Influence of Risk Factors on Incidence, Management, Recurrence, and Follow-up of Acute Diverticulitis.

Prashant Vinay Sharma

A thesis submitted for the degree of Master of Medical Science at the University of Otago, Dunedin, New Zealand

14 December, 2017
Abstract

Acute Diverticulitis is a significant problem, accounting for up to one third of acute surgical admissions. Despite significant and rapid advances in medical knowledge, it remains a poorly understood disease. Practice is influenced by historical studies which have significant flaws. Current practice may be a reflection of limitations of the past e.g. the lack of accurate Cross Sectional Imaging. Technology is advancing and historical practices such as routine colonoscopy after diverticulitis may not be required. Risk factors for acute diverticulitis and recurrent diverticulitis remain unclear. With western society changing, diseases such as obesity are increasing. These may have influence on acute diverticulitis, its course and recurrence. Similarly other poorly understood risk factors include use of Non-Steroidal and Steroid medications, and the influence of Diabetes and autoimmune diseases. This thesis is an attempt to clarify these questions. Chapter 1 addresses the historical research and evidence that formed the basis of current practice. In Chapter 2 we address the effect of BMI and other risk factors on acute diverticulitis, and found that obese patients may be at increased risk. In chapter 3 we addressed the role of colonoscopy and found that the risk of malignancy after a confirmed episode of uncomplicated diverticulitis is not significantly different to that of a screened asymptomatic population, while complicated diverticulitis still carries a significant risk. In chapter 4, we looked at recurrent diverticulitis, and found that uncomplicated disease at initial presentation, having an autoimmune disease and taking regular NSAIDS increased risk of recurrent disease.
Preface

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I,
I took the one less travelled by,
And that has made all the difference

- Robert Frost

This thesis would not have been possible without the help of numerous people along the way.

I would like to thank Professor Frank Frizelle and Associate Professor Tim Eglinton for their gentle encouragement, their unyielding support and invaluable insight, without which, none of this would have been possible. In Sanskrit, a Guru is a mentor who brings the ignorant from darkness to light. They have truly been my Gurus, and for this I will be forever grateful.

I would also like to thank the Department of Surgery at Christchurch Hospital, for their support and help in entire journey of this Thesis. To the Consultants at the department who helped and encouraged me as a fellow, the secretaries who showed an ignorant fellow everything from using the printer to accessing medical records. Without them I would never have reached the end.

And finally, to my wife, Intan, who encouraged me, put up with my idiosyncrasies with good humour, stood by me in times of despair without any complaints and lifted me up to be a better person than I ever thought I could me. This is dedicated to you, my love.

Publications and Presentations Arising From This Thesis


The influence of body mass index, medications and chronic illness on the disease course of acute diverticulitis. Wednesday Posters, Colorectal Disease Vol 16, 2014, W180, Page 194 DOI 10.1111/codi.12644_2


Table of Contents
Abstract ................................................................................................................................. 3

Preface ................................................................................................................................... 4

Chapters

I. Overview of Diverticular Disease ......................................................................................... 12

   ▪ 1. Introduction ............................................................................................................... 12

   ▪ 2. History ..................................................................................................................... 14
      ▪ 2.1 History of Diverticular Disease ......................................................................... 14
      ▪ 2.2 History of Surgery in Diverticular Disease ..................................................... 19

   ▪ 3. Diverticulosis ........................................................................................................ 20
      ▪ 3.1 Introduction ........................................................................................................ 20
      ▪ 3.2 Epidemiology of Diverticulosis ...................................................................... 20
         ▪ 3.2.1 Prevalence of Diverticular Disease ............................................................. 20
         ▪ 3.2.2 Effect of Age and Gender .......................................................................... 23
         ▪ 3.2.3 Regional and Ethnic Variations ................................................................. 24
            ▪ 3.2.3.1 Asian Countries and Right Sided Diverticular Disease ..................... 26
      ▪ 3.3 Pathogenesis of Diverticular Disease ............................................................... 27
         ▪ 3.3.1 Introduction ................................................................................................ 27
         ▪ 3.3.2 Summary of Proposed Models of Pathogenesis of Diverticular Disease .. 28
            ▪ 3.3.2.1 Smooth Muscle Hypertrophy and Role of Elastin, Collagen, MMP and TIMP .............................................................................................................. 28
            ▪ 3.3.2.2 Genetics and Connective Tissue Disorders ........................................... 29
            ▪ 3.3.2.3 Intraluminal Pressure, Colonic Transit Time (CTT) and Colonic Motility ......................................................................................................................... 29
            ▪ 3.3.2.4 Cellular, Myenteric and Molecular Signalling Dysfunction ................... 31
            ▪ 3.3.2.5 Dietary Fiber and Lifestyle Factors ....................................................... 32
            ▪ 3.3.2.6 Medical Conditions .............................................................................. 34
               ▪ 3.3.2.6.1 Hypothyroidism ............................................................................... 35
               ▪ 3.3.2.6.2 Diabetes ..................................................................................... 35
               ▪ 3.3.2.6.3 Hypertension ............................................................................ 35

   ▪ 4. Diverticulitis .......................................................................................................... 35
II. The Influence of body mass index, medications and chronic illnesses on the disease course of acute diverticulitis

- Abstract ..........................................................63
- Introduction .......................................................64
- Methods ..........................................................65
- Results ............................................................68
  - Patient Demographics ......................................68
  - Method of Initial Diagnosis .................................68
  - Nature and location of disease at presentation ........69
  - Management and colonic evaluation .....................70
  - Recurrence ....................................................71
  - Patient factors potentially influencing disease course 71
    - Chronic illnesses and medications ....................71
III. Role of Routine Colonic Evaluation after Acute Diverticulitis .................................................. 85

- Abstract ........................................................................................................................................... 85
- Introduction ....................................................................................................................................... 86
- Methods .......................................................................................................................................... 86
  - Data Source and Search Strategy .................................................................................................. 87
  - Study Inclusion Criteria ............................................................................................................... 87
  - Study Exclusion Criteria ............................................................................................................. 87
  - Study Selection .............................................................................................................................. 87
  - Data Synthesis and Analysis ....................................................................................................... 87
  - Assessment of Heterogeneity ...................................................................................................... 89
- Results ............................................................................................................................................... 89
  - Characteristics of Studies ........................................................................................................... 89
  - Findings of Malignancy and Non Malignant Colorectal Polyps ............................................... 92
  - Uncomplicated Diverticulitis ....................................................................................................... 95
  - Complicated Diverticulitis ........................................................................................................... 98
  - Discussion ..................................................................................................................................... 100
- References ...................................................................................................................................... 104

IV. Risk Factors for Recurrent Diverticulitis ...................................................................................... 106

- Abstract ........................................................................................................................................... 106
- Introduction ....................................................................................................................................... 107
- Methods .......................................................................................................................................... 109
- Results ............................................................................................................................................... 109
  - Recurrent Diverticulitis and patients undergoing surgery ......................................................... 111
  - Emergency Surgery and Recurrent Diverticulitis ...................................................................... 112
  - Outcomes of patients managed conservatively at index admission ........................................ 113
  - Effect of Age, Gender, BMI, Chronic Illnesses, Weight, Medications and Surgery in Recurrent Diverticulitis ........................................................................................................... 115
  - Malignancy after Diverticulitis and Recurrence ......................................................................... 118
- Discussion ....................................................................................................................................... 119
  - Factors Influencing Recurrent Diverticulitis ............................................................................... 120
    - Obesity ....................................................................................................................................... 120
    - NSAIDS, Oral Corticosteroids and Immunosuppressants ....................................................... 120
    - Nature of Disease at index episode ......................................................................................... 121
    - Autoimmune disease and Diabetes ......................................................................................... 121
    - Gender and Age ....................................................................................................................... 122
    - Surgery and Interventional Radiology .................................................................................... 122
V. Summary of Findings and Conclusions ................................................................. 127

- Introduction ........................................................................................................... 127
- Role of Obesity ..................................................................................................... 128
- Role of Surgery .................................................................................................... 131
- Role of NSAIDS, Corticosteroids, and other Immunosuppressive medications ...... 132
- Role of Chronic Autoimmune Diseases and Diabetes ............................................ 133
- Role of Routine Colonoscopy after Diverticulitis ............................................... 134
- Summary ............................................................................................................... 135
- References ........................................................................................................... 136
Chapter I
Table 1 – Reported Prevalence of Diverticular Disease
Table 2 – Summary of studies of mortality with colonic perforation in patients with solid organ transplants
Table 3 – Studies after 2010 of Recurrent Diverticulitis

Chapter II
Table 1 – Demographics of patients with diverticulitis
Table 2 – Method of Initial Diagnosis
Table 3 – Nature and Location of disease at presentation
Table 4 – Management of patients
Table 5 – Colonic evaluation of patients with Acute Diverticulitis
Table 6 – Effect of chronic illnesses and medication on nature of diverticulitis at initial presentation
Table 7 – Effect of chronic illnesses and medication on management of diverticulitis
Table 8 – Influence of chronic illnesses and medications on type of intervention
Table 9 – Mean Weight and BMI of patients
Table 10 – Influence of BMI on risk factors and management of acute diverticulitis

Chapter III
Table 1 – Baseline characteristics of studies included in systematic review
Table 2 – Nature of disease, methods and time of colonic evaluation
Table 3 – Nature of diverticulitis and crude proportion of malignancy in included studies
Table 4 – Finding of non-malignant colorectal polyps in reporting studies
Table 5 – Summary of findings in studies reporting patients with uncomplicated diverticulitis
Table 6 – Summary of Studies reporting complicated disease

Chapter IV
Table 1 – Demographics of patients with recurrent diverticulitis
Table 2 – Type of surgical procedure and recurrence of diverticulitis
Table 3 – Factors influencing Recurrence
Table 4 – Effect of age and weight on recurrent diverticulitis

List of Illustrations
Chapter I
Figure 1 - Definitions
Figure 2 – Natural History of Diverticulosis
Figure 3 – Relation of Blood Vessels to Diverticulae
Figure 4 – Prevalence of Colonic DD by Age, Gender and Region at Autopsy
Figure 5 – Reported prevalence of diverticulosis over time in countries
Figure 6 - mRNA Expression of the GDNF system in muscularis propria of the human colon
Figure 7 – Dietary Fiber Hypothesis
Figure 8 – Relative increase in hospitalization rates for diverticulitis in the US between 1998 and 2005, compared to reference year (1998) stratified by age group
Figure 9 – Effect of CRP on Recurrence

Chapter II
Figure 1 - Diagrammatic representation of ROIs and other measured anthropometric parameters
Figure 2 – Histogram of BMI of patients with acute diverticulitis
Figure 3 – Obesity (BMI>30) in patients with acute diverticulitis compared to general population of New Zealand

Chapter III
Figure 1 – PRISMA Flow Diagram of Study Selection Process
Figure 2 – Pooled estimate of proportion of colorectal cancer at colonic evaluation after acute diverticulitis
Figure 3 – Pooled estimate of proportion of non-malignant colorectal polyps at colonic evaluation after acute diverticulitis
Figure 4 – Estimated proportion of colorectal malignancy after an episode of uncomplicated colonic diverticulitis
Figure 5 – Estimated proportion of non-malignant colorectal polyps in patients with uncomplicated diverticulitis
Figure 6 – Pooled estimate of proportion of malignancy after an episode of complicated diverticulitis

Chapter IV
Figure 1 – Recurrence in patients with diverticulitis
Figure 2 – Outcomes of patients with emergency surgery
Figure 3 – Outcomes of patients managed conservatively at index presentation
Figure 4 – Histogram of Body Mass index of patients with recurrent diverticulitis

Chapter V
Figure 1 – Obesity incidence in patients with acute diverticulitis, recurrent diverticulitis and estimated NZ national Average
Figure 2 – Influence of obesity on Risk factors, Management and recurrence of acute diverticulitis
Abbreviations

AD – Acute Diverticulitis
AIDS – Acquired Immune Deficiency Syndrome
Ba – Total Body Area
BAPD – Anteroposterior diameter of body
BC – Body Circumference
BMI – Body Mass Index
BSA – Body Surface Area
BTD – Transverse diameter of body
COX – Cyclo-Oxygenase
CRP – C Reactive Peptide
CT – Computed Tomography
CTT – Colonic Transit Time
DD – Diverticular Disease
DNA – Deoxyribose Nucleic Acid
EPIC – European Prospective Investigation into Cancer
ESR – Erythrocyte sedimentation rate
GNDF – Glial Cell Derived Neurotrophic Factor
HPFS – Health Professional Follow-up Study
IAa – Intra-abdominal Area
L1A – Area of L1
L1a – Transverse diameter of L1 lumbar vertebrae
L1APD – Anteroposterior diameter of L1 lumbar vertebrae
MMP – Matrix Metalloproteinase
MOH – Ministry of Health
mRNA – Messenger RNA
NOD – Nucleotide Oligomerization Domain
NSAID – Non Steroidal Anti-Inflammatory Drugs
NZ – New Zealand
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RNA – Ribose Nucleic Acid
SCA – Spinal Canal Area
SQa – Ratio of subcutaneous fat to total body area
TGF – Tumour Growth Factor
TIMP – Tissue Inhibitors of MMP
TLR – Toll Like Receptors
UK – United Kingdom of Great Britain and Ireland
USA – United States of America
USD – United States Dollars
USS – Ultrasound Scan
Chapter I

Overview of Diverticular Disease

1.1 Introduction

Acquired colonic diverticulae, also known as diverticulosis are mucosal outpouchings occurring though the wall of the colon. These occur at areas of weakness in the muscle layer of the colonic wall. It has its highest prevalence, and is one of the commonest medical problems affecting western populations[1]. It affects 35.3% of New Zealanders over the age of 40[2].

Diverticular disease represents a spectrum of diseases rather than a single entity. This ranges from asymptomatic diverticulosis, to symptomatic disease. Symptomatic disease can be further classified into uncomplicated and complicated disease. Uncomplicated disease is usually defined as symptomatic disease from inflammation of colonic diverticula. Complicated disease is usually defined and presence of complications of diverticulosis and diverticulitis, including haemorrhage, inflammation, perforation, structuring, fistulation into surrounding organs, abscess formation and death.

Figure 1 - Definitions

Acute diverticulitis is thought to affect up to 20% of patients with diverticulosis[3]. The annual cost of diverticular disease was estimated at $USD 2.4 billion per year to the United States (US) alone in 2000, and is in the top 5 costliest gastrointestinal disease [4]. These costs are projected to increase.
Not all patients with diverticulosis get symptomatic disease. An estimated 20% of patients get diverticulitis. The majority of these are uncomplicated but a small proportion gets complicated disease.

The incidence of diverticulosis is thought to be increasing in western countries. Associated with this there has been significant rises in the incidence of diverticulitis and its complications. Traditionally this disease was thought to affect only older patients. Increasingly, younger patients are being seen with acute diverticulitis. It was believed that obesity was a risk factor for diverticulitis. This has never been demonstrated in a large scale study, but rather is from the personal experiences of surgeons from the turn of the century. There is conflicting evidence regarding this. We address this in Chapter 2.

Traditionally, surgery was the mainstay of management of DD. This has changed significantly over the last 20 years, with an increasing shift towards non-surgical management in both the acute and elective setting. Improvement in diagnostic techniques such as Computed Tomography (CT) scanning has led to greater accuracy in diagnosis of this disease and its complications. Evolution of non-surgical
techniques such as percutaneous drainage of abscess have revolutionised management, allowing many patients with abscesses to avoid an operation.

Despite being one of the most prevalent conditions requiring treatment in an acute surgical ward, various aspects of this disease remain shrouded in mystery. Portions of current management exist largely because of historical practices rather than sound scientific evidence. Current guidelines reflect limitations of previous technology and management practices. This includes practices such as routine colonoscopy after acute diverticulitis (discussed in chapter 3).

Historically, surgery was recommended after 2 episodes of diverticulitis, as it was believed that patients were less likely to respond to medical treatment in subsequent attacks. Aggressive surgical intervention was also advocated in younger patients as they were believed to have more virulent disease. Even up to 2000, surgery after 2 attacks of diverticulitis was recommended[5]. While some guidelines still endorse these practices, they have been largely abandoned. The role of surgery in an elective setting after diverticulitis remains unclear. While surgery does provide relief from recurrent episodes in a single affected segment, when to proceed to resection remains an unknown and highly contentious issue. The decision to operate relies heavily on knowledge of the natural history of diverticulitis and factors that influence this. However, to date there are many aspects of the natural history of the disease that remain unclear. It has been known for a while that a portion of patients get recurrent diverticulitis. There is a significant paucity of literature on risk factors that predict for recurrence. We address this issue in Chapter 4.

2. History

2.1 History of Diverticular Disease

The word diverticulum comes from the Latin “Diverto” or “to turn aside or divert”. A diverticulum therefore is a small turning aside. Abnormalities of the intestinal tract have been described by various authors, including Sommering, Schrock, Riolan etc without any clear differentiation of specific pathology[6].

The French anatomist Alexis Littre was probably the first to accurately intestinal diverticula in 1700. He believed that diverticula formed due to traction on intestinal wall due to part of the wall entering a hernia sac. He believed this resulted in the wall of the intestine being pulled out, resulting in diverticula [7]. He however did not differentiate colonic from other diverticula.
Giovanni Morgagni in 1761 recognised that not all diverticula could be related to traction, and said “for sometimes they belong to those intestines which area not situated in places where hernias happen”[8]. He recognised ileal diverticula separately in humans as well as geese, and hypothesized that these could be related to the vitellum. While he believed in Littre’s view of traction on the bowel, also believed in the views of Fabricius, that bowel content became harder and dryer as it progressed along the intestine, and exerted pressure from inside. He thought that this could also contribute to formation of diverticula.

Johann Meckel in 1812 described a protrusion in the ileum. He was the first to show that this diverticulum was formed congenitally, and not as a result of traction. He recognised this occurred only in the ileum, and recognised that it contained all layers of intestinal wall[8].

Colonic diverticulae were probably first described by Voigtel in 1804[9]. He said that it was not rare to find bags or sacks in the colon. He called these “Natürliche Anhängsel am Darmkanal” or “Naturally occurring appendages of the Intestinal Canal”. It is not clear however whether these were colonic diverticulae. Similarly Fleischmann in 1815 gave a description of diverticulae in the gastrointestinal tract, including bile duct and colonic outpouchings[10]. Again, he did not differentiate colonic from other diverticula. He was the first to use the term “Divertikel”

Monro in 1830 described diverticulitis causing death of a patient. He have a clear account, writing “the term diverticulum is to be understood a process of blind sac connected to the convexity of a portion of the intestinal canal which fully communicates with the cavity of the intestine excepting when inflammation has given rise to accretion of their opposite side”[11].

While this may have been the first description of diverticular disease, credit for the first accurate and clear description of colonic diverticula is usually attributed to the French anatomist and pathologist Jean Cruveilhier in 1834[8, 11, 12]. He performed multiple post mortem studies on human cadavers, and published the two volume *Anatomie pathologique du corps humain* in 1835. He wrote ‘we not infrequently find between the bands of longitudinal muscle fibers in the sigmoid a series of small, dark, pear-shaped tumours, which are formed by herniae of the mucous membrane through the gaps in the muscle coat”[9]. He called these “hernies tuniquaires” or hernias related to the tunica of colon. He was the first to use the term diverticulum and grouped them into congenital and acquired, without describing any difference in structure.

In 1896, the German anatomist Graser observed that diverticulae were associated with entrance or exit of blood vessel in the wall of the intestine[13]. He believed that areas of weakness occurred in the bowel wall where veins entered the colon. As veins are capacitance vessels needing to distend, space was needed around these vessels, leading to weakness. He thought that obstruction of drainage of
blood via the inferior mesenteric artery predisposed to weakness in the colonic wall and formation of diverticulae[9]. This was propounded by Sudsuki, who found venous congestion in 6 out of 15 cases of acquired diverticulae[14]. Graser was the first described the phenomenon of diverticulitis, or inflammation of a diverticulum, what he termed peri-diverticulitis.

Other anatomists and pathologists described diverticulosis and diverticulitis between 1850 and 1900 to varying degrees, including Klebs[15], Heschl[16], Hanau[17], Good[18], Hansemann[19] and Fischer[6]. Klebs reported that number of diverticulae were higher in obese patients, while Hansemann reported a higher number in lean people. Heschel, Hanau and Good attempted to recreate diverticulae by filling human cadaveric intestines with water under pressure and recording points of rupture. They concluded that the weakest part of the bowel was at the mesenteric border, where vessels from mesentery penetrated into colon. Chlumsky in 1899 attempted to replicate this experiment in live intestines of dogs[20]. He found in live animals, ruptures occurred more frequently at the anti-mesenteric border, whereas once the intestine was removed and dead, ruptures occurred in the mesenteric border. Despite this, the belief of the time was that DD occurred at the antimesenteric border due to high luminal pressures.

In 1904 Edwin Beer described complications of diverticular disease in 18 cases, including diverticulitis, abscess formation, stenosis and structuring, perforation, ulceration, fistula formation, as well as cancer. He tried to differentiate diverticulitis from malignant disease, and believed they were often mistaken. He recognised that the incidence was increasing, writing “Only 20 years ago Virchow spoke of acquired diverticulae as an unusual pathological condition, but during these 20 years our views have changed”[22].

In 1927 Spriggs and Marxer first attempted to identify the aetiology of diverticular disease. They classified diverticular disease into 4 stages based on appearances at Barium Enema[23]. It was believed that formation of diverticular disease progressed though these stages. Stage 1 was the “Prediverticular Stage” where there was loss of normal segmentation of the bowel. Stage 2 was the
“Stage of Irritation” where early diverticulae could be seen, and the bowel itself had a “concertina-like appearance”. Stage 3 was “Developed Diverticula”, where various diverticulae of various shapes and sizes were visible. Some contained all the coats of the bowel wall, while others had loss of muscle fibers. Often the diverticula had stercoliths. Stage 4 was “Diverticulitis”, where inflammation arose from the neck of the pouches, especially those containing stercoliths. According to the thinking at the time, formation of diverticulitis was inevitable, due to relentless progression of the disease though the stages.

As treatment, Spriggs recommended a healthy diet with fruit and vegetables. He also writes “The colon is washed out with saline every other day, for a time, but at low pressure, the funnel being not more than 18 inches above the level of the anus”. He also writes “If grave symptoms such as a rising pulse rate, collapse, and intractable vomiting are not present, and the diagnosis has been made radiologically, then castor oil (with laudanum) and hot fomentations and enema may be given with confidence”. He advocated surgery only for the complications of diverticular disease[23].

Lockhart-Mummery, while writing on the aetiology of diverticular disease in 1930, did not believe in the progressive stages of diverticular disease[24]. He writes “The secondary inflammation may never occur, or it may take place at almost any stage in the development of the pouches”. He also commented that he seldom saw thin people with diverticulitis.

The next stage in the search for aetiology of diverticular disease came in the 1960’s. Attention was turned towards the luminal pressure of colons with diverticulosis. In 1962 Painter reported the first study of intraluminal pressures in diverticulosis to the British Society of Gastroenterology [25]. He found that administration of morphine resulted in increased frequency and higher amplitude pressure waves in sigmoid colons with diverticular disease, and concluded that morphine should not be administered in diverticulitis.

Subsequently in 1964, Painter[26-30] and Arfwidsen[31] published studies measuring intraluminal pressures in diverticular disease. Painter, in a 4 part study found that under basal conditions, the intraluminal pressures were not different in the sigmoid colon with and without diverticular disease. In the presence of morphine and neostigmine however, the frequency and amplitude of pressure waves were much higher in colons with diverticulosis. When the muscle was paralysed by probanthine, the intraluminal pressures fell to a basal level in colons with diverticulosis, even with provocation. He concluded that morphine should be contraindicated in acute diverticulitis. Arfwidsen showed that segments of the sigmoid colon with diverticulosis were capable of producing higher pressures than normal bowel when stimulated by eating, emotions and by the drug prostigmine.
Attention was then turned to the muscular layer of the colon. Morson in 1963 showed that the pain experienced by patients in acute diverticulitis was most probably not due to inflammation[32]. He showed that about two thirds of cases of diverticulitis that underwent resection had no evidence of inflammatory disease in the pathological specimen. These instead had a significant degree of muscular thickening in the wall of the colon. Hughes in 1968 examined colons of 200 unselected cadavers and measured muscle thickness in the colon wall[33]. He found muscle wall thickening or abnormality present in 73% of colons with diverticula, and in only 8% of those colons without. He also noted that all cases with acute diverticulitis at the time of death showed marked muscle thickening.

This combined with the findings of Painter and Arfwiddsen led to the theory that diverticulosis was caused by pulsion of colonic mucosa by excessive intraluminal pressure. Due to muscular hypertrophy, excessive intraluminal pressures could be generated. During segmentation, the outflow of the colon is obstructed leading to a pocket of high pressure, causing pulsion of diverticula at areas of weakness. Because the underlying cause was thought to be due to muscular hypertrophy, this lead to the development of myotomy as an alternative to resection in diverticulitis[34].

Others however had different findings in colons with DD. Edwards in 1934 showed that in the “prediverticular stage”, the circular muscle of the colon developed ridges[35]. This resulted in an area between the ridges where the muscle coat was thin enough to allow close approximation of mucosa and serosa. He proposed irregular muscle spasm as a mechanism, leading to variability in muscle thickness.

Painter was also among the first to propose a dietary causation[36]. Amongst his travels he had noted that the incidence of DD was extremely low to non-existent in Sub-Saharan African populations as well as in the Pacific. He proposed a role for dietary fibre. He noted that during the years of World War II, the crude death rate from DD was stable. During this period due to scarcity of resources, the bread available was less refined and higher in fibre. Refined sugar was strictly rationed. After the war years, the mortality from DD steadily increased. Painter states that “Diverticulosis, like scurvy, is a deficiency disease, and therefore, should be preventable”[37].

Correlation however does not equal causation. There have been multiple studies reporting relatively low prevalence in geographical areas with high fibre diet. This is addressed later in this chapter. There are significant ethnic and regional variations as well, independent of diet.

Despite its prevalence, our understanding of the pathophysiology of DD has not improved appreciably for the past 30 years.
2.2 History of Surgery in Diverticular Disease

The first successful resections of diverticulitis was reported by Moynihan in 1907[38]. He described abdominal operations as “martyrology”, as two thirds of all patients died after abdominal section. In describing diseases of the large intestine, he describes “mimicry of malignant disease”. He reported operating on a patient with suspected carcinoma, “examination of which subsequently revealed no evidence whatsoever of a malignant grown”. He then describes the specimen as “A hyperplastic tuberculous tumour, dense inflammatory deposits on the serous covering, or the formation of many false diverticula with inflammation in and around them”. Later that year William Mayo and colleagues reported operating on 5 patients with strictures related to diverticular disease[39]. Mayo conjectured that diverticulosis resulted from a congenital defect in the muscular layer of the colon.

