duration of pressure recording. There was also a degree of variability around what constituted diverticular disease and its manifestations, as well as a wide range of different endpoints, making it difficult to compare the results of different studies. Additionally, there is a limit to the observations that can be gleaned from pressure measurements taken from single sensors or sensors that are between 7.5 and 15 cm apart. As a consequence of these methodological limitations, it is not possible to draw consistent and definite conclusions from the existing body of evidence to support the widely accepted role of abnormal intrasigmoid pressure in diverticulosis and diverticular disease.

It is important to note that all previous studies looking at colonic pressure profiles in diverticulosis and diverticular disease were limited by their use of low resolution methods of recording pressure, which require the observer to make inferences on wave characteristics, due to the pressure sensors being at least 7cm apart (179, 180). Low resolution designs are now known to risk significant misinterpretation of the frequency and polarity of colonic

propagating sequences, and were often associated with the use of non-specific tools such as the ‘motility index’, which conveys only a vague summary of the actual underlying motility profiles (179). As a result, the most significant factor limiting our understanding of the nature pressure profiles in diverticulosis has been the inability to obtain reliable and detailed data on large bowel contractile activity.

Consistent methodology and terminology is an essential consideration for planning future studies. Differentiating between asymptomatic diverticulosis, symptomatic uncomplicated diverticular disease, acute and chronic diverticulitis and rarer manifestations such as segmental colitis associated with diverticula is required in order to gain useful information from *in vivo* manometry. Bowel preparation may also have an effect on colonic pressure profiles and should be standardised. Additionally, the use of newer methods for measuring colonic pressure profiles may result in more accurate and reproducible pressure measurements. High resolution manometry (HRM) using fibre-optic catheters, for example, is a recently-developed tool that is now being applied to study colonic pressures in greater detail (181). As recording sensors are positioned 1cm apart, substantially more accurate information regarding the spatiotemporal patterns of pressure waves can be obtained. Studies on control participants and patients using HRM have already led to significant advances in the understanding of large bowel physiology (182, 183). The data obtained from HRM studies are very detailed, and small studies of fewer than 20 participants have shown significant differences in colonic pressure profiles (numbers of different types of propagating motor patterns, speed and distance of pressure wave propagation, and amplitude and duration of pressure events) when compared to controls with normal bowel function (183).

3.6. Limitations

This systematic review and meta-analysis was conducted in accordance with the code of practice as set out in the PRISMA statement (184) with the exception that this is a review of physiology studies. As assessed using the NOS, the studies which were included carry a significant risk of bias. Essential data were not reported in all studies (such as blinding of investigators for data collection, basic demographic data and key definitions) and there was considerable heterogeneity between studies in terms of defining patient selection and outcomes. Furthermore, the outcome data were variable and did not include consistent measures of variance or tests of statistical significance. It was not feasible to request unpublished data for the older studies.

3.7. Conclusions

The available evidence from manometric studies provides limited evidence which supports the role of abnormalities of colonic pressure profiles in the aetiology of diverticulosis or diverticular disease. Moreover, the interpretation of these data is critically limited by inconsistent study methodologies and the inadequacies of low resolution manometry. Additional studies that follow consistent definitions of disease status, standardised protocols, make use of high-resolution manometry and report consistent endpoints are needed to define conclusively the role of aberrant colonic pressures in diverticulosis and diverticular disease. Chapter 4 follows on from the findings of this review to define a standardised participant group (asymptomatic diverticulosis) in which to perform *in vivo* high resolution manometry.

Chapter 4. *In vivo* High Resolution Manometry - Colonic Motility in Established Diverticulosis

4.1. Background

As discussed in Chapter 1, the pathogenesis of diverticulosis and diverticular disease remain incompletely understood (143), despite their prevalence. High intra-colonic pressures and abnormal colonic motility have long been postulated as pivotal in the formation of diverticula (34, 170, 185, 186) and it is also thought that the diverticulosis colon is more active than healthy controls (51, 63, 172).

Although high intraluminal pressures and aberrant colonic motility are widely accepted theories for the aetiology of diverticulosis (76, 170), as outlined in Chapter 3, the evidence for their role is weak when systematically reviewed. Furthermore, the role of colonic motility on the symptomatology of diverticular disease is also based on limited evidence (157). The uncertainty regarding the causes of diverticulosis has been identified as a barrier to effective patient counselling and self-management of the chronic manifestations of diverticular disease (38, 52).

Previous studies examining the role of colonic motility and intraluminal pressure have all utilised of low-resolution manometry as a tool for measuring intraluminal pressure. This technique has been criticised as fewer pressure sensors leads to sparse spatial resolution, which often leads to misinterpretation of colonic pressure profiles, particularly with regards to lower amplitude events and the direction of pressure waves (179). The advent of high-resolution manometry (HRM) has improved our understanding of colonic physiology; enabling improved characterization and quantification of colonic motility profiles in health and at times of abnormal physiology (181, 182, 187-189).

4.2. Study Objectives

The aim of this *in vivo* manometry study was to accurately evaluate pressure profiles of the colon in participants with asymptomatic diverticulosis versus healthy controls, using HRM. The effect of meal consumption was also evaluated in both groups.

4.3. Study Methods

4.3.1 **Ethics Approval**

Ethical approval for the study was obtained from the Health and Disability Ethics Committee (HDEC 15/NTA/24) of New Zealand, and the Auckland District Health Board Research review committee (A+6568). All participants provided written, informed consent.

4.3.2 **Study Population**

1. Diverticulosis Group

The source population included all adult New Zealand citizens and permanent residents who lived in the Auckland District Health Board area. All diverticulosis participants were recruited from surveillance colonoscopy lists at Auckland City Hospital, this meant that people who opted to receive surveillance colonoscopies through privately funded health services were excluded from the source population. The waiting list was screened for participants who were due to have a surveillance colonoscopy for polyps and had a previous colonoscopy documenting sigmoid diverticulosis. Eligible participants were aged ≥18 years; able to give informed consent; had normal bowel function (between 1 bowel motion every 3 days to 3 bowel motions every day, absence of gastrointestinal symptoms) and not known to have previous symptoms of diverticular disease.

2. Control Group

The historical control group comprised of nine healthy human controls who were recruited from Flinders Medical Centre, in South Australia, and St. George Hospital in Sydney, New South Wales. All participants had a normal bowel habit, defined as between three bowel movements a day and one bowel movement every 3 days, with no gastrointestinal symptoms. Detailed population characteristics and study methodology have been previously published (182).

3. Exclusion Criteria

Exclusion criteria for both groups were: pregnancy; previous colorectal resection; presence of functional motility disorders; and metabolic, neurogenic or endocrine disorders known to cause colonic dysmotility.

4.3.3 **Recruitment and Consent**

1. Surveillance Colonoscopy

Surveillance colonoscopy is performed routinely in the outpatient setting for patients in New Zealand who have previously had colonic polyps removed (190). The main clinical indication for this is as a means for further detection of polyps. Patients who undergo surveillance colonoscopy through the public healthcare system are managed by the District Health Board for the area they reside in and are recalled for screening as clinically indicated. At Auckland District Health Board, this is overseen by the Auckland District Health Board Gastroenterology and Hepatology Department, that generates monthly colonoscopy waiting lists which include all patients who are due to undergo an outpatient colonoscopy during the following 1-3 month period.

2. Recruitment Process

Potentially eligible participants for the diverticulosis group were identified from the colonoscopy waiting list and contacted via telephone by the investigator (Rebekah Jaung) and provided with verbal information on research rationale and protocol.

Potential participants were then posted the Participant Information Sheet and Consent Form (Appendix A). When verbal consent was granted, contact was made with members of the clinical and administrative staff in order to schedule the participant's colonoscopy at a date which was appropriate for conducting a manometry study. Written informed consent was obtained from participants on the day of the colonoscopy, and participants were encouraged to contact study investigators during this process if they wished to discuss the study further.

4.3.4 **High Resolution Manometry**

The assessment of colonic pressure waves through the measurement of colonic intraluminal pressure (manometry) is a well-established method for investigating the role of elevated colonic pressures and increased colonic activity in the pathophysiology of diverticulosis and diverticular disease (34, 51, 63, 157, 172-176). Although manometric methods are used for clinical purposes in the management of upper gastrointestinal conditions (191), colonic studies are still limited to the area of research.

The present study utilised fibre-optic HRM catheters with 72 sensors spaced at 1 cm intervals in all participants except in one diverticulosis participant in whom a 36-sensor catheter was

used. These catheters were developed, designed and custom-built for the research purposes by the Commonwealth Scientific and Industrial Research Organisation (CSIRO), New South Wales, Australia. The development and clinical validation process for the catheters has been described in detail by the developers (181, 188).

In brief, fibre-optic HRM catheters contain multiple fibre optic strain gauges which are spaced at 10mm intervals along the length of the catheter and are encased in a protective silicone outer sleeve. The distal end of the catheter is watertight and ends in a notched plastic tip, and the proximal end consists of an optical connector for attachment to a spectral interrogator acquisition unit (FBG-scan 804; FOS&S, Geel, Belgium). The catheter diameter is 3mm.

The strain gauges consist of fibre Bragg grating (fbg) elements affixed to a pressure sensitive structure (a rigid metallic substrate and a flexible diaphragm) (188). The gauges are interrogated along a single fibre through the application of Wavelength Division Multiplexing (WDM) techniques (188). This arrangement overcomes the technical limitations of traditional water-perfused and solid state manometry catheters in terms of spatial resolution, catheter diameter and device flexibility (188).

Changes in intraluminal pressure cause the flexible diaphragm component of the strain gauges to bend against the section of the fibre associated with the specific fbg element – resulting in modification of the reflected Bragg wavelength of that element. These readings are compared to wavelengths which respond to standardised pressure readings obtained during catheter calibration to infer observed pressures (181, 188).

The spectral acquisition unit was used with a PC laptop system running a custom-written LabVIEW program (National Instruments, Austin, Texas, USA) which displayed all pressure changes in real time while recordings were taken, and also enabled significant events such as food intake and the occurrence of gastrointestinal symptoms to be marked as they happened. Recordings were saved as .txt files which were in turn analysed using a custom-designed software package (PlotHRM; Flinders University) (Figure 4-1).

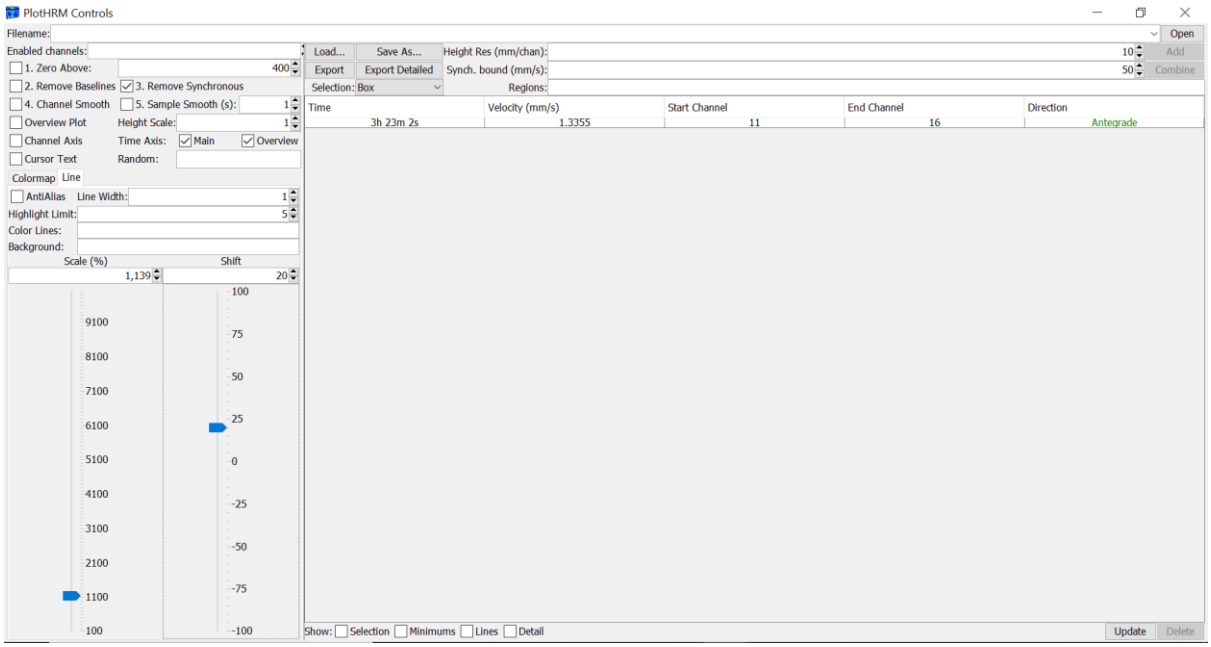


Figure 4-1 PlotHRM Software

4.3.5 **Study Procedures**

The techniques used in the study have been described and used in a number of previously published Australian and New Zealand manometry studies (189, 192-194).

1. HRM Catheter Preparation

The HRM catheter was calibrated one day prior to each case. This involved connecting the catheter to the acquisition box and placing it in a sealed cylindrical tube and manually raising and lowering the pressure applied to the catheter from 0-100mmHg. These readings were compared to a recordings made for a previously saved successful calibration PlotHRM.

Following calibration, a 10cm rubber over-tube was placed over the catheter. This over-tube protected the catheter from kinking or breaking during insertion and *in vivo* recording by allowing the catheter to move freely at the point where it enters the anal canal. A single loop of nylon thread was also attached to the notched tip of the catheter, this served as the attachment point during endoscopic insertion. This loop was secured with a double overhand knot and the knot was covered with Parafilm (Sigma-Aldrich, St. Louis, Missouri, USA) to prevent discomfort and irritation while the catheter was inserted and removed.

2. Colonoscopy

Study participants were booked as the first case on the list and were asked to arrive at the Endoscopy Unit at Auckland City Hospital at 0800h. All colonoscopies were performed by a single consultant Gastroenterologist endoscopist who was already familiar with the procedure for endoscopic insertion of HRM catheters from previous studies (189).

Participants received full bowel preparation (e.g. Pico-salax (sodium picosulphate with magnesium citrate) or Glycoprep-C (Fresenius Kabi, New South Wales, Australia)), and the procedure was performed under conscious sedation using fentanyl and midazolam.

3. HRM Catheter Placement

Following completion of the surveillance colonoscopy, participants moved into left lateral position. The catheter and colonoscopy were inserted per rectally and advanced up to the hepatic flexure. The catheter was attached to the colonoscope using a metal snare (Olympus, Centre Valley, Pennsylvania, USA) passed through the colonoscope, and attached to the loop of nylon tied to the tip of the catheter. Once the ascending colon was intubated, the loop of nylon on the catheter tip was secured to a colonic fold using a single Endoclip (Olympus, Centre Valley, Pennsylvania, USA).

The catheter was handled independently of the colonoscope by an assistant (Rebekah Jaung) for the duration of the insertion process, with care taken to prevent kinking and to ensure that the rubber over-tube remained within the anal canal. After securing the catheter with the Endoclip, the colonoscope was gently removed and the end of the catheter outside of the anal canal was secured to the participant's inner thigh using Tegaderm (3M, St. Paul, Minnesota, USA).

4. Radiographic Assessment of HRM Catheter Placement

After the catheter had been placed, participants were taken to the Radiology Department for a single plain film radiograph of the abdomen. This is to define the anatomical position of the catheter and enable spatiotemporal mapping of colonic motility. These methods have been used previously and advocated internationally (182).

5. HRM Catheter Recording

Following the endoscopic placement of the catheter and radiographic assessment of placement, study participants stayed in a private cubicle in the recovery area of the Endoscopy Suite for 4-6 hours for the remainder of the study. At this point, the catheter was connected to an

acquisition box and laptop containing the custom-made software package so that data could be obtained and stored. Free mobilisation through this time was limited by the presence of the HRM catheter and acquisition box, but if required (for example mobilising to the toilet), the catheter could be disconnected. The participant and nurses were shown how to disconnect and reconnect the catheter, and the study investigators were also available to assist with this at all times.

Recordings commenced within 60 minutes of participants waking from sedation and baseline recording was performed for a minimum of two hours. Each participant then received a 700-kcal meal consisting of a sandwich and 300 ml of a protein- and calorie-dense nutritional drink, and recordings then continued for an additional 2 hours.

6. HRM Catheter Removal

The catheter was removed by a study investigator (Rebekah Jaung) at the end of the study. The participant was asked to move into left lateral position, the catheter was disconnected from the acquisition unit and removed by applying gentle traction. This removal method is reliable, safe and painless.

7. Discharge Criteria

After catheter removal, participants were assessed by a study investigator (Rebekah Jaung) to ensure that they remain well. If clinically well and happy to go home, participants were discharged home.

8. HRM Catheter Sterilisation

The Parafilm and nylon components were removed from the tip of the catheter using scissors. The catheter was then transported to the Sterile Services Unit (SSU) at Auckland City Hospital for sterilisation. A standard high level disinfection protocol was followed by the SSU staff to disinfect the catheter, with care taken to ensure that the optical connector end of the catheter was not submerged during the process.

The disinfection process was determined in communication with the SSU at the start of the study and attached to the catheter at the time of delivery for sterilisation. The sterilised catheter was picked up from SSU by the study investigator (Rebekah Jaung) and stored in a locked cabinet between recordings.

4.3.6 **Manometric Data Analysis**

Manometric data analysis was performed using a PlotHRM. Detection of propagating contractions and pattern recognition were based on previously described methods and definitions (182). All propagating activity was analysed with an additional subgroup analysis of cyclic motor patterns (CMPs) in isolation. CMPs were defined as repetitive propagating contractions with a frequency between 2-6 cycles/minute for a duration of 3 minutes. Activity from sensors including propagating contractions between the splenic flexure and sigmoid flexure (descending colon) were analysed separately to activity from sensors including propagating contractions between the sigmoid flexure and the rectosigmoid junction (sigmoid colon), based on anatomical localisation using the radiographs (Figure 4-2). The total number of propagating contractions, antegrade propagating contractions, retrograde propagating contractions, mean amplitude (mmHg) of propagating contractions and the mean distance (mm) of propagating contractions in the pre- and postprandial state were calculated in MATLAB (r2018a; MathWorks).

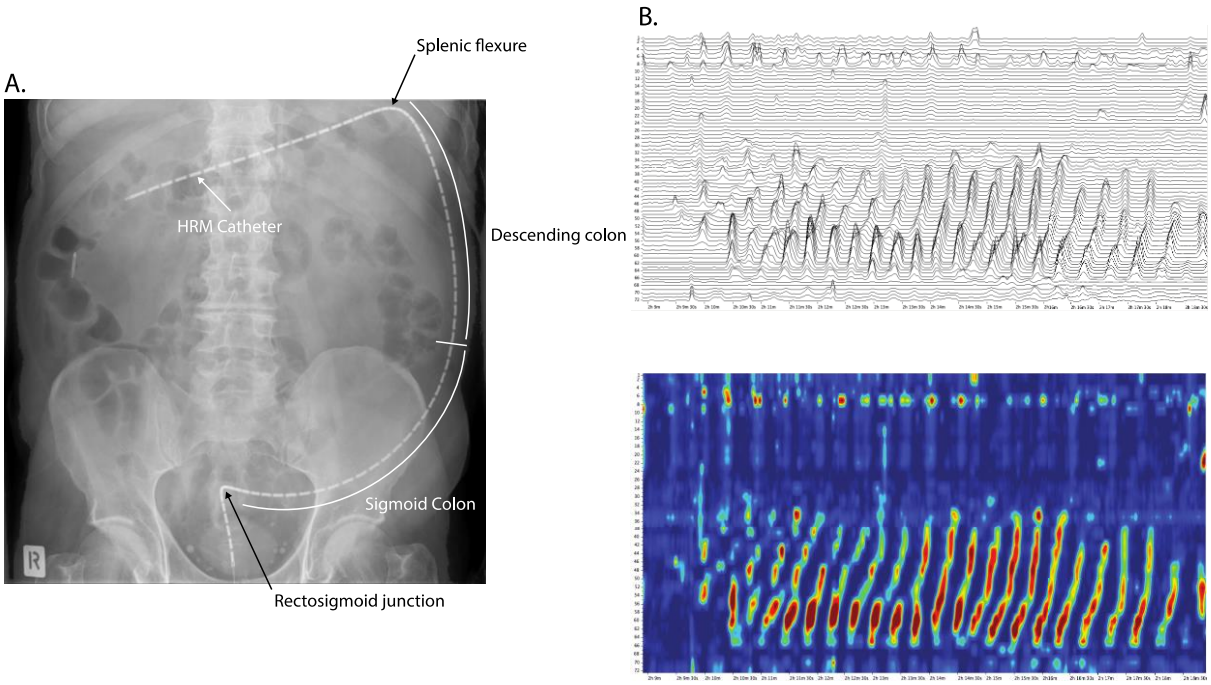


Figure 4-2 A – Abdominal radiograph of intracolonic high-resolution manometry catheter placement.

B – Line plot (above): each line represents a sensor with proximal sensors starting at the top and each peak represents an increase in pressure. Clouse plot (below) of manometric pressure recordings representing retrograde CMPs. Colour intensity represents amplitude of contraction, 0 mmHg (blue) to 75 mmHg (red).

4.3.7 **Statistical Analysis**

Data are presented as mean (standard error). Student's t test for parametric data and Mann-Whitney U test for non-parametric data were used to compare each metric of interest between controls and participants with diverticulosis. Paired samples student's t test and Wilcoxon signed-rank test were used to compare pre- and postprandial propagating contractions as appropriate. All statistical testing was conducted in R (R Foundation for Statistical Computing, Austria 2014) with $P<0.05$ considered statistically significant.

4.4. Results

4.4.1 **Participant Data**

1. Participant flow

The study population comprised of eighteen participants. Nine were healthy volunteers (historical controls) and nine had established, asymptomatic diverticulosis. Three participants with asymptomatic diverticulosis who were recruited and had some recordings taken but were excluded from the study as the HRM catheter unclipped during the recording time, compromising the data that were recorded.

2. Baseline characteristics

The control group was comprised of six women and three men with a median age of 51 (range 30-69) years. The diverticulosis group was comprised of three women and six men with a median age of 64 (60-76) years.

A total of 4815 minutes of data were analysed across all the participants. The minimum useable duration of recording was 80 minutes, hence a standardised duration of 80 minutes of pre- and postprandial data were analysed per participant (Figure 4-3). In all but one participant (several centimetres shy of the splenic flexure), the most proximal sensor reached beyond the splenic flexure.

4.4.2 **Descending Colon**

The pre-meal and post-meal metrics at the descending colon of the control and diverticulosis group are presented in Table 4-1. No statistically significant differences were observed in pre-meal propagating contractions between the control and diverticulosis groups (Table 4-1). The post-meal mean distance for propagating contractions was significantly lower in the diverticulosis group compared to the control group (10.8 (1.5) mm versus 20.0 (2.0) mm, p=0.03). The post-meal mean amplitude was lower in the diverticulosis group when compared to the control group (32.31 (17.2) versus 48.7 (17.5) mmHg), this approached but did not meet statistical significance (p=0.06). Other parameters for post-meal propagating contractions between control and diverticulosis groups also showed no differences.

The magnitude of the meal response, defined as the difference between post-meal and pre-meal activity was similar between the two groups (Table 4-1).

1. Cyclic Motor Patterns

There were no CMPs before meal-consumption in either control or diverticulosis participants. After consuming a meal, the CMPs of control participants propagated a greater mean distance than diverticulosis participants (17.1 (2.8) mm versus 6.0 (2.5) mm, $p = 0.01$). Post-meal cyclic activity of control participants also had higher mean amplitude than diverticulosis participants – 37.5 (7.2) mmHg versus 20.0 (8.0) mmHg, $p = 0.1$, however, this finding was not statistically significant. The magnitude of the post-meal increase in CMPs, defined as the difference between post-meal and pre-meal CMPs was not statistically significant in diverticulosis participants (Table 4-1).

Descending Colon		**Control (n = 9)**			**Diverticulosis (n = 9)**	
	Pre-meal	Post-meal	*p*	Pre-meal	Post-meal	*p*
All Activity†						
Total no. propagating contractions	7.3 (2.5)	64.3 (22)	0.04	11.8 (4.7)	46.8 (13)	0.012
No. antegrade propagating contractions	2.6 (1.5)	11.2 (3.1)	0.021	0.6 (0.3)	6.1 (3.0)	0.012
No. retrograde propagating contractions	4.0 (1.4)	50.6 (19)	0.039	8.6 (4.4)	27.0 (11)	0.09
Mean distance propagated (mm)	13.9 (4.2)	20.0 (2.0)*	0.25	7.3 (2.8)	10.8 (1.5)*	0.17
Mean amplitude (mmHg)	34.2 (9.6)	48.7 (5.8)	0.091	21.7 (6.8)	32.3 (5.7)	0.079
Cyclic Motor Patterns‡						
Total no. CMPs	-	32.44 (19)	0.014	-	16.44 (7.9)	0.10
No. of antegrade CMPs	-	2.89 (2.9)	1	-	2.11 (2.0)	0.37
No. Retrograde CMPs	-	26.00 (15)	0.022	-	12.78 (7.3)	0.10
Mean distance propagated of CMPs (mm)	-	17.08 (2.8)*	0.003	-	6.04 (2.5)*	0.10
Mean amplitude of CMPs (mmHg)	-	37.51 (7.2)	0.008	-	20.04 (8.0)	0.10

Table 4-1 Colonic motility patterns in the descending colon.