Smithwick in 1942 reporting experience with management of diverticular disease at Massachusetts General Hospital advocated an aggressive surgical approach to diverticular disease[40]. He described it as a comparatively rare disease. His data showed that roentgenologic evidence of diverticulitis was present in 25% of cases having diverticulosis. Of the patients with diverticulitis, medical management was unsatisfactory and unmanageable in 9.3% of patients. Of the patients operated on, 40% had perforation or fistulation into the bladder. An operation was required in 48% of all first attacks of diverticulitis. He compared different procedures, and reported best results from either proximal diversion or resection of the affected segment. He reported an overall mortality of 17.1%.

By 1955, with the introduction of better anaesthetic techniques, antibiotics and aseptic technique, the mortality of intestinal operations had reduced to about 5%. Todd in the Hunterian Lecture to the Royal College of Surgeons in England recognised the difficulties in operating on dense fixated fibrosed inflamed colons[41]. He described proximal diversion of the colon, or as he called it “Preliminary Colostomy”. He writes “Preliminary colostomy, placed well in the right half of the transverse colon to leave a long distal loop free for later resection and anastomosis, is advisable in all cases of complicated diverticulitis and also in those cases where symptoms or even a mass do not show rapid improvement with conservative therapy and chemotherapy”. Once the acute attack was treated, a delayed resection six to eight weeks down the track was performed. He also noted “Almost all the patients are fat.” Of the 29 operative cases described by Todd, only one death was reported, from undiagnosed bilateral pyelonephritis.

Up to this point, surgery in diverticular disease was reserved for complication of diverticulosis. In 1969, Parks published a seminal paper on the natural history of diverticular disease[42]. He reported a readmission rate of 24.6% in patients treated medically on their first admission for diverticulitis. Of the ones treated surgically he writes “The 138 patients who were surgically treated as a result of the presenting attack had a variable number of admissions, mostly related to staged procedures and are not further considered here”. He believed that progress of disease was more often within one segment rather than involving progressive segments. Parks reported that medical treatment was less
likely to be successful in subsequent attacks and that mortality increased significantly once patients developed complications of diverticular disease. His data showed only a 6% chance of success with medical treatment after the third attack. Based on this, surgery was recommended after 2 attacks of acute diverticulitis. This was the prevailing practice for the next 4 decades, despite the questionable findings and paucity of evidence.

In 1964 Reilly introduced Sigmoid Myotomy as an alternative to resection[34]. He reported performing a longitudinal myotomy on 8 patients. Unfortunately, the first 2 patients who underwent this procedure died immediately after the operation, the first within 24 hours of coronary thrombosis, and the second at day 10 of pulmonary embolism. In 1970 he published 5 year results of treating 50 patients with myotomy and found that 42 patients had a “satisfactory” result[43]. This was initially taken up enthusiastically as a therapeutic as well as a preventative procedure. Reilly’s results however could not be replicated in subsequent studies. Studies also showed recurrence of high intracolonic pressures after myotomy[44], as well as recurrent diverticulitis[45]. While still performed in some Eastern European centres, this procedure is now largely historical in the Western World.

3. Diverticulosis

3.1 Introduction

Diverticulosis affects a significant proportion of the population. The exact prevalence varies as discussed below. Not all diverticulosis is symptomatic, nor does all diverticulosis lead to acute diverticulitis. The incidence of diverticulosis increases with age. There are also significant ethnic, regional and gender variations in incidence of diverticulosis.

3.2 Epidemiology of Diverticulosis

3.2.1 Prevalence of Diverticular Disease

The exact prevalence of diverticulosis is not known. As about 80% of patients affected with diverticulosis are asymptomatic, the true prevalence of this disease can be difficult to ascertain. The risk of diverticular disease increases with age. It is estimated that up to 65% of people greater than 65 years old in industrialised countries have colonic diverticulae [21].

The prevalence of diverticular disease has been determined indirectly from radiological, autopsy studies and clinical studies including endoscopy. There are problems with each method of evaluation. The sensitivity and specificity of each test varies. Many studies were performed on a small number of patients, at a single institution or single geographical area. These results may not be a true reflection of incidence in the overall population. The inclusion criteria for patients into each study varied, as did the age of the population studied.
A summary of studies reporting prevalence of diverticular disease is shown in Table 1. The first radiological study looking at prevalence was performed by Spriggs and Marxer in 1925[10]. They looked at 1000 consecutive barium enemas, and found presence of colonic diverticulae in 10%. In 1930 William Mayo reported diverticulosis in 5% of autopsies at their clinic[12]. He thought about 12% of cases of diverticulosis developed diverticulitis. Rankin and Brown reported an incidence of 5.7% in 24,620 Barium enemas[46]. More recent studies have reported a much higher prevalence, ranging from 30 to 50%. It has been known for a long time that the incidence increases with age. Even correcting for age, there has been a shift towards increased prevalence over the past century.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Location</th>
<th>Method</th>
<th>Patients</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1925</td>
<td>Spriggs[10]</td>
<td>Wales, UK</td>
<td>Barium Enema</td>
<td>1000</td>
<td>10%</td>
</tr>
<tr>
<td>1930</td>
<td>Mayo[12]</td>
<td>Rochester, US</td>
<td>Xray Colon Autopsy</td>
<td>31,838</td>
<td>5.7%</td>
</tr>
<tr>
<td>1930</td>
<td>Rankin and Brown[46]</td>
<td>Rochester, US</td>
<td>Barium Enema (24,620) Autopsy (1925)</td>
<td>5.67%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Autopsy</td>
<td>1925</td>
<td>5.2%</td>
</tr>
<tr>
<td>1935</td>
<td>Ochsner[47]</td>
<td>Rochester, US</td>
<td>Autopsy</td>
<td>447</td>
<td>6.9%</td>
</tr>
<tr>
<td>1947</td>
<td>Pemberton[46]</td>
<td>Rochester, US</td>
<td>Barium Enema</td>
<td>47,000</td>
<td>8.5%</td>
</tr>
<tr>
<td>1946</td>
<td>Morton[49]</td>
<td>Rochester, US</td>
<td>Autopsy</td>
<td>8500</td>
<td>6.5%</td>
</tr>
<tr>
<td>1948</td>
<td>Cleland[50]</td>
<td>Adelaide, Australia</td>
<td>Autopsy</td>
<td>3000</td>
<td>2.8%</td>
</tr>
<tr>
<td>1949</td>
<td>Grout[51]</td>
<td>UK</td>
<td>Barium Enema</td>
<td>2179</td>
<td>8%</td>
</tr>
<tr>
<td>1959</td>
<td>Havia[53]</td>
<td>Sweden</td>
<td>Barium Enema</td>
<td>3563</td>
<td>15.8%</td>
</tr>
<tr>
<td>1961</td>
<td>Havia[53]</td>
<td>Finland</td>
<td>Barium Enema</td>
<td>3125</td>
<td>5.2%</td>
</tr>
<tr>
<td>1969</td>
<td>Havia[53]</td>
<td>Finland</td>
<td>Barium Enema Laparotomy</td>
<td>1215</td>
<td>12%</td>
</tr>
<tr>
<td>1967</td>
<td>Manousos[54]</td>
<td>Oxford, UK</td>
<td>Barium Enema</td>
<td>109</td>
<td>7.6%&lt;60 34.9%&gt;60</td>
</tr>
<tr>
<td>1964</td>
<td>Kim[55]</td>
<td>Korea</td>
<td>Barium Enema</td>
<td>1500</td>
<td>0%</td>
</tr>
<tr>
<td>1967</td>
<td>Suarez[56]</td>
<td>Puerto Rico</td>
<td>Barium Enema</td>
<td>971</td>
<td>1%</td>
</tr>
<tr>
<td>1969</td>
<td>Ghavami[57]</td>
<td>Iran</td>
<td>Barium Enema (247) Laparotomy (2149) Autopsy (1689)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>Eastwood[59]</td>
<td>Edinburgh UK</td>
<td>Barium Enema</td>
<td>12,335</td>
<td>22.9%</td>
</tr>
<tr>
<td>1974</td>
<td>Levy[60]</td>
<td>Israel</td>
<td>Barium Enema</td>
<td>1377</td>
<td>16.2% Ashkenazi 3.8% Sephardic 0.7% Arab</td>
</tr>
<tr>
<td>1984</td>
<td>Levy[61]</td>
<td>Israel</td>
<td>Barium Enema</td>
<td>880</td>
<td>17.3% Ashkenazi 12.3% Sephardic 5.4% Arab</td>
</tr>
<tr>
<td>1974</td>
<td>Bohrer[42]</td>
<td>Nigeria</td>
<td>Barium Enema</td>
<td>216</td>
<td>1.15%</td>
</tr>
<tr>
<td>1975</td>
<td>Narasaki[60]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>2662</td>
<td>1.7%</td>
</tr>
<tr>
<td>1975</td>
<td>Rios-Dalenza[54]</td>
<td>Bolivia</td>
<td>Barium Enema</td>
<td>500</td>
<td>0.2%</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Country</td>
<td>Procedure</td>
<td>Cases</td>
<td>Prevalence</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>---------</td>
<td>-----------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>1976</td>
<td>Sato[65]</td>
<td>Japan</td>
<td>Autopsy</td>
<td>771</td>
<td>1%</td>
</tr>
<tr>
<td>1976</td>
<td>Eide[64]</td>
<td>Norway</td>
<td>Autopsy</td>
<td>280</td>
<td>32.1%</td>
</tr>
<tr>
<td>1978</td>
<td>Archampong[67]</td>
<td>Ghana</td>
<td>Barium Enema</td>
<td>592</td>
<td>3.9%</td>
</tr>
<tr>
<td>1978</td>
<td>Calder[68]</td>
<td>Kenya</td>
<td>Barium Enema</td>
<td>226</td>
<td>6%</td>
</tr>
<tr>
<td>1978</td>
<td>Marigo[66]</td>
<td>Brazil</td>
<td>Autopsy</td>
<td>832</td>
<td>9.5%</td>
</tr>
<tr>
<td>1979</td>
<td>Rolon[69]</td>
<td>Paraguay</td>
<td>Autopsy</td>
<td>1364</td>
<td>0.73%</td>
</tr>
<tr>
<td>1979</td>
<td>Eide[66]</td>
<td>Norway</td>
<td>Autopsy</td>
<td>280</td>
<td>32.15%</td>
</tr>
<tr>
<td>1980</td>
<td>Vajrabukka[71]</td>
<td>Thailand</td>
<td>Barium Enema</td>
<td>289</td>
<td>4%</td>
</tr>
<tr>
<td>1981</td>
<td>Dabestani[72]</td>
<td>Iran</td>
<td>Barium Enema</td>
<td>690</td>
<td>1.6%</td>
</tr>
<tr>
<td>1981</td>
<td>Bohrer[73]</td>
<td>Guatemala</td>
<td>Barium Enema</td>
<td>300</td>
<td>2%</td>
</tr>
<tr>
<td>1982</td>
<td>Sim[2]</td>
<td>New Zealand</td>
<td>Barium Enema</td>
<td>1118</td>
<td>35.3%</td>
</tr>
<tr>
<td>1982</td>
<td>Nakib[74]</td>
<td>Kuwait</td>
<td>Colonoscopy</td>
<td>481</td>
<td>0.6%</td>
</tr>
<tr>
<td>1982</td>
<td>Kubo[75]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>12,505</td>
<td>7.8%</td>
</tr>
<tr>
<td>1983</td>
<td>Fatayer[76]</td>
<td>Jordan</td>
<td>Barium Enema</td>
<td>274</td>
<td>4%</td>
</tr>
<tr>
<td>1983</td>
<td>Pan[77]</td>
<td>China</td>
<td>Autopsy</td>
<td>6,896</td>
<td>0.12%</td>
</tr>
<tr>
<td>1983</td>
<td>Pan[77]</td>
<td>China</td>
<td>Colonoscopy</td>
<td>909</td>
<td>1.2%</td>
</tr>
<tr>
<td>1985</td>
<td>Burkitt[78]</td>
<td>Georgia, US</td>
<td>Barium Enema</td>
<td>277</td>
<td>52-60%</td>
</tr>
<tr>
<td>1985</td>
<td>Oguntbi[79]</td>
<td>Nigeria</td>
<td>Barium Enema</td>
<td>603</td>
<td>1.85%</td>
</tr>
<tr>
<td>1985</td>
<td>Coode[80]</td>
<td>Hong Kong</td>
<td>Autopsy</td>
<td>200</td>
<td>5%</td>
</tr>
<tr>
<td>1986</td>
<td>Lee[81]</td>
<td>Singapore</td>
<td>Autopsy</td>
<td>1,014</td>
<td>19.1%</td>
</tr>
<tr>
<td>1987</td>
<td>Ihekwaba[82]</td>
<td>Nigeria</td>
<td>Autopsy</td>
<td>1,420</td>
<td>0.01%</td>
</tr>
<tr>
<td>1987</td>
<td>Sugihara[83]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>625</td>
<td>13.3%</td>
</tr>
<tr>
<td>1987</td>
<td>Naraynsingh[84]</td>
<td>Trinidad</td>
<td>Barium Enema</td>
<td>971</td>
<td>24.6%</td>
</tr>
<tr>
<td>1991</td>
<td>Yap[85]</td>
<td>Singapore</td>
<td>Barium Enema</td>
<td>361</td>
<td>28%</td>
</tr>
<tr>
<td>1991</td>
<td>Chia[86]</td>
<td>Singapore</td>
<td>Barium Enema</td>
<td>524</td>
<td>20%</td>
</tr>
<tr>
<td>1993</td>
<td>Munakata[87]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>11,084</td>
<td>23.2%</td>
</tr>
<tr>
<td>1995</td>
<td>Nakada[88]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>6,849</td>
<td>15.7%</td>
</tr>
<tr>
<td>1998</td>
<td>Ogutu[89]</td>
<td>Kenya</td>
<td>Colonoscopy</td>
<td>247</td>
<td>5.3%</td>
</tr>
<tr>
<td>1998</td>
<td>Chan[90]</td>
<td>Hong Kong</td>
<td>Barium Enema</td>
<td>858</td>
<td>25.1%</td>
</tr>
<tr>
<td>2000</td>
<td>Miura[91]</td>
<td>Japan</td>
<td>Barium Enema</td>
<td>13,947</td>
<td>28.3%</td>
</tr>
<tr>
<td>2010</td>
<td>Lee[92]</td>
<td>Korea</td>
<td>Colonoscopy</td>
<td>1,030</td>
<td>19.7%</td>
</tr>
<tr>
<td>2010</td>
<td>Song[93]</td>
<td>Korea</td>
<td>Colonoscopy</td>
<td>848</td>
<td>12.1%</td>
</tr>
<tr>
<td>2011</td>
<td>Rondagh[94]</td>
<td>Netherlands</td>
<td>Colonoscopy</td>
<td>2,310</td>
<td>37%</td>
</tr>
<tr>
<td>2011</td>
<td>Prilepskaia[95]</td>
<td>Moscow, Russia</td>
<td>Colonoscopy</td>
<td>300</td>
<td>16.2%</td>
</tr>
<tr>
<td>2011</td>
<td>Elbatea[96]</td>
<td>Egypt</td>
<td>Colonoscopy</td>
<td>864</td>
<td>2%</td>
</tr>
<tr>
<td>2011</td>
<td>Golder[97]</td>
<td>UK</td>
<td>Barium Enema</td>
<td>1,000</td>
<td>44.7%</td>
</tr>
<tr>
<td>2012</td>
<td>Kamalesh[98]</td>
<td>India</td>
<td>Colonoscopy</td>
<td>3,022</td>
<td>9.9%</td>
</tr>
<tr>
<td>2013</td>
<td>Azzam[99]</td>
<td>Saudi Arabia</td>
<td>Colonoscopy</td>
<td>3,649</td>
<td>7.4%</td>
</tr>
</tbody>
</table>
There are significant and interesting regional variations in reported prevalence of diverticulosis. Diverticulosis is almost unheard of in certain South American states and in Africa. Recent studies have reported an increasing incidence of diverticulosis in Africa. Despite this, the reported incidence of diverticular disease in African and middle eastern countries remains much lower than that in western countries. There are interesting regional variations. Levy et.al. looked at the incidence of diverticulosis in various ethnic groups in Israel in 1974, and a follow-up study in 1984[60, 61]. He found that the incidence did not change in significantly in the Jewish population, but increased 5 fold in the Arab population. The cause of these regional variations is as yet unknown, and is potential areas of future study.

### 3.2.2 Effect of Age and Gender

It has been known for a long time that the prevalence of diverticulosis as well as the incidence of diverticulitis increases with age. William Mayo noted that diverticulosis was rare in younger patients. In his series of 1819 patients in the 1930's, only 20 patients were less than 40[12]. Multiple series since then have reported prevalence of 2-5% in patients less than 40, increasing to up to 60% in patients more than 70[100]. This is independent of regional variations.

Earlier studies reported a male preponderance in the incidence of diverticulitis. More recent data shows a female preponderance. A large series from 1974 to 1983 of symptomatic diverticulitis admitted at Massachusetts General Hospital showed 59.1% of all cases were Female[101]. In patients under 50, men predominated, but in patients over 50, women were predominant. Other studies have also shown a predominance of men in younger patients [102, 103].

Figure 2 shows incidence of diverticulosis with respect to region, age and gender. Correcting for regional variations, there is still an increase in incidence of diverticulosis with increasing age in Western Countries. In Singapore, the prevalence peaked at 65-74, and then decreased in older cohorts.
3.2.3 Regional and Ethnic Variations

There are significant ethnic as well as regional variations in the incidence of diverticulosis and diverticulitis. In a seminal paper published in 1969 by Painter, Diverticular disease was called a disease of Western Civilisations[37]. This stemmed from his experiences in Africa, where Painter had noticed that diverticular disease was almost unheard of.

South American countries have very low reported incidences of diverticular disease and its complications. Reported incidence included 0.2% in Bolivia[64], 1% in Puerto Rico[56] and 0.73% in Paraguay[70]. An interesting study conducted by Bohrer on the highland Mayan Indian tribes in Guatemala reported an incidence of 2%[73]. Their diet and lifestyle were reportedly largely unchanged with Western influence. A study from Brazil reported a higher incidence of 9.5%[69]. While this was much higher than other South American countries, it was still significantly lower than that of western countries.

Middle Eastern countries also have very low reported incidence of diverticular disease. In a study from Iran, Ghavami reported no diverticular disease found from almost 4000 patients[57]. Another study by Dabestani from Iran reported an incidence of 1.6%[72]. Other reports included an incidence of 0.6% in Kuwait[74], 2% in Egypt[96], 4% in Jordan[76] and 7.4% in Saudi Arabia[99].
The incidence of diverticular disease in Africa traditionally has been of great interest. This was the region that Painter initially noticed a very low incidence\cite{36}. He reported that diverticular disease was almost unknown in rural Africa, and seen only occasionally in more in 40 hospitals in Johannesburg and in Ibadan, Nigeria. Studies from the region report an incidence of 6\% in Kenya\cite{68}, and 3.9\% in Ghana\cite{67}. There have been multiple studies conducted in Nigeria. Bohrer reported an incidence of 1.15\% in a tribe in rural Nigeria\cite{62}. Ihekwaba reported an incidence of 0.01\% from an autopsy series on “Black Africa” in Nigeria\cite{82}. Ogunbiyi conducted a study in Ibadan, the area initially reported by Painter, and found an incidence of 1.85\%\cite{79}. Alatise et al reported only 40 cases of diverticular disease over a 5 year period in a tertiary hospital in Nigeria\cite{105}.

As immigration increases from non-western countries to western countries, the incidence of diverticulosis in these migrants has been studied. Migrants have been noted to have lower incidence for diverticular disease than native residents of western countries. Painter reported that the disease was rare amongst Japanese, but increased in Japanese migrants in Hawaii. He also noted that the incidence of diverticular disease and diverticulitis in Negro Americans was equivalent to that that of their white counterparts, while the disease was almost unheard of in Africa. Turkish migrants to the Zaanstreek region of Netherlands have a significantly lower incidence of diverticular disease (7.5\% vs 50\%)\cite{106}. Similarly, incidence of diverticular disease among Indian subcontinent migrants to UK is also significantly lower than that of native residents (6\% vs 23\%)\cite{107}.

Hjern et al looked at hospitalisations for diverticular disease amongst immigrants over a 10 year period in Sweden\cite{108}. After adjusting for age, sex and socioeconomic status, they found that incidence of diverticular disease among migrants from Western Europe, Australia, New Zealand and North America were not significantly different to that of the native Swedish population. Amongst migrants from Non Western countries, including Africa, Asia, South America and Eastern Europe, there was initially a much lower risk of admission. However, their incidence of diverticular related admissions increased sequentially the longer they lived in Sweden. No study has specifically looked at differences in diet among migrants or ethnic groups.

Figure 3 shows a graph of reported prevalence of DD over time in some countries. All countries except Jordan and Kenya showed an increase in prevalence. The largest rise was reported in Japan, where prevalence went from <5\% in 1975 to 28\% in 2000.
3.2.3.1 Asian Countries and Right Sided Diverticular Disease

Asian countries have been studied with great interest as the spectrum of disease is quite different to that of western countries. In western countries, diverticular disease affects the left side of the colon 90-99% of the times [97]. In Asian countries, diverticular disease is predominantly on the right side. Right sided diverticular disease is found in about 20% of asymptomatic patients in Asian countries vs. only about 5% in western countries. In western countries, diverticulitis involves the right side only about 1.5% of times vs. 75% in Asian countries [110]. The cause of this difference in distribution has not been explained to date. Within Asian countries, there are interesting variations.

In Singapore, autopsy data from more than 1000 patients showed a significantly higher incidence amongst ethnic Chinese (24%) compared to ethnic Indians (14.3%) and Malays (11.7%) [81]. They found that if a single diverticulum only was found, it was found in the right colon or transverse colon 87.1% of times. For multiple diverticulae, the right side was involved 67-95% of the times. This is in sharp contrast to distribution of disease among western countries, where right sided disease is found very rarely. Interestingly, the distribution of right sided disease was similar in all three ethnic groups studied. While there were ethnic variations in overall incidence, there was no significant difference in the distribution of the disease. This suggests an environmental factor predisposing to right sided disease.

An autopsy series from Japan, looking at 625 patients found right sided diverticular disease in 68.8% [83]. Of the 77 patients with diverticulitis in this series, 61 (79.2%) had right sided diverticulitis while only 16 (20.8%) had left sided disease. A South Korean study of 1030 patients undergoing
colonoscopy at a tertiary hospital in South Korea found diverticulosis in 203 (19.7%) of patients [92]. Of these 203 patients, Right sided diverticulosis (i.e. involving caecum and ascending colon) was found in 85%. The Left side was involved only 12.7% of the times. This distribution was also reflected in the incidence of diverticulitis. About 80% of the cases of diverticulitis were on the right side. There have also been multiple longitudinal studies looking at diverticulosis in Japan in from 1967 to 1993 [83, 87, 88]. This showed a significant increase from 2.1% in 1967 to 23% in 1993.

The cause of this East-West difference has not been explained. Studies on Japanese emigrants to Hawaii, and their children have shown a right sided predilection, compared to the indigenous Hawaiian population [58, 111]. This suggests a genetic predisposition as well as environmental factors in the pathogenesis. This is a potential area for future study.

3.3 Pathogenesis of DD

3.3.1 Introduction

The exact mechanism by which DD forms is as yet unknown. Rather than a single causative factor, multiple factors have been identified. Diverticular disease probably results from a complex interplay of Genetic, Lifestyle and Environmental factors. There may be a difference in aetiology of right sided disease vs left sided disease. In the western world left sided disease predominates, therefore our discussion focuses on this.

There are functional differences between the right and left side of the colon. The right colon receives ileal content, which is predominantly liquid. It has a relatively high concentration of carbohydrates and proteins that have escaped small bowel digestion. As this content moves through the colon, bacterial action causes fermentation and solubilisation. Further down the colon, the level of microbial action decreases as substrate for activity decreases. Coupled with this there is increase in absorption of water and electrolytes, resulting in a firmer content. By the time it reaches the descending colon, most of the absorption will have occurred. The sigmoid colon and rectum act as a holding reservoir for the bulk. As we progress distally from the sigmoid colon, the level of voluntary control increases, allowing for control of release of faecal matter.

The wall of the colon is composed of 3 layers, namely, the mucosa, muscularis, and serosa. The muscularis layer is composed of 2 layers of muscles, named after for their orientation in the colonic wall, i.e. Circular and longitudinal layers. The circular muscle layer thickens at regular intervals to form valvular flaps, called plicae circularis, that project into the lumen of the bowel. These act to slow down passage of effluent, as well as to increase absorptive area available. The longitudinal muscle layer also condenses into thick bands called the taeniae coli. This contracts to allow shortening of the colon which results in forward propulsion of content.
Historically models of pathogenesis include the staged model and herniation in areas of vascularity. These were discussed previously in the history of DD. The staged model has now been abandoned, and it is now known that DD can involve any portion of the bowel, and not just the mesenteric side with blood vessels.

3.3.2 Summary of Proposed Models of Pathogenesis for Diverticular Disease

3.3.2.1 Smooth Muscle Hypertrophy and Role of Elastin, Collagen, MMP and TIMP

Thickening of the Smooth Muscle layer has long been recognised as one of the most consistent features of diverticular disease[33, 112]. This was thought to be due to increased muscle hypertrophy, resulting in increased intraluminal pressures and subsequently, diverticular disease. It is now known that this is incorrect. Ultrastructural studies of the muscle cells of patients with uncomplicated DD have not shown hypertrophy or hyperplasia of muscle cells. Instead, studies have shown an increase in elastin laid down between muscle cells, resulting in altered muscle morphology. These changes are not unique to DD, as they have also been found as a natural feature of ageing[113, 114].

A role for collagen has long been suspected in the pathogenesis of DD and diverticulitis. Collagen Type I is responsible for mechanical strength in mature tissue. Collagen Type III is usually found in early phases of wound healing, and does not have the same tensile strength of Type I. Collagen is degraded by the synergistic action of Matrix Metalloproteinases (MMP), a family of zinc-dependant endopeptidase enzymes, and Tissue Inhibitors of MMP (TIMP). Colonic diverticula occur as a result of weakness in colonic wall, resulting in outpouchings of the mucosa and submucosa. Weakness of colonic wall could be the result of reduced Type 1 collagen, either from reduced deposition or from increased action of MMP and TIMP. Weakness could also result from increased deposition of Type III collagen.

Deposition of collagen in muscle layers has also been shown in patients with DD[115]. Studies of ratios of Collagen Type I to Type III in patients with DD have shown increased Type III collagen compared to colons free of diverticular disease[116, 117]. As Type III collagen is usually laid down after inflammation, this suggests inflammation and scarring in the pathogenesis. Increase in elastosis by greater than 200% as been shown in taenia coli of patients with DD[118]. Increased collagen crosslinking resulting in a less compliant colon has also been shown in patients with DD[119]

Studies of MMP and TIMP in patients with diverticulitis have been conflicting. Stumpf et.al. showed decreased expression of MMP[117], while Rosemar et.al.[120] found increased expression. Mimura
and colleagues found an 18 fold increase in TIMP mRNA expression in complicated diverticulosis compared to controls[121]. This upregulation of TIMP was also observed in Macrophages and fibroblasts in areas around blood vessels. Increased TIMP expression has been associated with increased severity of diverticulitis[121].