†Comparing magnitude of meal response between controls and diverticulosis participants: Number of propagating contractions; p=0.45, antegrade; p=0.14, retrograde; p=0.085, amplitude; p=0.82, distance; p=0.65, ‡No pre-meal CMPs therefore magnitude of difference is equal to post-meal responses, *$p \leq 0.01$ difference between controls and diverticulosis participants

4.4.3 **Sigmoid Colon**

The pre-meal and post-meal metrics of the sigmoid colon of the control and diverticulosis group are presented in Table 4-2.

Measurements for the diverticulosis group demonstrated fewer antegrade propagating contractions than the control group (0.56 (1.01) versus 2.6 (3.43), p = 0.06) before a meal was consumed. However, there were no other statistically significant differences between the control and diverticulosis in pre-meal propagating contractions (Table 4-2). Post-meal mean distance of propagating contraction was lower in the diverticulosis group than controls (10.8 (1.5) mm versus 20.2 (5.9) mm, p=0.01). Similarly, diverticulosis participants had fewer retrograde propagating contractions (27.0 (11) versus 54.1 (12), p=0.09) and lower mean amplitudes (32.3 (5.7) mmHg versus 46.9 (5.4) mmHg, p=0.08), however these findings did not reach statistical significance. There were no other post-meal differences between diverticulosis and control participants.

The magnitude of the meal response was similar between the two groups (Table 4-2), however, the control group had a greater increase in retrograde propagating contractions in response to a meal than the diverticulosis group (p = 0.04).

1. Cyclic Motor Patterns

There were no CMPs before meal-consumption in diverticulosis participants. After consuming a meal, control participants experienced a greater overall increase in total CMPs (50.2 (18) versus 16.9 (11), p = 0.08) and retrograde CMPs than diverticulosis participants (35.8 (11) versus 13.9 (9.6), p = 0.07). The magnitude of the increase in CMPs was consistently lower in diverticulosis participants (Table 4-2), however no metric reached statistical significance.

Sigmoid Colon		Control (n = 9)			Diverticulosis (n = 9)	
	Pre-meal	Post-meal	*p*	Pre-meal	Post-meal	*p*
All Activity†						
Total no. propagating contractions	9.9 (3.4)	79.2 (18)	0.051	11.8 (4.7)	46.8 (13)	0.012
No. antegrade propagating contractions	2.6 (1.1)	19.2 (9.2)	0.039	0.6 (0.3)	6.1 (3.0)	0.012
No. retrograde propagating contractions	5.9 (2.6)	54.1 (12)	0.032	8.6 (4.4)	27.0 (11)	0.090
Mean distance propagated (mm)	12.2 (3.3)	20.2 (5.9)*	0.34	7.3 (2.8)	10.8 (1.5)*	0.17
Mean amplitude (mmHg)	40.0 (9.0)	46.9 (5.4)	0.34	19.3 (6.5)	32.3 (5.7)	0.040
Cyclic Motor Patterns‡						
Total no. CMPs	0.9 (0.9)	50.2 (18)	0.024	-	16.9 (11)	0.18
No. of antegrade CMPs	-	9.2 (7.9)	0.10	-	2.6 (2.2)	0.18
No. retrograde CMPs	0.6 (0.6)	35.8 (11)	0.011	-	13.9 (9.6)	0.18
Mean distance propagated of CMPs (mm)	0.6 (0.6)	9.5 (2.0)	0.019	-	4.8 (2.5)	0.18
Mean amplitude of CMPs (mmHg)	2.7 (2.7)	33.0 (7.8)	0.082	-	17.3 (8.7)	0.18

Table 4-2 Colonic motility patterns in the sigmoid colon

†Comparing magnitude of meal response between controls and diverticulosis participants: Number of propagating contractions; p=0.13, antegrade; p=0.5, retrograde; p=0.042, amplitude; p=0.56, distance; p=0.6, ‡Comparing magnitude of meal response of CMPs between controls and diverticulosis participants: Number of propagating contractions; p=0.079, antegrade; p=0.43, retrograde; p=0.071, amplitude; p=0.41, distance; p=0.23, *p=0.01 difference between controls and diverticulosis participants

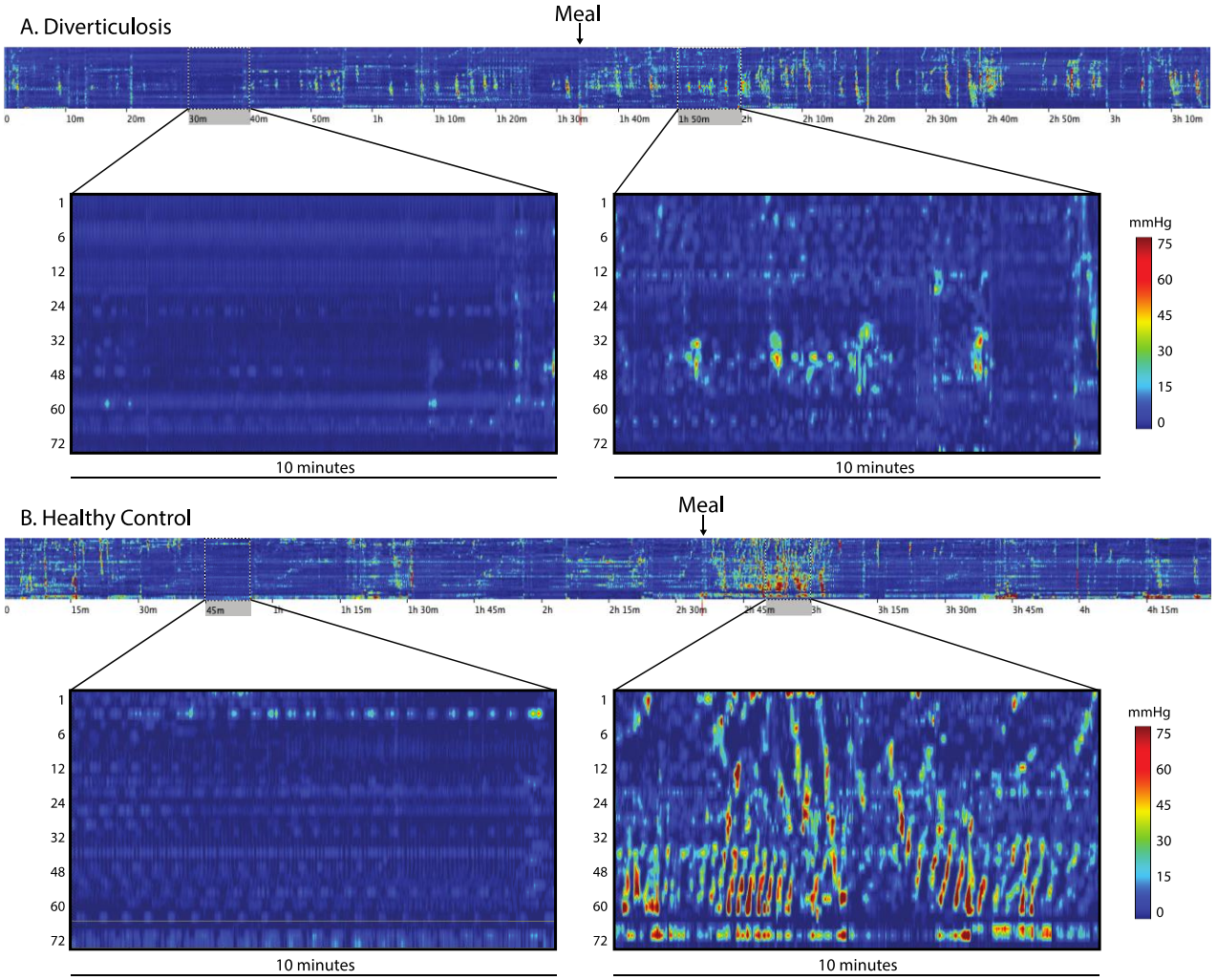


Figure 4-3 A. Colour map of high-resolution manometry recordings of diverticulosis participant. B - Colour map of high-resolution manometry recordings of control participant.

4.4.4 **High-Amplitude Propagating Contractions (HAPCs)**

No high-amplitude propagating contractions (HAPCs) were recorded in diverticulosis patients. However, one patient with diverticulosis had many antegrade short single contractions (as defined by Dinning et al.) with amplitudes > 100 mmHg (182). This is shown in Figure 4-4. HAPCs were identified in 5 control patients, all occurring post-meal (Table 3). In all but one control patient, no HAPC propagated into the sigmoid colon.

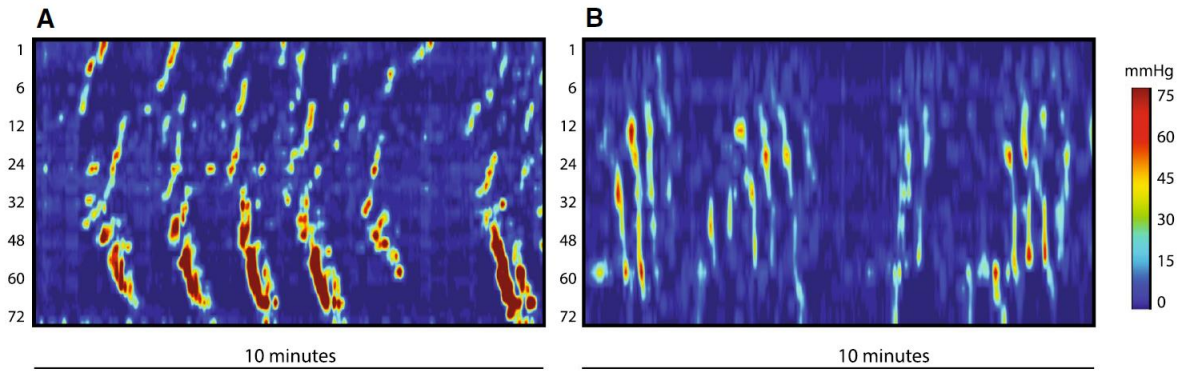


Figure 4-4 A. Color map of diverticulosis patient with high-amplitude, antegrade short single contractions.

B. Color map of the cyclic motor pattern seen in a diverticulosis patient

4.5. Discussion

This series of *in vivo* recordings with HRM failed to confirm the commonly taught conception that intracolonic pressures are increased in patients with diverticular disease compared to healthy controls. Contrary to this prevailing hypothesis, this study shows that the healthy colon tends to have a greater frequency of colonic propagating contractions both in the pre-prandial and postprandial state. Intra-sigmoid pressures also tend to be greater in healthy colons compared to diverticulosis colons. Furthermore, CMPs tend to occur less frequently in the diverticulosis colon with a more significant postprandial increases in CMPs seen in healthy participants. In combination, these results reject widely taught theories regarding colonic pressures and activity in diverticulosis.

The findings from this study are consistent with the systematic review described in Chapter 3, evaluating intracolonic pressures in diverticulosis in previous series. The review highlighted a lack of evidence showing increased intracolonic pressures in those with diverticular disease.

Previous data on intracolonic pressure were based on traditional low-resolution manometry which has been shown to under-report many activities in the colon, particularly regarding CMPs (179). Previous literature claiming higher intraluminal pressures and colonic activity in diverticular disease also lacked sufficient overall empirical data, as evidenced by often conflicting results (51, 63, 163, 164, 170, 172). This study is the first to use HRM to confirm a lack of evidence for the commonly postulated theory that higher intraluminal pressures are present in diverticular disease (185), and that diverticulosis colons are more active (51, 63, 172). This indicates that further research is still required to definitively elucidate the pathophysiological mechanisms of diverticulosis.

The findings of this study challenge currently held understandings about the role of intracolonic pressure in the pathophysiology of diverticulosis. This uncertainty is mirrored when considering the paucity of definitive evidence for the other proposed causes of diverticulosis. Clinically, this lack of clarity is a barrier when counselling those who have asymptomatic diverticulosis or diverticular disease, with implications for health literacy, quality of life and self-management (38, 52).

Several mechanisms may explain the findings of this study. The general decrease in overall activity, in particular CMPs, in this diverticulosis cohort may reflect changes in colonic pacemaker cells, the interstitial cells of Cajal (ICC) (66, 195) and decreased colonic compliance. Bassotti et al. reports ICC depletion in diverticular disease (66) which may help explain decreases in colonic activity. However, others have also reported no significant differences in ICC quantity and no change in the frequency of propagating contractions (195). Hence, these cellular changes require further investigation. Furthermore, the degree of collagen cross-linking, which increases with age, increases more so in diverticular disease independent of age (196, 197). This may result in decreased compliance and subsequently decreased colonic activity. Increased thickening of colonic circular muscle in diverticular disease may further contribute to this (198).

Collagen may have a second role in the pathogenesis of diverticula. The ratio of type I to type III collagen is seen to decrease in diverticular disease leading to weakened connective tissues (35). The weakened colonic wall may be sufficient substrate for diverticula to form without need for higher intracolonic pressures. Connective tissue disorders may therefore contribute more to the pathophysiology of diverticular disease than elevated pressures (38). Factors such as inflammation and low fibre diet are also likely involved (52, 199, 200).

Patients with diverticulosis may also have altered bowel habit with irritable-bowel-type symptoms in uncomplicated disease (although all participants in this study were asymptomatic) (93). Colonic dysmotility, namely the reduced propagating contractions and intracolonic pressures in the present study's diverticulosis participants may explain how these symptoms arise.

4.6. Limitations

The sample size of this study is small and the findings are only applicable to those with asymptomatic diverticulosis. A larger study may be beneficial to further validate the reduced pressures and intracolonic activity seen among this cohort of diverticulosis participants compared to controls. Furthermore, future studies should also investigate those with different manifestations of symptomatic disease to determine whether the patterns seen in this study are observed in those with symptomatic diverticular disease. The current study utilised a relative short recording time before and after meal consumption. An ambulatory high resolution colonic manometry has recently been developed (201), and prolonged 24 hour ambulatory recording may provide further insights into the condition. This analysis also focused mainly in the distal colon where diverticula are most commonly found, whether proximal colonic activity has a role in the pathogenesis of diverticular disease remains to be elucidated. Additionally, high-amplitude propagating contractions, a type of propagating motility pattern associated with the forward propulsion of colonic content (202), occurred too sparsely to be included in analysis.

4.7. Conclusion

This is the first study to use HRM to examine colonic pressures in diverticulosis and it has failed to demonstrate increased colonic pressure or motility when compared with measurements taken in control participants. Further studies utilising HRM, and comparable participant selection and data analysis strategies are required in order to support these initial findings and explore the role of aberrant colonic pressures in diverticular disease.

Chapter 5. Survey of Australasian Surgeons - Current Management of Acute Diverticulitis

5.1. Background

As described in Chapter 1 and demonstrated in part within Chapter 4, there are still significant gaps in our understanding of the pathophysiology of diverticular disease and how best to manage it. Although it is a relatively common condition, there is a paucity of high level evidence to support widely held views about its aetiology and management, and subsequently considerable variability among the guidelines produced by different regions and healthcare systems with regards to fundamental aspects of clinical management including disease classification, diagnostic methods, medical and surgical management (108). This is particularly the case when considering the management of uncomplicated acute diverticulitis, which accounts for 85-90% of cases of acute diverticulitis (11).

One factor contributing to this variability is the fact that many aspects of clinical management which had been previously considered routine have been challenged by new evidence. As discussed in Chapter 1, there are a number of trends in the management of acute diverticulitis which have led to changes in clinical practice and guidelines. Notably, the past decade has seen a shift towards a more conservative approach to managing uncomplicated acute diverticulitis with the aim of reducing unnecessary antibiotic use and hospital admissions, both of which entail risks to patients. Recent studies have demonstrated that patients with uncomplicated acute diverticulitis can be safely managed in an outpatient setting (20, 110, 111, 144, 145, 203) and with limited use of antibiotic therapy (23, 26, 101). Not only have these changes been adopted inconsistently across different regions, clinical research on acute diverticulitis management is limited by the use of inconsistent terminology and criteria for grading severity of disease.

A significant barrier to defining current practice, as well as the safety and acceptability of a more conservative approach to uncomplicated acute diverticulitis management in an Australasian context, is that there are currently no published national or regional clinical guidelines for this condition. There is a need to ascertain the degree to which trends in acute diverticulitis management have been adopted in this region, both as a means of auditing local clinical practices and in order to ascertain whether new practices endorse clinical equipoise.

5.2. Study Objectives

The aim of this survey of Australasian surgeons was to evaluate the current practice of colorectal specialists in Australasia and general surgeons in New Zealand with regards to the medical management of acute diverticulitis, to assess whether newer approaches to management were being translated into practice and to provide context for further local research into acute diverticulitis.

5.3. Study Methods

5.3.1 **Study Design**

This study was designed as a cross-sectional survey which was open to all members of the Colorectal Surgery Society of Australia and New Zealand (CSSANZ) and all general surgery consultants at the three tertiary centres in Auckland. Ethics approval for this study was obtained from the University of Auckland Human Participants Ethics Committee (#012408), as well as Auckland, Counties Manukau and Waitemata District Health Boards, prior to distribution of surveys.

5.3.2 **Survey Construction**

The survey was constructed in English. Uncomplicated acute diverticulitis was defined as acute diverticulitis with evidence of inflammation without abscess or perforation on CT scan (modified Hinchey criteria 1a) (12). Some questions required yes/no answers, while others asked for responses on a 5-point Likert scale, with 1 meaning always; 3 sometimes; and 5 never (Figure 5-1). Additionally, there were a number of questions where qualitative information was gained through free-text responses.

The six sections of the survey were designed to collect information about the number of patients with acute diverticulitis seen by participants, describe the rationale for hospital admission, identify the criteria used to assess severity, examine the current medical management of uncomplicated and complicated acute diverticulitis, and investigate the utilisation of selective use of antibiotics and anti-inflammatory agents in the management of acute diverticulitis. The content of the survey is summarised below, with italics indicating questions which were posed to the participants. Complete copies of both the colorectal specialist and general surgeon surveys can be found in Appendix B.

Section 1 (for General Surgeons): Experience managing acute diverticulitis

1. Main subspecialty area
2. Frequency of acute diverticulitis managed at participant's centre

Section 1 (for Colorectal Specialists): Experience managing acute diverticulitis

1. Country (New Zealand or Australia)

2. Frequency of acute diverticulitis managed at participant's centre

Section 2 (same in both versions): Rationale for hospital admission

Which of the following factors would you consider an absolute indication for admitting the patient with a clinical or radiological diagnosis of acute diverticulitis?

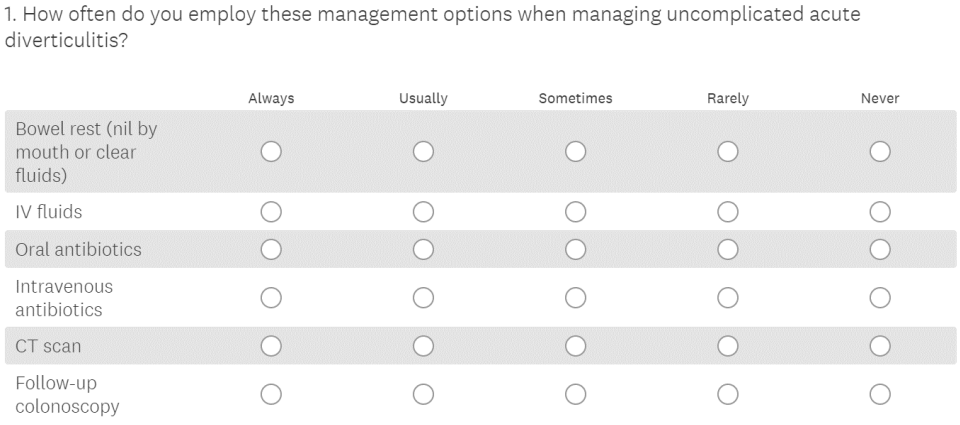
Section 3 *(same in both versions)*: Criterion for assessing disease severity

1. *Is there a severity score for acute diverticulitis that is routinely used in your centre? Y/N*

2. *Please tick any that you use and describe any that are not listed in the 'Other' section.*

Section 4 (same in both versions): Medical management of uncomplicated and complicated acute diverticulitis

Figure 5-1 demonstrates how a Likert Scale was used to ascertain how frequently different medical management techniques were utilised by the respondents.


1. How often do you employ these management options when managing uncomplicated acute diverticulitis?

	Always	Usually	Sometimes	Rarely	Never
Bowel rest (nil by mouth or clear fluids)	○	○	○	○	○
IV fluids	○	○	○	○	○
Oral antibiotics	○	○	○	○	○
Intravenous antibiotics	○	○	○	○	○
CT scan	○	○	○	○	○
Follow-up colonoscopy	○	○	○	○	○

Figure 5-1 Sample of Likert Scale used in online survey.

Section 5 (same in both versions): Use of anti-inflammatory medications in the treatment of diverticular disease

1. *Do you ever use anti-inflammatory medications in the treatment of any diverticular disease? Y/N*

2. If so, please state which medication and briefly describe the condition it was used to treat.

Section 6 (same in both versions): Use of corticosteroids in the treatment of diverticular disease

1. Do you ever use a short course of corticosteroids as an adjuvant therapy in acute diverticulitis? Y/N

2. Would you be willing to enrol patients in a randomised control trial to assess the use of a short course of corticosteroid in uncomplicated acute diverticulitis? Please add comments in the space below if you wish. Y/N

5.3.3 **Survey Publication and Dissemination**

The survey was published on published online using Survey Monkey (Palo Alto, California, USA) and the online version was beta-tested by clinicians who were not study investigators in order to assess clarity of the text and ease of participation. A link to the relevant version of the survey was emailed to all eligible clinicians in January 2015 using an email template developed for this purpose (Appendix C). CSSANZ members received the survey by email via the CSSANZ mailing list, and the general surgery consultants were contacted through the General Surgery Service at each centre. At one month after the initial email, a reminder email was sent out to increase response rate. The survey was closed two months after the initial email.

5.3.4 **Data Analysis**

Statistical analysis was performed using SPSS for Windows (Version 19; SPSS, Chicago, Illinois, USA). Descriptive statistics and figures were used to summarise the data. Univariate analysis was carried out using the χ^2 test for categorical data, one-way analysis of variance

(ANOVA) was used for parametric continuous data and the Mann Whitney U and Kruskal-Wallis test were used for non-parametric data.

When analysing responses which were measured using the five-point Likert Scale, consensus within the two study groups was defined as ≥ 80% of participants responding with either options 1-2 out of 5 or 4-5 out of 5.

5.4. Results

5.4.1 **Survey Response Rate and Frequency of Managing Diverticulitis**

Responses were received from a total of 99 of 200 (49.5%) colorectal surgeons and 19 of 36 (52.7%) general surgeons who were approached to participate in this study. Of the colorectal surgeons, 78 (78.8%) were based in Australia and 21 (21.2%) were based in New Zealand – the response rate for New Zealand members of CSSANZ was 65.6%. The majority of both groups saw patients with acute diverticulitis at least once a month (91.9% in the colorectal group and 84.2% in the general surgeon group). The median number of patients seen per week was 2 (1-5) and 5 (2-6.5) patients, respectively.

5.4.2 **Admission Criteria**

Factors seen as an absolute indication for hospital admission are listed in Table 5-1. General surgeons were more likely to include first episode of acute diverticulitis and a moderately raised CRP as an absolute indication for admission than colorectal surgeons. There were no significant differences between the responses of New Zealand and Australian colorectal surgeons.

Admission variable	**NZ colorectal surgeons (%)**	**General surgeons (% positive)**	**p-value**
First episode of AD	2 (9.5)	7 (36.8)	0.039
Patient age	0 (0.0)	0 (0.0)	-
Patient comorbidity	8 (38.1)	6 (35.3)	-
Temperature <36 °C or >38 °C	14 (66.7)	15 (78.9)	-
Heart rate >90 per minute	11 (52.4)	13 (68.4)	-
Respiratory rate >20 per minute	14 (66.7)	13 (68.4)	-
Signs of hypovolaemia	20 (95.2)	14 (73.7)	-

Localised peritonism	12 (57.1)	12 (63.2)	-
Rectal bleeding	4 (19)	5 (26.3)	-
Need for intravenous analgesia	20 (95.3)	15 (78.9)	-
Not tolerating oral intake	18 (85.7)	17 (89.5)	-
White blood cells <4x109/L or >12x109/L	6 (28.6)	7 (36.8)	-
CRP > 10	0 (0.0)	2 (10.5)	-
CRP >40	0 (0.0)	7 (36.8)	0.02
CRP >100	10 (47.6)	8 (42.1)	-

Table 5-1 Absolute indicators for hospital admission (New Zealand surgeons only).

A p-value <0.05 was considered to be significant. Underlining indicates positive consensus.

AD = acute diverticulitis, CRP = C-reactive protein

Comorbidities that were considered absolute indicators for admission by either group are displayed in Figure 5-2.