These studies have been conducted on a small number of patients who have undergone resection for acute diverticulitis. Whether these factors play a role in the formation of asymptomatic DD is unknown. In acute diverticulitis, there is increased expression of cytokines and pro-inflammatory mediators, which may alter expression of mRNA of MMP and TIMP’s[122]. It is also not known whether the increased ratio of Type III collagen is a result of previous bouts of inflammation or as a result of an acute process.

3.3.2.2 Genetics and Connective Tissue Disorders

There is evidence that weakness in connective tissue such as elastin and collagen can result in diverticular disease. The incidence of diverticular disease and diverticulitis is increased in patients with congenital disorders of elastin and collagen. Patients with Congenital Connective tissue disorders such as Marfans Syndrome and Ehlers Danlos Syndrome have an increased incidence and present at a younger age with diverticulosis and diverticulitis[123, 124]. Colonic diverticulae are present in up to 40% of patients with Ehlers-Danlos Type IV syndrome[125]. Perforated diverticulitis has also been described in adolescents with Williams-Beuren Syndrome, leading to operative intervention[126]. Diverticulosis is also present in high numbers in patients with Polycystic Kidney Disease on dialysis compared to renal failure patients without Polycystic disease and age matched controls [127].

3.3.2.3 Intraluminal Pressure, Colonic Transit Time (CTT), and Colonic Motility

While traditionally believed to the primary causative agent in the formation of DD, studies looking at intraluminal pressures and CTT have been conflicting and contradictory, and plagued with methodological flaws.

Burkitt in 1972 studied CTT, stool weight and dietary intake in UK, South Africa and Uganda. He found that increased fibre in diet resulted in shorter CTT and increased stool weight [128]. He hypothesised that low fibre resulted in smaller harder stools that took longer to pass through the colon, which resulted in the colon generating higher pressures to propel and expel stool. He proposed this as the underling mechanism for DD. Seminal work by Painter and Arfwiddsen also suggested a role for increased intraluminal pressures [26-31].
The evidence for the role of abnormal intracolonic pressure is weak. These studies generally did not control for age or gender, and they were performed on small number of patients, without adequate population matched controls. Colonic Transit times vary significantly in the population. It varies with diet, time of day, coexisting medical conditions, and age. More recent studies have questioned these findings. A meta-analysis of studies on addition of wheat bran did not show any increase in CTT or frequency of defaecation[129]. A study of colonic motility over a 24hr period in patients with DD has shown increased motility and propulsive force compared to health subjects[130]. A recent systematic review of manometry data showed significant heterogeneity and methodology, and recommended further high quality studies with standardized reporting using modern manometry techniques[131].

Traditionally, it was believed that patients with DD generated higher pressures during segmentation in their colons. Thickened smooth muscle was observed in colonic walls of patients with DD. It was thought that this caused a stronger contraction and generation of higher pressures. As discussed previously in page 28, it is now thought that the thickening is due to increased deposition of elastin and collagen rather than smooth muscle hypertrophy or hyperplasia. Studies on colonic resting pressures were performed in a small number of patients, and there have been methodological flaws in the studies themselves. The pressures were measured by inflating a balloon in the colon. Paradoxically, studies have shown that inflating balloons in the colons of patients with DD results in the muscle layer yielding more quickly than in healthy controls [132, 133]. Preparation of bowel for testing and introduction of transducers also alters resting states. Measurements therefore may not be a true reflection of native pressures. These studies were also performed for short periods of time, and may not be an accurate reflection of colonic pressures over a longer period of time.

The incidence of DD increases with age. Studies of CTT in the older patients have been conflicting, with some studies showing a slower rate of passage [134, 135], while others showing no difference [136, 137]. To date, there is no conclusive evidence of reduced CTT or increased pressure in colons of patients with DD compared to patients without.

While most motility studies show a reduction with DD, a study by Shafik et.al. showed two different electrophysiological activity patterns in DD[138]. In the early stages, there was elevated electrophysiological activity, suggesting hypermotility. In the later stages, there is a low or absent electrophysiological activity

3.3.2.4 Cellular, Myenteric Nervous and Molecular Signalling Dysfunction.

Strong evidence exists for neurophysiological disturbance in diverticular disease, especially in later stages of the disease. Multiple studies have shown aberrant responses to stimuli in colonic smooth muscle of patients with DD[139-141]. Most studies show decreased response to electrophysiological stimuli in ex-vivo specimens of patients with DD. Studies have described a reduction in myenteric
plexus in patients with diverticulosis [142, 143]. Studies have reported reduced ganglionic nerve cells in affected smooth muscle[143, 144]. Studies have also shown significant reduction in Glial Cell and Interstitial cells of Cajal, as well as reduced signalling between cells in resected sigmoid specimens containing diverticular disease[145, 146].

Animal models show a natural decrease in enteric nerve density with ageing [140, 141]. Histological studies on humans have also shown decrease in enteric nerve density and ganglia with ageing [140, 147, 148]. It has been hypothesized that with ageing, there is decrease in enteric neurons, resulting in impaired colonic motility, possibly resulting in DD. Studies on this however are conflicting as other studies have found increased, albeit disorganized ganglia in diverticular disease [114].

There is increasing evidence that Interstitial cells of Cajal act as pacemaker cells, and maybe responsible for generation of slow waves[149]. Disruption of these cells could result in relative colonic hypomotility.

The survival and maintenance of enteric neurons is dependent on neurotrophic factors, such as Glial Cell Line-derived Neurotrophic factor (GNDF). GNDF is a member of the TGF-B family of growth factors. Loss of the gene for GNDF leads to complete loss of enteric neurons. In a study by Bottner et. al., when colons of patients with diverticulosis were compared to patients without diverticulosis, there was significant downregulation of mRNA of GNDF and its receptors[145]. This research, while still in its infancy, represents a promising new avenue for the search of pathogenesis of diverticulosis, and possible avenue for gene therapy in the future.

![Figure 6 - mRNA Expression of the GDNF system in muscularis propria of the human colon](image)

*Figure 6 - mRNA Expression of the GDNF system in muscularis propria of the human colon*

*Figure 1. mRNA expression of the GDNF system in the muscularis propria of the human colon. mRNA expression of GDNF (A) and its receptors GFRa1 (B) and RET (C) is significantly down-regulated in patients with DD compared to controls. mRNA levels are determined by qPCR, expression of target genes is normalized to mRNA expression of the housekeeping gene HPRT. Data are shown as mean +/- SEM, n=20 (controls) and n=21 (DD), *p<0.05 vs. control.

doi:10.1371/journal.pone.0066290.g001

From Bottner et.al[145]
This is an area of future study. This evidence while interesting, is largely speculative because there remains a lack of an animal model for diverticular disease. Neuronal issues may lead to motility problems, but how this results in formation of diverticulae remains unclear. Most studies to date were performed in small numbers of patients, using specimens obtained from acute operations, i.e. complicated diverticular disease. Some studies used colon from patients with colorectal cancer as control. This may not be an accurate reflection of all patients with DD. It is not known if neuromuscular dysfunction is a factor in pathogenesis in early stages of disease, or in late stages. It is not known whether this occurs in asymptomatic patients. As yet, no conclusive evidence exists to date of neuromuscular dysfunction in the pathogenesis of DD.

### 3.3.2.5 Dietary Fiber and Lifestyle Factors

Insufficient dietary fibre intake was thought to be the cause of DD for half a century. In 1949 Carlson et al. conducted a study on rats fed low fibre and high fat diet, and found increased incidence of diverticulosis[150]. Subsequently, in Painter and Burkitt’s seminal work in 1960’s, dietary fiber was proposed in the pathogenesis of DD[36, 37, 128, 151]. Painter observed that DD was almost unheard of in Africa, where fibre intake was higher. They also observed that incidence of diverticulitis decreased among European migrants to Singapore, Fiji and Nigeria[37]. The proposed mechanism of pathogenesis was that deficiency in fibre led to passage of smaller harder stools, which required greater work by the colon to expel. This raised intraluminal pressures, resulting in diverticular disease. Painter stated that diverticulosis, like scurvy, is a deficiency disease, and therefore, should be preventable[36]. Painter then performed a study adding unprocessed bran in diets of 70 patients with symptomatic DD, and found marked relief of symptoms in 62[151]. This lead to the recommendation of addition of fibre to patients with symptomatic diverticular disease, a practice that is still endorsed by current guidelines and recommendations of professional bodies.

There are significant flaws in these studies and their conclusions. Painter and Burkitt’s work assumed diet to be uniform within the African countries. This is not true, as diet varies considerably depending on geographical location within the country, level of urbanisation, and socioeconomic status. There has been a shift towards western diet in the latter half of the century in Africa.

During the time of Painter’s studies, life expectancy in African countries was low. This has not changed significantly in recent years. The World Health Organisation (WHO) reports average life expectancy currently in South Africa is 52.62yrs, Nigeria is 51.86 years and in Kenya is 57.08 years. As incidence of DD increases with age, one would expect countries with low average life expectancy to have lower prevalence anyways. Data from the UK has also shown that while consumption of refined foods have increased and consumption of fibre has significantly decreased since the 1940’s, the age adjusted mortality from DD has not changed significantly[152].
Subsequent studies to confirm the low fibre pathogenesis theory have produced limited and conflicting results. There is a significant paucity of good quality studies on large number of patients. Most studies were observational interventional studies performed on small numbers of patients. Larger studies have focused on symptomatic patients or patients with diverticulitis only, ignoring the large majority of patients with asymptomatic disease.

Gear et.al. performed a study of asymptomatic diverticular disease among vegetarians and non-vegetarians in UK[153]. They found non-vegetarians had a significantly lower intake of fibre, and higher incidence of diverticular disease. Confounding this is the fact that in their study, vegetarians with diverticulosis consumed more fibre than non-vegetarians without diverticulosis.

A systematic review of the role of high dietary fibre in diverticulitis was performed by Unlu and colleagues in 2012[154]. They found only 3 randomised controlled studies and one case controlled study of sufficient quality for meta-analysis. The 3 randomised studies had inconsistent results. Two showed significant improvement in symptoms although a significant placebo effect was seen in one. The third study showed no effect of fiber. A similar review of clinical studies by Hume et.al. concluded that although fiber supplements were widely used and recommended, there was little evidence to support their use in uncomplicated DD, but some people may report improvement in symptoms[155].

Aldoori et.al. prospectively looked at dietary fiber and risk of symptomatic diverticular disease in 43,881 U.S. male healthcare professionals[156]. They found risk of symptomatic DD was higher in the quintile with lowest fiber intake. Similarly, the European Prospective Investigation into Cancer and Nutrition-Oxford Cohort (EPIC-Oxford) looked at 47,033 British men and women for an average of 12 years[157]. They found that adjusted relative risk of hospitalisation with symptomatic DD for patients in the highest category of fiber intake was almost half that of those with the lowest intake. The main criticisms of these studies are that they do not look at asymptomatic DD. These studies also included patients with diverticular bleeding in the category of symptomatic DD.

A more recent observational study by Peery and colleagues looked at 2104 patients undergoing colonoscopy[158]. These patients were then interviewed and diet and lifestyle information was collected. They found that DD was more prevalent in patients with high fiber diets. They also found a dose response relationship, with patients with >3 diverticulae having higher fiber diets than patients with <3 diverticulae. They concluded that a high fiber diet did not protect against asymptomatic diverticulosis.

These studies suggest that addition of fiber in patients with symptomatic DD results in improvement in symptoms, and reduction in hospital admissions and complications of DD. It has not been
conclusively shown that addition of fiber reduces incidence of asymptomatic DD. The risk factors transforming asymptomatic DD to acute diverticulitis and symptomatic DD are also poorly understood.

Other lifestyle factors such as smoking, alcohol, and caffeine intake have been looked at. Aldoori and colleagues, in the largest prospective study of risks of symptomatic DD in men, looked at a cohort of 47,678 men [159]. They found only 382 cases of acute diverticulitis (0.8%). There was no significant association between alcohol intake, caffeine intake or smoking with risk of acute diverticulitis. This however does not look at asymptomatic diverticulosis.

Physical activity has also been studied. Physical activity may be a surrogate marker of obesity. Reduced physical activity has been associated with increased DD in women in Sweden [160]. Women who exercised more than 30 minutes a day had a 46% lower risk of diverticular bleeding and 25% lower risk of diverticulitis. A small study of runners showed vigorous physical activity (running >8km/day) was associated with a 69% risk reduction for symptomatic DD, compared to runners who ran less than 2km/day[161].

3.3.2.6 Medical conditions

An increased incidence of diverticular disease has been noted in various medical conditions. As discussed previously, diverticulosis has been reported at a higher rate in patients with Polycystic kidney disease. Epidemiological studies on these are difficult, as diseases do not occur in isolation, but often in combination with other factors. Other acquired conditions that have been associated with DD include

3.3.2.6.1 Hypothyroidism

A large retrospective case control study of 3,175 patients in Israel showed a 2.4 times higher risk of diverticulosis if there was a diagnosis of hypothyroidism[162]. It is thought that hypothyroidism could result in colonic hypomotility and constipation, which could result in diverticular disease.

3.3.2.6.2 Diabetes

Studies on DD in patients with diabetes have been conflicting. The same Israeli study as above showed a decrease in incidence of DD in diabetics by about half. Another study in middle aged Japanese males however showed doubling of the incidence of DD in males with Diabetes[163]. Similarly, in a Korean study, Diabetes has found to be an independent risk factor for presence of DD[92]. A study in Saudi Arabia also showed increased DD in Diabetics[99]. These studies were conducted in Asian populations, which have a different pattern of disease compared to Western populations. It is not known if these results are generalizable to all diverticular disease.

3.3.2.6.3 Hypertension
Studies on hypertension have also been conflicting. Some studies have shown significantly higher incidence[99, 163], while others have shown no increase incidence[162].

4. **Diverticulitis**

4.1 Introduction

Acute diverticulitis (AD) results from inflammation of a diverticulum. Diverticulitis affects between 10-25% of people with diverticulosis. The cause is poorly understood. Most of the people will experience only a single episode of diverticulitis. A small proportion experience recurrent diverticulitis. The risk factors for recurrent diverticulitis are again, very poorly understood.

Clinically, diverticulitis can present in wide spectrum ranging from uncomplicated disease to abscess, to perforation, to fistula formation. Uncomplicated diverticulitis is usually defined as the presence of colonic diverticular disease with localised wall thickening and/or stranding of pericolic fat on CT. Complicated diverticulitis was defined as; the presence of abscess, perforation (including any pericolic or extraluminal gas), obstruction or fistula formation, protracted disease with symptoms, or an associated mass lesion.

Of all patients with AD, about a quarter present with complicated diverticulitis at first presentation. Not all patients with complicated disease have prior episodes of diverticulitis[164]. Previously it was thought that diverticulitis progressed in a linear fashion, but this is not thought to be the case now. Because of the variety of presentations, and lack of clear progression, these entities may have separate pathogenesis. Complicated and uncomplicated diverticulitis may be separate clinical entities, with differing pathogenesis, natural history and outcomes.

Clinically, diverticulitis is manifested by onset of abdominal pain and fever. Blood tests usually show an elevated White Cell Count and neutrophilia, and an elevated C-Reactive Peptide (CRP) and Erythrocyte Sedimentation Rate (ESR). Diagnosis is usually confirmed with cross sectional imaging or CT scan. CT scanning also allows for radiological classification of the disease into uncomplicated and complicated diverticulitis.

Acute diverticulitis accounts for a significant proportion of all acute surgical admissions. Annually there are about 152,000 yearly hospitalisations in the US alone for diverticulitis[165]. Of all patients with diverticulosis, up to 25% will developing symptomatic acute diverticulitis or complications of diverticular disease[166]. Hospitalisations for acute diverticulitis are also on the increase. In Finland cases of complicated diverticulitis have increased 50% over the last 20 years[167] Admission rates for
diverticular disease have increased by up to 16% over the past decade [168]. Of all the patients admitted with diverticulitis, about 32% will have at least one further admission within 1 year.

4.2 Pathogenesis of Diverticulitis

The underlying pathological mechanism that leads to diverticulitis remains unclear. Rather than a single causative factor, it is likely that a number of factors are involved in an as yet poorly understood mechanism. Historically, it was thought that diverticulitis occurred as a staged progression of DD, starting with development of diverticula, and progressing to pericolicitis, phlegmon formation, abscess and eventual perforation. This has now been disproven. The cause is likely to be due to complex interactions involving environmental and genetic factors. Some of the implicated factors in pathogenesis are discussed below.

4.2.1 Stasis, Obstruction and Inflammation

Similar to the theory of pathogenesis of appendicitis, this theory hypothesizes that the pathogenesis is diverticulitis is the result of faecal matter causing obstruction of a diverticulum[169]. A faecolith or hard inspissated faeces obstructs the narrow neck of a diverticulum. This results in a low grade inflammation from the continuous abrasion of the mucosa from hard faeces. Loss of mucosal barrier allows for translocation of colonic microbiota into the lamina propria, leading to inflammation of the mucosa[170, 171]. A second theory is that inspissated faeces in diverticula leads to obstruction, which then leads to bacterial overgrown in an anaerobic environment, and local tissue ischemia from increased pressure.

There are several flaws with these theories. Cultures of peritoneal fluid for perforated diverticular disease most commonly show mixed anaerobic and aerobic organisms[172]. This goes against obstruction and overgrowth in an anaerobic environment. Diverticulitis can also occur in the presence of large mouthed diverticulae, which do not obstruct. On cross sectional imaging and at histology, rarely are obstructing faecoliths found in diverticulae.

Progression of acute diverticulitis to complicated disease, including perforation and fistulation occurs in only a small proportion of patients. This goes against a constant irritation or obstruction theory.

It has been noted that mucosal inflammation can coexist with diverticular disease[173-175]. This so called “Segmental Colitis” or “Diverticular Colitis” has similar features histologically to inflammatory bowel disease. It has been known that a proportion of patients continue to have symptoms long after signs and symptoms of inflammation have abated. Segmental colitis has been proposed to be the
causative agent for their symptoms. Chronic low grade inflammation can also result in altered neurophysiology which can alter colonic motility.

### 4.2.2 Dietary Fiber Hypothesis

Dietary fiber has been implicated in pathogenesis of diverticulitis. A high fiber diet has experimentally been shown to alter colonic flora and micro-ecology of the colon of patients [176, 177]. This may result in a change in the immune response of the patient. Addition of probiotics to diet has been shown to modulate intestinal immune response, which may result in down regulation of intestinal inflammatory responses [178, 179]. A theoretical progression to diverticulitis from low fiber diet is shown below.

**Figure 7 - Dietary Fiber Hypothesis**

4.2.3 Microperforation

This model postulates that a microperforation in a diverticulum leads to an inflammatory response, which then progresses onto diverticulitis and its complications. Several potential causes for this microperforation have been proposed. Stasis and obstruction as mentioned earlier can lead to microperforation. The neck is usually the narrowest point of the diverticulum. This passes through the muscle layers, and can be compressed by contraction of the muscle. This can result in increased pressure on the head of the diverticulum, possibly resulting in microperforation. It can also result in obstruction and stasis[21]. This is currently accepted as the most likely cause of acute diverticulitis.
4.3 Risk Factors for Diverticulitis

4.3.1 Age and Sex

The incidence of diverticular disease increases with age, and as expected, the incidence of diverticulitis also increases with increasing prevalence. There is clearly an association with age and diverticulitis. Traditionally, diverticulitis was thought of as a disease of the elderly [180]. Recently however, there has been an increasing incidence of AD in younger populations. In a large review of admissions between 1998 to 2005 in the US population, the average age for AD decreased from 64.6 to 61.8 during the study period [181]. Incidence rates remained stable in the 65-74yo age group, but increased dramatically in the 18-44yo and 45-64yo age groups.

Sex differences have also been noted, but studies are conflicting. Early studies suggested a higher incidence in males [182]. Schauer and colleagues reported double incidence of diverticulitis in males compared to females in less than 40yo, and 1.5 times increased incidence in greater than 40yo[103]. More recent data from UK and Canada however have showed a higher incidence of hospitalisation in women compared to men [168, 181].

4.3.1.1 Younger Patients

Diverticulitis is relatively rare before the age of 40. Patients less than 40 yo account for only 2-5% of all patients with acute diverticulitis [102, 183]. There is evidence that the incidence of acute diverticulitis in this subgroup is increasing. Recent epidemiological studies have reported increased hospitalisations in these patients [1, 184]. Patients less than 50 account for the greatest relative increase in hospitalisations for diverticulitis
4.3.2 Medical Conditions

4.3.2.1 Hypertension

Hypertension has been associated with an increased risk of acute diverticulitis as well as complicated diverticulitis. A large prospective Swedish study by Rosemar and colleagues sowed an almost double risk of complicated diverticulitis in men with BP >146mmHg [185]. Diastolic pressure >102mmHg was also associated with a 2.2 times higher risk in the same study.

4.3.2.2 Renal Disease

Diverticular disease has been associated with polycystic kidney disease. Multiple studies have looked at diverticular disease in patients with chronic renal failure[186, 187]. While studies suggest mild to modest increase in risk of diverticular disease, the impact on diverticulitis is less clear. In the absence of polycystic disease, the risk of acute diverticulitis is not increased in renal failure[188]. A retrospective UK study on risk factors for death with perforated diverticulitis however showed increased odds (OR 18.7) for pre-existing renal disease[47].

4.3.3 Immunosuppression, Steroids and NSAIDS
Immunocompromised patients represent an “at risk” group of patients. These include patients with Acquired Immunodeficiency states, including AIDS, Immune suppressed patients such as solid organ transplant recipients and well as patients on chronic immunomodulatory drugs such as corticosteroids and anti-rheumatoid medications. This group has been studied extensively, as it was thought that these patients would have a more virulent form of diverticulitis and be more likely to have complications related to the disease.

Early case reports from 1971 from Washington University hospital reported a higher incidence of perforated diverticulitis among patients on chronic corticosteroids[189]. This trend was confirmed in multiple subsequent studies[190-193]. Prior to cross sectional imaging, the diagnosis was often based on clinical or operative findings, and therefore incidence of perforated disease was overestimated to an extent. Later studies combined accurate diagnosis with large numbers to analyse trends in patients on chronic corticosteroids. Humes et.al. performed a case-control analysis of 899 cases of perforated diverticular disease[194]. They found that 20% of patients with perforation had used oral corticosteroids, compared to 10% of controls. Overall, corticosteroid use was associated with a 70% increased risk of perforation. They also looked at NSAID use, and found a small, non-statistically significant increase in risk of perforation.

Studies on organ transplant recipients have largely been on small number of patients. These have however shown a very high mortality rate with colonic perforation in these patients. A summary of the studies is given below. The most well studied group are patients with renal transplants.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Organ Transplanted</th>
<th>Patients with Perforation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalla Valle[195]</td>
<td>2005</td>
<td>Kidney</td>
<td>8</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Church[196]</td>
<td>1986</td>
<td>Kidney</td>
<td>11</td>
<td>7 (63%)</td>
</tr>
<tr>
<td>Koneru[197]</td>
<td>1990</td>
<td>Kidney</td>
<td>11</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Squiers[198]</td>
<td>1991</td>
<td>Kidney</td>
<td>12</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Bardaxoglou[199]</td>
<td>1993</td>
<td>Kidney</td>
<td>6</td>
<td>4 (66%)</td>
</tr>
<tr>
<td>Benoit[200]</td>
<td>1993</td>
<td>Kidney</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Stelzer[201]</td>
<td>1996</td>
<td>Kidney</td>
<td>30</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Pirenne[202]</td>
<td>1997</td>
<td>Kidney</td>
<td>8</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Lederman[203]</td>
<td>1998</td>
<td>Kidney</td>
<td>13</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Catena[204]</td>
<td>2008</td>
<td>Kidney</td>
<td>15</td>
<td>7(46.7%)</td>
</tr>
<tr>
<td>Qasabian[205]</td>
<td>2004</td>
<td>Heart/Lung</td>
<td>8</td>
<td>1(12.5%)</td>
</tr>
<tr>
<td>OVERALL</td>
<td></td>
<td></td>
<td>127</td>
<td>45 (35.4%)</td>
</tr>
</tbody>
</table>
The risk of progression to diverticulitis and perforation among these patients is low. Hwang and colleagues performed a Meta-analysis of diverticulitis in transplant patients and patients on chronic corticosteroids. They report an overall incidence of progression to diverticulitis with or without perforation of 1% over a variable length of time. In patients with known DD, approximately 16% progressed to diverticulitis. Contrary to wide held beliefs, abdominal signs and symptoms in these patients were not masked due to immunosuppression. Hwang reported an overall mortality of 23% for an emergency colectomy and a mortality of 56% for patients not undergoing surgery[190].

Patients on NSAIDS and other Cyclo-oxygenase inhibitors represent a special category within these patients. These drugs have well known effects on suppression of metabolites of Arachidonic acid, and the subsequent suppression of host protective mechanisms and inflammatory responses. Well known complications of these drugs include gastrointestinal tract ulceration and reduction of adhesiveness of platelets, resulting in increased risk of bleeding. Small cohort studies have shown an increased risk of perforation among patients on regular NSAIDS[192, 206, 207]. A large study of 939 patients by Strate and colleagues found an increased risk of diverticular bleeding as well as diverticulitis with regular use of Aspirin and NSAIDS [208].

4.3.4 Geographical and Seasonal Factors

Seasonal variations and cyclical patterns have been observed in hospitalisations for AD in USA. Ricciardi and colleagues reported an increase in hospitalizations in summer months by about 25%[209]. This was noted to be independent of region, age, sex and race. Nguyen and colleague noted regional variations in USA, with highest incident for hospitalization for AD in North-eastern states, and lowest in the Western and Midwestern states[184]. Risk for hospitalization has been risked to sunlight exposure and Vitamin D levels. Higher Vitamin D levels have been associated with significantly lower risk of diverticulitis[210].

4.3.5 Diet and Lifestyle Factors

As previously the link between diet and DD is weak at best. Evidence for the role of fiber in Diverticulitis is marginally stronger. There have been at least 3 large epidemiological studies addressing this issue.

The Health Professional Follow-up Study (HPFS) of 48,000 men showed that men with the highest intake of fiber (>32g/day) had the lowest risk of symptomatic diverticulitis, with an estimated risk reduction of 42% compared to those with lowest fiber intake[211]. Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) study of 47,033 men and women from Scotland and England showed a 41% lower risk of hospitalisation in participants with the highest
 (>25g/day) intake of fiber [157]. Vegetarians also had lower risk. The Million Women Study of 690,075 middle aged women also showed reduced risk of admission and death in women with highest (>17.6g/day) Fiber intake[212]. In this study, the effect was noted to be different depending on fiber consumed, with strongest effect seen in cereal and fruit fiber.