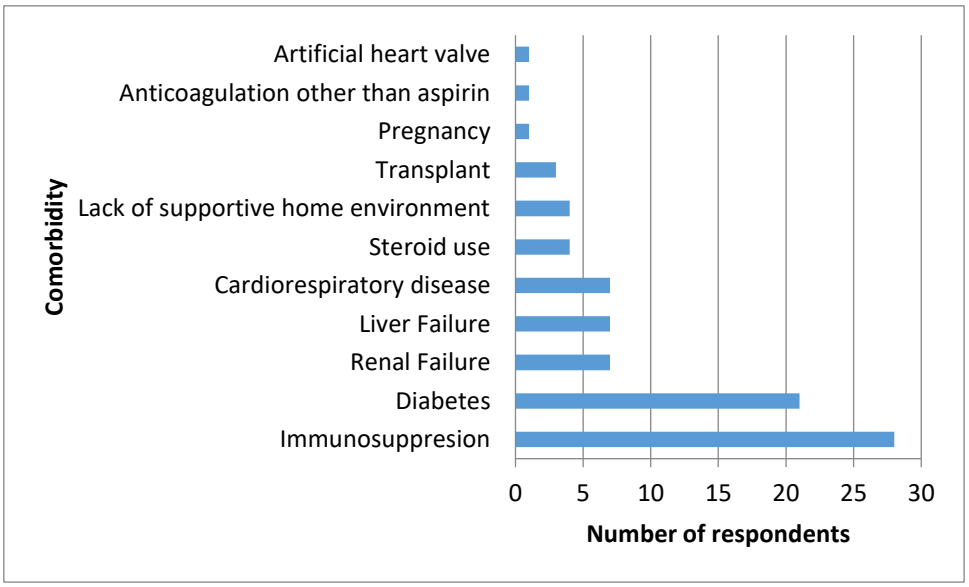


Figure 5-2 Absolute indicators for hospital admission.

5.4.3 **Assessment of Severity**

Twenty-eight (28.6%) colorectal surgeons and six (35.3%) general surgeons stated that there was a severity score they routinely used when assessing patients with acute diverticulitis. The majority of clinicians in both groups stated that they used the Hinchey Classification (67 (95.7%) of colorectal surgeons and 12 (92.3%) of general surgeons). The Mannheim Peritonitis Index (1 (1.4%) of colorectal surgeons and 1 (7.7%) of general surgeons) and Acute Physiology and Chronic Health Evaluation II (APACHE II) (10 (7%) of colorectal surgeons and 1 (7.7%) of general surgeons) were also used by a minority of respondents. There were no significant differences in the responses of the two groups.

5.4.4 **Management of Uncomplicated Acute Diverticulitis**

There was a wide variety of practice amongst the respondents. The use of inpatient colonoscopy met a 4/5 consensus, (rarely or never used) by all the respondents and was the only aspect of management where consensus was reached. The general surgeon group reached a 1/2 consensus (always or usually) regarding intravenous antibiotics, with 82.4% of respondents reporting their frequent use in managing uncomplicated acute diverticulitis. The

utilisation of key components of the medical management of uncomplicated acute diverticulitis are displayed in Table 5-2.

	Median Likert Scale Score (% agreement of 1 or 2)		p-value
	New Zealand colorectal surgeons	**General surgeons**	
Bowel rest (NBM or clear fluids)	2 (57.1)	3 (29.4)	-
IV fluids	2 (61.9)	2 (64.7)	-
Oral antibiotics	3 (42.9)	3 (23.5)	-
IV antibiotics	2 (57.1)	2 (64.7)	-
Inpatient colonoscopy *	5 (0.0)	5 (0.0)	-
Follow-up colonoscopy	2 (71.4)	2 (76.5)	-
Follow-up CT colonography	5 (9.5)	4 (5.9)	-

Table 5-2 Management of uncomplicated acute diverticulitis (New Zealand surgeons only).

A p-value <0.05 was considered to be significant. Underlining indicates positive consensus. * Indicates that there was negative consensus. NBM = nil by mouth, IV = intravenous, CT = computed tomography

5.4.5 **Management of Complicated Acute Diverticulitis**

Both groups used bowel rest, intravenous fluids, intravenous antibiotics and follow-up colonoscopy. Neither group routinely used inpatient colonoscopy. The utilisation of key components of the medical management of complicated acute diverticulitis are displayed in Table 5-3.

	Median Likert Scale Score (% agreement of 1 or 2)		p-value
	New Zealand colorectal surgeons	**General surgeons**	
Bowel rest (NBM or clear fluids)	2 (85.7)	2 (64.7)	-
IV fluids	1 (95.2)	1 (94.1)	-
Oral antibiotics	4 (20.0)	4 (11.8)	-
IV antibiotics	1 (100)	1 (94.1)	-

*Inpatient colonoscopy	5 (0.0)	5 (0.0)	-
Follow-up colonoscopy	2 (81.0)	2 (94.1)	-
Follow-up CT colonography	4 (14.3)	4 (5.9)	-

Table 5-3 Management of complicated acute diverticulitis (New Zealand surgeons).

A p-value <0.05 was considered to be significant. Underlining indicates positive consensus. * Indicates that there was negative consensus. NBM = nil by mouth, IV = intravenous, CT = computed tomography

5.4.6 **Selective Antibiotic Therapy**

Forty three colorectal surgeons and seven general surgeons stated that they sometimes did not use antibiotics in the management of diverticular disease. There was no statistically significant difference between the two groups or between colorectal surgeons working in differing countries. This question included the option to provide a free-text response. Key themes from the free-text responses are tabulated into Figure 5-3.

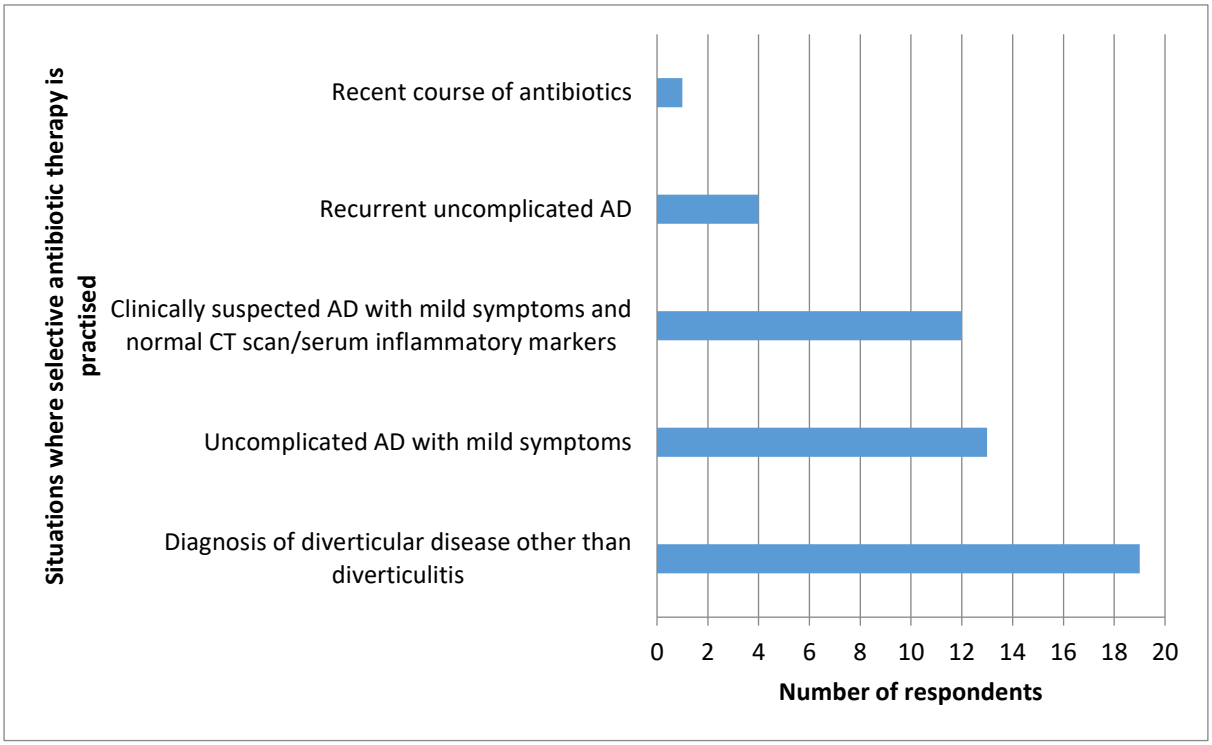


Figure 5-3 Rationale for selective antibiotic therapy.

AD = acute diverticulitis, CT = computed tomography

5.4.7 **Anti-inflammatory Medications**

Thirty-three (34%) colorectal surgeons and 10 (58.8%) general surgeons responded that they have used anti-inflammatory agents in the management of diverticular disease of any kind. There was no statistically significant difference between country and specialty. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly named agents amongst the free-text responses (4 responses) and analgesia was the most frequently stated purpose for the use of anti-inflammatory agents (8 responses). Four surgeons had used an anti-inflammatory agent in the management of segmental colitis with associated diverticulosis, and recurrent or refractory acute diverticulitis and symptomatic uncomplicated diverticular disease were both mentioned once.

A separate question enquired about the use of corticosteroids in any kind of diverticular disease. None of the respondents had used corticosteroids in this setting.

5.5. Discussion

This survey describes current practice and provides insight into the decision-making processes of clinicians who are currently managing patients with acute diverticulitis in Australasia.

Responses to this survey provided some information about the rationale for selecting inpatient care of patients with acute diverticulitis. Notably, serum markers of inflammation did not appear to weigh heavily on the decision to admit a patient. A minority of clinicians stated that age was an absolute indicator for admission, with a wide range of ages that were considered to be a reason to admit patients for admission. Immunosupression in general, as well as the specific circumstances of diabetes, steroid therapy, transplant, and organ failure were specified as comorbid conditions that were absolute indicators for hospital admission.

In our survey, there was little consensus regarding the management of uncomplicated acute diverticulitis. Routine use of antibiotics for patients with uncomplicated acute diverticulitis was still practised by a majority of respondents, and there was no consensus regarding this approach. This lack of consensus has also been reported internationally. A recent Delphi study demonstrated that, while there is expert consensus regarding the acceptability of outpatient management of patients with uncomplicated acute diverticulitis, there does not appear to be agreement regarding the important issue of selective use of antibiotics in this patient group (146).

Follow-up colonoscopy for patients with uncomplicated acute diverticulitis was practised ‘most of the time’ by both of the groups surveyed. This an area of some contention, as several systematic reviews (204-207), a retrospective study (208) and one large epidemiological study (209) have demonstrated that there are little data to support routine follow-up imaging in this patient group, other than as part of age-appropriate screening or in the management of patients with symptoms suggestive of an alternate diagnosis.

Responses to the focused question regarding the role of selective antibiotic therapy in diverticular disease showed that this approach was considered for non-inflammatory manifestations of the disease, as well as for mild acute diverticulitis. It would be interesting to observe whether these practices had changed or will proceed to change significantly over time. In the aforementioned international survey, a majority of respondents answered that there was a lack of high level evidence to support the use of antibiotics in these patients (146), a factor which is likely to explain, at least in part, why consensus is lacking.

The responses to the question regarding anti-inflammatory medication use reflect the uncertainties and new developments that have been made in this area. Anti-inflammatory agents are currently being considered for use in the management of select sub-types of diverticular disease. Mesalazine in particular, has been reported to be a helpful adjunct in the treatment of symptomatic uncomplicated diverticular disease (118, 119) and segmental colitis associated with diverticulosis (39, 40). There is a small and as yet inconclusive amount of data suggesting that it may be of use in uncomplicated acute diverticulitis by reducing damage caused by inflammation and aiding earlier resolution of the inflammatory response and associated symptoms. To date mesalazine has been shown to improve time to resolution of endoscopic and histologic evidence of inflammation following an episode of acute diverticulitis and also reduce the rate of recurrence (71, 126).

Corticosteroid use in the management of uncomplicated acute diverticulitis was not practised by any of the respondents. This question was included in the survey to investigate the possibility of performing an interventional trial, but the results of the survey indicated that this was not likely to meet clinical equipoise in the region.

5.5.1 **Survey of Patients with Diverticular Disease**

The lack of consensus regarding key aspect of diverticular disease management, especially the use of antibiotics and the role of outpatient management in uncomplicated acute diverticulitis, is also reflected in the wide range of positions demonstrated within different practice guidelines (21, 108). The challenge for health professionals and service providers is to ensure that this increasingly nuanced and constantly developing health information is delivered in an effective way to patients; however, there are no baseline data about health literacy in this patient group or about the effectiveness our current methods of health information delivery.

A survey of patients with diverticular disease was attempted in tandem with the current study. This study of patients with a history of hospital admission for acute diverticulitis aimed to provide baseline data about health literacy and disease-specific knowledge in this patient group, as well as examining the association between these and disease-specific health outcomes and quality of life. Ethics approval for this study was obtained from the Health and Disability Ethics Committee (17/CEN/80/AMO6) and a total of 150 patients were contacted regarding participation in the study.

The primary objective of this study was to ascertain whether there is a positive association between health literacy and quality of life:

- Health literacy was measured using the Health Literacy Questionnaire (210)
- Quality of life was measured by the NZ-WHOQOL-BREF (211)

The results of this study are not included as a separate chapter within this thesis due to the limitations presented by the low response rate of 20/150 responses (13.3%) and a summary of responses is attached as Appendix D. However, this survey represents a novel attempt to gauge how well changes in the diverticular disease knowledge base have been communicated to patients and what impact this increasingly nuanced discussion has had on their quality of life. Performing similar studies with methodology which is optimised to ensure satisfactory response rates from a broad range of patients would be valuable for ensuring that this aspect of diverticular disease management is not falling behind other dimensions of care.

5.6. Limitations

The most significant limitation of this study was the sub-optimal response rate. This may be in part due to self-selection by clinicians who do not treat patients with diverticular disease and felt that the survey was not relevant to their clinical practice. The number of responses could have been increased by surveying all New Zealand general surgeons, however, this was found to be logistically impractical due to the inability to gain access to all general surgeons either from the Royal Australasian College of Surgeons or through the District Health Boards. Despite these limitations, the results of this study are still useful for informing future local research into diverticular disease, including the acceptability of interventional studies which interrogate the utility and acceptability of newer techniques for managing acute diverticulitis.

5.7. Conclusion

Acute diverticulitis is a frequent indication for hospital admission under the General Surgery service, and the patients who are affected make up a heterogeneous group, with variable disease severity. However, even taking this into account, there is a striking lack of consensus regarding the approach to and management of acute diverticulitis, particularly the more common uncomplicated presentation. This lack of consensus may be explained by the paucity of high-level evidence in this group of patients. Expansion of the existing knowledge base and ability to utilise this new information in a cohesive, evidence-based approach to management will improve the efficiency and quality of care for patients presenting with this common condition.

Chapter 6. Retrospective Cohort Study – Predicting Complicated Acute Diverticulitis in a Tertiary Hospital Setting

6.1. Background

As discussed in Chapter 1, the characterisation of acute diverticulitis as complicated or uncomplicated, based on clinical and radiological features, is particularly useful when initiating clinical management. Uncomplicated disease, acute inflammation related to diverticula in the absence of abscess, perforation, fistula or bleeding (21), makes up approximately 90% of cases of acute diverticulitis (212) is a generally a self-limiting condition (213), while complicated disease may require acute operative management and can be life-threatening. These differences in severity and outcome must be considered in the context of the growing body of evidence supporting conservative approaches to managing uncomplicated disease such as outpatient treatment (110, 133) and selective antibiotic use (23, 101, 145, 214), while hospitalisation and routine antibiotic use are still recommended for complicated disease (21, 108). As the evidence supporting conservative management of uncomplicated acute diverticulitis increases and becomes more widely adopted by clinicians, the divergence in treatment pathways between complicated and uncomplicated disease will continue to increase.

In addition to the gold standard computed tomography (CT) scan (111), attempts have been made by researchers to identify clinical characteristics and laboratory test findings that correlate with complicated disease (28, 212), in the same way that risk classification systems for patients with peritonitis (215, 216) predict prognosis in this patient group. This field of research aims to construct a reliable means of identifying patients who are at risk of complicated acute diverticulitis at the time of initial presentation in order to enable clinicians to have greater certainty when advising patients about their expected disease course and provide patients the most appropriate level of management.

6.2. Study Objectives

The purpose of this retrospective cohort study was to apply a systematic approach to identifying factors associated with CT-proven uncomplicated acute diverticulitis in order to differentiate patients who can be managed safely in a conservative manner from those who are likely to have complicated disease.

6.3. Study Methods

6.3.1 **Ethics Approval**

Ethics approval for this study was obtained from the University of Auckland Human Participants Ethics Committee (#011311 and #9613), Auckland District Health Board and Counties Manukau District Health Board prior to data extraction and analysis.

6.3.2 **Study Population**

The study population was comprised of adults over the age of 18, who presented to Auckland City and Middlemore Hospital with symptoms and radiological or intra-operative evidence of acute diverticulitis and were admitted under General Surgery. At the time of the study, neither site had a formal treatment protocol for acute diverticulitis so management of the patients at both sites was stipulated by the admitting surgical teams,

1. Inclusion Criteria

Uncomplicated acute diverticulitis was defined as CT-proven diverticulitis which met the criteria for Hinchey 1a disease, as described by the Modified Hinchey Classification (12). The Modified Hinchey Classification was chosen as it is the most commonly used scale at the two study sites. Hinchey 1a disease correlates with radiological findings of colonic wall thickening with pericolic soft tissue changes on CT scan (217)

2. Exclusion Criteria

Exclusion criteria were diagnoses other than left colonic acute diverticulitis on CT scan or based on intra-operative findings, and those who did not have imaging, operative or histological findings that confirmed a diagnosis of acute diverticulitis. Patients not admitted under General Surgery were also excluded as they make up a small minority of patients and diagnosis and management may have been delayed due to atypical presentations.

6.3.3 **Data Collection**

As all cases of acute diverticulitis requiring hospital-level care are managed at public hospitals in New Zealand, our data can be seen as representative of all such cases of acute diverticulitis occurring in the Auckland City and Middlemore Hospital catchment areas during the study period. Cases were identified using discharge diagnosis (International Statistical Classification

of Diseases and Related Health Problems code K57 for diverticular disease) for the period January 2012 to June 2013 inclusive. Of these cases, codes pertaining to diverticular disease outside of the sigmoid colon, diverticular bleeds, elective hospital admissions and those indicating diverticulosis only were excluded to leave only those cases pertaining to sigmoid colon acute diverticulitis. Once cases were identified, each patient's National Health Index (NHI) number was used to access their electronic records for information pertaining to the relevant hospital admission. Data were then de-identified prior to data analyses and entered into an electronic database.

1. Patient Characteristics

Demographic data were collected. Individual patient factors were recorded, such as comorbidities and the use of the following medications, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants and chemotherapeutic agents. Regular (>4 days of use in the last week) steroid or (within the six months prior to presentation) immunomodulator/biologic use was combined into one parameter for data analysis.

2. Disease Characteristics

Presenting symptom(s), duration of illness, vital signs and initial blood test results were also collected. Initial vital sign recordings and laboratory results were used to determine whether patients met the criteria for systemic inflammatory response syndrome (SIRS) at the time of presentation. The criteria for SIRS used in this study were met if patients had two or more of the following: temperature <36 or >38 C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, PaCO2 >32 mmHg, white cell count <4 or >12 x 10^9/L or >10% bands (immature neutrophils) (109). Patient-reported pain score on admission was also collected; this number was recorded by the Emergency Department nursing staff on admission. Patients were asked to report their pain level on a scale of 0 to 10, with 10 being the worst pain they have ever experienced.

3. Inpatient Care

Management of the patients at both sites was guided by the admitting surgical teams, without a formal protocol. All patients included in the study received antibiotics; however, we recorded whether patients were prescribed antibiotics by the admitting clinician, based on a clinical diagnosis or later following CT scan, thus describing local practice at the time of the study. At

the time of the study, neither site had a policy of selective antibiotic treatment or hospital-led outpatient management for uncomplicated acute diverticulitis.

4. Primary and secondary outcomes

The primary outcome studied was disease status (uncomplicated or complicated according to the modified Hinchey classification). Other recorded endpoints were: length of hospital stay, requirement for procedural intervention, 30-day readmission, and in-hospital death.

6.3.4 **Statistical Analysis**

Statistical analysis was performed using SPSS for Windows (version 19; SPSS, Chicago, Illinois, USA). Descriptive statistics and figures were used to summarise the data. Univariate analysis was carried out using the χ^2 test for categorical data, one-way analysis of variance (ANOVA) was used for parametric continuous data, and the Mann–Whitney U test and Kruskal–Wallis test were used for nonparametric data.

Multivariate regression analysis using a logistic regression model was also carried out incorporating all factors which had a p value ≤ 0.1 on univariate analysis to examine the impact of multiple factors on the likelihood of the three endpoints—need for procedural intervention, prolonged hospital stay and 30-day readmission. Closely related parameters were input into separate regression models to avoid erroneous correction for each other. This method was also used to identify factors associated with a severe clinical course. Results were considered significant if p value <0.05. Parametricity was determined using the Shapiro–Wilk test, with normally distributed data being expressed as mean ± standard deviation (SD) and nonparametric data as median ± interquartile range (IQR).

Variables identified as independent predictors of complicated acute diverticulitis on regression analyses were then used to generate a risk stratification system. The discriminative capacity of each system was interrogated using receiver operating characteristic (ROC) curves. The area under the ROC curve (*c*-value of discrimination) was used to appraise predictive accuracy. An area-under-curve (AUC) of 1.0 indicates a perfect test while an area of 0.5 signifies an ineffective test; an area between 0.7-0.8 represents ‘fair discrimination’ at predicting a binary outcome (218).

6.4. Results

6.4.1 **Data retrieval**

After applying the exclusion criteria to the 676 admissions identified through clinical coding, there were 376 confirmed admissions for acute diverticulitis over the 18-month study period. Data for patients from Auckland City Hospital were retrieved through the electronic information system portal (Concerto) and the electronically-linked '3M Viewer' which contained scanned picture files of all hand-written clinical notes which are generated during a patient's hospital admission. Data for patients for Middlemore Hospital were retrieved through Concerto and directly extracting data from paper clinical notes.

6.4.2 **Incidence of Uncomplicated Acute Diverticulitis**

Of 376 confirmed cases of acute diverticulitis, there were 315 (83.8%) cases of uncomplicated acute diverticulitis. Overall, there were similar numbers of men and women in the study population, although younger men and older women were overrepresented. In total, 225 admissions (59.8%) were for patients under the age of 60. The median age for all admissions was 57 (46.5-66) years. The median age was 49.5 (43-66) years for men and 63 (54-72) years for women, the difference between these was statistically significant ($p = 0.0$). Further demographic data are displayed in Table 6-1.

	Total (n=375)	Women (n=186)	Men (n=189)
Median age (LQ-UQ)	57 (46.5-66)	63 (54-72)	49.5 (43-66)
Age group			
18-44 years (%)	79 (21)	23 (12.3)	56 (29.6)
45-59 years (%)	146 (38.8)	164 (32.1)	133 (45.5)
60-74 years (%)	112 (29.8)	75 (40.1)	37 (19.6)
≥75 years (%)	39 (10.4)	29 (15.5)	10 (5.3)
First episode of AD (%)	249 (66.6)	112 (59.9)	137 (72.5)
Charlson score ≥3 (%)	117 (31.2)	80 (43)	37 (19.6)
Current NSAID use † (%)	28 (7.4)	14 (7.5)	14 (7.4)
Steroid† or immunomodulatory/biologic use (%)	17 (4.5)	13 (7)	4 (2.1)

Table 6-1 Demographic data.

†> 4 days in past week, LQ = lower quartile, UQ = upper quartile, AD = acute diverticulitis, NSAID = non-steroidal anti-inflammatory drug

6.4.3 **Clinical Management Data**

Most patients (68.1%) were started on intravenous antibiotics by the first surgical doctor to assess them (prior to confirmation of diagnosis by CT scan). Some form of procedural management was required by 13.5% of patients during their admission (surgery - 31 patients (8.2%), or percutaneous drainage - 20 patients (5.3%)). Of the patients who required surgery: two underwent laparoscopic washouts and the remaining patients had either high anterior resection or Hartmann's procedure.

6.4.4 **Outcome Data**

There were 2 in-hospital deaths. One patient had acute diverticulitis with bowel perforation and was not a suitable candidate for acute surgery; the other underwent an operation but

subsequently died, with a diagnosis of post-operative shock. Eleven patients left the Auckland region and were lost to follow-up.

Median length of hospital stay was 3.0 days (2.11-4.09) in the uncomplicated group and 6.2 days (3.4-11.4) in the complicated group. There were 60 patients (16.0%) who required more than one week's hospital admission and 39 patients (10.4%) required readmission within 30 days of discharge. During the 12 months following the index admission, ten patients underwent operations for diverticular disease (2.3%). There were five deaths (1.3%); however none of these were related to diverticular disease. The results of univariate analysis of outcome variables are available in Table 6-2.