The main criticism of these large epidemiological studies is that hospital admission does not always equate to acute diverticulitis. These studies were conducted prior to the routine use of CT scanning to prove acute diverticulitis. It is difficult to know whether the symptoms and observed risk reduction represent Acute Diverticulitis, Symptomatic Diverticular Disease, Diverticular Complications or functional bowel problems associated with DD.

Other dietary factors that have been studied include Dietary Fat[93, 211], Red Meat[211], Dairy Products[213], Caffeine[159], Micronutrients (Potassium, beta carotene, Vitamin C and Magnesium)[211], and Nuts, corn and popcorn[214]. None of these have been associated with any significant increase in Acute Diverticulitis.

Lifestyle factors studied have included Alcohol Intake and Smoking. In the prospective HPFS study, there was a modest increase in risk (RR 1.38) of symptomatic diverticular disease in men with alcohol consumption greater than 30g/day[159]. In the EPIC study however, significance of the effect of alcohol disappeared after adjustment for smoking. In a study by Papagrigoriadis, there was no difference in alcohol consumption in patients with and without complicated diverticulitis[215].

Smoking has long been known to have a negative effect on the immune system and increase the risk of infectious complications. Hjern and colleagues, in a study of 36,000 Swedish women, found a 24% increased risk of hospitalization for DD in smokers, even after controlling for age, fibre, medical comorbidities, Medications, BMI and physical activity[160]. There was no clear link with number of cigarettes smoked. Similarly, the EPIC and HPFS studies both showed increased risk in smokers.

### 4.3.6 Diabetes

Diabetes is reaching almost epidemic proportions in western countries. Diabetes has well recognised effects on the immune system, with increased risk of infections[216, 217].

Diabetes may increase risk of acute diverticulitis by increasing risk of infection. A study by Cologne et.al. of 1019 patients with diverticulitis showed a higher Hinchey score in diabetics vs non
diabetics[218]. Despite this, the success rate of non-operative management was similar in both
groups. This suggests that diabetics may be at risk of having more advanced disease. This remains
a very poorly studied area, and is an area for study in this project.

4.3.7 Physical Activity and Obesity

Anecdotally, surgeons have noted that patients undergoing emergency operations for
diverticulitis and its complications have higher BMI’s than the general population. There is a
paucity of studies on obesity and diverticulitis. Current epidemiological trends show a worrying
increase in obesity in western countries. In the USA, the Centre for Disease Control estimates 36.5
% of all adults to be obese[219]

Smaller studies have suggested an increased risk of complicated diverticulitis in obese patients
[103, 220, 221]. Jeong and colleagues looked at visceral fat in patients with diverticulitis in 130
patients. They found that patients with higher visceral fat were significantly more likely to have
complicated disease [221]. Dobbins and colleagues performed a retrospective study that looked
at mean BMI among 61 patient, of whom 16 underwent an emergency colectomy[220]. They
found that patients with higher BMI’s had significantly higher risk of perforation and abscess
formation, as well as recurrent diverticulitis.

Two large prospective studies have looked at obesity and diverticular disease. Rosemar and
colleagues studied 7,500 men in Sweden over 28 years[185]. They found men with a BMI>30 had
4 times the risk of diverticulitis compared to men with a normal BMI, after adjusting for age,
smoking and blood pressure. Similarly, Strate and colleagues looking at the 18 year follow-up data
of the HPFS found that a BMI>30 was associated with a 79% greater risk of diverticulitis [222].

Aldoori first studied the link between physical activity and risk of symptomatic DD. Using the HPFS
data, a 4yr follow-up found that physical activity was inversely related to symptomatic diverticular
disease[223]. They found sedentary activity had increased risk of symptomatic DD (RR1.32), while
vigorous physical activity decreased risk (RR 0.6). A further 18 year follow-up of the HPFS data by
Strate and colleagues was published in 2009 [224]. They found that risk of complications from DD
was associated with lower physical activity, and this effect was greatest in men with a BMI≥30
kg/m². Obese men with low physical activity levels had a relative risk of 1.62 for diverticulitis, and
2.81 for bleeding from DD. Vigorous activity was associated with a 25% risk reduction of
diverticulitis.

Although a higher BMI has been correlated with diverticulitis, the mechanism for this is less clear.
Fat has well studied endocrine functions. There is significant crossover between endocrine and
immune function. One of the best studied is Leptin. Leptin is a cytokine released by adipocytes
that has effects on the thalamus resulting in regulation of satiety. Leptin also has effects on the
Immune system, with regulation of T cell proliferation and differentiation[225]. Abdominal fat has been associated with chronic diseases such as Type 2 Diabetes and Heart Disease, and is a central feature of the Metabolic Syndrome (Syndrome X) [226]. The immunomodulatory effects of uncontrolled Type 2 Diabetes are also well known.

Surgeons have known of the role of the omentum in adhering to inflamed tissue, such as perforated viscera. Similarly in Crohn’s disease, fat wrapping around the affected segment has also long been noted by surgeons, and used to delineate extent of disease[227]. Surgeons have also known for a long time that obese patients were more likely to get infectious complications after major surgery, including wound complications[228]. While usually attributed to the relatively ischaemic nature of fatty tissue, excessive fat probably has a role in down regulating immune response, making infections more likely. Fat cells express a range of receptors that mediate inflammation, including Toll Like Receptors (TLR) and Nucleotide Oligomerization Domains (NOD[229]). Visceral fat has been associated with degree of inflammation in Crohn’s disease. Precursors to Adipocytes in mice demonstrate phagocytic activity similar to Macrophages.

Fat probably has a greater role in the triggering and maintenance of inflammatory states than currently appreciated. All this could predispose obese patients to development of Acute Diverticulitis and for maintenance of symptomatic disease.

5. Natural History and Recurrence of Diverticulitis

The natural history of diverticulitis remains unclear. There is a paucity of literature on the long term follow-up and recurrence. The literature on diverticulitis is also conflicting. Prior to routine cross sectional imaging, diverticulitis was diagnosed clinically. Up to 34% of clinical diagnosis of diverticulitis change with cross sectional imaging [230]. Therefore studies on natural history of diverticulitis prior to accurate diagnoses with CT scanning have been plagued with methodological flaws. There is a lack of uniformity in definitions, terminology and outcomes in studies, making comparison even more difficulty.

Parks performed the first study on the natural history of DD. He looked at 521 patients admitted to a single centre for symptomatic diverticular disease. Although they do not specify what constitutes “medical management”, they found that the risk of hospital admissions increased significantly after the third admission for patients who were medically managed. They did not follow-up any of the patients managed surgically[42]. This led to the practice of performing a resection after 2 episodes of diverticulitis.
Traditionally surgery was the mainstay of treatment, and a large portion of the literature is dedicated to follow-up of patients after surgery. A long term benefit from resection, electively or in an emergency has not yet been shown. Over the past 2 decades, there has been an increasing trend towards conservative management. This has been shown to be safe in the long term [231]. It was also thought that conservative management was more likely to result in complicated disease, more likely to require a colostomy and have increased morbidity and mortality with poorer outcomes. This has also been shown to not be the case [164, 232].

The reported recurrence rate of diverticulitis varies in the literature. The largest study performed on 25,058 patients followed up for 14 years reported a recurrence rate of 19% [233]. Only 3.8% of patients had more than 1 admission. Quoted recurrence rates in the literature after an episode of diverticulitis range in literature from 7% to 62% [42, 231, 234-240]. In series without imaging based inclusion criteria, recurrence rates have been quoted from 13-47%. Studies with stricter imaging based criteria for acute diverticulitis have shown a lower recurrence rate than previously thought. A summary of studies looking at recurrence after 2010 is shown below.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>No of Patients</th>
<th>Design</th>
<th>Length of Followup</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahat [241]</td>
<td>2013</td>
<td>Israel</td>
<td>261</td>
<td>Prospective</td>
<td>88 mo</td>
<td>21.5%</td>
</tr>
<tr>
<td>Buchs [231]</td>
<td>2013</td>
<td>Switzerland</td>
<td>280</td>
<td>Prospective</td>
<td>24 mo</td>
<td>16.4%</td>
</tr>
<tr>
<td>Binda [237]</td>
<td>2012</td>
<td>Italy</td>
<td>743</td>
<td>Retrospective</td>
<td>10.7yr</td>
<td>17.2%</td>
</tr>
<tr>
<td>Hall [238]</td>
<td>2011</td>
<td>USA</td>
<td>672</td>
<td>Retrospective</td>
<td>42.8mo</td>
<td>36%</td>
</tr>
<tr>
<td>Makela [239]</td>
<td>2010</td>
<td>Finland</td>
<td>977</td>
<td>Retrospective</td>
<td>-</td>
<td>42%</td>
</tr>
<tr>
<td>Eglinton [240]</td>
<td>2010</td>
<td>NZ</td>
<td>320</td>
<td>Retrospective</td>
<td>101mo</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

The evidence suggests that recurrence after an episode of uncomplicated diverticulitis is uncommon, and recurrent disease is not more severe or more likely to require surgery [238, 240].

### 5.1 Risk factors for Recurrence of Diverticulitis

Recurrent diverticulitis is uncommon. Only 10-25% of patients with DD develop acute diverticulitis. Of the patients with acute diverticulitis, only 10-25% develop recurrent diverticulitis. Studies looking at recurrent diverticulitis in these patients have been plagued with the same methodological flaws as with most studies on diverticulitis prior to accurate diagnosis with Cross sectional CT scanning. Prior
to the widespread use of routine CT scanning, the diagnosis of diverticulitis was based on clinical findings alone. The accuracy of clinical diagnosis is low, and previous studies have overestimated incidence of recurrence. There are very few studies looking at recurrence with objective CT proven diagnosis.

It was initially believed that recurrent diverticulitis had a more virulent and severe course. Studies showed increased risk of perforation in recurrent disease. It was also believed that medical management of diverticulitis was not likely to be successful after the second episode. Based on these, recommendations were made for surgery after 2 confirmed episodes of diverticulitis. These recommendations were based on historically flawed studies. This recommendation persisted until the early 2000’s.

More recent studies have contradicted these historical findings. In a large cohort study of 25,058 patients with acute diverticulitis by Anaya and colleagues, patients with recurrent hospitalization for diverticulitis did not have a significantly higher risk of emergency surgery or disease associated mortality [233]. Other studies have confirmed these findings. It is now believed that recurrent diverticulitis does not carry a worse outcome that the initial episode. Some of the factors studied are discussed below.

5.1.1 Young Patients

There has been conflicting evidence about the incidence and natural history of diverticulitis in these patients. Earlier studies reported an incidence of diverticulitis between 2-7% in these patients [242-244]. Later studies report an incidence between 18-34% [245, 246]. It was also reported in earlier studies that these patients had a more severe course, and had a higher rate of recurrence, more visits to the emergency department as well as more complications from diverticulitis when managed medically [102, 103, 247, 248]. This led to the advocating by some authorities of performing resection surgery after a single episode in these patients [249, 250].

More recently, good quality studies with relatively long term follow-up have disproven this belief. Recent studies have not found a significant difference in rate of conservative management, need for emergency surgery or risk of recurrent disease [245, 251-253]. More current guidelines recommend that they should be treated no differently to older patients [254].

Younger patients have a longer life expectancy, and therefore would be expected to have more medical contact, and higher accumulated risk, rather than absolute risk. In the large study of 25,058 patients followed over 14 years, patients less than 50 were more likely to have recurrence than older
patients (27% vs 17%), were more likely to undergo emergency colectomy (RR 2.2) and were more likely to require a colostomy[233].

5.1.2 Extent of Surgical Resection and Level of Anastomosis

It has been known that a proportion of patients get recurrent diverticulitis even after surgery. As early as 1962, Leigh and colleagues reported recurrent diverticulitis in 72 patients from the Mayo clinic after apparently having undergone an adequate segmental resection for acute diverticulitis[255]. In another later study from Mayo clinic, Benn and colleagues reported a recurrence rate of 10.4% in 501 patients[256]. Interestingly, they showed that 71% of the patients had persistent diverticulae in barium enemas after a seemingly adequate resection. They found that a rectal anastomosis was associated with a lower rate of recurrence than a sigmoid anastomosis.

Other studies have not found an association with extent of resection and risk of recurrent disease [257, 258]. It was also believed initially that operating after recurrent attacks of diverticulitis may result in higher morbidity and mortality, due to advanced disease state, less pliable colonic wall, and increased age of the patient. In mathematical modelling however, it was showed that morbidity and mortality were not significantly different after the 4th episode of diverticulitis than the second episode [259, 260].

5.1.3 CRP

Buchs and colleagues looked at patterns of recurrence after an episode of uncomplicated diverticulitis [231]. Of the 280 patients included in their study, the overall recurrence rate was 16.4%, with more than half the recurrences in the first year. Of the patients with recurrent disease, only 2.1% were complicated and only 1.4% required an emergency colectomy. On univariate analysis, they found that the CRP on admission was strongly correlated with recurrence within the first six months. The cut-off value for CRP was about 240mg/l. The graph below shows probability of recurrence vs time to recurrence based on CRP.
5.1.4 Smoking and Lifestyle Factors

Smoking has well described effects on the immune system. Smokers have a vastly higher risk of infectious diseases, including respiratory infections, wound infections etc. [261]. Smoking has been directly correlated with increased risk of recurrence of autoimmune diseases such as Crohn’s disease [262]. While epidemiological studies have shown increased risk, the mechanism of this is less clear. Proposed mechanisms include immune dysregulation via toxins in tobacco smoke, structural changes in cilia and mucosa from smoking, and increased bacterial virulence in smokers.

Epidemiological studies on smoking and diverticular disease are conflicting. Two studies have associated smoking with increased risk of complicated diverticular disease [215, 263]. A larger epidemiological study, however, did not show increased disk of diverticular disease [159].

Similarly other lifestyle factors have been studied with mixed results. Physical activity and obesity have been addressed above. Other factors studied have included caffeine use, Nuts, Corn and Seed consumption, Red Meat consumption and alcohol use[264]. None of these factors have been shown to conclusively increase the risk of either diverticulosis or diverticulitis. There has been a weak association with increased risk of alcohol with diverticulosis, although it is hard to draw definitive conclusions given significant heterogeneity in the studied patients [159].
adjustment for smoking, the relationship between alcohol and diverticular disease was no longer significant in one study [157].

5.1.5 NSAIDS, Steroid Use and Autoimmune diseases

Non-steroidal anti-inflammatory medications (NSAID’s) are amongst the commonest over the counter medications in use today. Up to 26% of the US population using an NSAID regularly[265]. Oral corticosteroids are also widely used for a variety of conditions. Both these medications have well recognised effects on the immune system. NSAIDS have long been associated with loss of mucosal barrier and peptic ulceration due to inhibition of prostaglandin synthesis and the subsequent loss of the gastric mucosal barrier.

The role of both these drugs in Diverticular disease and diverticulitis has been studied. Regular NSAIDS have been associated with and increased risk of diverticular bleeding and diverticulitis [208, 266]. They have also been associated with an increased risk of complicated diverticulitis [267-269]. The mechanism for this, again, remains unclear.

Patients on oral corticosteroids have also been shown to have a higher risk of acute diverticulitis and complicated diverticulitis [194, 270]. This seems more so in immunosuppressed patients. Organ transplant patients on oral steroids have been shown to have a higher risk of diverticulitis, and higher mortality[190]. Patients with rheumatoid arthritis have also been shown to have a higher risk of complicated DD while on oral steroids [193].

Most of these studies have been epidemiological, and most looked at acute presentations of diverticulitis. There is significant paucity of literature on what effect these medications have on Recurrence of diverticulitis.

5.1.6 Family History and Genetics

While a genetic component of diverticular disease has not been shown, it has been recognised for a while that there may be a familial association. In 1926, Mackoy reported a familial group with long standing abdominal symptoms and diverticular disease on X-ray examinations of the bowel [271]. There is some evidence of a genetic component. An interesting study of the Swedish Twin Registry showed that the Odds Ratio of developing diverticular disease was 7.15 times higher if the co-twin was affected[272]. This correlation was higher in monozygotic than dizygotic twins.
The influence of a family history on the risk of recurrence has been studied. Hall et al. looked at 954 patients with diverticulitis had found that a family history of diverticulitis was associated with a higher risk of recurrence [238]. Further studies are needed to confirm this finding.

6. Summary and Conclusions

Despite significant advances in medical knowledge, diverticular disease remains an enigma. The history of diverticular disease has been plagued with flawed conclusions and inferences, leading to treatments which may not have been in the patient’s best interests. Historically flawed data has led to unclear and conflicting evidence on the pathogenesis of diverticular disease and diverticulitis. This has then resulted in flawed practice recommendations, which could result in harm to the patient. This has been demonstrated in the practice of performing resection after 2 confirmed episodes of diverticulitis.

Rapid advances in medical technology, especially in radiological imaging has resulted in greater accuracy in diagnoses, and allowed for management options which were not previously available.

Despite all this, basic questions remain unanswered about diverticular disease. The aim of this project is to look at risk factors for diverticulitis and recurrent diverticulitis. The main factors looked at are the least understood risk factors and risk factors that have conflicting literature. These include the influence of obesity, the influence of NSAIDS and oral corticosteroid medications, influence of autoimmune diseases and the influence of diabetes. Chapter 2 addresses the influence of these risk factors in acute diverticulitis, and chapter 4 addresses the influence of these on recurrent diverticulitis.

We also wish to examine areas of practice in the management of acute diverticulitis that may have stemmed from historical beliefs, which may not be relevant in the modern setting. Historically, diverticulitis was largely a clinical diagnosis. Clinical diagnosis is subject to error, and up to 40% of diagnoses change with Cross sectional imaging of the abdomen [230]. Colonoscopy has been recommended by practice guidelines after an episode of diverticulitis. This practice may, however, stem from historical inaccuracies in diagnosis. The role of colonoscopy in a modern setting with cross sectional imaging proven diverticulitis is not known, and is also an area of study for this project. This will be addressed further in Chapter 3.
References

95. Prilepskaia SI, Baryshnikov EN, Kosacheva TA et al. [Prevalence of diverticulosis and colon tumors among adult population of Moscow with constipation and symptoms of anxiety (according to population-based study MUSA)]. Eksp Klin Gastroenterol 2011; 22-26.
127. !!! INVALID CITATION !!!


253. Katz LH, Guy DD, Lahat A et al. Diverticulitis in the young is not more aggressive than in the elderly, but it tends to recur more often: systematic review and meta-analysis. J Gastroenterol Hepatol 2013; 28: 1274-1281.
Chapter II

The influence of body mass index, medications and chronic illness on the disease course of acute diverticulitis.

Abstract

Background
Colonic diverticulae are very common in older adults though usually asymptomatic. The reason why some develops diverticulitis while others do not is uncertain. Studies have suggested an increased risk of diverticulitis in the obese. Other studies have suggested an association between Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids and immunosuppressants with complicated diverticular disease. The aim of this study was to study effect of some chronic illnesses and these drugs on incidence of patients presenting with acute diverticulitis.

Methods

All patients admitted with a diagnosis of acute diverticulitis (AD) from January 1998 to Dec 2010 at Christchurch Public Hospital were included. Medical records were analysed for concurrent chronic illnesses, regular use of immunomodulatory drugs, management and follow-up. Using computerised tomography of the abdomen (CT) data, estimation was made of Body Mass Index (BMI) and weight.

Results

There were 1299 patients, 582 male and 716 female, median age 64, range (18-98). Of all patients, 79.6% had a BMI >25, and 55.2% of patients having BMI >30. Patients with diabetes were significantly more likely to have uncomplicated diverticulitis (54.2% vs 41.3%). BMI, weight, use of regular NSAIDS, steroids and immunosuppressants did not have a significant effect on nature of disease (complicated vs. uncomplicated) at presentation nor were they significant predictors for need for intervention. Recurrent diverticulitis will be addressed in Chapter IV.

Conclusion

Obesity is common in patients with diverticulitis and may be associated with an increased risk. Diabetes, Autoimmune diseases, NSAIDS, Steroids and Immunomodulatory drugs do not affect stage at presentation or subsequent management.

Introduction

Acute Diverticulitis (AD) represents a spectrum of disease, ranging from simple uncomplicated diverticulitis to perforated disease with generalised peritonitis. It is a significant problem, and in 2004 accounted for 312,000 admissions and 1.5 million days of inpatient care in the US alone[273]. Up to 60% of all people in industrialised countries will develop colonic diverticular in their lifetime, and of these, up to 25% will develop an episode of acute diverticulitis or its complications[274]. Admissions for acute diverticulitis have increased by up to 16% in the past decade[165, 168]. The rates of admission have increased in young patients. In the united states alone, admissions for patients less
than 44 yo increased by 82% between 1998 and 2005[273]. The incidence of complicated diverticulitis is also increasing, with a reported 50% increase in Finland over the last 20 years[167, 239].

There has been a considerable shift towards conservative management of this disease over the past 2 decades[275]. Despite the prevalence of this disease, the natural history is poorly understood. Why some patients get diverticulitis and others do not is not clear. The risk factors for getting acute diverticulitis are also poorly understood. Identification of risk factors for diverticulitis could potentially lead to better identification of patients likely to benefit from intervention.

Previous studies have shown an association between use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and complicated diverticular disease[268]. Aspirin (also an NSAID) has been associated with increased risk of diverticulitis and diverticular bleeding[208]. Corticosteroids and oral opiates have been associated with increased risk of perforated diverticular disease[194].

Obesity is also a risk factor of interest in studies of diverticulitis. Anecdotally, surgeons have noted patients undergoing emergency operations for diverticulitis to have higher BMI’s than the general population. In 1869, Klebs in writing the Handbook of Pathological Anatomy noted Diverticular disease was commoner in obese patients[15]. Todd, in the Hunterian Lecture at Royal College of Surgeons in 1955 noted “Almost all the patients are fat”[41].

Studies have shown an increased risk of complicated diverticulitis in obese patients[103, 220, 221, 228]. In patients requiring emergency colectomy, higher BMI’s have been associated with higher risk of perforation and abscess formation, as well as increased post-operative morbidity and costs[220, 276]. Increased physical activity has been associated with a lower risk of complications of diverticular disease[224]. Clearly obesity has a role in the course of AD, but the exact mechanism remains elusive.

Obesity is directly linked to insulin resistance and diabetes[277]. Diabetes has known effects on the immune system, resulting in an increased risk of infection[278]. Diabetes impairs phagocytic function of macrophages as well as T cells [217, 278, 279]. Chronic autoimmune diseases also impair immune responses, resulting in increased risk of infections [235]. The effect of these diseases on the risk of AD is unknown. Impaired immune responses could result in increased susceptibility to diverticulitis.

The purpose of this study was to assess the effects of chronic illnesses including diabetes, autoimmune diseases, weight and BMI, as well as the regular use of NSAIDs, corticosteroids and immunosuppressive drugs on the nature of diverticulitis at presentation and subsequent management.
Methods

A retrospective audit was performed of all patients admitted with a diagnosis of colonic diverticulitis and its complications at Christchurch Public Hospital. Christchurch Hospital is the largest tertiary centre and teaching hospital in South Island of New Zealand. It serves a wider population of about 566,000, and has about 8400 general surgical admissions annually.

Patients were identified from hospital discharge summary coding information. A search was performed of all patients admitted with a diagnosis code including diverticular disease of the colon from January 1998 to December 2010. Medical records were analysed to 2013, to allow a minimum of 3 years of follow-up after diagnosis. There was no restriction on age, sex or location of diverticulitis within the colon. Patients were excluded if the diagnosis was other than acute colonic diverticulitis, including small bowel diverticula.

The inpatient notes and discharge summaries of all potential patients were then analysed. A database was created. Demographic data collected included age and sex of patient. The date and method of first diagnosis was recorded (e.g. clinical diagnosis, CT scan, colonoscopy, surgery etc.). If cross sectional imaging was used in the initial diagnosis or if the patient underwent surgery, the location of diverticulitis was recorded.

If cross sectional imaging was performed, patients were then further divided into uncomplicated and complicated disease. Uncomplicated diverticulitis was defined as the presence of colonic diverticular disease with localised wall thickening and/or stranding of pericolic fat on CT. Complicated diverticulitis was defined as; the presence of abscess, perforation (including any pericolic or extraluminal gas), obstruction or fistula formation, or an associated mass lesion. The nature of disease was also recorded.

The drug charts and medical notes were then analysed for regular use of NSAID’s (including low dose aspirin), oral corticosteroids, and immunosuppressive medications. The dose of the drugs used was also recorded. The use of aspirin was divided into Low Dose (75 – 150mg once daily) and Regular Dose (500mg - 1g). The use of prednisone was divided into Low and High Dose. Low dose was defined as a combined daily dose less than 10mg per day, and high dose was defined as greater than 10mg per day. Medications were only recorded if they were used continuously. Intermittent or sporadic use of medications was not recorded. The presence or treatment of concurrent Diabetes and Autoimmune diseases were also recorded.
The management of diverticulitis at index admission, and recurrent admissions was recorded. If the patient underwent a surgical or interventional radiological procedure at any time from the diagnosis to completion of study, this was recorded. Data recorded included type of procedure, time from initial diagnosis to procedure, subsequent procedures (e.g. reversal of Hartmann’s).

Using a validated tool, if cross-sectional imaging was used in the diagnosis of diverticulitis, the body mass index (BMI) of the patient was calculated[280]. The following metrics were collected. All measurements were performed at the L1 lumbar vertebrae (Transpyloric plane).

- Circumference of body (BC)
- Total body area (Ba)
- Intra-abdominal area (IAa) - Circumference between abdominal musculature and outer fatty parameter
- Ratio of subcutaneous fat to total body area SQa (=Ba-IAa)
- Antero posterior body diameter (BAPD)
- Transverse body diameter (BTD)
- Spinal Canal Area (SCA)
- Transverse Diameter of L1 (L1a)
- Antero posterior diameter of L1 (L1APD)
- Area of L1 (L1A)
Using these anthropometric parameters, determinations were made of height, weight, Body Mass Index (BMI) and Body Surface Area (BSA) as outlined by Geraghty et al. [280]. In their validation study, comparisons of calculated values were statistically indistinguishable from actual measured values.

Data on colonic evaluation after initial diagnosis, including colonoscopy, barium enema etc were also recorded. If diverticulosis was reported at colonic evaluation, the site of diverticulosis was recorded. A finding of colonic malignancy at any time after diagnosis was also noted. Data was also collected on recurrence of diverticulitis. If the patient was admitted at any time after the index presentation, the time to recurrence, management and need for intervention was recorded. Patient deaths during the study period were also recorded.

All the data was then analysed using IBM SPSS Statistical Analysis Software package. The data was then analysed for differences in conservative management and surgical interventions. Surgical intervention was further subdivided into emergency and elective intervention. It was also divided on the type of procedure performed. The total patient population was then divided into subgroups, including patients with diabetes, autoimmune diseases, patients on regular NSAIDS, steroid medications and immunomodulatory drugs.
Results

- Patient Demographics

A total of 1299 patients were included for analysis. Table 1 lists the patient demographics for the study population. There were 583 males and 716 Females. There were no significant differences in age in the two genders.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients (n)</th>
<th>Standard Deviation/Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1299</td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>582</td>
<td>(44.8%)</td>
</tr>
<tr>
<td>- Female</td>
<td>716</td>
<td>(55.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Male</td>
<td>59.0</td>
<td>(21-98)</td>
</tr>
<tr>
<td>- Female</td>
<td>67.0</td>
<td>(18-98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>63.88</th>
<th>±15.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Avg Age Male</td>
<td>59.78</td>
<td>±15.51</td>
</tr>
<tr>
<td>- Avg Age Female</td>
<td>67.22</td>
<td>±13.93</td>
</tr>
</tbody>
</table>

- Method of Initial Diagnosis

Accuracy of clinical diagnosis of diverticulitis varies, with up to 37% of diagnosis changing with cross sectional imaging[230]. Cross sectional imaging is the most accurate way of confirming diagnosis and staging disease at time of diagnosis. The method of diagnosis for patients in the study period is listed in Table 2. A total of 948 patients were diagnosed by cross sectional CT scan at initial presentation, representing 72.92% of the total population of patients with diverticulitis. There were 168 patients who underwent immediate surgery without prior cross sectional imaging. Only 6% of patients had a
clinical diagnosis of diverticulitis at index presentation, without any confirmatory cross sectional imaging.

Table 5 - Method of initial diagnosis

<table>
<thead>
<tr>
<th>Method of Initial Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>948</td>
<td>72.9</td>
</tr>
<tr>
<td>Surgical Pathology/Surgery (including Laparoscopy)</td>
<td>168</td>
<td>12.9</td>
</tr>
<tr>
<td>Clinical</td>
<td>78</td>
<td>6.0</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>53</td>
<td>4.1</td>
</tr>
<tr>
<td>Barium Enema</td>
<td>48</td>
<td>3.7</td>
</tr>
<tr>
<td>MRI</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1299</td>
<td></td>
</tr>
</tbody>
</table>

- **Nature and location of disease at presentation**

The nature of the disease at presentation for patient who had a CT scan on admission is shown in Table 3. There were 533 patients with uncomplicated disease and 415 patients with complicated disease. Of the patients with complicated disease, 93 patients (22.4%) had more than one pathology found on the CT report. The location of diverticulitis was also noted on the CT report. The sigmoid colon was involved 90.3% of cases.

Table 6 – Nature of Disease at Presentation

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1299</td>
<td></td>
</tr>
<tr>
<td>Total with CT at Initial Presentation</td>
<td>948</td>
<td>100%</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>533</td>
<td>56.2%</td>
</tr>
<tr>
<td>Complicated</td>
<td>415</td>
<td>43.7%</td>
</tr>
<tr>
<td>- Perforation</td>
<td>201</td>
<td>48.4%</td>
</tr>
<tr>
<td>- Abscess</td>
<td>172</td>
<td>41.4%</td>
</tr>
<tr>
<td>- Fistula</td>
<td>29</td>
<td>6.9%</td>
</tr>
<tr>
<td>- Inflammatory Mass</td>
<td>38</td>
<td>9.1%</td>
</tr>
<tr>
<td>- Stricture</td>
<td>18</td>
<td>4.3%</td>
</tr>
<tr>
<td>- Obstruction</td>
<td>10</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Location of Diverticulitis

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Right Colon</td>
<td>20</td>
<td>2.1%</td>
</tr>
<tr>
<td>- Transverse Colon</td>
<td>9</td>
<td>0.9%</td>
</tr>
<tr>
<td>- Left Descending Colon</td>
<td>57</td>
<td>6.1%</td>
</tr>
<tr>
<td>- Sigmoid Colon</td>
<td>856</td>
<td>90.3%</td>
</tr>
<tr>
<td>- Rectum (inc Rectosigmoid Jn)</td>
<td>3</td>
<td>0.3%</td>
</tr>
<tr>
<td>- More than One Location</td>
<td>3</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
- **Management and colonic evaluation**

Of the 1299 patients, a total of 321 underwent surgery or an interventional radiological procedure at either index presentation or in subsequent follow-up. This is outlined in Table 4. At index admission, 1090 patients (83.9%) were managed conservatively, while 209 (16.1%) had an emergency procedure.

Of the 1090 patients managed conservatively at index admission, 106 patients (9.7%) subsequently had an elective procedure. Of these, 71 (67%) were for persistent symptoms, 11 (10.4%) were for a colonic stricture, 23 (21.7%) were for fistulae including colovesical fistulae, 1 was for persistent recurrent bleeding. There were an additional 6 patients who could not be classified into the above, due to lack of documentation regarding the procedure performed, or because of surgery performed in the past, prior to study commencement with lack of accurate notes.

A total of 32 patients underwent insertion of a percutaneous drain under radiological guidance. All except one were performed in an emergency setting. Of these 32 patients, 8 (25%) went on to have emergency surgery for failure of management with percutaneous drain. These patients were included in the final surgical procedure rather than percutaneous drainage category. A total of 24 patients were managed by percutaneous drain alone.

**Table 7 - Management of Patients**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative Management at Index Admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Procedure at Index Admission</td>
<td>1090</td>
<td>83.9%</td>
</tr>
<tr>
<td>• Colectomy and Anastomosis</td>
<td>67</td>
<td>32.1%</td>
</tr>
<tr>
<td>• Hartmann’s Procedure</td>
<td>111</td>
<td>53.1%</td>
</tr>
<tr>
<td>• Percutaneous Drainage</td>
<td>23</td>
<td>11.1%</td>
</tr>
<tr>
<td>• Laparoscopy / Other</td>
<td>8</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Elective Procedure after Index Admission</strong></td>
<td>106</td>
<td>9.7%</td>
</tr>
<tr>
<td>• Colectomy and Anastomosis</td>
<td>71</td>
<td>66.9%</td>
</tr>
<tr>
<td>• Hartmann’s Procedure</td>
<td>32</td>
<td>30.1%</td>
</tr>
<tr>
<td>• Percutaneous Drain</td>
<td>1</td>
<td>0.9%</td>
</tr>
<tr>
<td>• Laparoscopy / Other</td>
<td>2</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Unknown / Historical Procedure</strong></td>
<td>6</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Total Procedures</strong></td>
<td>321</td>
<td></td>
</tr>
<tr>
<td><strong>Total Colectomy and Anastomosis</strong></td>
<td>138</td>
<td></td>
</tr>
<tr>
<td><strong>Total Hartmann’s Procedure</strong></td>
<td>182</td>
<td></td>
</tr>
</tbody>
</table>
Table 8 - Colonic Evaluation of patients with AD

<table>
<thead>
<tr>
<th>Colonic Evaluation after diagnosis</th>
<th>788</th>
<th>60.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Barium Enema</td>
<td>86</td>
<td>6.6</td>
</tr>
<tr>
<td>- Colonoscopy Including Flexible Sigmoidoscopy</td>
<td>625</td>
<td>48.1</td>
</tr>
<tr>
<td>- Colonoscopy prior to index admission</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>- CT Including Colonography</td>
<td>63</td>
<td>4.8</td>
</tr>
<tr>
<td>- Unknown / No Evaluation/ Private study</td>
<td>511</td>
<td>39.4</td>
</tr>
</tbody>
</table>

Recurrence

Of the 1299 patients, 238 patients had a further admission for recurrence of diverticulitis within the study period, representing 18.3% of all patients. This includes all patients with recurrences of diverticulitis after surgery. Of these patients, 67 (5.15%) went on to develop a second recurrence, and 20 (1.54%) developed a third recurrence. Only 11 patients had more than 3 recurrences. Recurrent diverticulitis is further discussed in Chapter IV.

Patient factors potentially influencing disease course

- Chronic illness and medications

The presence of coexisting chronic illness and the use of regular NSAID, corticosteroid and immunosuppressive drugs are shown in Table 6. Patients could only be divided into uncomplicated and complicated disease if there was a CT scan performed at index admission. The p values were calculated using a two tailed, two proportion z-test for significance of difference between 2 independent proportions. The Null hypothesis is that there is no difference in incidence of complicated and uncomplicated disease, with the alternative hypothesis being that there is a difference.
There were a total of 107 patients with diabetes and 29 with autoimmune diseases. There were 126 patients taking an oral corticosteroid regularly, and 435 patients taking an NSAID regularly. Additionally, 25 patients (1.94%) took 2 or more NSAIDs regularly, 56 patients (4.3%) took an NSAID concurrently with a corticosteroid, and 14 patients (1.1%) took an NSAID concurrently with another immunosuppressive drug.

There were no significant differences in the proportions of uncomplicated and complicated disease in all the subgroups examined, except for patients with Diabetes. Diabetics were significantly more likely to have uncomplicated disease at presentation (p=0.013). There were no significant differences in rates of uncomplicated and complicated disease for patients on regular NSAIDs. NSAIDS were not associated with higher risk of complicated disease.

Table 9 - Effect of Chronic Illnesses and Medications on Nature of Diverticulitis at initial presentation

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Uncomplicated</th>
<th>Complicated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1299</td>
<td>533</td>
<td>415</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>107</td>
<td>8.24</td>
<td>58</td>
<td>26</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Autoimmune Disease</strong></td>
<td>29</td>
<td>2.23</td>
<td>15</td>
<td>11</td>
<td>0.878</td>
</tr>
<tr>
<td><strong>Regular Steroid</strong></td>
<td>126</td>
<td>9.69</td>
<td>51</td>
<td>42</td>
<td>0.773</td>
</tr>
<tr>
<td>- Prednisone &lt;10mg/day</td>
<td>48</td>
<td>38.09</td>
<td>18</td>
<td>16</td>
<td>0.694</td>
</tr>
<tr>
<td>- Prednisone &gt;10mg/day</td>
<td>66</td>
<td>52.38</td>
<td>29</td>
<td>25</td>
<td>0.701</td>
</tr>
<tr>
<td>- Dexamethasone</td>
<td>12</td>
<td>9.52</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Regular NSAIDs</strong></td>
<td>435</td>
<td>33.48</td>
<td>181</td>
<td>135</td>
<td>0.644</td>
</tr>
<tr>
<td>- Aspirin (Low Dose)</td>
<td>367</td>
<td>84.36</td>
<td>165</td>
<td>106</td>
<td>0.067</td>
</tr>
<tr>
<td>- Aspirin (Full Dose)</td>
<td>3</td>
<td>0.68</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>- Diclofenac</td>
<td>28</td>
<td>6.43</td>
<td>14</td>
<td>11</td>
<td>0.982</td>
</tr>
<tr>
<td>- Ibuprofen</td>
<td>24</td>
<td>5.51</td>
<td>11</td>
<td>12</td>
<td>0.411</td>
</tr>
<tr>
<td>- Naproxyn</td>
<td>7</td>
<td>1.61</td>
<td>3</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>- Piroxicam</td>
<td>1</td>
<td>0.22</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Indomethacin</td>
<td>1</td>
<td>0.22</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Celecoxib</td>
<td>1</td>
<td>0.22</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Other Immunosuppressants</strong></td>
<td>26</td>
<td>2.01</td>
<td>17</td>
<td>11</td>
<td>0.627</td>
</tr>
<tr>
<td>- Adalimumab</td>
<td>1</td>
<td>3.84</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>- Azothioprine</td>
<td>7</td>
<td>26.92</td>
<td>6</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Colchicine</td>
<td>1</td>
<td>3.84</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Ciclosporin</td>
<td>1</td>
<td>3.84</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Leflunomide</td>
<td>1</td>
<td>3.84</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>- Mesalazine</td>
<td>2</td>
<td>7.69</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>- Methotrexate</td>
<td>13</td>
<td>50</td>
<td>6</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>
Patients were then analysed method of management against presence of diabetes, autoimmune diseases, and use of medications. This is summarised in Table 7. There were no significant differences in conservative management and surgical intervention in all of the subgroups examined. Patients with chronic illnesses and on NSAIDS, steroids and other immunomodulatory drugs were no more likely to be managed surgically than patients without these factors. There was a trend towards more interventions in patients taking regular NSAIDS, but this was not statistically significant.

Table 10 - Effect of Chronic Illnesses and Medications on Management of Diverticulitis

<table>
<thead>
<tr>
<th>Total</th>
<th>Conservative Management</th>
<th>p</th>
<th>Emergency (%)</th>
<th>Elective (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>978 (75.3%)</td>
<td></td>
<td>209 (65.1%)</td>
<td>106 (34.9%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>107</td>
<td>81 (75.7%)</td>
<td>26 (24.3%)</td>
<td>0.918</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>29</td>
<td>20 (68.9%)</td>
<td>9 (21.1%)</td>
<td>0.425</td>
<td>5 (55.5%)</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>435</td>
<td>304 (69.9%)</td>
<td>131 (30.1%)</td>
<td>0.086</td>
<td>72 (54.9%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>126</td>
<td>91 (72.2%)</td>
<td>35 (27.8%)</td>
<td>0.401</td>
<td>22 (60%)</td>
</tr>
<tr>
<td>-Prednisone &lt;10mg</td>
<td>48</td>
<td>35</td>
<td>13</td>
<td>0.698</td>
<td>8</td>
</tr>
<tr>
<td>-Prednisone &gt;10mg</td>
<td>66</td>
<td>45</td>
<td>21</td>
<td>0.169</td>
<td>1</td>
</tr>
<tr>
<td>Other Imunosuppressant</td>
<td>29</td>
<td>25 (86.2%)</td>
<td>4 (13.8%)</td>
<td>0.627</td>
<td>0</td>
</tr>
</tbody>
</table>

For patients who had a surgical procedure or an interventional radiological procedure, the procedure performed and relation to chronic diseases and medications was recorded. This is shown in the Table 8 below. There were no significant differences in proportions of patients in intervention categories in all the subgroups examined.

Table 11 - Influence of Chronic Illness and Medication on Type of Intervention

<table>
<thead>
<tr>
<th>Total</th>
<th>Colectomy + Anastomosis</th>
<th>Hartmanns</th>
<th>Laparoscopy</th>
<th>Percutaneous Drain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>138</td>
<td>182</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>11 (7.53%)</td>
<td>12 (8.11%)</td>
<td>1 (25%)</td>
<td>2 (8.33%)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>3 (2.05%)</td>
<td>6 (4.05%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Patients who underwent a CT scan had BMI, BSA, height and weight calculated using the methods outlined above. Out of a total of 948 patients who had CT at index presentation, a total of 849 had images available on a Picture Archiving system (PACS) to assess and measure cross sectional images for calculation of Body Mass Index. There were 99 patients who had a report only, and did not have electronically retrievable images that could be used to calculate BMI.

Of all patients, 3.9% were classified as underweight, with BMI <20 kg/m². Approximately 16.5% of patients were classified as normal, with a BMI between 20 and 25 kg/m². A significant proportion of patients with diverticulitis were overweight and obese. Approximately 79.6% of all patients had a BMI higher than 25, with 55.2% of patients classified as Obese (BMI>30 kg/m²). Figure 2 shows the distribution of BMI for all patients with diverticulitis.

<table>
<thead>
<tr>
<th>NSAIDS</th>
<th>53 (36.30%)</th>
<th>57 (38.51%)</th>
<th>2 (50%)</th>
<th>9 (37.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>17 (11.64%)</td>
<td>14 (9.46%)</td>
<td>3 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>-Prednisone &lt;10mg</td>
<td>5 (3.43%)</td>
<td>8 (5.41%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>-Prednisone &gt;10mg</td>
<td>11 (7.53%)</td>
<td>7 (4.73%)</td>
<td>2 (8.33%)</td>
<td></td>
</tr>
<tr>
<td>Other Immunomodulators</td>
<td>4 (2.74%)</td>
<td>5 (3.38%)</td>
<td>1 (4.17%)</td>
<td></td>
</tr>
</tbody>
</table>
The patients with calculated BMI were then further subdivided into nature of disease at presentation, use of studied medications, presence of autoimmune disease and diabetes, management of disease, recurrence, diagnosis of malignancy and death. This is shown in Table 9 below.
Patients with a BMI of <18 are considered underweight. Patients with BMI between 18-25 are considered normal, BMI between 25 to 30 are considered overweight and BMI> 30 are considered obese. The patients with a calculated BMI were then classified into these categories. Table 10 below shows the distribution of these patients against gender, nature of disease at presentation, management and recurrence. Comparison was then made between obese patients (BMI>30) to non obese patients (BMI<30) and tested for significance of the difference between the two proportions as outlined in methods.

Table 12 - Mean Weight and BMI of patients

<table>
<thead>
<tr>
<th></th>
<th>Mean Age</th>
<th>Mean Weight (kg)</th>
<th>Mean BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>63.87</td>
<td>89.29</td>
<td>31.10</td>
</tr>
<tr>
<td>- Male</td>
<td>59.77</td>
<td>104.38</td>
<td>32.71</td>
</tr>
<tr>
<td>- Female</td>
<td>67.21</td>
<td>76.52</td>
<td>29.74</td>
</tr>
<tr>
<td>Uncomplicated Diverticulitis</td>
<td>60.75</td>
<td>90.92</td>
<td>31.86</td>
</tr>
<tr>
<td>Complicated Diverticulitis</td>
<td>62.81</td>
<td>89.85</td>
<td>30.88</td>
</tr>
<tr>
<td>Diabetic</td>
<td>65.44</td>
<td>96.04</td>
<td>33.52</td>
</tr>
<tr>
<td>Autoimmune Disease</td>
<td>65.01</td>
<td>88.06</td>
<td>31.50</td>
</tr>
<tr>
<td>Regular Steroids</td>
<td>67.23</td>
<td>83.08</td>
<td>30.45</td>
</tr>
<tr>
<td>Regular NSAIDs</td>
<td>67.26</td>
<td>87.56</td>
<td>30.89</td>
</tr>
<tr>
<td>Other Immunosuppressive Drugs</td>
<td>64.55</td>
<td>86.73</td>
<td>31.21</td>
</tr>
<tr>
<td>Surgical Intervention</td>
<td>63.59</td>
<td>88.30</td>
<td>30.58</td>
</tr>
<tr>
<td>- Emergency Surgery</td>
<td>63.91</td>
<td>86.60</td>
<td>29.81</td>
</tr>
<tr>
<td>- Elective Surgery</td>
<td>62.69</td>
<td>91.99</td>
<td>32.13</td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Colectomy + Anastomosis</td>
<td>61.20</td>
<td>88.67</td>
<td>31.03</td>
</tr>
<tr>
<td>- Hartmann's</td>
<td>64.20</td>
<td>90.49</td>
<td>30.65</td>
</tr>
<tr>
<td>- Percutaneous Drainage</td>
<td>70.13</td>
<td>78.51</td>
<td>28.74</td>
</tr>
<tr>
<td>- Laparoscopy</td>
<td>67.25</td>
<td>101.53</td>
<td>34.37</td>
</tr>
<tr>
<td>Recurrent Diverticulitis</td>
<td>61.15</td>
<td>91.57</td>
<td>31.75</td>
</tr>
<tr>
<td>Malignancy</td>
<td>69.733</td>
<td>82.25</td>
<td>28.49</td>
</tr>
<tr>
<td>Death</td>
<td>76.99</td>
<td>79.55</td>
<td>27.96</td>
</tr>
</tbody>
</table>
Table 13 - Influence of BMI on Risk Factors and Management of Acute Diverticulitis

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>&lt; 18</td>
<td>18-25</td>
<td>25-30</td>
<td>&lt;30</td>
<td>&gt;30</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>849</td>
<td>13</td>
<td>160</td>
<td>206</td>
<td>379</td>
<td>44.6</td>
<td>470</td>
<td>55.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>389</td>
<td>4</td>
<td>52</td>
<td>84</td>
<td>140</td>
<td>35.9</td>
<td>249</td>
<td>64.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>460</td>
<td>9</td>
<td>108</td>
<td>122</td>
<td>239</td>
<td>51.9</td>
<td>221</td>
<td>48.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>485</td>
<td>11</td>
<td>83</td>
<td>103</td>
<td>197</td>
<td>40.6</td>
<td>288</td>
<td>59.4</td>
<td>&lt;0.0002</td>
<td></td>
</tr>
<tr>
<td>Complicated</td>
<td>364</td>
<td>6</td>
<td>91</td>
<td>85</td>
<td>182</td>
<td>50.0</td>
<td>182</td>
<td>50.0</td>
<td>0.3124</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>84</td>
<td>0</td>
<td>11</td>
<td>13</td>
<td>24</td>
<td>6.3</td>
<td>60</td>
<td>12.8</td>
<td>0.0018</td>
<td></td>
</tr>
<tr>
<td>Conservative Rx</td>
<td>624</td>
<td>10</td>
<td>102</td>
<td>145</td>
<td>257</td>
<td>67.8</td>
<td>367</td>
<td>78.9</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>Perc Drain</td>
<td>31</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>19</td>
<td>5.1</td>
<td>12</td>
<td>2.5</td>
<td>0.0574</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>216</td>
<td>2</td>
<td>53</td>
<td>51</td>
<td>106</td>
<td>28</td>
<td>110</td>
<td>23.4</td>
<td>0.129</td>
<td></td>
</tr>
<tr>
<td>- Emergency</td>
<td>133</td>
<td>2</td>
<td>32</td>
<td>36</td>
<td>70</td>
<td>18.5</td>
<td>63</td>
<td>13.4</td>
<td>0.0435</td>
<td></td>
</tr>
<tr>
<td>- Elective</td>
<td>83</td>
<td>0</td>
<td>19</td>
<td>15</td>
<td>34</td>
<td>9</td>
<td>49</td>
<td>10.4</td>
<td>0.4783</td>
<td></td>
</tr>
<tr>
<td>Recurrences</td>
<td>238</td>
<td>3</td>
<td>31</td>
<td>46</td>
<td>80</td>
<td>21.1</td>
<td>115</td>
<td>24.5</td>
<td>0.2473</td>
<td></td>
</tr>
<tr>
<td>- 2 Recurrences</td>
<td>59</td>
<td>1</td>
<td>10</td>
<td>14</td>
<td>25</td>
<td>6.6</td>
<td>34</td>
<td>7.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>- 3 Recurrences</td>
<td>19</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>1.8</td>
<td>12</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &gt;3 Recurrences</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.8</td>
<td>8</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Recurrence</td>
<td>19</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>2.4</td>
<td>10</td>
<td>2.1</td>
<td>0.8088</td>
<td></td>
</tr>
<tr>
<td>After Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were 9 patients who initially underwent a percutaneous drainage procedure, and then subsequently had surgery. While overall there was no significant difference in rates of obesity between males and females, a male patient was significantly more likely to be obese at initial presentation.

Obese patients were significantly more likely to have uncomplicated disease at initial presentation. Obesity did not have a significant effect on incidence of complicated disease at presentation. Obese patients were significantly more likely to be diabetic. Obese patients were significantly more likely to be managed conservatively, and were significantly less likely to undergo emergency surgery. There was no significant effect of BMI on rate of elective surgery. Of the patients with CT proven diverticulitis at index admission, 248 patients developed recurrent diverticulitis in the study period, accounting for 28% of all patients.

Figure 3 below shows the estimated rate of obesity among patients with acute diverticulitis against estimated obesity rates in New Zealand. Obesity rates in New Zealand were obtained from the Ministry of Health Social Indicators report on Obesity [281]. In all subgroups, obesity was significantly higher in patients with diverticulitis compared to that of the general New Zealand population.
Mortality

There were a total of 107 deaths during the study period, representing 8.23% all patients over a 12 year period. Not all deaths were directly related to diverticulitis. On subgroup analysis there was no significant effect of having Diabetes, Autoimmune diseases, or taking regular NSAIDS, steroids and immunomodulatory medications on the risk of death.

Discussion
Despite its prevalence, risk factors for development of acute diverticulitis are not well understood. There is significant heterogeneity in the literature about potential risk factors. These include lifestyle factors, use of concurrent medications and previous diverticulitis.

The prevalence of obesity is increasing in western societies. Obesity has long known association with development of chronic diseases such as Type 2 diabetes, hypertension, Osteoarthritis, Obstructive Sleep apnoea, Gastroesophageal reflux disease etc. Obesity has long been associated with increased risk of infection. In surgical patients, obesity increases the risk of surgical site infection by up to 2.5 times[282].

Adipose tissue have a significant neurohormonal function that is only just now beginning to be recognised. Adipose cells release a variety of inflammatory mediators, including Leptin, Adiponectin, cytokines and chemokines[283]. Leptin has been recognised as regulator of CD4+ T cell mediated inflammation[225]. Patients with genetic deficiency of Leptin have significant immune system dysfunction associated with severe obesity, and are increased risk of death from infectious causes[284]. Obesity has been associated with increased risk of surgical site infections, nosocomial, odontogenic, respiratory, Urogenital, biliary, bone and joint as well as skin infections [285]. Adipose cells clearly have a role in the mediation of inflammation.

The role of obesity in diverticulitis has been studied. Anecdotally, surgeons have noted that the patients undergoing surgery for diverticulitis were obese. In a review of the American College of Surgeons NSQIP Database, Morbidly obese patients were younger at presentation when undergoing surgery for diverticulitis, and had higher preoperative systemic inflammatory response syndrome (SIRS)/Sepsis and Septic shock[286]. Smaller studies have shown an increased risk of complicated diverticulitis in obese patients[103, 185, 220, 221, 287]. Conflictingly, other studies have not shown any increased risk[288, 289].

Many of these studies were performed at a time when cross sectional imaging was not routinely used in the diagnosis of diverticulitis. This unfortunately places significant bias on the available literature, as up to 37% of clinical diagnosis of diverticulitis changes with cross sectional imaging[230]. Our study represents the largest study of patients with CT proven diverticulitis in the literature to date.

Obesity is a significant problem in our society. According to the New Zealand Ministry of Health Adult Nutrition Survey 2008/09, 27.8% of adults over the age of 15 were obese[290]. Our data shows that the incidence of obesity in patients with acute diverticulitis is much higher than the general population. In our study, about 80% of the patients with diverticulitis had a BMI greater than 25, and about 55% of patients were clinically obese.
In our study, there was no increased incidence of complicated disease in obese patients. There was however, a significantly higher proportion of obese patients with uncomplicated disease at index presentation. Surgery is generally reserved for patients who have failed conservative management and for complicated disease. Interestingly, while there was no increased risk of complicated diverticulitis in obese patients, there patients were significantly more likely to be managed conservatively, and significantly less likely to undergo emergency surgery.

The cause of this discrepancy is not immediately clear. Obese patients are clinically more difficult to examine[291]. Peritoneal signs may be masked or underestimated on serial examinations due to presence of a large abdominal wall. Surgery on the obese is also technically more difficult, and is associated with higher risk of morbidity and mortality as well as costs associated with the surgery[276, 292]. Due to these factors, there may be a reluctance or a higher threshold used by surgeons in deciding when to operate on obese patients.