	All (n = 376)	**Complicated AD (n = 61)**	**Uncomplicated AD (n = 315)**	**p-value**
Patient demographics				
Age (years) (LQ-UQ)	57.1 (46.5-66)	55 (44-63)	59 (47-69)	0.06*
18-44 (%)	79 (21)	10 (16.4)	69 (21.9)	0.39
45-59 (%)	146 (38.8)	26 (42.6)	120 (38.1)	0.39
60-74 (%)	112 (29.8)	17 (27.9)	95 (30.2)	0.76
≥75 (%)	39 (10.4)	8 (13.1)	31 (9.8	0.49
Female (%)	187 (50.3)	27 (44.3)	160(50.8)	0.4
Ethnicity				
European (%)	293 (78.3)	48 (78.7)	245 (78.3)	0.55
Māori (%)	35 (9.4)	9 (14.8)	26 (8.3)	0.15
Pasifika (%)	33 (8.8)	1 (1.6)	32 (10.2)	0.03*
Indian (%)	11 (2.9)	5 (8.2)	6 (1.9)	0.02*
Other (%)	11 (2.9)	0 (0)	11 (3.5)	0.24
Patient factors				
First episode (%)	249 (66.6)	41 (67.2)	208 (66.5)	0.58
Smoking status				0.39

Current smoker (%)	66 (17.8)	12 (19.7)	54 (17.5)	
Ex-smoker (%)	82 (22.2)	17 (27.9)	65 (21.0)	
Never smoked (%)	222 (60)	32 (52.5)	190 (61.5)	
Duration of symptoms (days) (LQ-UQ)	2 (1-4)	4 (1-7)	2 (1-4)	0.01*
<1 day (%)	129 (34.5)	18 (29.5)	111 (35.5)	0.46
>5 (%)	80 (21.3)	37 (60.7)	43 (13.6)	0.0*
>7 (%)	39 (10.4)	13 (21.3)	26 (8.3)	0.01*
Charlson score >3 (%)	117 (31.2)	20 (32.8)	97 (30.9)	0.77
Current steroid† or immunomodulator/biologic use (%)	17 (4.5)	8 (13.1)	9 (2.9)	0.0*
Current NSAID use† (%)	28 (7.4)	6 (9.8)	22 (7.0)	0.43
Physical examination				
Temperature on admission (◦C) (SD)	36.8 (0.8)	37 (0.9)	36.8 (0.8)	0.05*
Heart rate on admission (beats per minute) (SD)	84 (17)	93 (19)	82 (16)	0.0*
Respiratory rate on admission (breaths per minute) (SD)	18 (4)	18 (3)	17 (4)	0.54
SIRS criteria met	105 (28.5)	27 (45)	78 (24.9)	0.0*
SIRS criteria met for temperature (%)	98 (26.2)	20 (32.8)	78 (24.9)	0.21
SIRS criteria met for heart rate (%)	111 (29.6)	30 (49.2)	81 (25.8)	0.0*
SIRS criteria met for respiratory rate (%)	26 (7.2)	8 (13.6)	18 (5.9)	0.05*
Patient reported pain score (0-10)				
Pain score ≥2	245 (78.5)	34 (75.6)	211 (79)	0.56
Pain score ≥4	107 (34.3)	18 (40)	89 (33.3)	0.40
Pain score ≥6	107 (34.3)	18 (40)	89 (33.3)	0.24

Pain score ≥8	25 (8)	5 (11.1)	20(7.5)	0.28
Presence of peritonism	111 (30.3	25 (41)	86 (28.2)	0.26
Admission blood tests				
White cell count (x 10^9/L) (LQ-UQ)	12 (10-14)	13 (10-16)	12 (10-14)	0.17
Neutrophil count (x 10^9/L) (LQ-UQ)	8.57 (6.36-10.88)	10.1 (7.6-11.93)	8.4 (6.2-10.6)	0.02*
SIRS criteria met for white cell count (%)	164 (43.6)	31 (50.8)	133 (42.2)	0.26
C-reactive protein (mg/L)				
CRP ≥50 (%)	206 (59)	47 (81)	159 (54.6)	0.0*
CRP ≥100 (%)	107 (30.7)	35 (60.3)	72 (24.7)	0.0*
CRP ≥150 (%)	52 (14.9)	22 (37.9)	30 (10.3)	0.0*
CRP ≥200 (%)	28 (8)	13 (22.4)	15 (5,2)	0.0*
Serum sodium (mmol/L) (IQR)	138 (3)	137 (4)	138 (3)	0.0*
Hyponatraemia (<135mmol/L) (%)	41 (11.1)	14 (23)	27 (8.8)	0.0*

Table 6-2 Results of univariate analysis.

All continuous variables are non-parametric and expressed as median±IQR and all discrete variables are expressed as count (percentage). * p-value <0.1, †> 4 days in past week. IQR = inter-quartile range, NSAID = non-steroidal anti-inflammatory drug, CT = computed tomography, CRP = C-reactive protein, ICU = intensive care unit

6.4.5 **Multivariate Analysis**

The multivariate analyses of independent predictors for complicated acute diverticulitis are displayed in Table 6-3. These results were used to construct a risk stratification system (Table 6-4).

Variable	OR	95% CI	p-value
Meets SIRS criteria	2.3	1.2-4.1	0.08
Meets SIRS criteria for HR	2.1	1.1-4.0	0.020
Duration of symptoms >5 days	3.5	1.8-6.6	0.01
Serum sodium <135mmol/L	2.7	1.2-5.9	0.014
CRP ≥150 mg/L	4.6	2.3-9.2	0.01

Table 6-3 Results of multinomial logistic regression.

Variable	Points allocated	
Duration of symptoms >5	Yes = 2	No = 0
SIRS	Yes = 1	No = 0
Serum sodium <135mmol/L	Yes = 1	No = 0
CRP ≥150 mg/L	Yes = 2	No = 0

Table 6-4 Risk score for predicting disease severity

SIRS criteria was chosen over the heart rate component in isolation as the SIRS criteria as a whole is a well-known and widely used score for assessing seriously unwell patients with sepsis. We adjusted this model by giving the variables 'CRP ≥150' and 'duration of symptoms >5 days' double weighting and this improved the predictive ability of our model slightly, resulting in an AUC of 0.75 (Figure 6-1). This analysis only included the 337 patients for whom all data required for the risk score were available.

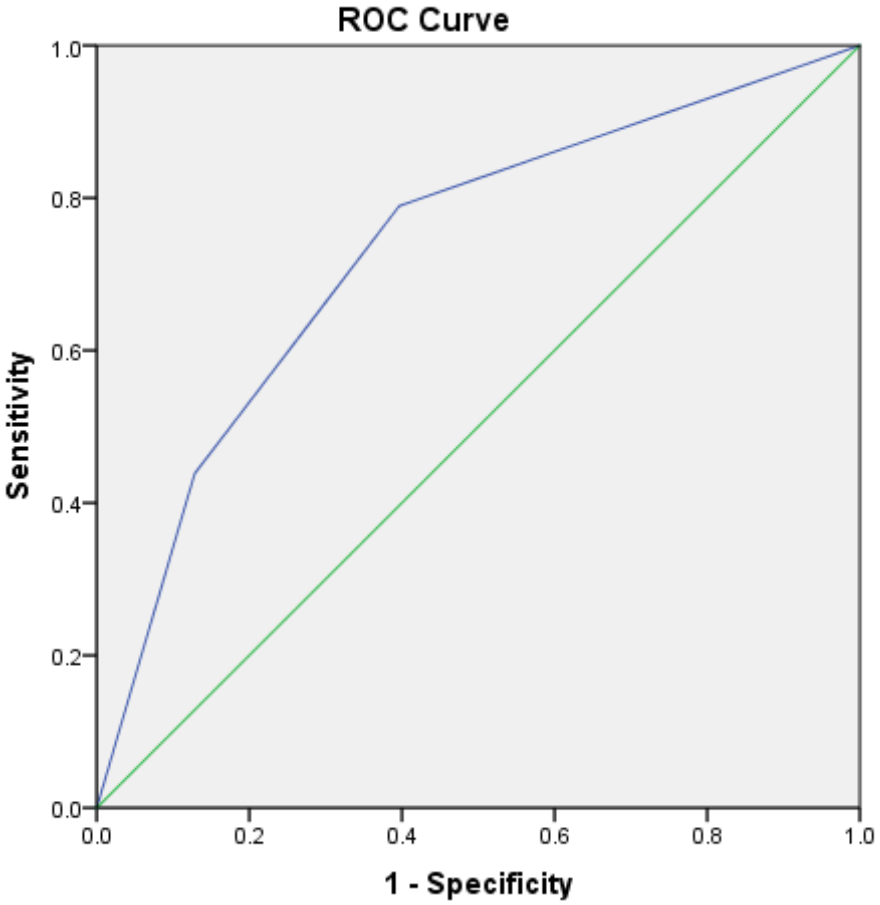


Figure 6-1 ROC curve for composite risk score (AUC = 0.73, 95% CI 0.7-0.8)

Figure 6-2 compares risk scores by disease status and shows the incidence of complicated acute diverticulitis at the three cut-off points, indicating low, moderate and high-risk groups for complicated disease. The incidence of complicated acute diverticulitis increased six-fold between the low (6.6%) and high-risk groups (41.0%) (Table 6-5). The positive predictive value of the risk score was poor at 41.0% but the negative predictive value was high at 94.0%.

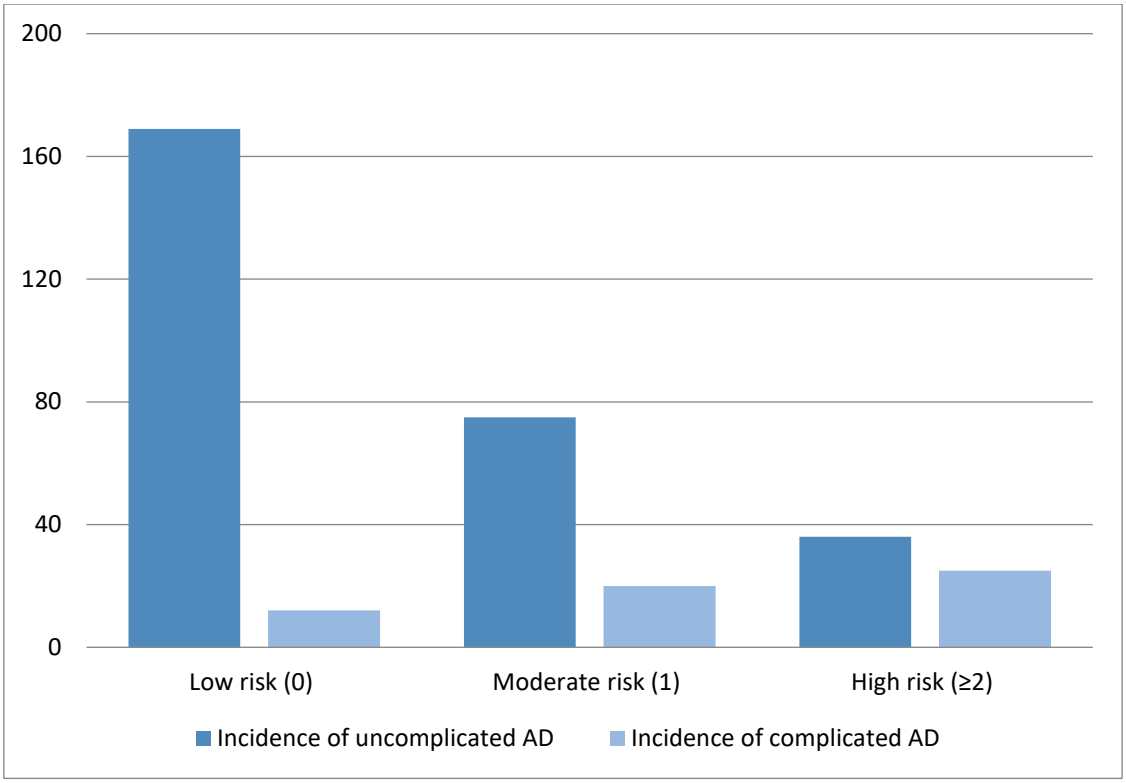


Figure 6-2 Risk prediction versus observed disease status

Risk score	Incidence of complicated AD
Low risk 0 (181)	6.6%
Moderate risk 1 (95)	21.1%
High risk ≥2 (61)	41.0%

Table 6-5 Incidence of complicated AD by risk score.

6.5. Discussion

This study has shown that a composite risk score for complicated acute diverticulitis (CT scan showing >1a modified Hinchey disease) consisting of meeting SIRS criteria, CRP > 150, duration of symptoms ≥5 days and hyponatraemia, had a 'fair' predictive ability and has the potential to be developed into a simple clinical decision-making tool to use in the triaging of patients with acute diverticulitis. Two previous systematic review and meta-analyses have identified similar risk factors - namely high CRP, symptom severity, comorbidities and steroid/non-steroidal anti-inflammatory drug use but were limited by the heterogeneous nature of the available published literature when defining complicated acute diverticulitis and examined risk factors (28, 212).

Traditionally, the severity of acute diverticulitis was classified according to the Hinchey Classification for colonic perforation associated with diverticulitis (12, 13). A number of variations of the Hinchey classification have also been proposed to stratify disease severity and risk in acute diverticulitis; however, they are not widely used in current clinical practice. As outlined in Chapter 1, more recent literature proposes that acute diverticulitis should be divided into uncomplicated or complicated disease using a combination of clinical and radiological features. This approach acknowledges the utility of CT for assessing severity of an episode as well as diagnostic purposes (29).

As demonstrated through the survey of Australasian colorectal specialists and general surgeons described in Chapter 5, the Hinchey classification is the most commonly used system to determine the severity of acute diverticulitis, however this system does not take patient characteristics into account nor does it generate an idea of expected risk. Other, less commonly used scores were those which were used to assess the severity of general abdominal infections (Mannheim Peritonitis Index (216) and Acute Physiology and Chronic Health Evaluation (APACHE) score (215)). These have a number of commonalities with the risk factors identified by this study, namely, duration of symptoms prior to presentation (MPI) and elements of SIRS and hyponatraemia (APACHE). However, the respective outcomes of death and ICU admission are not applicable to the vast majority of patients who do not become systemically unwell (only 28.5% of patients in this study met the criteria for SIRS), advancing the need for a disease-specific risk prediction system.

The utility of an institutional protocol for acute diverticulitis has been investigated by a limited number of studies. Some of these studies focus exclusively on the management of

uncomplicated acute diverticulitis (17, 112, 219), while one study has described a single-institutional experience of implementing a diverticulitis clinical pathway based on radiologic criteria (220). This pathway utilised the modified Neff (mNeff) classification as the basis for differentiating between uncomplicated and complicated acute diverticulitis, and guiding clinical decision-making around the admitting service (surgical versus non-surgical), consideration of outpatient management, choice and duration of antibiotic therapy and need for procedural intervention (220). The authors found that clinician compliance was high for documentation of the patient's mNeff classification and admission to the appropriate service based on the pathway, but low overall, largely due to non-compliance with regards to antibiotic choice and duration of treatment (220).

The pathway utilised in this study represents one version of the type of decision-making tool that could be used to improve the management of acute diverticulitis. Improving our ability to identify patients who are more or less likely to have complicated acute diverticulitis at an early stage of hospital admission enables clinicians to offer patients more targeted advice regarding their expected outcome, and appropriate application of management options based on disease severity. The auditing of clinical protocols which differentiated between high and low-risk patients with modifications such as prioritised imaging to rule out complicated disease (to allow for earlier discharge and reduce unnecessary overnight admissions), a shorter, narrow-spectrum or delayed antibiotic regimen, and outpatient-based management is an important area for further research to ensure that patients with acute diverticulitis are managed consistently and appropriately.

6.6. Limitations

This study is limited by its retrospective design. The quality of the dataset is dependent on appropriate documentation by a large number of medical and nursing staff, and missing data are a minor but persistent confounding factor. A larger-scale and prospective dataset may identify additional independent risk factors and is ultimately required to validate this scoring system. In addition, the risk factors identified will need to be confirmed in other populations of acute diverticulitis patients to assess suitability for wider application. This study is not representative of the majority of cases of uncomplicated acute diverticulitis which are managed outside the hospital in an outpatient setting and hospital-led outpatient management of uncomplicated acute diverticulitis is not routine practice at the two included sites.

6.7. Conclusion

The management and expected clinical course for patients with uncomplicated and complicated acute diverticulitis diverge significantly. Carrying out a risk assessment for complicated acute diverticulitis in the early stages of the consultation process will help ensure that patients are managed according to the most appropriate management pathway. When implemented in conjunction with an evidence-based protocols which outline the most appropriate management for differing levels of disease severity, this stratified approach should lead to a more efficient use of health resource, reduce unnecessary hospitalisation and delays in care, and improve patient satisfaction and quality of life for those with acute diverticulitis.

Chapter 7. Retrospective Cohort Study of Uncomplicated Acute Diverticulitis – Predicting Severe Course in Uncomplicated Acute Diverticulitis

7.1. Background

Over the past decade, there has been a trend towards more conservative management of acute diverticulitis. This is particularly the case with uncomplicated disease which makes up the vast majority of cases, and while it is a self-limiting condition with a good prognosis, it is associated with significant healthcare costs, use of broad-spectrum antibiotics and hospital admissions.

A more conservative approach to uncomplicated acute diverticulitis management has been supported by a number of studies which have investigated the safety and utility of outpatient management of uncomplicated cases (20, 110, 111, 133, 144, 145, 221, 222) and questioned the need for intravenous (103) or indeed any (23, 101, 145, 214) antibiotics in this group of patients. In parallel with these changing paradigms, there have been efforts to further classify acute diverticulitis into different categories (15, 20) in order to identify the patients for whom conservative management is most appropriate. Accurate early assessment of the severity of the acute diverticulitis will enable clinicians to have greater certainty when advising patients about their expected disease course, reduce the number of unnecessary hospital admissions and interventions, and allow for more appropriate distribution of health resources.

7.2. Study Objectives

The purpose of this retrospective study was to identify factors associated with CT-proven uncomplicated acute diverticulitis in order to differentiate patients who can be managed safely in a conservative manner from those who are likely to have a more severe clinical course.

7.3. Study Methods

7.3.1 **Ethics Approval**

Ethics approval for this study was obtained from the University of Auckland Human Participants Ethics Committee (#011311 and #9613), Auckland District Health Board and Counties Manukau District Health Board prior to data extraction and analysis.

7.3.2 **Study Population**

The study population was made up of adults over the age of eighteen, who presented to Auckland City and Middlemore Hospital with symptoms and radiological or intra-operative evidence of uncomplicated acute diverticulitis and were admitted under General Surgery. Management of the patients at both sites was guided by the admitting surgical teams, without a formal protocol.

1. Inclusion Criteria

Uncomplicated acute diverticulitis was defined as CT-proven diverticulitis which met the criteria for Hinchey 1a disease, as described by the Modified Hinchey Classification (Table 7-1) (12). The Modified Hinchey Classification was chosen as it is the most commonly used scale at the two study sites (see Chapter 3) and in practice guidelines for acute diverticulitis (21, 108). Hinchey 1a disease correlates with radiological findings of colonic wall thickening with pericolic soft tissue changes on CT scan (217).

Classification	**Definition**
0	Mild clinical diverticulitis (not confirmed by imaging or intraoperative findings)
Ia	Confined pericolic inflammation or phlegmon
Ib	Pericolic or mesocolic abscess
II	Pelvic, distant intra-abdominal, or retro-peritoneal abscess
III	Purulent peritonitis
IV	Faecal peritonitis

Table 7-1 Modified Hinchey Classification (12)

2. Exclusion Criteria

Exclusion criteria were evidence of complicated acute diverticulitis or diagnoses other than left colonic acute diverticulitis on CT scan or based on intra-operative findings, and those who did not have imaging, operative or histological findings that confirmed a diagnosis of uncomplicated acute diverticulitis. Patients not admitted under General Surgery were also excluded as they make up a small minority of patients and diagnosis and management may have been delayed due to atypical presentations.

7.3.3 **Data Collection**

As all cases of acute diverticulitis requiring hospital-level care are managed at public hospitals in New Zealand, our data can be seen as representative of all such cases of acute diverticulitis occurring in the Auckland City and Middlemore Hospital catchment areas during the study period. Cases were identified using discharge diagnosis (International Statistical Classification of Diseases and Related Health Problems code K57 for diverticular disease) for the period January 2012 to June 2013 inclusive. Of these cases, codes pertaining to diverticular disease outside of the sigmoid colon, diverticular bleeds, elective hospital admissions and those indicating diverticulosis only were excluded to leave only those cases pertaining to sigmoid and descending colon acute diverticulitis. Once cases were identified, each patient's National Health Index (NHI) number was used to access their electronic records for information pertaining to the relevant hospital admission. Data were then de-identified prior to data analyses and entered into a password protected electronic database.

1. Patient Characteristics

Demographic data were collected. Individual patient factors that were recorded were comorbidities and the use of the following medications: steroids, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, biologics and chemotherapeutic agents. Regular (>4 days of use in the last week) steroid or (within the six months prior to presentation) immunomodulator/biologic use was combined into one parameter indicated pharmacological immunocompromise for data analysis.

2. Disease Characteristics

Presenting symptom(s), duration of illness, vital signs and initial blood test results were also collected. Initial vital sign recordings (temperature, heart rate, respiratory rate and blood

pressure) and laboratory results were used to determine whether patients met the criteria for systemic inflammatory response syndrome (SIRS) at the time of presentation. The criteria for SIRS used in this study were met if patients had two or more of the following: temperature <36 or >38 C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, $PaCO^2$ >32 mmHg, white cell count <4 or >12 x 10^9/L or >10% bands (immature neutrophils) (109). Patient-reported pain score on admission was also collected; this number was recorded by the Emergency Department nursing staff on admission. Patients were asked to report their pain level out of ten, with ten being the worst pain they have ever experienced and zero being no pain.

3. Inpatient Care

Management of the patients at both sites was guided by the admitting surgical teams, without a formal protocol. All patients included in the study received antibiotics; however, we recorded whether patients were prescribed antibiotics by the admitting clinician, based on a clinical diagnosis or later following CT scan, thus describing local practice at the time of the study. At the time of the study, neither site had a policy of selective antibiotic treatment or hospital-led outpatient management for uncomplicated acute diverticulitis.

4. Endpoints

The following endpoints were considered to identify patients with a more severe clinical course:

1. Need for intervention (an acute or semi-acute operation during hospital admission or percutaneous drainage).

2. Prolonged hospital stay due to acute diverticulitis only (admission greater than 7 days).

3. Readmission to hospital within 30 days.

Univariate and multivariate regression were performed for these endpoints individually and as a combined endpoint (severe clinical course) for patients who had one or more of these outcomes.

7.3.4 **Statistical Analysis**

Statistical analysis was performed using SPSS for Windows (version 19; SPSS, Chicago,

Illinois, USA). Descriptive statistics and figures were used to summarise the data. Univariate analysis was carried out using the χ^2 test for categorical data, one-way analysis of variance (ANOVA) was used for parametric continuous data, and the Mann–Whitney U test and Kruskal–Wallis test were used for nonparametric data.

Multivariate regression analysis using a logistic regression model was also carried out incorporating all factors which had a p value ≤0.1 to examine the impact of multiple factors on the likelihood of the three endpoints—need for procedural intervention, prolonged hospital stay and 30-day readmission. Closely related parameters were input into separate regression models to avoid erroneous correction for each other. This method was also used to identify factors associated with a severe clinical course. Results were considered significant if p value was <0.05. Parametricity was determined using the Shapiro–Wilk test, with normally distributed data being expressed as mean ± standard deviation (SD) and nonparametric data as median ± interquartile range (IQR).

7.4. Results

7.4.1 **Data retrieval**

After applying the exclusion criteria to the 676 admissions identified through clinical coding, there were 376 confirmed admissions for acute diverticulitis over the 18-month study period. Data for patients from Auckland City Hospital were retrieved through the electronic information system portal (Concerto) and the electronically-linked '3M Viewer' which contained scanned picture files of all hand-written clinical notes which are generated during a patient's hospital admission. Data for patients for Middlemore Hospital were retrieved through Concerto and directly extracting data from paper clinical notes which were requested through the Clinical Records Department.

7.4.2 **Incidence of Uncomplicated Acute Diverticulitis**

Of 376 confirmed cases of acute diverticulitis, there were 315 cases of uncomplicated acute diverticulitis. There was no gender bias evident in this study population, and 190 admissions (59.6%) were for patients under the age of 60. The median age for all admissions was 56 (46–66) years. The median age was 52 (43–61) years for men and 62 (52–69) years for women, and the difference between these was statistically significant ($p = 0.01$). Additional demographic data are outlined in Table 7-2.

	Total (n=314**)**	**Men** (n=155**)**	**Women** (n=159**)**
Median age (IQR)	56 (46-66)	52 (42-60)	62 (52-69)
Age group			
18-44 years (%)	68 (21.9)	49 (31.6)	19 (11.9)
45-59 years (%)	120 (38.1)	66 (42.6)	54 (34.0)
60-74 years (%)	95 (30.2)	32 (20.6)	63 (39.6)
≥75 years (%)	31 (9.8)	8 (5.2)	23 (14.5)
First episode of AD (%)	208 (66.5)	111 (71.6)	96 (61.1)
Charlson score ≥3 (%)	97 (30.9)	32 (20.6)	65 (41.1)
Current NSAID use † (%)	22 (7.0)	11 (7.1)	11 (6.9)
Steroid† or immunomodulator/biologic use (%)	9 (2.9)	2 (1.3)	7 (4.4)

Table 7-2 Demographic data.

†> 4 days in past week, IQR = interquartile range, SD = standard deviation, AD = acute diverticulitis, NSAID = non-steroidal anti-inflammatory drug

7.4.3 **Clinical Data**

Not all patients exhibited signs of systemic illness at the time of their presentation, and temperature >38 or <36 C was present in 74 patients (24.9%), heart rate >90 beats per minute in 84 (26.5%) and respiratory rate >20 breaths per minute in 19 (6.2%) patients. The SIRS criteria were met by 74 patients (24.9%). The severity of acute diverticulitis was assessed objectively at the time of CT using the Modified Hinchey Classification (Table 7-1).