The effect of drugs including NSAIDS and corticosteroids have also been studied in acute diverticulitis. NSAIDS have long been known to have deleterious effects on the upper gastrointestinal tract by inhibiting the cyclooxygenase mediated prostaglandin synthesis pathway. This results in a breakdown of mucosal protective barrier. Evidence now exists that NSAIDS have the same effect on the lower gastrointestinal tract. Previous studies have suggested an associated between NSAIDS and diverticulitis.[208, 266] NSAIDS have also been associated with an increased risk of perforated diverticulitis[192, 206, 267-269].

In our study approximately 34% of patients were on a regular NSAIDs. Approximately 5% were on a regular NSAID and corticosteroid medication. The commonest NSAID used was low dose aspirin. Almost 10% of patients were on regular corticosteroid medications with more than half of these taking more than 10mg per day. We found women were more likely to be on steroid medications than men. There was no significant increased risk of complicated disease among regular users of these medications. Use of these medications was not a statistically significant predictor for surgical intervention, nor was it a predictor for emergency intervention. Our data suggests that the effect of these medications, if any, is modest.

Diabetes mellitus is a chronic illness associated with macro and microvascular complications. Patients with diabetes are more likely to have infections than non-diabetics. Studies have shown reduced humoral responses as well as impaired cellular innate responses, including impaired chemotaxis and phagocytosis in diabetic polymorphonuclear cells[216, 217]. Studies have suggested an increased prevalence of Type 2 diabetes in patients with diverticulosis[162, 163]. We hypothesized that these patients could have increased risk of diverticulitis and complicated diverticulitis and have an increased risk of surgical intervention.
Our data shows that diabetic are not at increased risk of complicated diverticular disease. There is a significantly higher proportion of obesity amongst diabetic patients. This is not unexpected, as diabetes and insulin resistance is directly linked to abdominal fat. Despite this, there was no demonstrable differences in management of these patients, nor was there a significantly higher risk of recurrent disease.

Studies on patients with chronic autoimmune diseases such as rheumatoid arthritis have shown an increased risk of diverticulitis[191]. This could be related to use of immunomodulatory drugs rather than the disease itself. We looked at the effect of these diseases on nature of disease and management. The total population pool of these patients was small in our study. No significant differences were found in rates of uncomplicated and complicated disease. There was a trend towards more surgical interventions in this group, however, this was not statistically significant. Autoimmune diseases were not a predictor for surgical intervention.

The rate of malignancy after uncomplicated diverticulitis was low. Only 0.9% of patients with uncomplicated diverticulitis subsequently had a colonic malignancy diagnosed in the area of concern on cross sectional imaging. This is addressed in Chapter 3. There were other colonic malignancies discovered incidentally, as well as later which were unrelated to the initial diverticulitis. Overall, the risk of malignancy after acute uncomplicated diverticulitis was low.

There are several limitations to our study. While our overall population of patients was high, the numbers of patients in some subgroups were low. These included patients with diabetes, steroids, and autoimmune diseases. It may be that our study was underpowered to find a significant difference in these groups. Our study only looked at regular use of NSAIDS and steroids. There are patients who are intermittently on these medications. These were not included and their overall effect is unknown. The estimations for Body mass index and weight were based on measurements and calculations performed on CT scan. There could be errors in measurement, leading to errors in final results. In the validation study by Gerrarty et al., errors in measurement resulted in a maximum error of +1.5%. The calculation were based on CT scans on patients without significant pathology. While unlikely, it is possible that patients with abdominal pathology may have altered body morphology, resulting in further error in calculations.

Management of diverticulitis is evolving and changing. Our study was an audit of patient management from 1998 to 2010. Management of diverticulitis has changed somewhat since this audit, and it may be that our audit is a reflection of historical practices, rather than current management. Most management trends are driven by what evidence was available at the time, and what most experts felt was safest. This has changed significantly in management of diverticulitis. An example of this is that there was a trend to operate on younger patients, because it was felt they had more virulent
disease, and had longer to live, therefore were more likely to get recurrent disease. This has now been disproven, and does not factor into management.

Our audit has a low rate of percutaneous drainage and interventional radiological procedures and a relatively higher rate of immediate operative intervention. It is now routine to perform cross sectional imaging on all patients with suspected diverticulitis. In the previous decade, CT scanning was reserved for patients who were diagnostic dilemmas, and for patients who did not respond to management as expected. This may factor into decision making for management.

Factoring in to the decision to operate may have been the relative novelty of interventional radiological procedures at the time of the audit. It was not known then whether percutaneous drainage was safe in the long term in complicated diverticulitis, or whether it was just delaying the inevitable surgery. When the technology was emerging during the time period of the audit, percutaneous drainage was initially reserved for patients who were poor candidates for surgery, as it was felt that this would not be as successful in the long term. It is now known that in the long term, it is safe to percutaneously drain diverticular abscesses rather than proceeding to an operation and indeed, is the first line of management for these. In today’s practice, percutaneous drainage is more common, and immediate surgery is extremely uncommon. This is because the techniques, equipment, expertise and availability of these once novel treatments have become more commonplace. The decision to operate varies between surgeons and this may factor into the high rate.

Conclusion

We found that the majority of patients with acute diverticulitis were overweight or obese. This may be a factor in the pathogenesis of acute diverticulitis. We found that while there is no difference in proportion of complicated disease in the obese, they were significantly less likely to undergo surgery and significantly more likely to be managed conservatively. We also found that regular use of NSAIDS and steroids, diabetes and autoimmune diseases were not significant predictors for complicated disease or need for surgical intervention.

REFERENCES


Chapter III

Role of Routine Colonic Evaluation after Acute Diverticulitis
ABSTRACT

**Background:**
Acute diverticulitis accounts for 152,000 hospitalisations in the US alone. Current guidelines recommend routine colonic evaluation after acute diverticulitis to confirm the diagnosis and exclude malignancy. However, research suggests the yield of colorectal cancer following CT proven uncomplicated diverticulitis may be low. In the era of widespread CT scanning for diverticulitis, routine colonic evaluation after diverticulitis may represent a non essential burden on health care resources.

**Methods:**
The PubMed (MEDLINE), EMBASE, BIREME, CINAHL, and the Cochrane Library databases were searched. Original studies of colonic evaluation after proven acute diverticulitis were included. Meta-analysis of data from included studies was performed using a DerSimonian Laird random effect proportion analysis.

**Results:**
Eleven studies from seven countries were included in the analysis. Out of a pooled population of 1970 patients, cancer was found in 22. The pooled proportional estimate of malignancy was 1.6% (95% confidence interval 0.9-2.8%). Of the 1497 patients with uncomplicated diverticulitis, cancer was found in 5 (proportional estimate of risk 0.7% (0.3-1.4%)). Of the 79 patients with complicated disease, cancer was found in 6 (proportion estimate of risk 10.8% (5.2-21.0%)).

**Conclusions:**
The risk of malignancy after a radiologically proven episode of acute uncomplicated diverticulitis is low. In the absence of other indications, routine colonoscopy may not be necessary. Patients with complicated diverticulitis still have a significant risk of colorectal cancer at subsequent colonic evaluation.
INTRODUCTION

Diverticulosis and diverticulitis are significant problems in Western countries. The incidence has increased over the past century[1] Up to 60% of people living in industrialised countries will develop colonic diverticula [293]. Acute diverticulitis is one of the commonest causes of acute surgical admission. It affects up to 25% of patients with diverticulosis. The annual costs of diverticular disease have been estimated at around 2.7 billion USD per year, with around 152,000 yearly hospitalizations.[4, 165]

The management of acute diverticulitis has evolved over the past two decades. There is greater use of computed tomography (CT) to confirm the diagnosis and a trend to conservative management instead of resection [294, 295]. Current internationally accepted guidelines and professional bodies recommend routine colonic evaluation after an episode of acute diverticulitis to confirm the diagnosis and exclude malignancy.[296, 297] However, this practice dates back to the time before widespread use of cross-sectional imaging to diagnose acute diverticulitis. This may be a reflection of limitations in diagnosis and diagnostic methods previously used, rather than a true indication of risk of malignancy.

Improvement in the accessibility of CT has led to its routine use in the diagnosis of diverticulitis and its complications. Technological improvement in quality and resolution of CT has led to better evaluation of the colon in the affected segment and accurate staging of complications of diverticulitis.[298] Due to this, the role of routine colonic evaluation after acute diverticulitis has been questioned.

Routine colonoscopy after acute diverticulitis places a significant resource burden on already stretched healthcare systems.[299] There is also a small, but real risk of morbidity and mortality associated with invasive procedures. In addition, endoscopy may be technically more difficult in these patients due to bowel spasm, luminal narrowing, and fixation of the colon due to inflammation and pericolic fibrosis.

To our knowledge, there are no prospective, randomised trials demonstrating a benefit of routine colonic evaluation after acute diverticulitis. Current recommendations are based largely on small to medium sized cohort studies performed before the widespread use of CT.

The objective of this study was to perform a systematic review and meta-analysis of published studies of colonic evaluation after an episode of diverticulitis to determine the yield of colorectal cancer and non-malignant colorectal polyps.

METHODS

The meta-analysis was performed in concordance with the PRISMA Statement for preferred reporting of Systematic Reviews and Meta-Analyses.[300]
Data Source and Search Strategy

A search of online databases, including, PubMed (Medline), EMBASE, BIREME, CINAHL, and the Cochrane Library was performed. All published articles and abstracts were included. The following search terms were used: Diverticulitis, Colonoscopy, Acute Diverticulitis, Colon Cancer, Endoscopy, Colonography, Colonic evaluation, Cancer risk after diverticulitis. There was no predetermined study design type, language limit or publication year.

Study Inclusion Criteria

Studies were eligible if patients received direct colonic evaluation associated with an episode of acute diverticulitis. Studies were included if diverticulitis was diagnosed with radiological confirmation. We included patients who received Flexible sigmoidoscopy alone, Computed Tomographic Colonography (CTC) alone, incomplete colonoscopy, or contrast enema studies. All potentially relevant studies were then screened by 2 researchers (Consultant Colorectal Surgeon and Surgical Fellow). The full texts of relevant articles were obtained. A further evaluation was performed of the bibliographies of the articles to identify further potentially relevant studies not identified in the initial search. Data from the included studies was then extracted, tabulated and analysed.

Study Exclusion Criteria

Studies were excluded where the diagnosis of diverticulitis was made solely on clinical grounds. Studies or data from studies was excluded if there was no direct colonic evaluation. This included follow-up of patients via Cancer Registry alone. Studies where the primary method of evaluation of the affected segment was from histopathology after surgery were excluded. Studies on emergency surgery in diverticulitis without prior colonic evaluation were also excluded.

Study Selection

The flowchart in Figure 1 demonstrates the method of literature review. Out of a total of 691 articles identified, 11 were included for meta-analysis. There was complete agreement between the authors as to inclusion of studies.
Data Synthesis and Analysis

Data was extracted from included studies and tabulated. The data was then analysed using MetaAnalyst Beta 3.13 Software [301] (Tufts Medical Center, USA).

The primary outcome of the systematic review was the yield of colorectal cancer in all patients who underwent routine colonic evaluation after an episode of acute diverticulitis. A DerSimonian Laird random effect proportion analysis of this data was undertaken using MetaAnalyst 3.13 software.

The included studies were then further analysed for reporting of uncomplicated and complicated diverticulitis. Uncomplicated diverticulitis was defined as the presence of colonic diverticular disease with localised wall thickening and/or stranding of pericolic fat on CT. Complicated diverticulitis was defined as; the presence of abscess, perforation (including any pericolic or extraluminal gas), obstruction or fistula formation, protracted disease with symptoms, or an associated mass lesion. Crude and pooled malignancy proportions were then calculated.

All included studies were then analysed for reporting of non-malignant colorectal polyps and crude and pooled proportion analysis was also performed on this data.
Assessment of Heterogeneity

Heterogeneity in the included studies was assessed using Cochran’s Q test. The Q test was also performed on all subgroup analyses.

RESULTS

Characteristics of Studies

The baseline characteristics of the included studies are summarised in Table 1. Of the included studies, four were performed in Israel, two in Sweden, one each in Australia, New Zealand, France, USA and the Netherlands. Ten articles were published in full, while one article was only published as an abstract.

Table 1 – Baseline characteristics of studies included in systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Total Patients</th>
<th>Patients with Colonic Evaluation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradel et.al.</td>
<td>1997</td>
<td>France</td>
<td>Prospective Cohort</td>
<td>64</td>
<td>26</td>
<td>Only patients with diverticulitis and colonic evaluation included</td>
</tr>
<tr>
<td>Sakhnini et.al.</td>
<td>2004</td>
<td>Israel</td>
<td>Prospective Longitudinal</td>
<td>122</td>
<td>93</td>
<td>Early colonoscopy in diverticulitis.</td>
</tr>
<tr>
<td>Hjern et.al.</td>
<td>2007</td>
<td>Sweden</td>
<td>Prospective Cohort</td>
<td>50</td>
<td>50</td>
<td>Compared CTC to colonoscopy</td>
</tr>
<tr>
<td>Lahat et.al.</td>
<td>2007</td>
<td>Israel</td>
<td>Prospective Longitudinal</td>
<td>154</td>
<td>73</td>
<td>Early colonoscopy in diverticulitis</td>
</tr>
<tr>
<td>Lahat et.al.</td>
<td>2008</td>
<td>Israel</td>
<td>Prospective Longitudinal</td>
<td>306</td>
<td>224</td>
<td>Early colonoscopy in patients with protracted symptoms and acute diverticulitis</td>
</tr>
<tr>
<td>Elramah et.al.</td>
<td>2010</td>
<td>USA</td>
<td>Retrospective Longitudinal</td>
<td>188</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Lau et.al.</td>
<td>2011</td>
<td>Australia</td>
<td>Retrospective Cohort</td>
<td>1088</td>
<td>319</td>
<td>769 followed up by Cancer Registry alone</td>
</tr>
</tbody>
</table>
All studies had CT as the primary method of diagnosis of acute diverticulitis. One study used Ultrasound Scan (USS) and CT in all patients, while another used USS or CT. Three studies looked at the role of early or inpatient colonoscopy in acute diverticulitis. One study looked at the role of colonoscopy in protracted symptoms of diverticulitis. One study looked at role of antibiotics in acute diverticulitis, 1 compared CTC to Colonoscopy, and one study compared USS to CT.

The nature of diverticular disease, methods and time of colonic evaluation reported in the included studies are summarised in Table 2. There was significant heterogeneity in the design as well as the primary outcomes of these studies.

**Table 2 - Nature of Disease, Methods and Time of Colonic Evaluation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Nature of Disease</th>
<th>Colonic Evaluation</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradel (1997)</td>
<td>CT and USS</td>
<td>All acute diverticulitis</td>
<td>Colonoscopy, Contrast enema and Surgery</td>
<td>Within 120 days</td>
</tr>
<tr>
<td>Sakhnini (2004)</td>
<td>CT</td>
<td>Uncomplicated and complicated diverticulitis</td>
<td>Colonoscopy</td>
<td>At Index admission</td>
</tr>
<tr>
<td>Hjern (2007)</td>
<td>CT</td>
<td>All acute diverticulitis</td>
<td>Colonoscopy and CT Colonography</td>
<td>Within 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Nature of Disease</th>
<th>Colonic Evaluation</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westwood et al.</td>
<td>2011 New Zealand</td>
<td>Retrospective Longitudinal</td>
<td>292</td>
<td>205</td>
</tr>
<tr>
<td>Chabok et al.</td>
<td>2012 Sweden</td>
<td>Multicenter Randomised</td>
<td>582</td>
<td>545</td>
</tr>
<tr>
<td>Schmilovitz-Weiss et al.</td>
<td>2012 Israel</td>
<td>Retrospective Cohort</td>
<td>220</td>
<td>100</td>
</tr>
<tr>
<td>Van der Wall et al.</td>
<td>2012 Netherlands</td>
<td>Retrospective Cross sectional</td>
<td>307</td>
<td>205</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>3358</td>
<td>1970</td>
</tr>
<tr>
<td>Study</td>
<td>Method</td>
<td>Disease Definition</td>
<td>Exclusion Criteria</td>
<td>Timing</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Lahat (2007) [305]</td>
<td>CT</td>
<td>Uncomplicated diverticulitis</td>
<td>Colonoscopy</td>
<td>Early (Within 6 weeks) or Late (Within 1 year)</td>
</tr>
<tr>
<td>Lahat (2008) [306]</td>
<td>CT</td>
<td>Complicated (Symptoms failing to resolve after 1 week of conventional treatment)</td>
<td>Colonoscopy</td>
<td>At index admission</td>
</tr>
<tr>
<td>Elramah (2010) [307]</td>
<td>CT</td>
<td>All acute diverticulitis</td>
<td>Colonoscopy</td>
<td>Within 6 months</td>
</tr>
<tr>
<td>Lau (2011) [308]</td>
<td>CT</td>
<td>All left sided diverticulitis</td>
<td>Colonoscopy</td>
<td>Within 1 year</td>
</tr>
<tr>
<td>Westwood (2011) [309]</td>
<td>CT</td>
<td>Uncomplicated diverticulitis</td>
<td>Colonoscopy</td>
<td>Within 2 years</td>
</tr>
<tr>
<td>Chabok (2012) [310]</td>
<td>CT</td>
<td>Uncomplicated diverticulitis</td>
<td>Colonoscopy, Barium Enema or CT Colonography</td>
<td>Within 8 weeks of discharge</td>
</tr>
<tr>
<td>Schmilovitz-Weiss (2012) [311]</td>
<td>CT</td>
<td>All acute diverticulitis, excluding haematochezia</td>
<td>Colonoscopy</td>
<td>Within 6 weeks</td>
</tr>
<tr>
<td>Van der Wall (2012) [312]</td>
<td>CT, USS or both</td>
<td>All Acute diverticulitis</td>
<td>Colonoscopy</td>
<td>Within 6 weeks</td>
</tr>
</tbody>
</table>

Out of a total population of 3358, 1970 patients underwent colonic evaluation. Colonoscopy was the commonest method of colonic evaluation in almost all studies, followed by CTC. Two studies used either CTC or colonoscopy, 1 study used CTC concurrently with colonoscopy. Only one study by Pradel et al [302] had a significant proportion of patients with surgery. In this study, patients presenting acutely with abdominal pain were assessed with CT and ultrasound and followed up for a final diagnosis. From this study, only patients with a final diagnosis of acute diverticulitis who subsequently underwent colonic evaluation were included. Patients who had emergency surgery at index admission, surgery without colonic evaluation and a final diagnosis other than acute diverticulitis were not included in the final analysis.

Out of the total population pool of 3358 patients with acute diverticulitis, 1388 patients were excluded from the final analysis. The commonest reason for exclusion was lack of direct colonic evaluation. Where stated, the reported reasons for not performing a colonic evaluation included lack of radiological evidence of diverticulitis, refusal of consent for procedure, severe medical comorbidities precluding a safe procedure, and proceeding to surgical resection without prior colonic evaluation. Three studies primarily considered the role of early colonoscopy in diverticulitis and excluded patients with evidence of perforation on initial CT. While 769 of the 1388 patients that did not receive colonic evaluation were followed up using regional cancer registries alone, they were still excluded from the final analysis.
The timing of colonic evaluation after an episode of acute diverticulitis is also shown in Table 2. Two studies performed colonoscopy at index admission. Most studies performed colonic evaluation within 6-8 weeks following the index attack. One study performed it within 3 months, one within 1 year and one within 2 years. The approach of different studies to prior evaluation of the colon was also heterogeneous. Out of the 11 included studies, four excluded patients who had received colonic evaluation up to one year prior to index admission[303, 305, 306, 308] Four studies did not report if colonic evaluation had been performed prior to that related to the index attack.[302, 304, 307, 310] Schmillovitz et al.[311] reported 11% of patients had received a colonoscopy prior to the index admission for diverticulitis, but did not report the timing of this. One study specified colonic evaluation was performed if this had not been carried out within 1 year prior to admission.[310] Finally, one study considered colonic evaluation only within the study period of 4 years.[312]

Of the 11 studies, 8 further divided patients into uncomplicated or complicated diverticulitis groups. Three studies were in patients with only uncomplicated diverticulitis. Only one study was targeted primarily at patients with complicated disease. This was performed on patients with protracted symptoms despite adequate treatment.

**Findings of Malignancy and Non Malignant Colorectal Polyps**

All of the 11 included studies reported the number of malignancies found. Table 3 summarises the overall finding of malignancies in the included studies, as well as the reported numbers of patients with uncomplicated and complicated disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Patients</th>
<th>Mean /Median Age</th>
<th>Patients with Uncomplicated Diverticulitis</th>
<th>Patients with Complicated Diverticulitis</th>
<th>Patients with Malignancy % (Crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradel (1997) [302]</td>
<td>26</td>
<td>64</td>
<td>na</td>
<td>na</td>
<td>2</td>
</tr>
<tr>
<td>Sakhnini (2004)[303]</td>
<td>93</td>
<td>63</td>
<td>87</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hjern (2007) [304]</td>
<td>50</td>
<td>56</td>
<td>na</td>
<td>na</td>
<td>0</td>
</tr>
<tr>
<td>Lahat (2007) [305]</td>
<td>73</td>
<td>60.3</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lahat (2008) [306]</td>
<td>224</td>
<td>na</td>
<td>201</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Elramah (2010) [307]</td>
<td>130</td>
<td>63.7</td>
<td>115</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Lau (2011)[308]</td>
<td>319</td>
<td>59.8</td>
<td>na</td>
<td>na</td>
<td>9</td>
</tr>
<tr>
<td>Westwood (2011)[309]</td>
<td>205</td>
<td>60(M)</td>
<td>205</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chabok (2012)[310]</td>
<td>545</td>
<td>57.1</td>
<td>545</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Out of a pooled population of 1970 patients, a colorectal malignancy was found in 22. The crude proportion of encountering a malignancy was 1.12%. DerSimonian Laird proportional analysis showed a pooled proportion of 1.6% (95% confidence interval 0.9-2.8%). There was no significant heterogeneity, the $Q$ value was 0.938 ($p=0.117$). Figure 2 illustrates the Forrest plot of the estimated proportion of malignancy after an episode of acute diverticulitis.

Seven studies reported findings of non-malignant colorectal polyps. In two studies, the polyps were further stratified to include advanced adenoma. Advanced adenomas were defined as an adenoma of 10 mm or greater in diameter, or with high-grade dysplasia, or with greater than 25% villous components. Table 4 summarises the findings of non-malignant colorectal polyps in these studies. Non-malignant colorectal polyps were found in 220 patients out of a pooled population of 1125 patients. The crude proportion of finding a non-malignant polyp was 19.5%. The estimated pooled proportion of finding a non-malignant polyp was 16.5% (95% confidence interval 11.2-23.8%). There was significant heterogeneity, the $Q$ value was 0.977 ($p<0.001$). Figure 3 shows the Forrest plot.
plot of the estimated proportion of non-malignant colorectal polyps per patient after an episode of acute diverticulitis. As only two studies reported advanced adenomas within this subset of colonic polyps, proportional analysis of this subset was not performed.

Table 4 – Finding of non malignant colorectal polyps in reporting studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Patients</th>
<th>Patients with Non Malignant Polyps (% Crude)</th>
<th>Reported Histology of Polyps Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakhnini (2004) [303]</td>
<td>93</td>
<td>9(9.6 %)</td>
<td>11 polyps in 9 patients, 9 Adenoma, 1 TVA, 1 TVA with cancer</td>
</tr>
<tr>
<td>Lahat (2007) [305]</td>
<td>73</td>
<td>5(6.8%)</td>
<td>8 polyps in 5 patients, 2 VA, 5 TA, 1 TVA</td>
</tr>
<tr>
<td>Elramah (2010) [307]</td>
<td>130</td>
<td>2(1.5%)</td>
<td>TA in 2 patients.</td>
</tr>
<tr>
<td>Lau (2011) [308]</td>
<td>319</td>
<td>82(27.5%)</td>
<td>TA/VA in 42%, HP 40%</td>
</tr>
<tr>
<td>Westwood (2011) [309]</td>
<td>205</td>
<td>50(24.4%)</td>
<td>HP in 20 patients, Adenoma in 19 patients, Advanced adenoma in 10 patients</td>
</tr>
<tr>
<td>Schmilovitz-Weiss (2012) [311]</td>
<td>100</td>
<td>32(32%)</td>
<td>42 polyps, 5 HP, 36 Adenoma, 1 advanced adenoma</td>
</tr>
<tr>
<td>Van der Wall (2012) [312]</td>
<td>205</td>
<td>40 (19.5%)</td>
<td>HP in 15 patients, Adenoma in 18 patients, Advanced adenoma in 7 patients.</td>
</tr>
</tbody>
</table>

Total: 1125 patients, 220 (19.5%)

HP = Hyperplastic Polyp, TA = Tubular Adenoma, VA =Villous Adenoma, TVA = Tubulovillous Adenoma
Of the 11 included studies, 3 did not classify patients into uncomplicated or complicated diverticulitis. Five studies reported patients with uncomplicated and complicated diverticulitis. Three studies were performed solely on patients with uncomplicated diverticulitis. Table 5 summarises the findings of studies reporting uncomplicated diverticulitis. In these 8 studies, a pooled population of 1497 patients had uncomplicated diverticulitis, representing 76% of the total population in all included studies. Within the 8 studies in this subgroup, unless performed solely on patients with uncomplicated diverticulitis, uncomplicated disease accounted for more than 95% of patients.