7.4.4 **Clinical Management Data**

The median time taken from presentation to CT scan was 16 hours (8–23) from time of admission. All but one patient underwent a CT scan (0.3%). This patient was diagnosed with uncomplicated acute diverticulitis intra-operatively during a laparoscopic appendicectomy

based on a clinical diagnosis of appendicitis and was excluded from our analysis. Most patients received bowel rest and intravenous fluids (84.9% and 85.8%), and 67% were started on intravenous antibiotics by the first surgical doctor to assess them.

Of the patients who had a CT showing uncomplicated acute diverticulitis, 3.8% required some form of procedural management during their admission [surgery—8 patients (2.5%) or percutaneous drainage—3 patients (0.9%)]. Patients who required surgery for severe symptoms (pain and SIRS) or failure to improve with conservative management underwent either a Hartmann's procedure or an anterior resection (6 Hartmann's procedures and one high anterior resection). Inpatient colonoscopy was performed in 5.3% of patients, and 25.2% were referred for outpatient colonoscopy. However, only 20 patients (6.7%) went on to undergo an outpatient colonoscopy.

7.4.5 **Outcome Data**

There were no in-hospital deaths. Five patients left the Auckland region and were lost to follow-up. Further statistical analysis was not performed for mortality data due to the low event rate. Median length of hospital stay was 3.0 days (2.11–4.09). There were 22 patients (6.9%) who required more than one week's hospital admission and 31 patients (9.8%) required readmission within 30 days of discharge. A total of 49 individual patients met one or more of the criteria for inclusion in the combined endpoint for severe clinical course—the factors associated with this endpoint on univariate analysis are outlined in Table 7-3.

During the 12 months following the index admission, none of the patients underwent operations for diverticular disease. There were two deaths (0.6%); however, these were not related to diverticular disease. There was no difference in prolonged hospital stay, need for intervention or the combined endpoint between patients who had intravenous antibiotics started by the admitting clinician and those who did not.

	Severe clinical course (49)	Expected Clinical course (265)	All (314)	p-value
Patient demographics				
Age (years) (IQR)	56 (42-65)	56 (47-66)	56 (46-66)	0.5
18-44	14 (28.6)	54 (20.4)	68 (31.7)	0.14
45-59	16 (32.7)	104 (39.2)	120 (38.2)	0.24
60-74	13 (26.5)	82 (30.9)	95 (30.2)	0.33
≥75	6 (12.2)	25 (9.4)	31 (9.9)	0.35
Gender				
Female	27 (55.1)	132 (49.8)	159 (50.6)	0.3
Ethnicity				
European	35 (71.4)	204 (77.0)	239 (76.1)	0.37
Māori	7 (14.3)	17 (6.5)	24 (7.7)	0.06
Pacific	3 (6.1)	31 (11.8)	34 (10.9)	0.18
Indian	2 (4.1)	4 (1.5)	6 (1.9)	0.24
Other	2 (4.1)	9 (3.4)	11 (3.5)	0.54
Patient factors				
First episode	30 (62.5)	177 (67.0)	207 (66.3)	0.32
Smoking status				0.54
Current	10 (20.4)	44 (66.8)	54 (17.5)	
Ex-smoker	12 (24.5)	53 (20.0)	65 (21.1)	
Never	26 (53.1)	163 (61.5)	189 (61.4)	
Duration of symptoms (days)	2 (1-3)	2 (1-4)	2 (1-4)	0.3
Charlson score >3	15 (69.4)	82 (31.1)	97 (31.0)	0.55
Current steroid† or immunomodulatory/biologic use	4 (8.3)	5 (1.9)	9 (2.9)	0.03*
Current NSAID use†	6 (12.2)	16 (6.0)	22 (7.0)	0.11

Physical examination				
Temperature on admission (◦C)	36.9 (36.5-37.3)	36.6 (36.2-37.2)	36.7 (36.2-37.2)	0.05*
Heart rate on admission (beats per minute)	81 (70-96)	81 (73-91)	81 (72-92)	0.85
Respiratory rate on admission (breaths per minute)	18 (16-19)	17 (16-18)	18 (16-18)	0.055*
SIRS criteria met	15 (31.3)	63 (24.2)	78 (25.0)	0.2
SIRS criteria met for temperature	13 (26.5)	65 (24.7)	78 (25.0)	0.46
SIRS criteria met for heart rate	15 (30.6)	66 (25.0)	81 (25.9)	0.26
SIRS criteria met for respiratory rate	3 (6.3)	15 (5.9)	18 (5.9)	0.57
Patient reported pain score (0-10)				
Pain score ≥2	38 (88.4)	172 (77.1)	210 (78.9)	0.07*
Pain score ≥4	33 (76.7)	136 (61.0)	169 (63.5)	0.03*
Pain score ≥6	21 (48.8)	68 (30.5)	89 (33.5)	0.02*
Pain score ≥8	9 (20.9)	11 (4.9)	20 (7.5)	0.01*
Presence of peritonism	13 (27.7)	72 (28.0)	85 (28.0)	0.56
Admission blood tests				
White cell count (x 10^9/L)	12 (10-14)	12 (9-14)	12 (10-14)	NS
Neutrophil count (x 10^9/L)	8.6 (7.6-11.6)	8.3 (6.0-10.4)	8.36 (6.2-10.6)	NS
SIRS criteria met for white cell count	23 (46.9)	109 (41.1)	132 (45.4)	0.27
C-reactive protein				
CRP ≥100	11 (17.0)	64 (26.2)	75 (23.8)	0.12
CRP ≥200	5 (10.6)	10 (4.1)	15 (5.2)	0.08*

Serum sodium (mmol/L)	138 (136-139)	138 (137-140)	138 (136-140)	NS
Hyponatraemia (<135mmol/L)	3 (6.1)	23 (8.9)	26 (8.5)	0.38

Table 7-3 Results of univariate analysis.

All continuous variables are non-parametric and expressed as median±IQR and all discrete variables are expressed as count (percentage). * p-value <0.1, †> 4 days in past week. IQR = interquartile range, NSAID = non-steroidal anti-inflammatory drug, CT = computed tomography, CRP = C-reactive protein, ICU = intensive care unit

7.4.6 **Multivariate Analysis**

Multivariate regression analyses identified the following independent predictors for a more severe clinical course. Meeting SIRS criteria was identified as an independently associated risk factor [OR 4.6 (1.3–17.0)] for requiring an operation or percutaneous drainage. Factors associated with readmission within 30 days were pain score ≥8 [OR 6.1 CI (2.0–18.7)] and first episode of acute diverticulitis [OR 2.5 CI (1.1–6.8)]. Admission >7 days was also associated with a pain score ≥8 out of 10 [OR 5.7 CI (1.4–23.8)]. Regular steroid or immunomodulator/biologic use [OR 4.3 (1.1–2.3)], higher temperature [OR 1.5 (1.0–2.3)], CRP C200 mg/L (OR 4.1 (1.2–14.1) and pain score ≥8 out of 10 [OR 5.9 (2.1–16.6)] were associated with a higher risk of a severe clinical course (Table 7-4). Further statistical models were not constructed as confidence intervals were wide.

	OR	**95%CI**	**p-value**
Pain score ≥8	5.9	2.1-16.6	0.0
Temperature on admission (per ◦C)	1.51	1.0-2.3	0.04
Steroid or immunomodulatory/biologic use	4.3	1.1-17.7	0.04
CRP ≥200	4.1	1.2-14.1	0.03

Table 7-4 Results of multinomial logistic regression.

7.5. Discussion

This study has identified first episode of acute diverticulitis, SIRS criteria and its components, regular steroid/immunomodulatory/biologic use and high patient-reported pain score as factors that can be used to predict patients with uncomplicated acute diverticulitis who are likely to have a more severe clinical course, as defined by the need for procedural intervention, prolonged hospital stay or readmission, individually and as a combined endpoint. The present study differs from existing studies in that we identified several clinical parameters that were significantly associated with severe clinical course in patients with CT-proven uncomplicated acute diverticulitis. This is the first time that risk prediction has been examined within a group of patients with uncomplicated acute diverticulitis, rather than as a means of differentiating uncomplicated acute diverticulitis from complicated disease.

Research to date has focused on identifying factors associated with poor outcomes amongst patients with more severe forms of acute diverticulitis, rather than defining the patients who can be safely treated conservatively from a population with mild acute diverticulitis. First episode of acute diverticulitis, having ≥1 comorbidity, or CRP >200 mg/L are factors which have been found to be associated with the likelihood of having a perforation (91, 223). Renal dysfunction, hypoalbuminaemia, the presence of comorbidities and older age have been identified as risk factors for post-operative mortality or major morbidity in patients with acute diverticulitis (224, 225). One retrospective study of 639 patients with first episode acute diverticulitis found that most patients required minimal hospitalisation and that intra-abdominal free air or fluid was associated with a more severe clinical course (133). In this instance, female gender and comorbidity (Charlson score >2) were found to be significantly associated with treatment failure. Another retrospective study of 42 patients found that patients with ‘mild’ acute diverticulitis on a CT scan performed within 24 hours of admission could safely be discharged for outpatient management (17).

A risk prediction score which incorporates these easily accessible variables could be a useful and simple tool for assisting in the objective assessment of whether a patient would be a candidate for conservative management, which includes outpatient treatment and selective antibiotic prescribing. It also strengthens the case for a protocol specific to the management of uncomplicated acute diverticulitis, which utilises early CT scan to confirm the diagnosis of uncomplicated disease, selective use of antibiotics and places a greater emphasis on outpatient management.

CT scan is the tool which is most commonly used to diagnose and stage acute diverticulitis in New Zealand (150), and the most widely used to trials investigating the safety of conservative management approaches in uncomplicated acute diverticulitis (17, 23, 101, 110, 111, 144, 145, 221). One retrospective study examining the impact of an acute diverticulitis protocol which included a recommendation that all patients with clinically suspected acute diverticulitis receive a CT scan in the Emergency Department found that implementation of the protocol significantly reduced the number of hospital admissions and total duration of hospital admission when compared to the initial practice of admitting these patients to the surgical ward for intravenous antibiotics while awaiting CT scan (112). Importantly the study found that this reduction in hospital admission was not associated with a corresponding increase in adverse events such as increased rates of readmission and that even accounting for the increase in demand for CT scans, overall healthcare expenditure decreased (112). The median time taken for a CT scan in our cohort was sixteen hours, which represents a significant delay for patients who do not need to be hospitalised.

The practice of routine antibiotic therapy in the treatment of uncomplicated acute diverticulitis has been brought into question by a number of recent studies that have indicated that antibiotics do not improve outcomes (23, 24, 101, 145). Although this is by no means universally accepted, there is an increasing shift towards selective use of antibiotics rather than treating every patient with acute diverticulitis with intravenous antibiotics on admission to hospital. Indeed, the lack of standardised criteria for selecting such patients may be an important factor restricting the application of this management option. At the two centres included in this study, there was no protocol for antibiotic use in uncomplicated acute diverticulitis and only 67% of patients were started on intravenous antibiotics by the admitting clinician prior to CT scan. There was no difference in disease severity between the two groups and the group who were prescribed antibiotics early did not have better outcomes.

In the two published randomised control trials investigating the safety of omitting antibiotics in uncomplicated diverticulitis, the exclusion criteria included: evidence of complicated acute diverticulitis or another diagnosis, immunosuppression, high fever, sepsis or peritonitis, and excessive comorbidities (23, 101). Although there are many commonalities between these criteria and the variables that we have identified, there is scope to improve the predictive capacity of these criteria in order to develop a tool which can be used in clinical practice as well as in research contexts.

Determining whether a patient with uncomplicated acute diverticulitis is a candidate for outpatient management is another significant clinical decision, and one which is endorsed by most published treatment guidelines for acute diverticulitis (21, 108). The evidence supporting this approach includes one randomised control trial (144), multiple prospective studies (221), and one prospective trial in which patients were managed as outpatients and without antibiotics (145). These studies indicate that treatment failure rates with outpatient treatment were comparable to inpatient treatment, and also resulted in lower healthcare expenditure (221). Exclusion criteria applied by these studies are similar to those described in the antibiotic trials but also include failure to improve following the first dose of antibiotics and/or analgesia, dehydration requiring intravenous fluids and patients who could not be safely managed at home (144, 145). This broader selection of exclusion criteria indicates that a suitable risk prediction tool must also consider factors which are not directly related to acute diverticulitis in isolation but must also consider the patient's social context. Although the impact of socioeconomic position and other social factors on patient experiences of acute diverticulitis and diverticular disease have not been a research focus to date, these may become increasingly important as the trend of increasing outpatient and self-management continues.

Improving our ability to predict those patients whose uncomplicated acute diverticulitis will follow a more severe course at an early stage of the hospital admission would enable clinicians to offer patients more targeted advice and counselling regarding a patient's expected outcome, and to reduce overtreatment by application of evidence-based management specific to the patient's expected clinical course. Ultimately, a streamlined management pathway could be designed for low-risk patients with modifications such as prioritised imaging to rule out complicated disease (to allow for earlier discharge), a modified or delayed antibiotic regimen, and outpatient-based management. Increasing the number of patients safely managed in the community could also be an important cost-saving measure, as described in the DIVER trial (144).

7.6. Limitations

This study is limited by its retrospective design. The quality of the data is dependent on appropriate documentation by a large number of medical and nursing staff, and missing data are a minor but persistent confounding factor. We have included only patients with CT-proven acute diverticulitis, which means that cases that were diagnosed clinically may have been missed. As all patients included in the study had proven acute diverticulitis, however, the diagnostic uncertainty that surrounds some retrospective studies of acute diverticulitis was avoided. Furthermore, patients who are deemed not to require imaging are presumed not to be unwell enough to warrant hospital admission and intensive management. This study is not representative of the majority of cases of uncomplicated acute diverticulitis which are managed outside the hospital in an outpatient setting and hospital-led outpatient management of uncomplicated acute diverticulitis is not routine practice at the two included sites. The relatively small dataset and the low event rate for patients with uncomplicated acute diverticulitis resulted in statistically significant odds ratios with wide confidence intervals. We also found a number of clinical and laboratory parameters that were significant on univariate analysis that may, in fact, be significantly associated with disease severity on multivariate analysis of a larger dataset. A larger-scale and prospective dataset is required and will allow for the construction of a risk prediction model with clinical application. In addition, the risk factors identified will need confirmation in other populations of acute diverticulitis patients to assess suitability for wider application.

7.7. Conclusion

By using the criteria identified (SIRS, regular steroid/ immunomodulator use, pain score ≥8, first episode) as a starting point, it may become possible to objectively identify the patients with uncomplicated acute diverticulitis for whom conservative management approaches such as foregoing antibiotics or opting for outpatient management would be appropriate. When implemented in conjunction with an evidence-based protocol for outpatient management of acute diverticulitis, this stratified approach should lead to a more efficient use of health resource, reduce unnecessary hospitalisation, and improve patient satisfaction and quality of life for those with acute diverticulitis.

Having attempted to characterise the patient group which can be treated with a more conservative approach, the next chapter describes a clinical trial which aimed to investigate that efficacy of foregoing antibiotics in the management of such patients.

Chapter 8. Double-Blinded Randomised Controlled Trial – Antibiotics in Uncomplicated Acute Diverticulitis

8.1. Background

Acute diverticulitis is one of the most common indications for hospital admission under General Surgery and admissions for acute diverticulitis are rising both internationally (111, 132, 213) and within New Zealand (150). Antibiotics have historically been a cornerstone in the management of both uncomplicated and complicated acute diverticulitis (226), however, as described in Chapter 1 and demonstrated by the lack of clinician consensus observed in Chapter 5, this appears to be changing in the case of uncomplicated disease.

As discussed in previous chapters, the management of uncomplicated acute diverticulitis has evolved significantly over the last decade, with increasing support for outpatient management (110, 133) and judicious use of antibiotics, (23, 101, 103, 145, 214). The need for routine antibiotic use in antibiotics has been challenged by two randomised controlled trials of antibiotics versus no antibiotics in uncomplicated acute diverticulitis. These demonstrated the non-inferiority of observation without antibiotics but these trials were not placebo-controlled (23, 101).

The findings of these trials, along with a growing awareness about the issue of antimicrobial resistance and the potential adverse events associated with antibiotic use, are all drivers for more selective use of antibiotics in the management of uncomplicated acute diverticulitis. Studies of risk prediction within this patient group, as attempted in Chapter 7, are also vital for ensuring that this change to practice occurs in a safe manner. Strengthening the evidence base for a more conservative approach to uncomplicated acute diverticulitis is key to ensuring that clinical equipoise is fulfilled when implementing changes to patient management.

8.2. Study Objectives

The STAND study (Selective Treatment with Antibiotics for Non-complicated Diverticulitis) was an international (New Zealand and Australia), multi-centre (four sites), placebo-controlled double-blinded randomised trial, which aimed to compare standard antibiotic therapy to placebo in the treatment of computed tomography scan (CT)-proven Hinchey 1a uncomplicated acute diverticulitis. The primary outcome for this study was the length of hospital admission in hours, from registration in the emergency department to discharge into the community.

8.3. Study Methods

8.3.1 **Ethics Approval**

Ethics approval was obtained from the Ministry of Health National Ethics Committee (15/NTA/65) before trial commencement. Site-specific ethics approval was also obtained as follows: Auckland District Health Board's (Auckland City Hospital) Research Review Committee (A+5600), Waitemata District Health Board Management Approval of Research (North Shore Hospital), Counties Manukau Health Research Office (Middlemore Hospital) and Westmead Hospital (HREC/16/WMEAD/186, SSA Ref: SSA/16/WMEAD/379). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) on 18/03/2015, trial identifier: ACTRN: 12615000249550.

8.3.2 **Study Population**

Participants were recruited from three New Zealand hospitals; Auckland City (December 2015 – March 2019), Middlemore (July 2016 – July 2017) and North Shore (April 2016 – May 2019) and one Australian hospital; Westmead (June 2018 – May 2019). All adult patients (≥18 years) who presented acutely to the on call General Surgical service with clinically suspected acute diverticulitis were screened for eligibility during the recruitment period at each site. Admission under the General surgical service is the typical patient pathway for acute diverticulitis in both New Zealand and Australia.

1. Inclusion Criteria

Confirmation of uncomplicated acute diverticulitis was defined as CT-proven acute diverticulitis which met the criteria for Hinchey 1a disease, as described by the Modified Hinchey Classification, namely acute diverticulitis of the descending/sigmoid colon with no evidence of perforation, abscess or peritonitis (12). The Modified Hinchey Classification was chosen as it is the most commonly used scale at the study sites, as identified in the survey described in Chapter 3.

Assessment of CT scan was performed by a radiology registrar or consultant as per usual hospital practice. If CT results changed from uncomplicated to complicated disease following randomisation patients were removed from the study and received standard care which included antibiotics at the clinical team’s discretion.

As the primary outcome was time-dependent, potential participants were excluded if study medication could not be administered within 24 hours of hospital admission.

2. Exclusion Criteria

Potential participants were excluded if they met any of the following exclusion criteria:

- met ≥2 criteria for Systemic Inflammatory Response Syndrome (SIRS) (227) upon presentation to hospital (temperature <36° or >38° Celsius, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO3 <32mmHg, white cell count <4 or >12 x 10 9/L)
- not fluent in English
- were unable to give consent or answer symptom-related questions due to cognitive impairment
- had previous drug reactions to the antibiotics used in the study
- had a lactose allergy (the placebo contained lactose)
- used steroids for greater than five days prior to presentation
- had been administered regular immunomodulators or biologics within the six months prior to presentation
- used regular non-steroidal anti-inflammatory drugs for greater than a week prior to presentation
- had been administered >1 dose of intravenous or >2 doses of oral antibiotics during this illness but prior to enrolment in the study
- were pregnant
- had an American Society of Anesthesiologists physical status classification (ASA) ≥4
- had CT evidence of complicated acute diverticulitis

8.3.3 **Trial Site Preparation**

The trial was pragmatically designed, in consultation with General Surgeons, Radiologists, Emergency Medicine and Infectious Diseases Physicians.

1. Antibiotic Regimen

The antibiotic regimen used in the trial was chosen in consultation with General Surgical and Infectious Diseases Medicine specialists at one of the study sites (Auckland City Hospital). The chosen treatment closely resembled the regimen that was already in use at all four study

sites and was appropriate as the initial treatment of both complicated and uncomplicated acute diverticulitis. The antibiotic regimen featured in the trial was:

- Upto 48 hours of 400mg of oral metronidazole three times a day and 750mg of intravenous cefuroxime every eight hours.
- Followed by five days of 625mg of oral Augmentin (amoxicillin/clavulanic acid), three times a day.

2. Timing of CT-scan

We aimed to have patients enrolled in the study and receiving their first dose of study medication within 24 hours of admission. Retrospective data from two of the study sites (Auckland City Hospital and Middlemore Hospital) showed that patients with uncomplicated AD have a CT scan at a mean time of 16.7 (SD 15.5) hours following admission (Chapter 7), leaving approximately 7 hours for recruitment and administering the first dose of study medication.

Study investigators consulted with the Radiology Departments at each study site in order to assess the feasibility of potential participants receiving a diagnostic CT-scan within 24 hours of their admission to hospital. It was determined that this would be possible for the majority of participants. Those who were excluded due to not receiving their CT-scan within 24 hours were recorded as missed potential participants.

3. Emergency Department Management

The Emergency Department was the entry point into hospital for a significant proportion of patients who are admitted with acute diverticulitis and in some cases, is where antibiotic treatment is commenced. In order to reduce the number of potentially eligible study participants receiving antibiotics in the Emergency Department, a study investigator met with Emergency Department medical and nursing staff prior to study commencement at each study site. This meeting was used to introduce the study to the staff and ensure that risk to potential participants was minimised through a clear understanding of the study's inclusion and exclusion criteria. In addition, information about the study was displayed in clinical areas in the Emergency Departments at each study site (Figure 8-1).

Figure 8-1 Poster for the STAND study used at Auckland City Hospital

4. Surgical Management

The study protocol was developed in collaboration with a senior member of the Acute Surgical Unit at Auckland City hospital (Li Hsee). The details of the study were presented to each

General Surgical Department prior to commencing recruitment at each study site, and further teaching sessions were undertaken following the changeover of junior staff. Blinded interim study results including adverse events were also presented to the surgical teams during the study period.

8.3.4 **Recruitment and Consent**

Patients were given verbal information about the trial when a diagnosis of uncomplicated acute diverticulitis was clinically suspected. Following CT confirmation of Hinchey 1a acute diverticulitis (12) of the descending/sigmoid colon, patients were given written and verbal information about the trial from the local study investigator, and written informed consent was obtained (Appendix E).

Upon radiological confirmation of a diagnosis of uncomplicated acute diverticulitis, a brief review of the patient's notes was undertaken to ensure that the patient was eligible based on the inclusion and exclusion criteria. Potential study participants were be approached in person by the study investigator (Rebekah Jaung for Auckland City Hospital, Bruce Su'a for Middlemore Hospital, Sherry Nisbet for North Shore Hospital, and Martijn Pieter Gosselink/Angelina Di Re for Westmead Hospital) and if convenient, a brief summary of the intended research was given. If the patient was open to taking part in the study, a more detailed overview was given.

If eligible for enrolment, patients were given detailed information regarding the study. All questions were answered, and patients were encouraged to contact investigators at a later time if they had any further questions or concerns. Potential participants were also given written information about the study. This included information specifically on the risks, benefits and actual process of administering the study medication and undergoing study assessments. Potential participants were also given the time and opportunity to discuss their participation in the study with family and whānau.

As it was not possible to contact potential participants in advance, due to the acute nature of the condition, particular care was be taken to ensure that patients are able to understand the benefits and risks of participating in the study and were be able to contact the site-specific and overall study investigators with further questions at any time.

8.3.5 **Study Procedure**

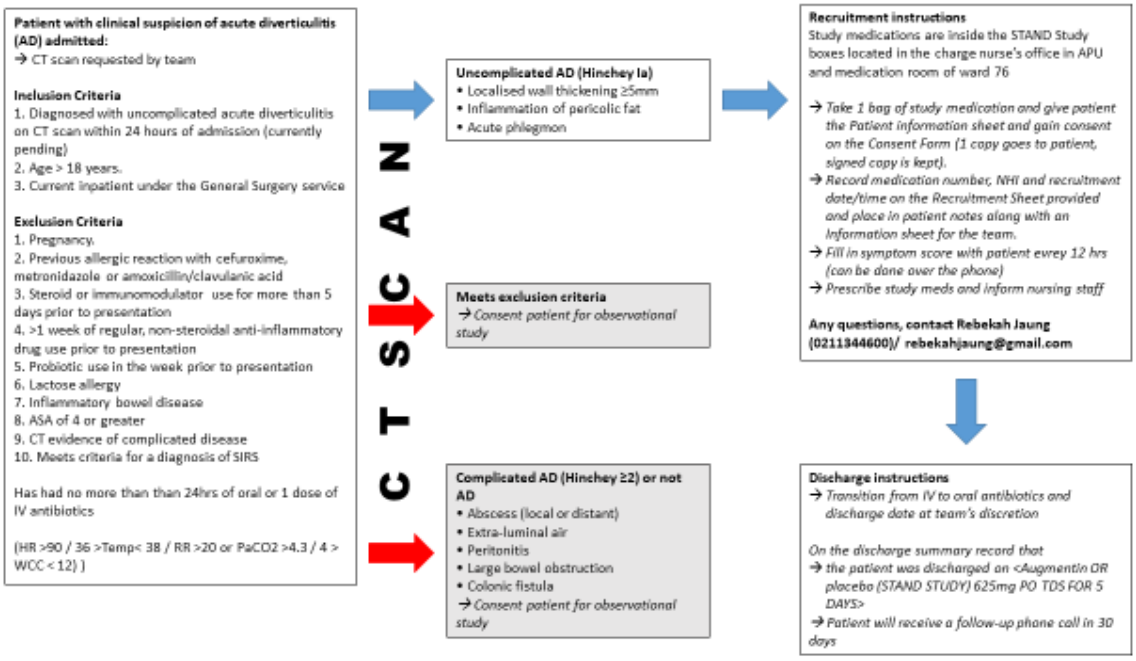


Figure 8-2 Study process overview for Auckland City Hospital. AD = acute diverticulitis, CT = computed tomography, ASA = American Society of Anesthesiologists physical status classification system, SIRS = systemic inflammatory response syndrome, IV = intravenous, HR = heart rate, Temp = temperature, RR = respiratory rate, $PaCO_2$ = partial pressure of carbon dioxide, WCC = white cell count, APU = admission and planning unit, STAND = Selective Treatment with Antibiotics for Non-complicated Diverticulitis

Figure 8-2 is a diagrammatic overview of the study process at one of the study sites (Auckland City Hospital). Different versions of this image were used at teaching sessions for the surgical team at each of the study sites. A form detailing the process was also inserted into the clinical notes of study participants (Figure 8.3).