Table 5 – Summary of findings in studies reporting patients with uncomplicated diverticulitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Patients</th>
<th>Patients with Uncomplicated Disease</th>
<th>Patients with Malignancy</th>
<th>% (Crude)</th>
<th>Patients with Non Malignant Colorectal Polyps</th>
<th>% (Crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakhnini (2004)</td>
<td>93</td>
<td>87</td>
<td>1</td>
<td>1.1%</td>
<td>9</td>
<td>10.3%</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Cases</td>
<td>Outcomes</td>
<td>Proportion</td>
<td>Rate</td>
<td>Total Rate</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>------</td>
<td>-------</td>
<td>----------</td>
<td>------------</td>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>Lahat (2007) [305]</td>
<td>73</td>
<td>73</td>
<td>0</td>
<td>0%</td>
<td>5</td>
<td>6.8%</td>
</tr>
<tr>
<td>Lahat (2008) [306]</td>
<td>224</td>
<td>201</td>
<td>0</td>
<td>0%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Elramah (2010) [307]</td>
<td>130</td>
<td>115</td>
<td>1</td>
<td>0.9%</td>
<td>2</td>
<td>1.7%</td>
</tr>
<tr>
<td>Westwood (2011) [309]</td>
<td>205</td>
<td>205</td>
<td>1</td>
<td>0.5%</td>
<td>50</td>
<td>24.4%</td>
</tr>
<tr>
<td>Chabok (2012) [310]</td>
<td>545</td>
<td>545</td>
<td>0</td>
<td>0%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Schmilovitz-Weiss (2012) [311]</td>
<td>100</td>
<td>86</td>
<td>0</td>
<td>0%</td>
<td>32</td>
<td>32%</td>
</tr>
<tr>
<td>Van der Wall (2012) [312]</td>
<td>205</td>
<td>185</td>
<td>2</td>
<td>1.1%</td>
<td>40</td>
<td>21.6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1575</td>
<td>1497</td>
<td>5</td>
<td>0.3%</td>
<td>138</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

A colorectal malignancy was found in 5 patients. The crude proportion of the finding of a malignancy after an episode of acute diverticulitis was 0.3%. The pooled proportional rate of a colorectal malignancy in patients with uncomplicated diverticulitis was 0.7% (95% confidence interval 0.3-1.4%). There was no significant heterogeneity. The Q value was 0.774 (p≤0.458). Figure 4 illustrates the Forrest plot of estimated effect.
Out of these 8 studies, 6 reported findings of non-malignant colorectal polyps. Out of 1497 patients, 138 were reported to have non-malignant polyps. This however represents polyps in the total pool of patients rather than polyps in patients with uncomplicated disease alone. Unless the study was performed solely on uncomplicated diverticulitis, no study specifically reported polyps in uncomplicated disease alone. As the proportion of patients with uncomplicated diverticulitis within these studies was more than 95%, a reasonably accurate estimate can be obtained from the data. The crude proportion of non-malignant colorectal polyps at subsequent colonic evaluation was 9.2%. The pooled proportional estimate was 15.1% (95% confidence interval 8.7-24.9%). There was significant heterogeneity, the Q value was 0.977 (p≤0.001). Figure 5 shows Forrest Plot of estimated effect. No study specifically reported the age of patients with non-malignant colorectal polyps.
Complicated Diverticulitis

Of the 8 studies reporting the nature of disease, 5 had patients with complicated disease. Table 6 summarises the findings of studies included in this group. In total there were 79 patients with complicated diverticulitis, representing less than 5% of the total pool of all included patients.

Table 6 – Summary of Studies Reporting Complicated Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Patients</th>
<th>Patients with Complicated Disease</th>
<th>Malignancy</th>
<th>% (Crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakhnini (2004)</td>
<td>93</td>
<td>6</td>
<td>1</td>
<td>16.7%</td>
</tr>
<tr>
<td>Lahat (2007)</td>
<td>224</td>
<td>23</td>
<td>3</td>
<td>13.1%</td>
</tr>
<tr>
<td>Elramah (2010)</td>
<td>130</td>
<td>15</td>
<td>2</td>
<td>13.3%</td>
</tr>
<tr>
<td>Schmilovitz-Weiss (2012)</td>
<td>100</td>
<td>14</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 5 – Estimated proportion of non malignant colorectal polyps in patients with uncomplicated diverticulitis.

Pooled Proportion = 15.1% (8.7-24.0%)  Q=0.977(p<0.001)
Six colorectal malignancies were reported in these patients. The crude rate of finding a malignancy was 7.6%. The proportional pooled rate of finding a malignancy in this patient population was 10.8% (95% confidence interval 5.2-21%). Heterogeneity was not statistically significant with a Q value of 0.716 (p=0.391). As the number of patients was low and no study reported the specific rate of finding polyps in patients with complicated disease, subgroup analysis for this was not performed. Figure 6 shows the Forrest plot of estimated effect among patients.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahnini (2004)</td>
<td>0.167 (0.023, 0.631)</td>
</tr>
<tr>
<td>Lahat (2008)</td>
<td>0.130 (0.043, 0.335)</td>
</tr>
<tr>
<td>Ebrani (2010)</td>
<td>0.133 (0.034, 0.406)</td>
</tr>
<tr>
<td>Schmalovitz-Meiss (2012)</td>
<td>0.000 (0.000, 0.366)</td>
</tr>
<tr>
<td>Van Der Wall (2012)</td>
<td>0.000 (0.000, 0.277)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.106 (0.052, 0.210)</td>
</tr>
</tbody>
</table>

Pooled proportion = 10.8% (5.2-21%) \[ Q=0.716 \ (p=0.391) \]
DISCUSSION

Routine colonic evaluation after an episode of diverticulitis has been standard practice for the past few decades, as reflected by recommendations of professional bodies and accepted international guidelines [296, 297, 313], however, there is a paucity of literature supporting this practice.

Prior to the widespread use of cross sectional imaging, the diagnosis of acute diverticulitis was based on clinical findings and contrast enema studies. The accuracy of the clinical diagnosis of acute diverticulitis is low, with up to 37% of diagnoses changed with cross sectional imaging [230]. While contrast enema has a high sensitivity and specificity for diverticulosis, accurate recognition of an associated neoplasm within a colon with diverticulitis can only be made about 50% of the time [314]. Contrast enema is also dependant on operator experience and the quality of the images obtained. The origin of the practice of routine colonic evaluation stems from these initial difficulties in differentiating acute diverticulitis from colorectal cancer.

CT scan has revolutionised the diagnosis and management of diverticular disease. CT has a sensitivity and specificity approaching 99% for the diagnosis of diverticulitis and its complications [315]. CT guidance allows for percutaneous drainage of diverticular abscesses. Most tertiary institutions now use multidetector CT scans, capable of producing high resolution images with thinner slices than previously available. Improvements in technology have allowed for high resolution reconstruction of images in coronal and sagittal sections, leading to better evaluation of the target area [298]. These improvements in diagnostic accuracy have raised the question of the necessity of routine colonic evaluation after an episode of diverticulitis.

In this systematic review and meta-analysis, the risk of encountering a malignancy with routine colonic evaluation after an episode of acute diverticulitis in all patients was 1.6% (0.9-2.8%). On stratifying for disease severity, those with complicated diverticulitis diagnosed by imaging still had a high yield of malignancy at subsequent colonoscopy (10.8%), however, in those with CT diagnosed uncomplicated diverticulitis, the yield was low (0.7%).

A recent meta-analysis by Niv et al [316] of colorectal cancer screening with colonoscopy in an asymptomatic population showed an invasive cancer rate of 0.78% (95% confidence interval 0.13–2.97%) in a pooled population of 68,324 patients. Comparing this data with the present study suggests that the risk of colorectal malignancy after an episode of radiologically proven acute uncomplicated diverticulitis is not significantly different to that of the general asymptomatic population. This suggests that a selective approach to colonoscopy following CT proven diverticulitis may be acceptable practice.

The yield of non-malignant colorectal polyps of 19.5% (11.2-23.8%) in the present study was also similar to that documented by Niv et al. In that analysis of screened asymptomatic individuals at least one adenoma was found in 19% of patients (15-23%) [316]. This finding has to be interpreted with caution however, as there was...
significant heterogeneity evident in the present meta-analysis when polyps were considered. Of the included studies, only two specifically reported findings of advanced adenoma within the subgroup of colorectal polyps. The most widely accepted definition of advanced adenoma includes adenomas of greater than 10mm diameter, or with high grade dysplasia, or with more than 25% villous architecture. In the present review Van der Wall et al[312] and Westwood et al [309] reported advanced adenoma in 3.4% and 5.4% of patients respectively. These findings are once again comparable to Niv et al’s aforementioned large study of asymptomatic screened individuals where advanced adenoma was found in 5% of cases.

It has been well documented that the risk of colorectal neoplasia increases with age and therefore, age may be expected to influence the yield of colonoscopy following an episode of acute diverticulitis. Unfortunately, the vast majority of studies in the present meta-analysis did not specify the ages of the patients with colorectal neoplasia separately. The only included study that addressed age did not find a statistically significant difference in the rate of advanced colorectal neoplasia in patients less than 50 years and those over 50.[309] The median ages of the included study populations ranged from 57 to 64 years. This was once again similar to the age range in the screening population used here for comparison and reinforces the fact that the yield of malignancy at colonoscopy after CT proven diverticulitis is likely to be similar to that population.

There is no internationally agreed acceptable yield of colonoscopy and this figure will depend on the population investigated. As with any invasive procedure, the indications depend on the potential risks and benefits to the individual patient, in addition to the resources available to the community. All invasive procedures carry a small but real risk of morbidity and mortality. Colonoscopy and CTC have a colonic perforation rate of 0.1-0.2% and 0.02% for respectively.[317] There are significant regional variations and local patterns in colorectal cancer, and the provision of colonoscopy has to take this into account. Many countries report a gap between the provision of and demand for colonoscopy.[299, 318] The fact that colorectal cancer outcomes are improved with early diagnosis and treatment increases the importance of targeting the available colonoscopy resources to those at greatest risk.

Many countries now offer national CRC screening programmes and faecal occult blood tests, flexible sigmoidoscopy and colonoscopy have all been demonstrated to be effective strategies. Non-targeted CT without Colonography has a sensitivity of 72% in the detection CRC.[319] Non targeted CT performed for diverticulitis should not be used as a substitute for CRC screening. If sufficient resource is available, colonoscopy after CT proven diverticulitis may present an opportunity to offer de facto screening, however, in the setting of an effective screening programme it is likely redundant. Given the rising prevalence of diverticular disease and the ageing population, a strategy of routine colonoscopy following CT proven uncomplicated diverticulitis may limit the timely provision of colonoscopy to those at greater risk of colorectal carcinoma.

There are a number of limitations in this meta-analysis that deserve further consideration. Any systematic review and meta-analysis is limited by the quality of the studies included and the data from these studies. There was
significant variability in design and methodology in the individual studies. The patient populations studied were also heterogeneous, ranging from acute admissions with uncomplicated diverticulitis, to patients with persisting symptoms despite adequate treatment. Out of the 11 included studies, five were retrospective. The study populations in many reports were small with only one study containing more than 500 patients, and this accounted for approximately 25% of the total pooled population. Despite these differences in the population, design, methodology and primary outcomes amongst studies, there was no significant heterogeneity in the pooled estimate of malignancy from the meta-analysis. In addition, no significant heterogeneity existed for the pooled estimates related to the uncomplicated and complicated diverticulitis subgroups, suggesting the studies produced consistent estimates of the risk of malignancy.

Of the 3358 patients in the 11 studies, 1388 patients were excluded from this analysis as they did not undergo colonic evaluation. Patients who went to surgery directly were excluded as the affected segment was removed hence it was neither available for colonic evaluation nor at risk of a missed cancer. Some 769 of the patients that did not receive colonic evaluation were followed up using cancer registry data. While this was not included in the meta-analysis, the cancer registry data did not suggest a high risk of CRC in these patients. In fact, when Westwood et al included accurate national cancer registry follow up with the group that underwent colonic evaluation, the rate of malignancy after acute diverticulitis dropped from 0.5% to 0.3%.[309]

The timing and method of colonic evaluation were also variable. Colonic evaluation was performed at differing time points ranging from the initial inpatient admission with acute diverticulitis to within two years of the episode. Colonoscopy was the most popular method of evaluation followed by CTC. While CTC has a similar sensitivity to colonoscopy for colorectal cancer,[320] contrast enemas have a lower accuracy.[321] The heterogeneity described limits the conclusions that can be drawn from this data and a well-designed, prospective, multicentre study investigating the incidence of malignancy after CT confirmed diverticulitis could provide more conclusive evidence in the future.

In using a selective approach for colonoscopy after acute uncomplicated diverticulitis, there are several other factors that need to be considered. The reporting of the initial diagnostic CT is operator dependent and accuracy will vary amongst institutions and with the experience of radiologists. There are significant regional variations in the incidence of CRC, and local institutions need to consider these. At the individual patient level, clinical history, family history and examination findings must all be considered in the decision whether or not to perform colonoscopy. Clinical features may exist that mandate colonoscopy irrespective of the CT findings. Most acute uncomplicated diverticulitis responds rapidly to treatment. Persistence of symptoms after optimal treatment should be an indication for further investigation. This meta-analysis focused on CRC, however other pathology, such as inflammatory bowel disease (IBD), may require exclusion depending on the clinical circumstances. It is noteworthy that the only studies considering alternative colorectal pathology also showed a very low rate of diagnosis of IBD after CT diagnosed diverticulitis[310, 317].
Despite the aforementioned limitations, the available data presented in this meta-analysis suggest the yield of malignancy at colonoscopy after CT proven acute *uncomplicated* diverticulitis is low. This data supports a selective approach to colonoscopy after an episode of CT proven diverticulitis. Patients with *uncomplicated* diverticulitis have a low risk of malignancy and can be prioritised similarly to the asymptomatic population. Patients with *complicated* diverticulitis represent a much higher risk group, and should undergo routine colonic evaluation. However, in view of the overall paucity of high quality data, further large scale studies are needed before practice recommendations can be made.

**References**

CHAPTER IV

Risk Factors for Recurrent Diverticulitis
ABSTRACT

Background

Diverticulosis is common in the older population, with up to 25% developing acute diverticulitis. After an initial episode of diverticulitis, most patients do not have recurrent diverticulitis. Risk factors for recurrence are poorly understood. Studies have suggested an association between corticosteroids, Non-Steroidal Anti-Inflammatory Medications (NSAID’s) and obesity with acute complicated diverticulitis. The purpose of this study was to study the effect of weight, body mass index, regular NSAID’s, corticosteroid, immunosuppressive medications, and chronic illnesses of diabetes and autoimmune diseases on risk of recurrent diverticulitis.

Methods

All patients admitted with a diagnosis of acute diverticulitis (AD) from January 1998 to Dec 2010 at Christchurch Public Hospital were included. Medical records were analysed for chronic illnesses, regular use of immunomodulatory drugs, management and follow-up. Using computerised tomography of the abdomen (CT) data, estimation was made of BMI and weight. Patients were follow-up up to assess recurrence of diverticulitis.

Results

1299 patients were identified with an initial attack of diverticulitis, of which, 238 patients had at least one recurrent episode (18.32%) Recurrent diverticulitis was significantly more likely in patients on regular NSAIDS (p<0.001), patients with Autoimmune diseases (p=0.006), and uncomplicated disease at index presentation (p<0.001). Surgery and interventional radiological procedures were associated with a significantly lower risk of recurrence (P<0.0001). Obesity, Age, Gender, and Diabetes were not associated with a higher risk of recurrence.

Conclusions

Patients with uncomplicated disease at initial presentation, autoimmune disease and regular NSAIDS are significantly more likely to have recurrent diverticulitis. Surgery was associated with a lower risk of recurrent diverticulitis. Diabetes and Obesity was not associated with a greater risk of recurrence.

INTRODUCTION
Diverticular disease is a significant problem in western countries. Up to 70% of the population greater than 70 have acquired colonic diverticula [7, 322]. Of these, 25-30% will develop at least one episode of symptomatic acute diverticulitis (AD) in their lifetime [7, 166]. Admissions for diverticulitis are increasing significantly in western countries, as is the incidence of complicated diverticulitis [165, 167, 168].

There has been a significant change in the diagnosis and management of diverticular disease and its complications over the past two decades[295]. Routine cross sectional imaging has allowed an accuracy of diagnosis of diverticulitis and its complications approaching 99%[323]. Cross sectional imaging has also allowed for percutaneous intervention with success rates similar to that of surgery [324].

The role of emergency surgery in acutely unwell patients, and patients with diffuse peritonitis due to complicated disease is clear. The role of elective surgery for prevention of recurrent diverticulitis and its complications remains a very controversial area. Up until early 2000, the American Society of Colon and Rectal Surgeons (ASCRS) recommended resection after 2 confirmed episodes of diverticulitis [325, 326]. The intention of elective surgery was to prevent further episodes of diverticulitis, and to prevent complicated disease in the future.

The initial rationale for this approach was based on data published in 1969 by Parks [42]. He found that medical management of diverticulitis was unlikely to be successful after the second episode. His data showed a 70% response to medical therapy with the first episode, and only 6% response after the third episode, although the definition of response was not provided. He also reported that mortality increased from 4.7% at first episode to 7.8% at subsequent episodes. Interestingly, the recurrence in patients that underwent surgery was not assessed in his original paper. Diverticulitis was also believed to be a progressive disease, and it thought that recurrent diverticulitis was likely to have a more virulent course than the initial episode[164].

Subsequent studies have questioned these findings and beliefs. There is a significant paucity of evidence to support resection after 2 episodes of diverticulitis [295]. Medical management has been shown to be much more successful than initially thought, leading to an increasing shift towards conservative management [259]. Mathematical modelling has shown that morbidity is not significantly different after the 4th episode of diverticulitis than the second episode [260]. A large cohort study has shown that patients with recurrent hospitalizations for diverticulitis did not have a significantly higher risk of emergency surgery or mortality [233].

The exact rate of recurrence after a single attack of diverticulitis is not known. Quoted recurrence rates in the literature range from 7% to 62%[42, 231, 237-241]. Many earlier studies were plagued
with methodological flaws. Traditionally, diagnosis of diverticulitis and its recurrence was based largely on clinical criteria. Up to 37% of diagnoses change with cross sectional imaging [230]. Older studies often report a higher risk of recurrence, and hence advocate for surgery. Later studies that use routine cross sectional imaging have a narrower range of reported recurrences, but still quote rates of 17-42% [17-22].

The risk of recurrent episodes of diverticulitis after the first episode of recurrence is also unknown. Parks showed a higher risk of failure of medical management and higher mortality after the second episode of recurrence. Most studies classify disease into recurrent disease without stratifying the number of episodes of recurrence and the individual risk. It was initially thought that recurrent disease was more likely to be complicated disease [327, 328]. More recent studies have questioned this belief [231, 270].

The shift away from surgery has also been supported by studies which show that surgery does not necessarily prevent recurrent diverticulitis [234]. After a seemingly adequate resection, up to 70% of patients have persistent diverticula on barium enema [329]. In a systematic review of literature, recurrent abdominal symptoms occurred in 1-10%, and re-resection was required in 0.3 -1% [234]. Quoted recurrence rates for diverticulitis after surgery vary in the literature from 5-25% [3, 255, 325, 329], depending on length of follow up and definition of recurrence (e.g. clinical vs radiological).

Despite its prevalence, risk factors for recurrent diverticulitis are poorly understood. There is a significant paucity of literature on this. There is conflicting evidence about the extent of resection on recurrence, with some showing a lower recurrence with extensive resection, while others showing the opposite [3, 325, 329]. A rectal anastomosis has been associated with a lower risk of recurrence [3, 330]. A C-Reactive Peptide titre greater than 240mh/L has been correlated with a higher risk of recurrence [231]. Several studies have suggested an association between non-steroidal anti-inflammatory medications (NSAID) and corticosteroid medication with complicated diverticulitis [194, 264, 268], although their effect on recurrence is unknown.

Obesity is a significant problem in western societies. Studies have also suggested an increased risk of complicated disease in obese patients [220, 228, 276, 287, 331]. The US Health Professional study showed a higher risk of diverticulitis in men with higher BMI, Waist to Hip Ratio and waist circumference [222]. Obesity also significantly increases costs associated with management of the disease and its complications [276]. The effect of obesity on the risk of recurrent diverticulitis is unknown.
The purpose of this study was to assess the effect of body mass index (BMI), weight, chronic illnesses including diabetes and autoimmune diseases, and use of regular use of medications including NSAID’s, corticosteroids, and other immunomodulatory drugs on risk of recurrent diverticulitis.

Methods

A retrospective analysis was performed of all patients admitted with Diverticulitis using methodology described in Chapter 2. Estimation of BMI was obtained using Cross sectional CT data as described in Chapter 2.

Data was collected on recurrence. Recurrent diverticulitis was defined as a radiologically, surgically or histopathologically confirmed diagnosis of acute diverticulitis after discharge from hospital for an episode of AD. If the patient was admitted at any time after the index presentation, the time to recurrence, management and interventions performed were recorded. Patients with clinical and biochemical signs of diverticulitis but without confirmation of diagnosis with the means mentioned were not included in recurrence. Patients with a final diagnosis of colitis or inflammation in the absence of inflamed diverticula on cross section imaging were also excluded. Patients with a final diagnosis of Inflammatory Bowel disease, or Colitis of an aetiological source other than diverticulitis (e.g. infectious colitis, Ischaemic Colitis etc.) were also excluded from recurrence. Patients with pelvic abscesses in the absence of active diverticulitis on CT were also excluded from recurrence.

All data was then analysed using International Business Machines (IBM) Statistical Package for Social Science (SPSS) statistical analysis software. Comparison of BMI and weight in these subgroups was performed using Pearsons Chi Squared test with a p value <0.05 considered statistically significant. Differences between in subgroups were performed using a 2 sided Students t-test, with a with a p value <0.05 considered statistically significant, where sample size was less than 30. In comparing proportions with sample size greater than 30, the significance of difference between 2 proportions was calculation using a 2 tailed Z-test, with a p value <0.05 considered significant.

RESULTS

There were a total of 1299 patients analysed. Of these, there were 238 patients who were admitted with recurrent diverticulitis after an initial episode of diverticulitis over the study period. The demographics of these patients are given in the table below. Of all the patients with recurrence, only 224 (85.3%) had a CT scan at the index presentation. All patients with recurrence had confirmation with CT scanning at time of admission for recurrence. Of the 238 patients with confirmed recurrences, a total of 195 patients had images retrievable though an electronic Picture Archiving system (PACS) to
allow for calculation of Body Mass index. There were 43 patients who had a CT report only or had imaging performed at a different institution that did not allow access to retrievable cross sectional imaging.

Table 1 shows demographics of patients with recurrence, compared to patients without recurrence. There were no significant differences in gender or age.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients with Recurrence</th>
<th>Patients without Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>238</td>
<td>1061</td>
</tr>
<tr>
<td>- Female</td>
<td>124 (52.1%)</td>
<td>593 (55.84%)</td>
</tr>
<tr>
<td>- Male</td>
<td>114 (47.9%)</td>
<td>468 (44.16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Female</td>
<td>66.00 (38-93)</td>
<td>67.92 (18-98)</td>
</tr>
<tr>
<td>- Male</td>
<td>54.84 (21-90)</td>
<td>60.00 (23-99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Female</td>
<td>65.81</td>
<td>67.51</td>
</tr>
<tr>
<td>- Male</td>
<td>56.09</td>
<td>60.00</td>
</tr>
</tbody>
</table>

Figure 1 shows the frequency of incidence of recurrent diverticulitis in all patients with an index presentation with AD. This includes patients managed conservatively and surgically. Of the 238 patients who developed recurrent disease, 67 (28%) patients went on to a second recurrence. Of these patients, only 20 patients developed a third recurrence. Of these 20, only 11 had more than 3 episodes of recurrent diverticulitis. Out of 1299 patients with AD, 18.3% (238 patients) developed a first recurrence, 5.2% (67) developed a second recurrence, and 1.5% (20) developed a third recurrence. Only 0.8% of patients had more than three recurrences. The risk of recurrence decreased with every episode, and greater than 3 recurrences was rare.

Figure 1 – Recurrence in patients with diverticulitis
- **Recurrent Diverticulitis and Patients undergoing Surgery**

Of the 1299 patients, 24.7% (321) underwent a surgical procedure including Interventional radiological procedure during the study period. Of these, 65.1% (209) were Emergency procedures, and 34.5% (106) were planned Elective procedures. There were 6 (0.4%) patients who had surgery at an institution other than ours, details of which could not be obtained.

Table 2 summarizes the type of procedure and recurrent diverticulitis after the procedure. There were a total of 15 confirmed recurrences after Surgery and Interventional Radiological procedures. Of these, there were a total of 10 confirmed recurrences after a colectomy, representing 3.4% of all colectomies, and 3.1% of all interventions. There were 4 confirmed recurrences after percutaneous drainage, representing 16.7% of all percutaneous drainage procedures. There was one recurrence in a patient who underwent a laparotomy and washout, without colectomy in an emergency setting.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>Recurrence</th>
<th>%</th>
<th>No Recurrence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Surgery</strong></td>
<td>321</td>
<td>15</td>
<td>4.67%</td>
<td>306</td>
<td>96.33%</td>
</tr>
<tr>
<td>Emergency Surgery</td>
<td>209</td>
<td>10</td>
<td>4.7%</td>
<td>199</td>
<td>95.3%</td>
</tr>
<tr>
<td>- Percutaneous Drain</td>
<td>23</td>
<td>3</td>
<td>13.1%</td>
<td>20</td>
<td>86.9%</td>
</tr>
<tr>
<td>- Hartmann’s Procedure</td>
<td>111</td>
<td>4</td>
<td>3.6%</td>
<td>107</td>
<td>96.4%</td>
</tr>
<tr>
<td>- Colectomy and Anastomosis</td>
<td>67</td>
<td>2</td>
<td>2.9%</td>
<td>65</td>
<td>97.1%</td>
</tr>
<tr>
<td>- Laparoscopy / Other</td>
<td>8</td>
<td>1</td>
<td>12.5%</td>
<td>7</td>
<td>87.5%</td>
</tr>
<tr>
<td><strong>Elective Surgery</strong></td>
<td>106</td>
<td>5</td>
<td>4.7%</td>
<td>101</td>
<td>95.3%</td>
</tr>
<tr>
<td>- Percutaneous Drain</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>- Hartmann’s Procedure</td>
<td>35</td>
<td>2</td>
<td>5.7%</td>
<td>33</td>
<td>94.3%</td>
</tr>
<tr>
<td>- Colectomy and Anastomosis</td>
<td>74</td>
<td>2</td>
<td>2.7%</td>
<td>72</td>
<td>97.3%</td>
</tr>
<tr>
<td>- Laparoscopy/Other</td>
<td>2</td>
<td>-</td>
<td>0.0%</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Unknown Procedure</strong></td>
<td>6</td>
<td>-</td>
<td>0.0%</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td><strong>No Intervention</strong></td>
<td>978</td>
<td>223</td>
<td>22.8%</td>
<td>755</td>
<td>77.2%</td>
</tr>
<tr>
<td><strong>Colectomy</strong></td>
<td>287</td>
<td>10</td>
<td>3.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emergency</td>
<td>178</td>
<td>6</td>
<td>3.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Elective</td>
<td>109</td>
<td>4</td>
<td>3.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were 24 patients who underwent an interventional radiological procedure, 23 as an emergency, and 1 in an elective setting. There were 7 patients who had laparoscopy and washout as an emergency, and one electively. One patient underwent a laparotomy and washout as an emergency. There were also 6 patients who had undergone a colectomy historically prior to the commencement.
of the study. While this most probably was a colectomy, no further information on the nature of the procedure could be obtained. There were no recurrences in this group.

Of the patients undergoing surgery, only 4.7% developed a recurrence, while 17.9% of patients without surgery developed recurrence. Patients who had surgery were significantly less likely to develop a recurrence than patients without intervention \((p<0.0002)\). There was no significant difference in recurrence rates between the emergency and elective intervention groups \((p=0.9785)\). Overall, percutaneous drainage and laparoscopic washout had higher incidence of recurrence, but this could not be tested for statistical significance due to small numbers.