Please place inside patient's notes. Patient Label

The STAND study
-Selective Treatment with Antibiotics in Non-complicated Diverticulitis

- Hypothesis: antibiotics are not mandatory in patients with UAD
- Primary objective: To determine whether antibiotic administration results in a difference in length of hospital stay when compared to a placebo through a double-blinded randomised control trial.

Recruitment information sheet

1. When admitting a patient who may have diverticulitis, screen the patient using the STAND Study Recruitment Sheet (available in the charge nurse's office in APU and medication room of ward 76 inside the STAND Study medication boxes. This sheet goes inside the patient's notes.
2. Consent/recruitment
    a. If the patient meets inclusion criteria, give them a Patient Information Sheet and gain written consent on the Consent Form if the patient is happy to proceed. Withhold antibiotics until after CT scan UNLESS the patient develops SIRS.
    b. If the patient likely has COMPLICATED acute diverticulitis, treat as usual but pass on their details to Rebekah Jaung **(021 134 4600 or rebekahjaung@gmail.com).**
3. Request CT scan and await results. Complete the Recruitment Sheet according to CT scan results.
4. If the CT confirms COMPLICATED acute diverticulitis or an alternative diagnosis, please pass these details onto Rebekah Jaung by text or email
5. If CT confirms UNCOMPLICATED acute diverticulitis, gain consent if not already gained and start study medications. These are located in boxes of four packs in the medication rooms of the above wards.
    a. Place patient labels onto the allocated bag and the individual medication containers. This pack must travel with the patient if they are moved from ED to the wards and the Augmentin will be the oral medication that they are discharged on.
    b. Record medication number, NHI and recruitment date/time on the recruitment sheet.
    c. Prescribe as follows:
    -Cefuroxime OR placebo (STAND STUDY) 750mg IV Q6H FOR 48 HRS or until stopped by team
    -Metronidazole OR placebo (STAND STUDY) 400mg PO TDS FOR 48 HRS or until stopped by team

    When above is completed/stopped:
    -Augmentin OR placebo (STAND STUDY) 625mg PO TDS FOR 5 DAYS
6. Criteria for withdrawal from the study are as follows:
    a. An increase in severity of symptoms or signs after 24 hours of study medication.
    b. No improvement in symptoms after 48 hours of study medication.
    c. Development of SIRS at any point during inclusion in the study.

Please contact Rebekah Jaung on 0211344600 or rebekahjaung@gmail.com if you have questions or concerns.

ADHB Research Review Committee **A+6807** / Ethics Reference Number: **15/NTA/65**

Figure 8-3 STAND Study Recruitment Information Sheet for Auckland City Hospital.

UAD = uncomplicated acute diverticulitis, CT = computed tomography

1. Management of Acute Diverticulitis

A standardised protocol for the management of uncomplicated acute diverticulitis with regards to analgesia, antiemetic therapy, dietary modification and discharge criteria was applied to all

study participants (Appendix F). At the time of study, only one study site (North Shore Hospital) had a formal protocol for the management of acute diverticulitis and the study protocol was informed by this document (Figure 8-4).

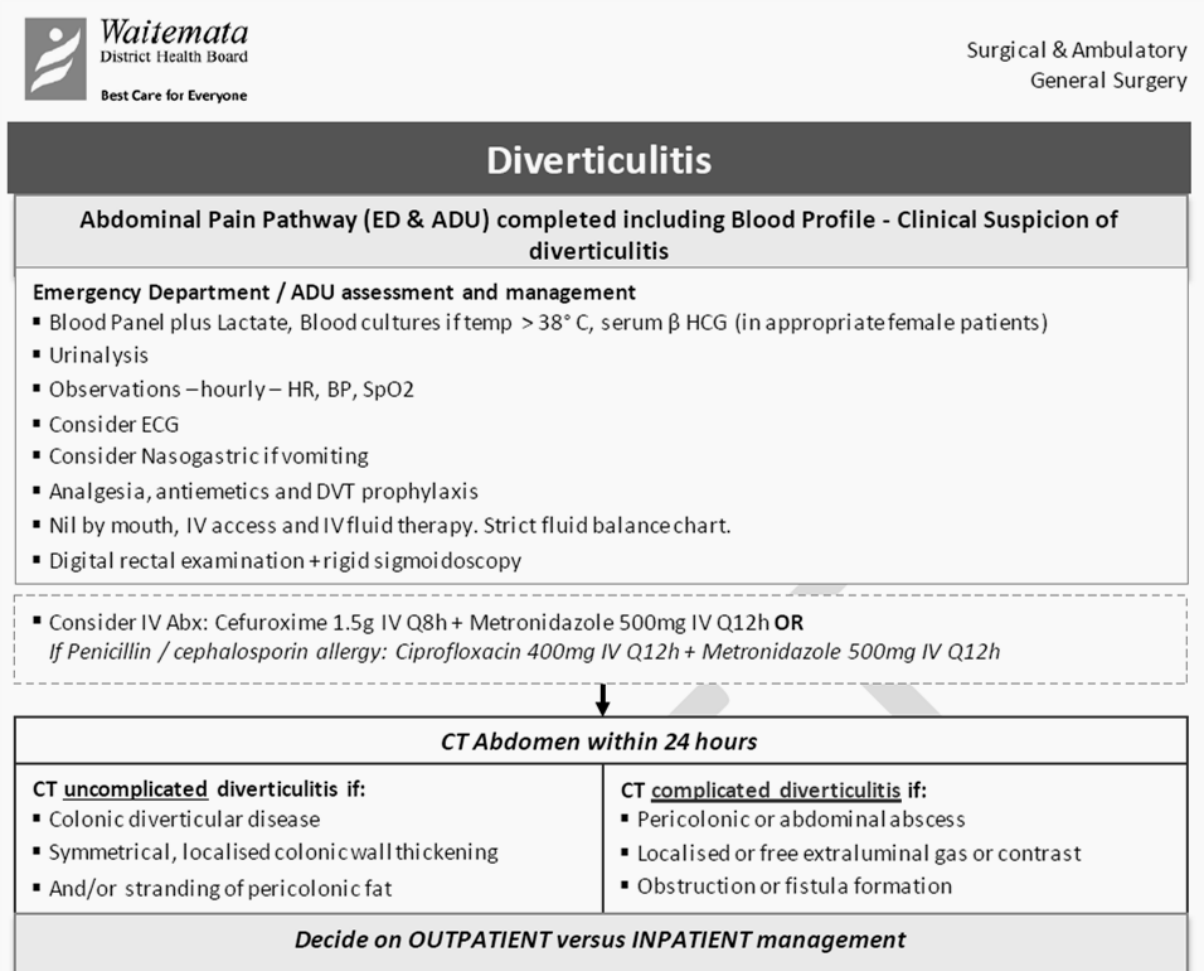


Figure 8-4 Abdominal Pain Pathway for Clinical Suspicion of Diverticulitis.

ED = Emergency Department, ADU = Assessment and Diagnostic Unit, β-HCG = beta- Human chorionic gonadotropin, HR = heart rate, BP = blood pressure, SpO_2 = peripheral capillary oxygen saturation, ECG = electrocardiogram, DVT = deep vein thrombosis, IV = intravenous, Abx = antibiotics, Q8h = every eight hours, Q12h = every twelve hours

2. Study Intervention

Figure 8-5 Study Medication Pack

Upon confirmation of eligibility and enrolment, the study medication regimen was administered within 24 hours of admission by a registered nurses not associated with the study.

Each study medication pack contained: the initial regimen (intravenous cefuroxime 750mg every 6 hours and oral metronidazole 400mg three times a day), and oral antibiotics (Augmentin (Amoxicillin/clavulanic acid) 625mg three times a day) – or placebo. Participants were prescribed the intravenous or oral regimen at the discretion of the surgical team, with a minimum treatment duration of 5 days of the oral regimen and a maximum treatment duration of 48 hours for the intravenous regimen and 5 days for the oral regimen (a total of 7 days of study medication). Participants requiring longer durations of treatment were regarded as having delayed recovery and started on conventional management which included antibiotics at the clinical team's discretion.

3. Patient Assessment

Study investigators met with participants every twelve hours for the first 48 hours and then daily until discharge. Assessments involved the completion of the Global Symptom Score (Table 8-1) – a pain and symptom questionnaire that had previously been developed for use in assessing symptoms of diverticular disease (71, 124), as well as recording of vital signs, laboratory test results and evidence of any adverse events or criteria for exiting the study.

	None	Close to none	Mild	Moderate	Moderately severe	Severe
Abdominal discomfort/pain						
Abdominal tenderness						
Nausea/vomiting						
Bloating						
Mucus in stool						
Constipation						
Diarrhoea						
Urgency when opening bowels						
Painful straining when opening bowels						
Fever						
Dysuria (pain on passing urine)						
Rectal bleeding						

Table 8-1 Global Symptom Score for Diverticular Disease

4. Deterioration and Treatment Failure

All patients who were enrolled in the trial had a CT-confirmed uncomplicated acute diverticulitis, which is the gold standard for imaging and staging AD (14). Patients with uncomplicated disease on CT have been shown to have very low rates of readmission and progression to requiring surgical intervention (17) at baseline, meaning that our study population is a low-risk population on which to trial this selective antibiotic use.

Retrospective data from cases of CT-proven uncomplicated acute diverticulitis from Auckland City and Middlemore Hospitals, two of the study sites, were used to identify variables which were associated with a poorer outcome, both in terms of longer hospital stay (a week or more) and the need for surgery or percutaneous drainage (Chapter 7). Factors associated with these outcomes were used to inform the exclusion criteria for the present study.

Deterioration during the study was defined as:

1. An increase in severity of symptoms or signs after 24 hours of study medication.
2. No improvement in symptoms after 48 hours of study medication.
3. Development of SIRS at any point during inclusion in the study.

These events were specified in the study documentation that was inserted into the participant's clinical notes (Figure 8-3) and were checked for during study assessments. If any of these outcomes occurred, participants were removed from the study and managed according to the clinical team's discretion.

5. Discharge from Hospital

Participants were discharged when they were afebrile on oral study medication, able to tolerate oral diet, able to manage pain exclusively with oral analgesia, able to mobilize safely and manage their activities of daily living. The final decision on whether participants were discharged was made by the clinical team who were blinded to allocation status. Participants were followed up with a telephone call 30 days after discharge to assess readmission, additional antibiotic prescriptions, ongoing symptoms, or adverse events. Readmission and the prescription of further courses of antibiotics were also assessed through the participants' electronic medical records.

8.3.6 **Sample Size**

An *a priori* power calculation was undertaken on the basis of previously published data on the incidence and duration of hospital admissions for uncomplicated acute diverticulitis (Chapter 7). There were 204 cases of uncomplicated acute diverticulitis during this time, with a mean length of stay of 88.9h (SD 70.6) per episode. Using these data, a power calculation was performed to determine the number of participants required to assess non-inferiority of the

intervention. The distribution of these data were symmetric under a logarithmic (base 10) transformation (SD 0.3).

A change in length of stay of 24 hours was deemed to be clinically significant for both participants and for hospital services. Assuming a non-inferiority margin of 24 hours, using an independent-samples t-test on log-transformed length of stay data and common SD of 0.245 it was determined that 89 participants would be required in each arm to achieve 80% power and one-sided alpha-error of 0.025.

8.3.7 **Randomisation**

Screened patients who consented to enrolment in the study were randomised following CT confirmation of uncomplicated acute diverticulitis, with the aim of allowing allocation to the antibiotic and placebo groups in a 1:1 ratio. The actual process of patient randomisation was achieved using a computer-based random number generator utilised by the external pharmacy where the study medication was manufactured. Randomisation was blocked into groups of four to ensure a comparable allocation to treatment and placebo groups. Heterogeneity was addressed by the randomisation process, and *post hoc* stratification analyses were undertaken as a secondary outcome.

The antibiotics and placebo were packaged in identical vials and bottles by an external pharmacy along with a study identification number (Figure 8-5). The oral placebos (metronidazole and Augmentin) were formulated from dextrose. The intravenous cefuroxime placebo was formulated from dextrose and lactose.

Successively registered patients were allocated consecutive sets of medication containing 48 hours-worth of intravenous medication and 5 days-worth of oral medication in sequence.

8.3.8 **Blinding**

Trial participants, investigators and clinical staff were blinded to participant allocation status. The randomisation code were available to the external pharmacy and one clinician who was not a study investigator at each study site as a safety mechanism in case there was a need for allocation to be revealed during the study (e.g. in an emergency such as anaphylaxis where allocation may have influenced clinical outcome).

8.3.9 **Outcomes**

1. Baseline Data

Participant demographic data were prospectively collected for age, gender and self-identified ethnicity.

Baseline clinical variables were prospectively collected through interviews with participants, supplemented by reviewing their clinical records. The following data points were collected:

- ASA, height, weight
- Previous history of diverticular disease
- Comorbidities, regular medications, medication allergies and reactions
- Baseline (usual) bowel habit

Regular (>4 days of use in the last week) steroid or (within the six months prior to presentation) immunomodulator/biologic use was combined into one parameter for data analysis.

2. Inpatient Variables

Inpatient variables were recorded twice daily for the first 48 hours and daily until discharge from hospital for participants, regardless of whether they remained on the study pathway or were removed for clinical or other reasons. The following data points were collected:

- Vital signs (Temperature, heart rate, blood pressure, respiratory rate)
- Pain score out of ten
- Analgesia consumption
- Anti-emetic consumption
- Daily blood tests (haemoglobin, white cell count, neutrophil count, C-reactive protein, sodium, potassium, creatinine)
- CT scan findings and time taken to CT scan
- Intravenous fluid intake
- Dietary status (nil by mouth, clear fluids, soft diet, full diet)

3. Primary Outcome

The primary outcome for this study was the length of hospital admission in hours, from registration in the emergency department to discharge into the community.

4. Secondary Outcomes

The secondary outcomes of this study were: participant drop-out or withdrawal rate, occurrence of adverse events, readmission within 1 week and 30 days, procedural intervention, change in serum markers of inflammation and patient-reported pain score at 12 and 24 hours.

8.3.10 **Statistical Analysis**

Statistical analysis was performed on an intention-to-treat basis. Statistical analysis was performed using Stata for Windows (Version 16, StataCorp. College Station, TX). Parametric data were expressed as mean (95% confidence intervals) and nonparametric data as median (interquartile range). An independent samples t-test was used for parametric continuous variables and Mann-Whitney U test for non-parametric continuous variables. Univariate analysis was carried out using the chi-square test for categorical variables and linear regression was performed to analyses relationships between the different variables and the primary outcome of length of stay. Results were considered statistically significant if $p < 0.05$.

8.3.11 **Adverse Events**

All adverse events were recorded, whether they related to administration of the study medication or not. These events were graded according to severity by the Common Terminology Criteria for Adverse Events (CTCAE) (228) and Clavien-Dindo (229) classification systems.

An adverse event was defined as any untoward medical event affecting a clinical trial participant, where the occurrence does not necessarily have a causal relationship with the intervention. For the purposes of this trial, this included symptoms of acute diverticulitis if they led to deviations from the study pathway.

A serious adverse event was defined as an event that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability.

1. Assessing Causality of Adverse Events

Each initial adverse event was considered for causality and expectedness as well as severity. A definition of adverse event causality based on the New Zealand Medicines and Medical Devices Safety Authority guidelines was used for the present trial (230). A summary of the grading is as follows:

- Unclassified - Where more data are required
- Unclassifiable Where the data available were insufficient or contradictory, and further data could not be obtained
- Unrelated - Where the adverse event is clearly not related
- Unlikely - Where the adverse event does not have a clear relationship to the intervention
- Possible - Where the adverse event follows a known pattern of response
- Probable - Where the adverse event reduces or ceases with withdrawal of the intervention
- Definite - Where the adverse event ceased with withdrawal of the intervention and recurs with re-exposure

2. Data Safety and Monitoring Committee

A data monitoring committee (DMC) was set up to oversee the trial. The DMC consisted of two clinicians and a biostatistician who were independent of the study and met six monthly for the duration of the study.

Prior to each meeting the study statistician (Associate Professor Lindsay Plank) provided the Committee with a report containing unblinded aggregate data including:

- Recruiting log
- Baseline characteristics by treatment allocation.
- Primary and secondary outcome data by treatment allocation (except outcomes that are only measured at the end of the study).

- Adverse event data by treatment allocation, graded by system and severity according to the CTCAE classification and the Clavien-Dindo classification.
- SAEs should also be listed separately by treatment allocation.
- Post-randomisation withdrawals and missing data accounted for.

In addition, all serious adverse events (SAEs) were reported to the DMC within 3 working days (Dr Greg O'Grady was the primary contact for adverse event reporting).

The following events were defined as events which should initiate discussion regarding early stopping of the trial:

- ≥3 deaths in placebo group
- A significantly higher number of (Clavien-Dindo ≥3) complications in the placebo group, assessed at the 6 monthly meetings, with p-values based on the O'Brien-Fleming rule.
- Lower than expected recruitment rate (as determined by the study investigators prior to the scheduled meetings)

8.3.12 **Funding Sources**

This study was funded by competitive grants awarded from the following bodies:

- Colorectal Surgical Society of Australia and New Zealand project grant (2015-2018).
- Auckland Medical Research Foundation Doctoral Scholarship (2014-2018)

8.4. Results

8.4.1 **Participant Flow**

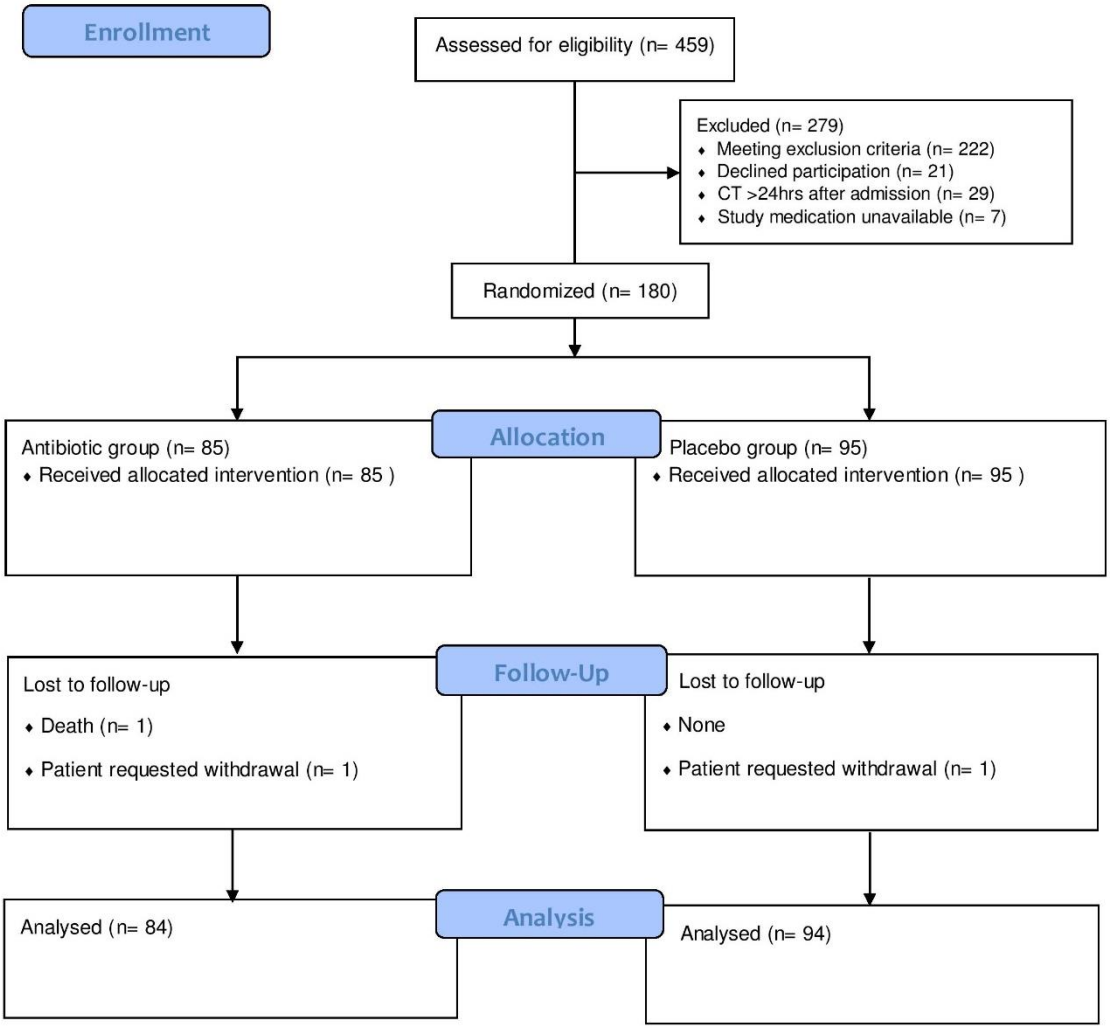


Figure 8-6 CONSORT 2010 Participant Flow Diagram.

The recruitment process is summarised in Figure 8-6. A total of 459 participants were screened for eligibility and 279 were excluded. In total, 180 participants were randomised to the antibiotics (n= 85) or placebo group (n= 95), one participant from each group was excluded from analysis at the request of the participants.

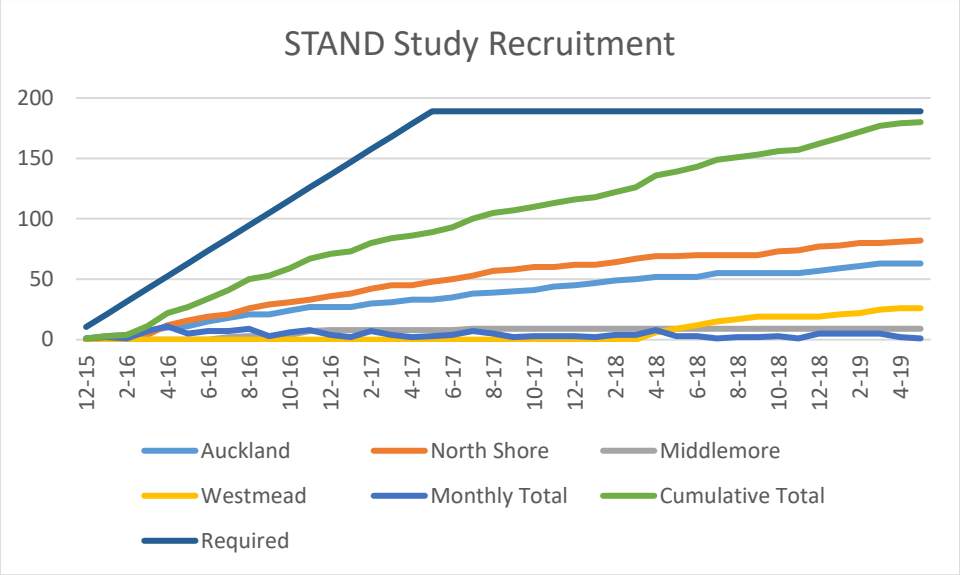


Figure 8-7 Graph of Expected versus Actual Recruitment by Study Site.

Figure 8-7 summarises recruitment rate for the trial by study site. The anticipated end of recruitment was April 2017, however the actual end date of the study was April 2019. Recruitment rate was highest at North Shore and Auckland Hospitals, and remained steady throughout the duration of the study.

8.4.2 **Baseline Characteristics**

Demographic characteristics were evenly distributed between the antibiotic and placebo groups (Table 8-2). Table 8-2 presents the baseline clinical characteristics of both groups at time of hospital admission. These did not differ significantly between the antibiotic and placebo groups, except participants in the placebo group had a longer mean time to CT scan (mean 9.8 (6.1-8.6) vs. 7.3 (8.3-11.2) hours; p = 0.01).

Characteristic	Antibiotic group (n = 84)	Placebo group (n = 94)
Age (years) (IQR)	56 (53-59)	59 (57 -62)
Female n, (%)	50 (60)	53 (56)
Ethnicity, n (%)		
European	69 (82)	74 (78)
Māori	7 (8)	8 (9)
Pacific	1 (1)	2 (2)

Asian	5 (6)	4 (4)
Other	2 (2)	6 (6)

Table 8-2 Demographic data. IQR = Inter-quartile range.

8.4.3 **Primary Outcome**

Length of hospital admission was not prolonged in the placebo group when compared with the antibiotic group (p= 0.15), see Table 8-3. The median length of hospital stay was 40.0 (24.4-57.6) hours in the antibiotic group and 45.8 (26.5-60.2) hours in the placebo group. The difference between medians (placebo group –antibiotic group) was 5.9 (-3.7-15.5) hours. The non-inferiority of this result when compared with the predetermined margin of 24 hours difference is demonstrated in Figure 8-8. Similar results were found when the analysis was adjusted for the difference in time to CT scan between the groups (p = 0.34). The observed length of stay (42.8 hours) was shorter than that used for the sample size calculation (88.9 hours) and would imply that fewer participants would be needed to detect a difference of 24 hours, given similar standard deviations for the log-transformed data.

Figure 8-8 Median difference in length of hospital admission (Placebo group-Antibiotic group) and non-inferiority margin.

Outcome	**Antibiotic group** **(n = 84)**	**Placebo group** **(n = 94)**
Median length of hospital stay (hours)	40 (24-58)	46 (26-60)
Reduction in white cell count at 24 hours ($x10^9$/L)	3 (3-4)	3 (2-3)
Reduction in pain score at 12 hours (0-10)	2 (1-3)	3 (2-3)
Reduction in pain score at 24 hours (0-10)	3 (2-4)	3 (2-4)
Discontinued study treatment, n (%)	8 (10)	14 (15)
Participant requested withdrawal, n (%)	3 (4)	4 (4)
Non-protocol discontinuation, n (%)	1 (1)	3 (3)
Need for procedural intervention, n (%)	2 (2)	0
1-week readmission, n (%)	5 (6)	1 (1)
30-day readmission, n (%)	5 (6)	10 (11)
Mortality, n (%)	1 (1)	0
Adverse event, n (%)	10 (12)	11 (12)
Serious adverse event, n (%)	3 (4)	0
Inpatient adverse events, n (%) Met SIRS criteria Met one condition of SIRS criteria IV line infection Positive MSU Positive blood culture Complicated AD requiring surgery	3 (4) 1 0 0 0 1 1	8 (9) 3 2 2 1 0 0
Outpatient adverse events	7 (8)	3 (3)

Readmission for AD	0	1
Pericardial effusion	1	0
UTI	1	1
Positive blood culture	1	0
Ongoing pain	1	1
Diarrhoea/high inflammatory markers	1	0
Pneumonia	1	0
Stroke	1	0

Table 8-3 Outcomes by allocation status.

AD = acute diverticulitis, IV = intravenous, MSU = mid-stream urine, SIRS = systemic inflammatory response syndrome, UTI = urinary tract infection

8.4.4 **Secondary Outcomes**

All but three participants completed 30 day follow up, one participant in the antibiotic group died during the follow up period and two requested withdrawal from the trial (one in each group).

There were no significant differences in the secondary outcomes as shown in Table 8-3. One week (6% vs 1%; p = 0.07) and 30 day re-admission (6% vs 11%; p = 0.3), need for procedural intervention (2% vs 0%; p = 0.1), and mortality (1% vs 0%; p = 0.3) were not significantly different between the groups. There was no difference in mean reduction in white cell count (2.9 (2.3-3.5) vs 2.7 (2.2-3.3), p = 0.7) nor mean pain score at 24 hours (3.2 (2.4-3.9) vs 3.0 (2.3-3.7), p = 0.9).

One participant in the antibiotic group died four days after being discharged, following a stroke and aspiration pneumonia which was unrelated to the episode of diverticulitis. Two participants (both allocated to the antibiotic group) required procedural intervention. One participant had their diagnosis revised to complicated diverticulitis after worsening symptoms prompted review of their CT scan; this participant discontinued study medication and required a Hartmann's procedure. The other participant was re-admitted within 1 week with a left-sided pneumonia and associated effusion which required ultrasound-guided drainage.

Twenty two participants discontinued study medication, seven of these participants chose to withdraw from the study. The differences in treatment discontinuation (10% vs 15%; p = 0.3) and withdrawal rate (4% vs 4%; p = 0.8) between the study groups were not statistically significant. Reasons for discontinuation of study medication were (antibiotic versus placebo): participant's wishes (7 participants; 3 vs 4); SIRS (4 participants; 1 vs 3); non-clinical protocol deviation (4 participants; 1 vs 3); failure to improve on study medication (1 in antibiotic group); diagnosis of complicated diverticulitis (1 in antibiotic group); positive blood culture (1 in antibiotic group); positive urine specimen (1 in placebo group); intravenous line infection (2 in placebo group); see Table 8-3.

Adverse events and serious adverse events are summarised in Table 8-3. There were no significant differences adverse events between antibiotic and placebo groups (12% vs 12%, p = 0.97) nor serious adverse events (4% vs 0%, p = 0.65). There were differences in the number of inpatient and outpatient adverse events in the placebo group compared to the antibiotic group ((9% vs 4% inpatient events; p = 0.2, 8% vs 3% outpatient events; p = 0.1) but these were not statistically significant. The three serious adverse events include two participants who required procedural interventions and one participant who died during the study follow-up period (30 days).

8.5. Discussion

This is the first double-blinded randomised control trial of placebo versus antibiotics for the management of uncomplicated acute diverticulitis. This study demonstrates that the use of placebo is non-inferior to antibiotics when comparing length of hospital admission context.

Previously, two open label non-blinded randomised control trials have compared antibiotics with no antibiotics for the treatment of uncomplicated acute diverticulitis. These trials found no difference between the two approaches in resolution of symptoms, recurrence, complications and length of hospital admission (23, 101). The first of these trials had a similar study population to that presented here and they enrolled participants with CT-proven diverticulitis without, "complications such as abscess, free air or fistula," (23). The other trial included participants with confined small pericolic abscesses (101), i.e. both Hinchey 1a and 1b acute diverticulitis (12, 13) participants were included, while the STAND study included participants with Hinchey 1a diverticulitis only.

A recent systematic review reported that selective antibiotic use did not confer any benefit over no antibiotics in uncomplicated acute diverticulitis, and not using antibiotics was associated with a shorter hospital admission (231). Long-term follow-up of the randomised control trial of Hinchey 1a acute diverticulitis only showed no difference between the two approaches in terms of complications, recurrence, and surgery for diverticular disease at a median of 11 years follow-up (232).

Clinical guidelines have been changing to reflect this growing body of evidence. A systematic review of published clinical guidelines for diverticular disease management, published in 2018, revealed three differing positions on antibiotic use in uncomplicated acute diverticulitis. The guidelines either recommended: not using antibiotics and managing these patients as outpatients (Danish Colorectal Cancer Group, Netherlands Society of Surgeons, Italian Society of Colon and Rectal Surgery); selective antibiotic use (American Academy of Family Physicians, German Society for Gastroenterology, Digestive and Metabolic Diseases/German Society for General and Visceral Surgery, American Gastroenterological Association, Association of Polish Surgeons); or using antibiotics (American Society of Colon and Rectal Surgeons, European Association for Endoscopic Surgery) (108). The authors of the review cautioned that these guidelines referenced only one of the existing randomised clinical trials and suggested that further evidence, particularly further randomised clinical trials, may lead to changes in the guidelines.

Similarly, expert opinion is yet to reach consensus with regards to antibiotic use in uncomplicated acute diverticulitis. A Delphi study which recruited experts from Australasia, Asia, Europe and North America found that internationally opinions on selective antibiotic use were divided (146). However, the American and Australasian experts reached consensus in favour of antibiotic use (146, 233).

The decision to employ a selective approach to antibiotic use in uncomplicated acute diverticulitis must be considered in the context of the global issue of antibiotic resistance (154) and surgeons must also take responsibility for antibiotic stewardship (234). Antibiotic use in uncomplicated acute diverticulitis has been identified as an area in which prescribing practices could change based on new evidence (153). Given that patients with diverticular disease continue to have high antibiotic exposure in the community (155), this potentially represents a significant reduction in unnecessary antibiotic use.

The growing weight of evidence in favour of selective antibiotic therapy in uncomplicated acute diverticulitis, necessitates that institutions revisit their position and incorporate selective antibiotic therapy into clinical protocols. These changes will need to be subjected to clinical audit to ensure that they are appropriate and optimised for the complex clinical context. The applicability of selective antibiotic therapy in community settings also needs to be systematically investigated. Research is needed to define the patient group in which selective antibiotic use is appropriate, including refining the radiological and clinical characteristics that define uncomplicated acute diverticulitis, and identifying patients who should be exempt from this change in practice.

8.6. Limitations

This trial was powered to detect differences in length of hospital stay greater than 24 hours, so the sample size may be inadequate to detect differences in the other clinical outcomes assessed. The follow-up after discharge from hospital was shorter than the two other randomised clinical trials (30 days compared to 24 months (235) and 11 years (232)) so may also have missed clinically significant, longer term outcomes. The inclusion and exclusion criteria also limit the generalizability of these results to the wider population.

8.7. Conclusion

The STAND study is the first double-blind randomised control trial to assess non-inferiority of placebo compared to antibiotic management of uncomplicated acute diverticulitis. This result provides arguably the strongest evidence to date in support of omitting antibiotics in selected patients presenting with uncomplicated acute diverticulitis.

SUMMARY OF RESULTS

This thesis sought to answer the following questions:

1. What is the role of colonic dysmotility in diverticular disease?
2. How is acute diverticulitis currently managed in Australasia?
3. Which clinical factors predict a more severe clinical course in acute diverticulitis?
4. Are antibiotics necessary in the management of uncomplicated acute diverticulitis?

The introduction presented an overview of key concepts in the field of diverticulosis and diverticular disease. The terminology and clinical manifestations of diverticular disease were outlined, and the classical approach to classifying acute diverticulitis according to the Hinchey classification was compared to the commonly used clinical classification of uncomplicated versus complicated acute diverticulitis. The evidence supporting different aspects of the pathophysiology of diverticula formation and progression to diverticular disease was discussed with reference to genetic susceptibility, fibre intake, disordered colonic motility, abnormal connective tissue, the role of inflammation and the gut microbiome. Changes to the management of patients with uncomplicated acute diverticulitis were also described in the context of evolving disease classifications and understandings of disease aetiology.

The first study was a systematic review which aimed to review evidence for abnormal colonic motility and pressure profiles in diverticulosis. All published studies which used manometry to investigate colonic pressure in patients with diverticulosis were searched in three databases (Medline, Embase, and Scopus). No language restrictions were applied. Any manometry studies in which patients with diverticulosis were compared with controls were included. The Newcastle−Ottawa Quality Assessment Scale (NOS) for case−control studies was used as a measure of risk of bias. Ten studies (published 1962−2005) met the inclusion criteria. The studies followed a wide variety of protocols and all used low-resolution manometry. Six studies compared intra-sigmoid pressure, with five of six showing higher pressure in diverticulosis vs controls, but only two reached statistical significance. This systematic review of manometry data demonstrated that evidence for abnormal pressure in the sigmoid colon in patients with diverticulosis is currently weak. Existing studies utilised inconsistent methodology, showed heterogeneous results and were of limited quality. These findings highlighted the need for higher quality studies using modern manometric techniques, and standardised use of diverticular disease-related terminology and reporting methods in order to clarify the role of colonic pressure in diverticulosis.

The second study attempted to apply the findings of the systematic review to further investigate the role of elevated intracolonic pressures and increased colonic activity in the pathophysiology of diverticulosis. High-resolution colonic manometry was used before and after a meal in participants with established, asymptomatic diverticulosis and in healthy controls. Antegrade and retrograde propagating contractions, distance of propagation (mm), and mean pressures (mmHg) in the descending and sigmoid colon were compared for all propagating contractions and cyclic motor patterns independently. In the descending colon, diverticulosis participants had lower post-meal mean distance of propagation of all contractions (10.8 (SE 1.5) mm versus 20.0 (SE 2.0) mm, p=0.03), and cyclic motor patterns (17.1 (SE 2.8) mm versus 6.0 (SE 2.5) mm, p = 0.01). In the sigmoid colon, diverticulosis participants had lower post-meal mean distance of propagation of all contractions (10.8 (SE 1.5) mm versus 20.2 (SE 5.9) mm, p=0.01), and a greater post-meal increase in retrograde contractions (p = 0.04). Mean pressures trended lower in diverticulosis participants. This is the first high-resolution manometry study of participants with diverticular disease. Fewer propagating contractions and lower intracolonic pressures were identified in diverticulosis participants compared to healthy controls. Although the reliability of these findings is limited by the size of this study, it nonetheless indicates the need for further studies of this nature in order to clarify the role that pressure and motility play in the formation of diverticula.

The third study shifted focus to the clinical management of acute diverticulitis and aimed to evaluate the current practice and degree of consensus amongst Australasian surgeons regarding non-surgical management of acute diverticulitis and to determine whether newer approaches to management are being translated into practice. An online survey was distributed to all Australasian colorectal surgeons and all general surgeons in the Auckland region starting in January 2015. Responses were collected over two months and analysed to identify points of consensus and areas of significant difference in opinion between these groups. Responses were received from a total of 99 of 200 (49.5%) colorectal surgeons, and 19 of 36 (52.7%) general surgeons. The Hinchey Classification was the most commonly used measure of disease severity, used by 67 (95.7%) colorectal surgeons and 12 (92.3%) general surgeons. There was lack of consensus around important aspects of acute diverticulitis management, including antibiotic therapy, and use and modality of follow-up imaging. Selective antibiotic therapy and use of anti-inflammatory medication as adjuncts to treatment were practised by a small minority of those surveyed. The low response rate limits the reliability of these findings. However, the lack of consensus regarding management of acute

diverticulitis may be a consequence of a paucity of high-level evidence to support specific management approaches, particularly in patients with uncomplicated acute diverticulitis.

Two retrospective cohort studies were performed in order to investigate the potential role of risk prediction in managing acute diverticulitis. The first of these studies aimed to identify risk factors for complicated acute diverticulitis in patients managed by a tertiary hospital surgical unit. Patients admitted to General Surgery at two New Zealand tertiary centres over a period of 18 months were included. Univariate and multivariate analyses were carried out in order to identify factors associated with complicated acute diverticulitis, defined as a contrast computed tomography (CT) scan showing Hinchey ≥1b disease. A total of 375 patients with acute diverticulitis were identified, 61 had complicated disease. Fifty one patients (13.5%) required procedural intervention and there were two in-hospital deaths. Meeting systemic inflammatory response syndrome (SIRS) criteria, delayed presentation >5 days, C-reactive protein (CRP) ≥150 and hyponatraemia were identified as independent risk factors. These variables were entered into a risk prediction model, which when evaluated with a receiver operating characteristic (ROC) curve had an area under the curve of 0.75 indicating fair predictive ability. There was a six-fold increase in the incidence of complicated acute diverticulitis between low and high-risk groups. Following validation with a prospective dataset, these findings have the potential to inform treatment decisions in this patient group, both in terms of expediting treatment in unwell patients with complicated disease, and avoiding overtreatment in those who are likely to have a mild disease course.

Acknowledging that the management of uncomplicated (Modified Hinchey Classification 1a) acute diverticulitis (AD) has become increasingly conservative and that clear criteria for patient selection are required to implement this safely, we performed a separate analysis in the same group of patients which aimed to identify risk factors for severe clinical course in patients with uncomplicated acute diverticulitis. Univariate and multivariate analyses were carried out in order to identify factors associated with a more severe clinical course. This was defined by three endpoints: need for procedural intervention, admission >7 days and 30-day readmission; these were analysed separately and as a combined outcome. Uncomplicated AD was identified in 319 patients. Fifteen patients (5%) required procedural intervention; this was associated with SIRS (OR 3.92). Twenty-two (6.9%) patients were admitted for >7 days; this was associated with patient-reported pain score >8/10 (OR 5.67). Thirty-one patients (9.8%) required readmission within 30 days; this was associated with pain score >8/10 (OR 6.08) and first

episode of AD (OR 2.47). Overall, 49 patients had a severe clinical course, and associated factors were regular steroid/immunomodulator use (OR 4.34), pain score >8/10 (OR 5.9) and higher temperature (OR 1.51) and CRP ≥200 (OR 4.1). Although the validity of these findings are limited by the retrospective nature and size of the dataset, this study represents an novel attempt to identify which patients with uncomplicated acute diverticulitis could be managed more conservatively. These findings have the potential to inform prospective treatment decisions in this patient group as strategies such as selective antibiotic use and outpatient management become more common.

Antibiotic treatment is still widely regarded as standard care in the management of uncomplicated acute diverticulitis. This practice is based on low level evidence, and has been challenged by two randomised trials which were not placebo-controlled. In order to answer the final question pursued by this thesis, an international (New Zealand and Australia), multi-centre, placebo-controlled and double-blinded randomised control trial was carried out in order to investigate the non-inferiority of foregoing antibiotics in this patient group. Participants with CT scan-proven Hinchey 1a uncomplicated acute diverticulitis were randomised to receive antibiotics or placebo. The primary endpoint was length of hospital admission and the main secondary endpoints were occurrence of adverse events and readmission within one week and 30 days. A total of 180 participants were randomised to receive antibiotics (n = 85) or placebo (n = 95). Length of admission was not prolonged in the placebo group when compared with the antibiotic group; median 45.8 (95% CI 26.5-60.2) versus 40.0 (95% CI 24.4-57.6) hours respectively (p= 0.2). The difference between medians (placebo – antibiotics) was 5.9 (95% CI -3.7-15.5) hours. No significant differences were found for the main secondary endpoints between the two groups: adverse events (12% vs 12%, p = 1.0), readmission within one week (6% vs 1%; p = 0.1) and 30 days (6% vs 11%; p = 0.3). Foregoing antibiotic treatment did not prolong length of hospital admission. This result provides arguably the strongest evidence to date in support of omitting antibiotics in selected patients presenting with uncomplicated acute diverticulitis.

CONCLUSIONS

The research presented in this thesis can be drawn upon in order to make the following conclusions.

Significant heterogeneity exists within the terminology and classifications of diverticular disease which are used in research into the pathophysiology of the disease as well as clinical research. In particular, there is a need to differentiate between those with diverticulosis and diverticular disease, and to use standard definitions for uncomplicated and complicated acute diverticulitis and less common types of diverticular disease such as symptomatic uncomplicated diverticular disease and sigmoid colitis with associated diverticulosis. The use of inconsistent terminology results in difficulties in collating and comparing the findings of different studies and standardising the management of different manifestations of diverticular disease.

The evidence base surrounding the role of disordered colonic motility and high intraluminal pressure in the pathophysiology of diverticulosis formation and diverticular disease is limited. When high resolution manometry was performed on a small group of patients with diverticulosis, those in the diverticulosis group had fewer propagating contractions and cyclic motor patterns when compared to controls. They also tended to have lower intra-sigmoid pressure measurements. The use of new techniques for measuring colonic pressure wave activity and a standardised approach to classifying study populations may provide new insights and challenge existing theories about this aspect of disease aetiology.

Although there is a high level of agreement about the use of the Hinchey classification system and about approaches to complicated acute diverticulitis among Australasian clinicians, there is a lack of consensus regarding many aspects of the clinical management of diverticular disease. This is particularly the case with approaches to management which have been changing significantly over the past decade, including the role of selective antibiotic use in uncomplicated acute diverticulitis.

Risk prediction is a potentially useful tool in the clinical assessment of patients with both undifferentiated and suspected uncomplicated acute diverticulitis. Independent risk factors for complicated acute diverticulitis (SIRS criteria, CRP > 150, duration of symptoms ≥5 days and hyponatraemia) were used to construct a risk stratification system which had a ‘fair’ predictive ability. Meeting SIRS criteria, regular steroid/immunomodulator use, pain score ≥8 and experience one’s first episode of acute diverticulitis were associated with a more severe

clinical course with uncomplicated disease but a risk stratification system could not be constructed based on the data that was used to perform this analysis.

The non-inferiority of placebo when compared to antibiotics in the management of uncomplicated acute diverticulitis was demonstrated in a double-blinded randomised control trial which examined the primary end point of length of hospital admission. This trial also adds to the evidence base regarding the safety of foregoing antibiotics in the management of this group of patients.

FUTURE DIRECTIONS FOR RESEARCH

This thesis has attempted to explore and add to the knowledge base surrounding both the pathophysiology and clinical management of diverticulosis and diverticular disease. In this process, it has also identified areas in which future research is warranted.

The pathophysiology of diverticula formation and diverticulitis is complex, and there is limited and heterogeneous evidence available to support the different proposed causal mechanisms. This thesis specifically interrogated the role of colonic pressure and motility, and has identified that further *in vivo* studies are warranted in order to characterise the difference in colonic pressure waves in participants with diverticulosis and different types of diverticular disease when compared to control participants. The use of high resolution manometry, consistent terminology and standardised study protocols are key elements to consider when planning future studies of this type.

Furthering our understanding of the pathophysiology of diverticular disease is vital for developing targeted treatment modalities and optimising the clinical management of this condition. Studies of the role of inflammation and microbiome in particular have already contributed the inception of clinical trials of selective antibiotic use, anti-inflammatory agents and agents which modify the gut microbiome. These attempts are invaluable when considering how few evidence-based management options there currently are for patients with chronic manifestations of diverticular disease.

Although the role of risk prediction has been investigated by multiple studies comparing uncomplicated to complicated acute diverticulitis, there have been few attempts at identifying those who are at risk of a more severe clinical course within the cohort of patients with uncomplicated disease. The risk factors identified by the retrospective cohort study in this thesis require large-scale, prospective validation. The development of a risk stratification system in this patient group would increase the safety of implementation and further research into conservative management approaches in uncomplicated acute diverticulitis.

The evidence base which supports the selective use of antibiotics in the management of uncomplicated acute diverticulitis is growing, however, there are still a number of aspects which require clarification. The majority of cases of uncomplicated acute diverticulitis are managed in the community, however the safety, acceptability and feasibility of selective antibiotic use has not been investigated in this context. When considering the need for antibiotic stewardship and in order to ensure that a greater proportion of those with diverticular disease receive optimal clinical management, high quality evidence about

selective antibiotic use in a community setting is a priority research area. In the tertiary hospital context, the effectiveness and safety of the conservative approach to uncomplicated acute diverticulitis such as selective antibiotic use and outpatient management must be assessed through clinical audit and longer-term prospective studies.

The terminology of diverticular disease is complex and the evidence base supporting known pathophysiologic pathways and optimal clinical management is shifting significantly. In particular, the management of mild or uncomplicated AD, which makes up the majority of cases, is currently undergoing a significant change and knowledge about the condition and its management that was previously considered to be standard is being revisited. The use of newer approaches to management requires a more nuanced discussion of risk versus benefit with patients compared to more traditional approaches. It is unclear whether health information that is available to patients takes these recent advances into account, and the challenge for health professionals and service providers is to ensure that this increasingly complex health information is delivered in an effective way to patients. This is an area which has not been extensively investigated, however ensuring the effective delivery of health information and strengthening health literacy will be key for ensuring that more conservative and outpatient approaches to care are adopted in a safe manner.

APPENDIX A *IN VIVO* HIGH RESOLUTION MANOMETRY - COLONIC MOTILITY IN ESTABLISHED DIVERTICULOSIS: (PATIENT INFORMATION SHEET AND CONSENT FORM)

Patient information sheet

Pressure wave movement in large bowel affected by diverticular disease

Principal Investigator:		**Associate Investigator**:	
Name:	**Ian Bissett**	Name:	**Dr. Rebekah Jaung**
Position:	**Professor of Surgery**	Position:	**PhD Candidate**
	Head of Department	Address:	**Department of Surgery**
Address:	**Department of Surgery**		**University of Auckland**
	University of Auckland		**Private Bag 92019**
	Private Bag 92019		**Auckland Mail Centre 1142**
	Auckland Mail Centre 1142	Phone No:	**021 134 4600**
Phone No:	**09 373 7599 ext 89821**	Email:	**rebekahjaung@gmail.com**
Email:	**i.bissett@auckland.ac.nz**		

You are invited to take part in a research study looking at pressure wave movement in large bowel affected by diverticular disease.

Please take your time to think about this study and decide whether you wish to take part in it. Taking part is completely voluntary and if you decide you do not wish to take part, it will not affect your continuing healthcare in any way.

This Participant Information Sheet will help you decide if you would like to take part. It describes our aims, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. Please feel free to talk about the study with other people, such as family, whānau, friends, or healthcare providers.

If you agree to take part in this study, you will be asked to sign a Consent Form. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

What is it all about?

Pressure waves in the gastrointestinal tract help break down and move food through its different parts, aiding in digestion and absorption of nutrients. It has been shown scientifically that pressure wave movement occurs first in the small intestine, then the stomach, and finally the large intestine (pictured to the right).

Diverticular disease (DD) is the term used to describe symptomatic diverticulosis, a chronic condition associated with a number of lower abdominal symptoms including pain, altered bowel habit and bloating. The effect of DD on bowel motility has not been well described. We intend to carry out the first research using high resolution manometry (HRM) to study bowel motility in patients with DD. HRM has already provided new insight into the patterns of bowel motility in normal and abnormal bowel.

The study will involve placing a catheter within the large intestine at the time of your scheduled colonoscopy, and recording information from it for 4 hours after the procedure.

We plan to include a total of 20 patients in this study and 12 control participants. Patients such as yourself will be approached if they are over the age of 18, and have previously been noted as having diverticulosis on endoscopy.

This study has been approved by the Northern A Health and Disability Ethics Committee. The Principal Investigator for the study is Professor Ian Bissett, Professor of Surgery and Head of Department of Surgery at the University of Auckland. If you have any questions about the study, please feel free to contact Professor Bissett – his contact details are listed on the front page of this document.

Why are you being asked?

You have previously been noted as having diverticulosis on endoscopy. It is now time for your scheduled surveillance colonoscopy, and this makes you an eligible candidate for our planned study should you wish to participate (please see full details below).

Please note that if you **do** choose to participate in this study it will not have any effect on your colonoscopy or future follow-up. However, it will require you to stay for approximately 4 hours after the procedure (rather than 1-2 hours which is the norm). The study is purely observational, and you are free to withdraw from it at any point.

Likewise, if you **don't** choose to participate, there will be no difference in the quality of care you receive.

What happens during the study?

On the day of your planned colonoscopy, we will ask that you come in to hospital at 8am. We will meet you at this time and take you through to the Endoscopy Suite.

The colonoscopy will take place as normal, with sedation and pain relief being given as required. At the end of this procedure, while the scope is being removed, the pressure-recording catheter will be attached to the inside of the bowel wall. This is safe and painless, and will take only a few minutes to perform.

The catheter is attached to a data recorder by a cable. This cable can easily be disconnected and reconnected, allowing you to move around freely. We will show both you and the nursing staff how this is done, and encourage you to contact us if you are unsure of anything.

We estimate that your colonoscopy will be finished by 9am, and ask that you stay in hospital until around 2pm in the afternoon. During this time we will obtain recordings from the catheter, and ask that you note the time at which you eat, drink, and pass wind/stool. A study investigator (Rebekah Jaung) will visit you 4 times through the day while you are in hospital to ensure there are no concerns – if there are the study will be stopped immediately. After about 4 hours of monitoring the bowel pressure, the catheter will be disconnected, and you will be transported to the radiology department of an x-ray of the abdomen.

After the x-ray, you will return to the endoscopy suite. The catheter will be removed by applying gentle traction. You will be assessed prior to discharge to ensure they are clinically well and happy to go home. There will be no further appointments or follow-up needed for this study.

We strongly encourage you to contact the study investigators at any point if you have any questions or concerns. Our contact details can be found at the top of first page of this information sheet.

What are the possible benefits and risks to you of participating?

There will be no direct benefit to you by participating in this study.

The information we obtain from this study will benefit scientific knowledge greatly, and will likely form the basis for new treatments aimed at improving quality of life for those who suffer from diverticular disease. Furthermore, the study may provide us with insight into why diverticulosis occurs and possible ways in which to prevent it.

There is a small risk of bowel injury associated with any colonoscopy. The addition of the catheter to the procedure should not add to that risk except for the chance of bleeding from the mucosal site that the catheter is clipped on. This is a very minor mucosal injury, similar to a biopsy that is routinely performed, and to date has not been associated in demonstrable bleeding in 25 cases in Auckland.

A possible inconvenience of this study is that the catheter limits free mobilisation. However it can be easily disconnected and reconnected, either by you, the nursing staff or a study investigator.

There will be no change to the colonoscopic technique (and findings) or the quality of care you receive whether you choose to participate or not.

This study involves the use of x-ray radiation. This will be at a level that is routinely used for patient care and carried out by qualified radiographers in the Radiology Department and interpreted by a qualified radiologist. A single abdominal x-ray carries a very low risk to patients.

What would happen if you were injured in the study?

In the unlikely event of an injury, you may be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What are the rights of participants in this study?

Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part, you will receive the usual care.

Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue.

If you do agree to take part, you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future health care.

Participants have the right to access information about them collected as part of the study.

No material which could personally identify you will be used in any reports on this study.

Your GP can be informed about your participation in the study if you would like this.

We are happy to send you a lay summary of the results of this study upon its completion. It is expected results will be published as a journal article and presented at various international conferences. Please note that a significant delay may occur between data collection and publication of the results.

Access to Clinical Records

Information regarding your age, height, weight, other previous abdominal procedures, other medical conditions, and current medications will be obtained from Auckland DHB electronic records.

What will happen after the study ends, or if you pull out?

The data from the study will be kept for 10 years. Professor Ian Bissett, Department of Surgery, University of Auckland will be responsible for the safe keeping of the data. After this time all data will be destroyed using confidential data destruction procedures.

Your data will be de-identified (made anonymous) following collection. All data will be stored digitally on hardware at the University of Auckland.

Members of the research team (present and future) will have access to the raw data and/or your clinical records during, or after, the study, but only where ethical approval has been attained. Future studies may wish to include this data. Where such use goes beyond that outlined in the present application, further ethical approval will be sought.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Name:	Prof. Ian Bissett	Name:	Dr. Rebekah Jaung
Phone:	09 373 7599 ext 89821	Phone:	021 134 4600
Email:	i.bissett@auckland.ac.nz	Email:	rebekahjaung@gmail.com

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) at Auckland City Hospital by telephoning 09 486 8324 ext 2324.

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by telephoning 09 486 8920 ext 3204.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:
Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

Thank you for making the time to read about and consider taking part in this study.

Pressure wave movement in large bowel affected by diverticular disease

Request for interpreter: (please circle yes or no)

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

Consent clauses:

- I have read and I understand the information sheet dated 16 February 2016 for volunteers taking part in the study investigating pressure wave movement in large bowel affected by diverticular disease.
- I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I have had the opportunity to use family/whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the investigation will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had ample time to discuss with whanau/family and friends when a decision is required or when making a decision.
- I know who to contact if I have any questions about the study.

- The data from the study will be kept for 10 years. After this time the data will be destroyed using confidential data destruction procedures.
- I consent to members of the research team having access to my data and/or clinical records during, or after, the study.
- I agree to my data or other information being stored for use in a different study for which ethics committee approval would be required. YES / NO
- I would like the researchers to send me details of the outcomes of the study in due course. YES / NO
- I agree to my GP or other current provider being informed of my participation in this Study. YES / NO

Please tick ethnicity (ies) with which you identify:

Maori ( )	NZ European ( )	Samoan ( )	Cook Island Maori ( )
Tongan ( )	Niuean ( )	Chinese ( )	Other European ( )
Indian ( )			

Other (e.g. Japanese, Tokelauan) please specify _____

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name:

Signature:	Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature:	Date:

APPENDIX B SURVEY OF AUSTRALASIAN SURGEONS - CURRENT MANAGEMENT OF ACUTE DIVERTICULITIS: (COLORECTAL SPECIALIST AND GENERAL SURGEON SURVEYS)

Section 1 – for Colorectal Surgeons

1. Please tick the country in which you work in
   -Australia

   -New Zealand

2. Do you regularly manage patients with acute diverticulitis?

3. Please give an estimate of how many cases of acute diverticulitis you would see in a week at your centre.

Section 2

Which of the following factors would you consider an absolute indication for admitting the patient with a clinical or radiological diagnosis of acute diverticulitis?

-First episode of acute diverticulitis **Y/N**

-Age of patient, please give an estimate of what age **Y/N**

-Comorbidities, please state which in particular **Y/N**

-Temperature >38 **Y/N**

- Heart rate >100 **Y/N**

-signs of hypovolaemia **Y/N**

-Localised peritonism **Y/N**

-PR bleeding **Y/N**

-Need for intravenous analgesia **Y/N**

-Not tolerating oral intake **Y/N**

Section 3

1. Is there a severity score for acute diverticulitis that is routinely used in your centre? **Y/N**
2. Please tick any that you use and describe any that are not listed in the 'Other' section.

-Hinchey Classification **Y/N**

-Mannheim Peritonitis Index **Y/N**

-Peritonitis Severity Score **Y/N**

-APACHE II **Y/N**

- Other:

Section 4

How often do you employ these management options?

	Always	Usually	Sometimes	Rarely	Never
Management					
Bowel rest (NBM or clear fluids)					
IV fluids					
Oral antibiotics					
Iv antibiotics					
CT scan					
Follow-up colonoscopy					

Section 5

1. Do you ever forgo antibiotics in the treatment of any diverticular disease? **Y/N**
2. If so, briefly describe the situation where you would not use antibiotics.
3. Do you ever use anti-inflammatory medications in the treatment of any diverticular disease? **Y/N**
4. If so, please state which medication and briefly describe the condition it was used to treat.

Section 6

Do you ever use a short course of corticosteroids as an adjuvant therapy in acute diverticulitis?

Y/N

Would you be willing to enrol patients in a randomised control trial to assess the use of a short course of corticosteroid in uncomplicated acute diverticulitis? Please add comments in the space below if you wish.

Y/N

Section 1 – for General Surgeons

1. Do you regularly manage patients with acute diverticulitis?

2. Please give an estimate of how many cases of acute diverticulitis you would see in a week at your centre.

Section 2

Which of the following factors would you consider an absolute indication for admitting the patient with a clinical or radiological diagnosis of acute diverticulitis?

-First episode of acute diverticulitis **Y/N**

-Age of patient, please give an estimate of what age **Y/N**

-Comorbidities, please state which in particular **Y/N**

-Temperature >38 **Y/N**

- Heart rate >100 **Y/N**

-signs of hypovolaemia **Y/N**

-Localised peritonism **Y/N**

-PR bleeding **Y/N**

-Need for intravenous analgesia **Y/N**

-Not tolerating oral intake **Y/N**

Section 3

3. Is there a severity score for acute diverticulitis that is routinely used in your centre? **Y/N**
4. Please tick any that you use and describe any that are not listed in the 'Other' section.

-Hinchey Classification **Y/N**

-Mannheim Peritonitis Index **Y/N**

-Peritonitis Severity Score **Y/N**

-APACHE II **Y/N**

- Other:

Section 4

How often do you employ these management options?

	Always	Usually	Sometimes	Rarely	Never
Management					
Bowel rest (NBM or clear fluids)					
IV fluids					
Oral antibiotics					
Iv antibiotics					
CT scan					
Follow-up colonoscopy					

Section 5

5. Do you ever forgo antibiotics in the treatment of any diverticular disease? **Y/N**
6. If so, briefly describe the situation where you would not use antibiotics.
7. Do you ever use anti-inflammatory medications in the treatment of any diverticular disease? **Y/N**
8. If so, please state which medication and briefly describe the condition it was used to treat.

Section 6

Do you ever use a short course of corticosteroids as an adjuvant therapy in acute diverticulitis?

Y/N

Would you be willing to enrol patients in a randomised control trial to assess the use of a short course of corticosteroid in uncomplicated acute diverticulitis? Please add comments in the space below if you wish.

Y/N

APPENDIX C SURVEY OF AUSTRALASIAN SURGEONS - CURRENT MANAGEMENT OF ACUTE DIVERTICULITIS: (EMAIL TO SURGEONS)

Dear Consultant Surgeon,

You have been invited to take part in a survey of current practice in the management of acute diverticulitis in Australasia. This survey is part of a project on acute diverticulitis that is based at the University of Auckland.

In particular, we are interested to see if more conservative approaches to management are being considered for use or are currently being used. This survey is comprised of 5 sections of largely short answer questions and should take five to ten minutes to complete.

Please feel free to contact me if you would like any further information.

Thank you for your time,

Kind regards,

Dr Rebekah Jaung

Cell phone: 021 134 4600

Email: rebekahjaung@gmail.com

PhD Candidate

Department of Surgery

University of Auckland

APPENDIX D SURVEY OF AUSTRALASIAN SURGEONS - CURRENT MANAGEMENT OF ACUTE DIVERTICULITIS: (SUMMARY OF RESULTS FROM PATIENT'S SURVEY)

	Total (n=20)	**Women (n=10)**	**Men (n=10)**
Mean age (SD)	70.5 (5.8)	70.4 (6.1)	70.6 (5.4)
Age Range	61-80	61-78	62-80
European (%)	14 (70)		
Māori (%)	2 (10)		
Other (%)	2 (10)		
Not stated (%)	2 (10)		

Table 1. Demographic data

	Total (n=20)
Hospital admission for DD in the last 6 months (%)	5 (25)
GP admission for DD in the last 6 months (%)	11 (55)
Antibiotics for DD in the last 6 months (%)	11 (55)
Concerns about level of disease-specific knowledge (%)	2 (10)

Table 2. Disease-related outcomes

	Mean score (SD)
How much does illness affect your life?	4.4 (3.2)
How long do you think your illness will continue? (a very short time to forever)	6.4 (3.4)
How much control do you feel you have over your illness?	5.1 (2.8)
How much do you think your treatment can help your illness?	6.7 (2.2)
How much do you experience symptoms from your illness?	5.6 (3.3)
How concerned are you about your illness?	5 (3.2)
How well do you feel you understand your illness?	7.8 (2.1)
How much does your illness affect you emotionally?	5.3 (3.1)

Table 3. Brief Illness Perception Questionnaire.

Response from 0 to 10 (not at all, to completely/severely).

	Answered correctly (n=20)
Location of diverticular disease	6 (30)
Diverticula are permanent	13 (65)
What percentage are symptomatic	10 (50)
Identifying symptoms	14 (70)
Need for hospital admission for all episodes of diverticulitis	16 (80)
Need for antibiotics admission for all episodes of diverticulitis	9 (45)
Situations requiring urgent medical care correctly identified	
Bleeding from the bowel	13 (6.5)
Abdominal infection due to burst bowel	19 (95)
Blockage of the bowel	8 (40)
Need for surgical management	19 (95)
Risk of bowel cancer	11 (55)
Range of diagnostic tests correctly identified	
Colonoscopy	18 (90)
CT scan	18 (90)
Blood test	8 (40)
Barium enema x-ray	5 (25)

Table 4. Disease-specific knowledge

Scale name (abbreviation)	Mean score (SD)
Part 1	
Feeling understood and supported by healthcare providers (HPS)	3.4 (0.3)
Having sufficient information to manage my health (HSI)	3.2 (0.3)
Actively managing my health (AMH)	3.2 (0.4)
Social support for health (SS)	3.1 (0.4)
Appraisal of health information (CA)	2.9 (0.5)
Part 2	
Ability to actively engage with healthcare providers (AE)	3.9 (0.3)
Navigating the healthcare system (NHS)	3.9 (0.5)
Ability to find good health information (FHI)	3.8 (0.4)
Understand health information well enough to know what to do (UHI)	4.1 (0.4)

Table 5. Health Literacy Questionnaire

Part 1 - Scales 1 to 5: How strongly you disagree or agree with the following statements (Strongly disagree/Disagree/Agree/Strongly agree).

Part 2 - Scales 6 to 9: How easy or difficult the following tasks are for you to do now (Cannot do or always difficult/usually difficult/sometimes difficult/usually easy/always easy).

Domains	Mean score (0-100)
Physical health	64.6
Psychological wellbeing	66.7
Social relationships	63.8
Environment	81.3

Table 6. NZ-WHOQOL-BREF. Screening cut-off for individuals with poor/unsatisfactory <60.

APPENDIX E DOUBLE-BLINDED RANDOMISED CONTROLLED TRIAL – ANTIBIOTICS IN UNCOMPLICATED ACUTE DIVERTICULITIS: (PATIENT INFORMATION SHEET AND CONSENT FORM)

Participant Information Sheet:

Trial of antibiotics compared to a placebo in uncomplicated acute diverticulitis

Principal Investigator:		**Associate Investigator**:	
Name:	**Ian Bissett**	Name:	**Dr. Rebekah Jaung**
Position:	**Professor of Surgery**	Position:	**PhD Candidate**
	Head of Department	Address:	**Department of Surgery**
Address:	**Department of Surgery**	**University of Auckland**	
University of Auckland		**Private Bag 92019**	
Private Bag 92019		**Auckland Mail Centre 1142**	
Auckland Mail Centre 1142		Phone No:	**021 134 4600**
Phone No:	**09 373 7599 ext 89821**	Email:	**rebekahjaung@gmail.com**
Email:	**i.bissett@auckland.ac.nz**		

You are invited to take part in a study investigating the usefulness of antibiotics in acute diverticulitis (AD). This study forms part of a PhD project being undertaken by Dr. Rebekah Jaung. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. We expect this will take about 30 minutes. You may also want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign a Consent Form. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

Why are you being asked?
Diverticulosis is the term used to describe out-pouchings of the lining of the large intestine, a common abnormality which is found in 70% in those over 80 years of age. To date, we have no clear ideas about why diverticulosis occurs or why it sometimes causes illness.

Diverticular disease includes any symptoms that occur because of diverticulosis, from occasional pain that goes away without any treatment, to acute diverticulitis (AD) – inflammation of the out-pouching, that sometimes require hospital admission, and in severe cases an operation. A CT scan is the best way we know of determining the severity of AD, and it is generally classified as uncomplicated or complicated, depending on how severe the inflammation is.

AD is a very common cause for hospital admission under the care of surgical doctors, and the mainstay of management is bowel rest, pain relief and antibiotics. Some cases are very mild and can be managed in the community by general practitioners; this also usually involves antibiotics in tablet form.

Although most of those effected only need to come to hospital once, in some people AD occurs multiple times throughout their lifetime, requiring multiple hospital visits and treatment with antibiotics. Recently, there has been a lot of research into the best way to treat uncomplicated AD, including finding strategies which minimise hospital stay and identifying the aspects of treatment that are actually effective for improving symptoms and recovery.

One question that has come up from this research is *whether antibiotics are necessary for people with uncomplicated AD*. It has never been shown that there are infectious agents involved in the inflammation process in patients with mild disease, and there has been one study which showed that patients given a placebo medication did just as well and had no more worse outcomes than similar patients who were given standard antibiotic therapy. The main outcome we are looking at is whether patients who get antibiotics have a shorter stay in hospital compared to those who do not get antibiotics. This outcome was chosen as it was practical and of interest to both healthcare professionals and patients.

We hope to add to the knowledge about the usefulness of antibiotics in AD. *If antibiotics are of no additional use, then reducing the amount of times a patient with acute diverticulitis needs to take antibiotics will be a benefit for the patient and also help prevent the development of antibiotic-resistant 'super bugs.'*

Inclusion criteria for this study are: age > 18 years, currently admitted to hospital with uncomplicated AD on CT scan within 24 hours of admission, does not exhibit systemic inflammatory response syndrome, able to understand risks/benefits of the study and complete patient-reported symptom scores, able to give informed consent.

Exclusion criteria for this study are: pregnancy, previous allergic reaction with cefuroxime, metronidazole or amoxicillin/clavulanic acid use, steroid or immunomodulator use for more than 5 days prior to presentation, greater than 1 week of regular, steroid or other immunosuppressor drug use for more than 5 days prior to presentation, inflammatory bowel disease, CT evidence of complicated disease, meets criteria for a diagnosis of SIRS.

You are being asked to consider joining this study because your CT scan shows that you have uncomplicated AD, and an examination of your medical history shows that you do not have any characteristics that would make it unsafe for you to participate in this study.

Please note that if you **do** choose to participate in this study, the only change to your care will be whether or not you get an antibiotic. You are free to withdraw from this study at any point.

Likewise, if you **don't** choose to participate, there will be no difference in the quality of care you receive.

This study has been approved by the Northern A Health and Disability Ethics Committee.

The Principal Investigator for the study is Associate Professor Ian Bissett, Associate Professor of Surgery and Head of Department of Surgery at the University of Auckland. If you have any questions about the study, please feel free to contact A/Professor Bissett – his contact details are listed on the front page of this document.

What would your participation involve?

You will be randomly allocated (like the flip of a coin) into either the antibiotics or placebo group. This is done so that you and the clinicians involved in your care are not influenced by which group you are in. Only the pharmacy, where the medications come from, will know which group you are in. You will receive the study medication in an intravenous (into the vein) form until your doctors transfer you onto tablet medication. In total, you will take 7 days of antibiotic or placebo.

While you are in hospital, a study investigator will visit you twice a day for the first two days and then daily after that. The visits should take 5-10 minutes and will involve asking you about your symptoms and performing a brief examination of your abdomen. We will also be recording your vital signs and blood test results from your clinical notes.

The rest of your management, including other medications, diet and when you are ready to be discharged home will be the same, regardless of the group you are allocated to.

A study investigator will call you 1 month after you are discharged to ask about your recovery and make sure that you haven't experienced any adverse events associated with being involved in the study.

We strongly encourage you to contact study investigators at any point if you have any questions or concerns. Our contact details can be found at the top of this leaflet.

What are the possible benefits and risks to you of participating?

There will be no direct benefit to you by participating in this study.

However, the information we obtain from this study will benefit scientific knowledge greatly, and will likely form the basis for a new way of managing patients with uncomplicated AD, as well as reducing the use of unnecessary antibiotics.

There are no major risks associated with this study.

There is a small chance that you do not recover as expected with the standard management for AD – this may mean that you actually had complicated AD that was not seen on the CT scan. In this case, you will be removed from the trial and we will reveal which group you were in, and the surgical doctors will continue to treat you based on standard clinical practice. If your surgical doctors decide that you need antibiotics, you will be taken out of the study. In other words, taking part in the study will not prevent you from getting treatment that your doctors think you require. Furthermore, the study process should not keep you in hospital any longer than is standard practice.

There will be no change to the quality of care you receive whether you choose to participate or not.

What would happen if you were injured in the study?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What are the rights of participants in this study?

Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part, you will receive the usual care.

Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue.

If you do agree to take part, you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future health care.

Participants have the right to access information about them collected as part of the study.

No material which could personally identify you will be used in any reports on this study.

Your GP can be informed about your participation in the study if you would like this.

We are happy to send you a lay summary of the results of this study upon its completion. It is expected results will be published as a journal article and presented at various international conferences. Please note that a significant delay may occur between data collection and publication of the results.

What will happen after the study ends, or if you pull out?

Your data will be de-identified (made anonymous) following collection. All data will be stored digitally on hardware at the University of Auckland.

De-identified records from the study will be kept for 10 years. Associate Professor Ian Bissett, Department of Surgery, University of Auckland will be responsible for the safe keeping of the data. After this time all data will be destroyed using confidential data destruction procedures.

Members of the research team (present and future) will have access to the de-identified records during, or after, the study, but only where ethical approval has been attained. Future studies may wish to include this de-identified data. Where such use goes beyond that outlined in the present application, further ethical approval will be sought.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Name: Ian Bissett, Associate Professor of Surgery

Phone: 021 347 442

Email: i.bissett@auckland.ac.nz

Name: Rebekah Jaung, PhD Candidate and Research Fellow

Phone: 021 134 4600

Email: rebekahjaung@gmail.com

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) at Auckland City Hospital by telephoning 09 486 8324 ext 2324.

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by telephoning 09 486 8920 ext 3204.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050

Fax: 0800 2 SUPPORT (0800 2787 7678)

Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

Thank you for making the time to read about and consider taking part in this study.

Patient consent form:

Trial of antibiotics compared to a placebo in uncomplicated acute diverticulitis

Request for interpreter: (please circle yes or no)

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

Consent clauses:

- I have read and I understand the information sheet dated 22 May 2015 for volunteers taking part in the study comparing antibiotics versus no antibiotics for the management of uncomplicated acute diverticulitis.
- I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I have had the opportunity to use family/whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
    - I have had ample time to discuss with whanau/family and friends when a decision is required or when making a decision.
    - I know who to contact if I have any questions about the study
    - The data from the study will be kept for 10 years. After this time the data will be destroyed using confidential data destruction procedures.
    - I consent to members of the research team having access to my data and/or clinical records during, or after, the study.
    - I agree to my data or other information being stored for use in a different study for which ethics committee approval would be required. YES / NO
    - I would like the researchers to send me details of the outcomes of the study in due course. YES / NO
    - I agree to my GP or other current provider being informed of my participation in this Study. YES / NO

Please tick ethnicity (ies) with which you identify:

Maori ( )	NZ European ( )	Samoan ( )	Cook Island Maori ( )
Tongan ( )	Niuean ( )	Chinese ( )	Other European ( )
Indian ( )			

Other (e.g. Japanese, Tokelauan) please specify _____

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

APPENDIX F DOUBLE-BLINDED RANDOMISED CONTROLLED TRIAL – ANTIBIOTICS IN UNCOMPLICATED ACUTE DIVERTICULITIS: (MANAGEMENT GUIDELINES FOR UNCOMPLICATED DIVERTICULITIS)

Antibiotics

Intravenous regimen (up to 48 hours)

Cefuroxime 750mg IV Q6H

Oral metronidazole 400mg TDS

Oral antibiotics (on discharge or once afebrile for 24 hours)

Augmentin 625mg PO TDS for 5 days

Analgesia

1. Paracetamol 1g PO QID/PRN
2. Tramadol 50-100mg PO
3. Sevredol 10-20mg PO Q1H
4. Morphine 2mg IV Q5MIN for up to 10mg

Anti-emetics

1. Ondansetron 4-8mg PO/IV Q8H
2. Metoclopramide 10mg PO/IV Q8H

Diet

Patients will be made nil by mouth with intravenous fluids while awaiting CT scan. Following this (assuming uncomplicated diverticulitis), patients will be reviewed by a clinician and in the absence of peritonism, nausea and vomiting they will be able to eat.

Discharge

Patients will be deemed fit for discharge when:

1. Afebrile on oral antibiotics or placebo
2. Pain controlled on oral, non-opioid analgesia.
3. Able to tolerate oral diet
4. Able to safely mobilise and carry out activities of daily living

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