- **Emergency Surgery and Recurrent Diverticulitis**

Of the 1299 patients admitted with AD, 209 (16.1%) underwent emergency surgery during the study period. Of these, 191 (14.7%) underwent an emergency surgery at index admission. Of the 1108 patients managed conservatively at index admission, 109 patients underwent elective surgery. Only 18 (1.62%) of patients out of the 1108 patients managed conservatively at index presentation required further emergency surgery for diverticulitis during the study period. Of the 191 patients managed surgically at index operation, 2 required a further surgical procedure during the study period.

Figure 2 demonstrates the outcome of patients managed with emergency surgery. Of the 209 patients, there were 10 patients who developed recurrent diverticulitis. Of these 10 patients, 2 required further surgery, including 1 percutaneous drain insertion and one Hartmann's procedure.

---

*Figure 2 - Outcomes of patients with an Emergency Surgery*
Figure 3 outlines the outcomes of patients managed conservatively at index admission. Conservative management was successful in 1108 (85.3%) of all patients.
Figure 3 – Outcomes of patients managed conservatively at index presentation

Conservative management at index presentation with Acute Diverticulitis (n=1108)

Elective Surgery (n=106)
Persisting Symptoms – 77
Stricture/Obstruction – 9
Fistula - 18
Malignancy / Suspicion - 2

No Further Recurrence /Intervention (n=101)

1st Episode of Recurrent Diverticulitis (n=5)

Conservative Management (n=5)

Conservative Management (n=1002)

No Further Recurrence /Intervention (n=780)

1st Episode of Recurrent Diverticulitis (n=223)

Surgery / Intervention (n=12)
Colectomy + Anastomosis – 9
Hartmann’s Procedure 2
Percutaneous Drain - 1

Conservative Management (n=211)

2nd Episode of Recurrent Diverticulitis (n=67)

Surgery / Intervention (n=3)
Colectomy + Anastomosis – 2
Hartmann’s Procedure -1

Conservative Management (n=64)

3rd Episode of Recurrent Diverticulitis (n=20)

Surgery / Intervention (n=3)
Colectomy + Anastomosis - 3

Conservative Management (n=17)

More than 3 Recurrences (n=11). No further Surgery in this group
Of these patients, 106 underwent elective surgery after index admission. The commonest indication for an elective procedure was for persistent symptoms related to diverticular disease, followed by fistulating disease, stricture and obstruction, and finally malignancy or suspicion of malignancy. Within the elective surgery group, there were 5 (4.7%) confirmed recurrences. These were all managed conservatively, with no further surgery in this group. There were no second episodes in this group.

Of the remaining 1002 patients managed conservatively, 18 required an emergency procedure during the study. Overall, only 1.79% of patients managed conservatively at index presentation and not undergoing elective surgery required emergency surgery.

- Effect of Age, Gender, Body Mass Index (BMI), Chronic Illnesses, Weight, Medications and Surgery in Recurrent Diverticulitis

Figure 4 shows a histogram of the BMI of all patients with recurrent diverticulitis. Of the 195 patients, 8 (4.2%) had a BMI<20, 26 (13.4%) had a BMI between 20 and 25, 46 (23.6%) had a BMI between 25 and 30, and 115 (58.9%) had a BMI greater than 30. Using the World Health Organization classification of BMI, 82.3% of patients with recurrent diverticulitis were classified as overweight or obese.
Patients with recurrent diverticulitis were then compared to patients without recurrent diverticulitis across a number of subgroups. These included gender, nature of disease at presentation, presence of diabetes and autoimmune diseases, use of regular medications, surgical intervention and type of procedure, presence of malignancy and death. Table 3 summarizes the overall number of patients in each subgroup. Total number of patients represents all the patients included in study, including ones that went straight to surgery without radiological confirmation prior to surgery. The total number of patients for calculation of BMI was 849, due to lack of availability of a retrievable imaging for measurements and calculation. There were a total of 948 patients who had cross sectional imaging, 99 of whom had a report only that confirmed the diagnosis. These are included in the data for diverticulitis, as it was confirmed, but cannot be included in BMI calculation due to above mentioned factors. Analysis was then carried out to assess for effect of each subgroup for difference in recurrence. For example, Patients with BMI>30 and recurrence were compared to patients with BMI<30 and recurrence and assessed for significance. Patients with Complicated disease at index presentation and recurrence were compared to patients with Uncomplicated disease at index presentation with recurrence. For the Risk factors of Diabetes, autoimmune diseases, NSAIDS, steroids and immunomodulators, comparison was made of proportion in recurrence group with the
no recurrence group. For patients undergoing surgery, the proportion of recurrence was compared to overall recurrence rate to assess for significance of difference.

Table 3 - Factors influencing Recurrence

<table>
<thead>
<tr>
<th>Total</th>
<th>Recurrence</th>
<th>No Recurrence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (All patients)</td>
<td>1299</td>
<td>238</td>
<td>1061</td>
</tr>
<tr>
<td>BMI (n=849)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BMI&lt;30</td>
<td>379</td>
<td>80</td>
<td>299</td>
</tr>
<tr>
<td>- BMI&gt;30</td>
<td>470</td>
<td>115</td>
<td>355</td>
</tr>
<tr>
<td>Nature of Disease (n=948)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Uncomplicated Disease at initial Presentation</td>
<td>533</td>
<td>159</td>
<td>374</td>
</tr>
<tr>
<td>- Complicated Disease at initial Presentation</td>
<td>415</td>
<td>79</td>
<td>336</td>
</tr>
<tr>
<td>Diabetes</td>
<td>107</td>
<td>17</td>
<td>90</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>29</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>435</td>
<td>105</td>
<td>330</td>
</tr>
<tr>
<td>Steroids</td>
<td>126</td>
<td>29</td>
<td>97</td>
</tr>
<tr>
<td>- Prednisone &lt;10mg</td>
<td>48</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>- Prednisone &gt;10mg</td>
<td>66</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td>Other Immunomodulators</td>
<td>26</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Surgery</td>
<td>321</td>
<td>15</td>
<td>268</td>
</tr>
<tr>
<td>- Emergency</td>
<td>209</td>
<td>10</td>
<td>199</td>
</tr>
<tr>
<td>- Elective</td>
<td>106</td>
<td>5</td>
<td>101</td>
</tr>
</tbody>
</table>

Overall recurrence rate was 18.3%. This is comparable to published literature. There was no increased proportion of recurrence in patients with a BMI>30. At index presentation, 533 patients out of 948 (56.2%) had uncomplicated disease. Of all patients with recurrent disease, 159 (66.8% of all recurrences) had uncomplicated disease at index presentation. There was a statistically significantly higher proportion of patients with uncomplicated disease at index presentation with recurrences compared to all uncomplicated disease at index presentation (66.8% vs 57.1%). The proportion of complicated disease at index presentation was not significantly different at initial presentation and at recurrence.

The proportion of patients with autoimmune diseases was significantly higher in the recurrence group than in all patients at index presentation. There was no increased risk in patients with Diabetes, steroid medications and other immunomodulatory. Patients on Non-Steroidal medications were significantly over-represented in patients with recurrence, with 44.1% of patients in recurrence group being on regular NSAIDS, vs 33.8% in all patients at index presentation.

There were only 15 recurrences in patient who had undergone surgery representing 4.6% of all patients who had undergone surgery. There were 223 recurrences in 978 Patients who had not had
surgery, representing 22.8% of patients. Patients who had surgery were significantly less likely to be in the recurrence group (p<0.0002). The total number of patients with recurrence after surgery was too small to perform subgroup analysis, but overall, there did not seem be any difference in emergency vs elective surgery on rate of recurrence.

Table 4 shows the estimated mean age and weight of patients across all studied risk factors, adjusted for recurrent diverticulitis. Overall, there were no statistically significant differences in mean age or weight across the groups studied.

Table 4 - Effect of Age and Weight on Recurrent Diverticulitis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recurrence (n=238)</th>
<th>No Recurrence (n=1061)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Age</td>
<td>Mean Weight (kg)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>61.1</td>
<td>91.6</td>
</tr>
<tr>
<td>- Female</td>
<td>65.8</td>
<td>77.7</td>
</tr>
<tr>
<td>Uncomplicated Diverticulitis</td>
<td>60.4</td>
<td>90.7</td>
</tr>
<tr>
<td>Complicated Diverticulitis</td>
<td>60.5</td>
<td>94.3</td>
</tr>
<tr>
<td>Diabetic</td>
<td>63.1</td>
<td>99.6</td>
</tr>
<tr>
<td>Autoimmune Disease</td>
<td>59.1</td>
<td>100.3</td>
</tr>
<tr>
<td>Regular Steroids</td>
<td>62.5</td>
<td>89.9</td>
</tr>
<tr>
<td>Regular NSAIDs</td>
<td>62.8</td>
<td>92.1</td>
</tr>
<tr>
<td>Other Immunomodulators</td>
<td>60.9</td>
<td>91.4</td>
</tr>
<tr>
<td>Surgical Intervention</td>
<td>59.3</td>
<td>96.0</td>
</tr>
<tr>
<td>- Emergency Surgery</td>
<td>59.8</td>
<td>95.3</td>
</tr>
<tr>
<td>- Elective Surgery</td>
<td>58.4</td>
<td>99.7</td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Colectomy + Anastomosis</td>
<td>57.1</td>
<td>95.2</td>
</tr>
<tr>
<td>- Hartmann’s</td>
<td>63.0</td>
<td>95.6</td>
</tr>
<tr>
<td>- Percutaneous Drainage</td>
<td>60.6</td>
<td>98.0</td>
</tr>
<tr>
<td>- Laparoscopy</td>
<td>71.5</td>
<td>106.8</td>
</tr>
<tr>
<td>Malignancy</td>
<td>68.0</td>
<td>80.1</td>
</tr>
<tr>
<td>Death</td>
<td>76.0</td>
<td>80.9</td>
</tr>
</tbody>
</table>

Malignancy after Diverticulitis and Recurrence

There were a total of 42 patients who had a diagnosis of a malignancy during the study period. In the colon there were 22 Colon cancers, 3 Rectal cancers, 1 anal cancers. These represent 2% of all patients.
with diverticulitis. There were also 6 diagnoses of Prostate cancer, 3 bladder cancers, 4 breast cancers, 2 haematological cancers and 1 Lung cancer.

Only 4 patients had malignancy diagnosed within a year of diagnosis of diverticulitis, and all of these had an initial presentation with complicated disease. Two of these patients had emergency surgery at presentation, with finding of malignancy on histology. One had a colovesical fistula that underwent urgent elective surgery, with finding of malignancy on histology. The other one had an urgent elective operation for a stricture, initially managed as benign diverticular stricture. Histology showed a malignancy in the stricture. The rest of the colon cancers were diagnosed more than a year after index presentation, and ranged from appendiceal and right sided tumors (n=10), Transverse colon tumors (n=3), Left sided cancers (n=5), Rectal cancers (unrelated to initial are of concern on CT) (n=3), Anal cancer (n=1).

There were 8 malignancies identified in patients with recurrent diverticulitis, representing 3.4% of all patients with recurrence. Of these, there was 1 prostate adenocarcinoma, 1 Bladder tumour with invasion into sigmoid colon, and 1 anal canal carcinoma. There were 5 colonic carcinomas (2.1%). Of these, 1 was a focal carcinoma in a polyp in the rectum, and 1 was a right colon cancer, both unrelated to initial diverticulitis. Only 3 malignancies were identified in area of recurrent diverticulitis, representing an overall malignancy rate of 1.26%. These were diagnosed at 2 years, 4yrs and 9 years after index presentation. All these 3 patients had colonoscopy after index presentation, with no immediate finding of malignancy.

**DISCUSSION**

Recurrent Diverticulitis is relatively uncommon. Of all patients with AD, between 25-30% will develop a recurrent episode [7, 166]. Risk factors for recurrence remain poorly understood.

Management of diverticulitis is changing significantly, with an increasing emphasis on conservative management. Elective surgery for diverticulitis based on a fixed number of episodes has now largely been abandoned in favour of a patient centric model, with surgery being offered only for severely symptomatic patients[332]. This is reflected by most recent international guidelines [254, 333].

In our study, recurrent diverticulitis affected 238 of 1299 (18.3 %) patients. This is consistent with the reported rate of 10-25% in literature [3, 255, 329, 330]. Our data shows that the risk of recurrent diverticulitis decreased with every subsequent attack. Of all patients with diverticulitis, 18% developed one recurrence, 5% developed 2 recurrences, and only 1.5% developed 3 recurrences. More than 3 recurrences were rare.
We have attempted to identify risk factors for recurrent diverticulitis. Some were found to be significant, while others were not, as discussed below.

**Factors Influencing Recurrent Diverticulitis**

**Obesity**

Obesity is a significant problem in New Zealand, with 27.8% of adults over the age of 15 being obese[290]. Obesity has been associated with in increased risk of diverticulitis [222, 334], and increased physical activity has been associated with a lower risk of complications of diverticular disease [224]. The effect of obesity on recurrent diverticulitis is not known.

In Chapter 2, we have shown that the proportion of obese patients with diverticulitis is significantly higher than that of the general population, with 55% of patients with diverticulitis being obese. In this study of patients with recurrent diverticulitis, obese patients accounted for about 44% of all patients.

Overweight and obese patients were overrepresented in patients with recurrent diverticulitis. Of all patients with recurrence, 67.6% were overweight (BMI>25) and 44.6% were obese (BMI>30). There was no significant difference in the proportions of patients with BMI less than 30 and no recurrence. Compared to the overall NZ population, obesity is overrepresented in patients with diverticulitis and recurrence, but there is no significant difference in proportions of obesity amongst patients with initial episode of diverticulitis and patients with recurrence.

**NSAIDS, Oral Corticosteroids and Immunosuppressants**

Oral corticosteroids, NSAIDS and opiates have been associated with complicated diverticulitis [194, 208, 264, 268]. NSAIDS are associated with an increased risk of perforation [193, 267, 335]. NSAIDS are known to inhibit the Cyclooxygenase mediated prostaglandin synthesis pathways. This affects inflammatory response, results in breakdown of mucosal protective barrier and may result in diverticulitis [194, 266]. Oral corticosteroids and immunosuppressants have well documented immunomodulatory effects and the risk of subsequent infection. The effect of these medications on recurrence of diverticulitis is not known.
Our data shows that patients on Non-Steroidal Anti-inflammatory medications were also significantly over-represented in patients with recurrent diverticulitis compared to patients without recurrence (44% vs 31%). The proportion of patients on NSAIDS was also higher in patients with recurrence compared to index presentation (44% vs 33%).

Interestingly, and somewhat counterintuitively, there was no increased risk in patients with steroid medications and other immunomodulatory. The cause for this is not immediately clear. Non Steroidals have a role in degradation of mucosal barriers by inhibiting arachidonic acid metabolites and prostaglandins which normally stimulate and maintain gastric and other enteric mucosal barriers. NSAIDS have been shown to cause colonic ulceration and inflammation[336], activate quiescent inflammatory bowel disease[337, 338], and is also associated with complicated diverticulitis[269]. It is well known that regular NSAIDS result in loss of mucosal barriers in the Upper GI tract resulting in peptic ulceration.

Non Steroids have a role in degradation of mucosal barriers by inhibiting arachidonic acid metabolites and prostaglandins which normally stimulate and maintain gastric and other enteric mucosal barriers. NSAIDS have been shown to cause colonic ulceration and inflammation[336], activate quiescent inflammatory bowel disease[337, 338], and is also associated with complicated diverticulitis[269]. It is well known that regular NSAIDS result in loss of mucosal barriers in the Upper GI tract resulting in peptic ulceration.

It is possible that NSAIDS result in a loss of mucosal protection of the colon, which could result in translocation of bacteria, or micro perforation in areas of weakness such as diverticulae. This may increase risk of diverticulitis. Corticosteroids, while reducing immune responses via a cellular mechanism, do not have the same immediate effects on mucosa. It may be possible that this is why steroids are not associated with an increased risk of recurrence.

**Nature of disease at index episode**

There were a significantly higher proportion of patients with uncomplicated disease at index presentation in the recurrence group, than patients with uncomplicated disease at initial presentation (66.8% vs 56.2%) This difference was significant. There was no statistically significant difference in proportion of patients with complicated disease at index presentation at recurrence compared to complicated disease at initial presentation (33.2% vs 43.7%).

The cause for this is again not clear. It is possible that a proportion of patients with severe complicated disease at index presentation underwent surgery. As discussed below, surgery has a much lower risk of recurrence. These patients may have been excluded from the natural course of the disease. The number of patients with uncomplicated disease is also higher. Overall difference between the 2 groups is about 10%, but only the difference in the uncomplicated groups approached statistical significance. It is possible that the study was underpowered for patients with complicated disease.

**Autoimmune disease and Diabetes**
Autoimmune diseases result in impaired immune responses, which can exacerbate ongoing infectious
diseases or predispose to increased risk of infection [235]. This could be related to the disease itself,
or related to ingestion of immunomodulatory medications required to manage this disease. Diabetes
also has well documented effects on the immune system and risk of infection [278].

Our data shows that the proportion of patients with autoimmune diseases was significantly higher in
the recurrence group than in all patients at index presentation (4.6% vs 1.1%). In our study, there were
significantly more patients with chronic autoimmune diseases in the recurrence group than the no
recurrence group (p=0.006). There was no significant difference in proportion of Diabetes in both
groups. As the total number of patients with autoimmune diseases was low, no meaningful subgroup
analyses could be performed. This is an area for further study.

**Gender and Age**

We found that there were no significant differences in gender or age of patients with recurrent
diverticulitis. Median ages across the groups were similar. Age did not significantly affect recurrence
rates.

**Surgery and Interventional Radiology**

There were only 15 recurrences in patient who had undergone surgery representing 4.6% of all
patients who had undergone surgery. There were 223 recurrences in 978 Patients who had not had
surgery, representing 22.8% of patients. Patients who had surgery were significantly less likely to be
in the recurrence group (p<0.0002). The total number of patients with recurrence after surgery was
too small to perform subgroup analysis, but overall, there did not seem be any difference in
emergency vs elective surgery on rate of recurrence.

Our data also shows that patients who underwent surgery or an interventional radiological procedure
had a significantly lower risk of developing recurrent diverticulitis. We specifically excluded patients
undergoing reversal of Hartmann's procedure from the surgery group, as this procedure was not
related to recurrent diverticulitis. In our study, approximately 4.7 % of all patients who underwent
these procedures developed recurrent diverticulitis. This is consistent with reported rates in the
literature [3, 255, 329].

There were a total of 15 recurrences out of 321 patients with surgical or radiological interventions. If
we look specifically at patients who had a colectomy, and then subsequently developed a recurrence
of diverticulitis, there were only 10 recurrences out of 287 colectomies (3.5%). This recurrence rate was significantly lower than that of patients without any intervention. Interventional radiological procedures seemed to have a higher recurrence rates (4 out of 24 patients, 16.6%). This could not be tested for statistical significance due to low overall numbers.

The median time to recurrence after surgery was 6 months for conservatively managed patients and 9 months after surgery. There were no significant differences in time to recurrence with or without surgery.

**Limitations of study**

There are several limitations to our study. The course of diverticulitis may be affected by multiple other factors, including length of medical treatment, family history and environmental factors such as smoking [159, 266]. We did not examine the effect of these factors. Overall, the number of patients with recurrent disease is small, with subgroups being even smaller. Our study may not have sufficient power to detect a small difference between these subgroups. We only looked at regular use of the medications studied. The effect of intermittent use of these medications is not known. We also calculated BMI and weight using morphological data obtained from CT scanning. While this method is validated, there is a chance of error associated with measurement, which may result in over or underestimation of metrics.

There may be also an additive or cumulative effect of risk factors. For example, patients with autoimmune disease may also be on NSAIDS or oral corticosteroids. Because of small numbers we could not analyse for significant differences within these subgroups.

Our definition of recurrence after surgery was very strict. Patients with a solely clinical diagnosis of recurrence were excluded. There were a number of patients who were admitted after an index operations with clinical and biochemical signs consistent with diverticulitis. Radiologically however, there was no evidence of diverticulitis. These were excluded. There were also patients with colitis, pelvic abscesses and other pathology seen on CT, without any evidence of diverticulitis. These were also excluded from recurrence. Whether these pathologies were related to diverticulitis is debatable. Their effects were also excluded. There is a chance our recurrence rate may underestimate the true recurrence rates.

**Conclusions**
Our study shows that patients with uncomplicated disease at initial presentation, autoimmune disease and regular NSAIDs are significantly more likely to have recurrent diverticulitis. Patients who had surgery or an interventional radiological procedure were significantly less likely to develop recurrence.

References


Chapter V
Summary of Findings and Discussion

Introduction

Medical knowledge has advanced significantly over the past century and is increasing at an almost exponential rate. It was estimated that the doubling time of medical knowledge in 1950 was 50 years. In 2020, the doubling time of medical knowledge is projected to be just 73 days[339]. Despite this huge leap in knowledge, a common and prevalent condition such as Acute Diverticulitis still remains shrouded in mystery.

The history of diverticulitis has been shrouded by incorrect assumptions, flawed methodology, and treatments based on very little evidence. These historical errors led to practices which are very difficult and slow to change.

Diverticulitis was initially only thought to affect an older age group. Due to medical advances, life expectancy has increased. Associated with this, the number of patients afflicted by diverticulitis has also increased. American NIS data has shown that between 1998 and 2005, the domestic US population aged 18 and older grew by 9.6%. The greatest increase was in individuals older than 75, by 33%[273]. In this time period, admissions for acute diverticulitis increased by 26%[273]. This trend is by no means restricted to United States alone. Analysis of acute hospital admissions in New Zealand has shown a similar trend, with an increase from 1,443 admissions in 2001 to 2,701 admissions in 2011 [340].

Despite advances, there remains significant heterogeneity in management of diverticulitis. Experts disagree significantly on most issues. A recent Delphi study questioned international experts on 20 items related to management of Acute Diverticulitis[341]. Questions ranged from Definition of Diverticulitis, use of biochemical markers, Use of imaging, Management with antibiotics and role of surgery and colonoscopy. They found that there was more non-consensus than consensus among experts.

The pathophysiology of Acute Diverticulitis is not understood. There are a number of risk factors identified that have been causally linked to Diverticular Disease and Diverticulitis. Some of these such as Dietary Fibre and Intraluminal Colonic Pressures have very conflicting results. There is a significant lack of good quality evidence to suggest a role for this in the pathogenesis of Diverticulosis,
Diverticulitis or recurrence. It is very difficult, if not impossible to accurately gauge exact dietary fibre intake in a general population because of significant variations in diet.

Diverticular disease occurs over a long time period, and there are no studies looking at role of Dietary Fibre in pathogenesis of diverticulosis over a long period of time.

**Role of Obesity**

Obesity is a huge problem in Western societies. According to the World Health Organization, obesity has tripled since 1975, and in 2016, 29% of adults aged 18 and over were overweight or obese [342]. These figures are projected to increase. Obesity is now considered one of the most serious public health issues of the 21st century. Numerous factors have contributed to this, including diet, mass urbanisation, sedentary lifestyles, social attitudes and societal changes etc.

Obesity has long been associated with an increased risk of surgical site infection. This association has been confirmed in epidemiological studies [282, 343]. This is not simply confined to abdominal surgery [344]. Obesity has been associated with increased morbidity and mortality with non-surgical infections, such as the 2009 Influenza Pandemic (H1N1) [345].

Obesity has been associated with a chronic low grade inflammatory state [346, 347]. Adipose cells have a significant neurohormonal function, which have a role in the proliferation, maturation and activity of immune cells. A study by Nieman and colleagues showed reduced lymphocyte proliferation, raised white cell and lymphocyte subset counts and higher monocyte and granulocyte phagocytosis in obese patients [348]. Another study by Ghanim and colleagues showed increased transcription of pro-inflammatory genes in Mononuclear cells of the obese [349]. Both these suggest that immune cells of obese patients exist in a pro-inflammatory state.

The hormonal function of adipose cells is again, only now being recognised. Adipose cells produce Leptin. Leptin is released predominantly by adipose cells and inhibits hunger to maintain energy balance. It acts opposite Ghrelin, which stimulates hunger. Both these hormones act on the hypothalamus [350]. Leptin has also been shown to have significant immunological function. It has been shown to regulate CD4+ T cells [225]. Patients with genetic deficiency of Leptin have significant immune dysfunction [284]. It is associated with increased risk of infections and death from infectious causes, as well severe obesity. Similarly, leptin deficient murine models show reduced circulating CD4+ cells and impaired T cell proliferation [351]. Adiponectin is another hormone which has raised levels in the obese [352]. It has been shown to induce anti-inflammatory cytokines in leucocytes, resulting in reduced phagocytic activity in macrophages [283]. Obesity has also been linked to other
immunological dysfunction. Obese patients have been shown to have a poor antibody response to vaccination[353]. Obese patients are also more susceptible to viral infections such as HSV1[354]

Epidemiological studies have suggested a link between obesity and diverticulitis [185, 222, 223]. The Health Professionals Follow-up Study and the Swedish Male study showed an increase in symptomatic diverticular disease in patients with obesity and reduced physical activity [185, 223]. These however, did not specifically look at acute diverticulitis. In a follow-up study of 47,228 health professionals by Strate et.al., patients with a BMI>30 had almost double the relative risk of acute diverticulitis compared to patients with BMI<21kg/m² [222].

While this looked at obesity and diverticulitis, to our knowledge, no study to date has looked at obesity in patients with diverticulitis alone. Therefore, our data represents the largest study of Body Mass Index in patients with confirmed diverticulitis alone.

Our data shows that overweight and obese patients are significantly over-represented in patients with acute diverticulitis and recurrence. Figure 1 shows percentage of obese patients in those with acute diverticulitis and recurrent diverticulitis against the estimated national average. Data for national average was obtained from Ministry of Health National Health Survey 2014/2015 [355].

The proportion of obese patients decreases with age. The percentage of obese patients was higher in every age group up to 74. Overall, in patients with acute diverticulitis, obesity was almost double the national average. Patient with recurrence seemed to have a lower proportion of obesity than patients with acute diverticulitis, but were still much higher than national average up to the age of 74.
Our data shows male patients were significantly more likely to be obese at index presentation of acute diverticulitis compared to female patients. This trend of diverticulitis in obese males has been observed in other studies[103, 289]. Obese patients were also significantly more likely to have uncomplicated disease at presentation, with 64.7% of obese patients having uncomplicated disease, vs 47% of non-obese patients. There was no significant difference in proportion of complicated and uncomplicated disease in the Obese and Non Obese. Figure 2 below shows the percentage of patients in obese and non-obese groups against the factors studied. There was a statistically significant increase in uncomplicated disease, diabetes and conservative management in the obese group at index presentation.
Role of Surgery

The results for surgery deserve further analysis. There has been a significant shift away from elective surgery in patients with diverticulitis. Traditional criteria have been for resection after 2 episodes of confirmed diverticulitis [325, 356]. These patients were at index presentation for diverticulitis, so elective surgery was not offered for this philosophy. Of the 106 patients that underwent elective surgery, 77 were for persisting symptoms, 9 for stricture and obstruction, 18 for colovesical fistula and 2 for suspicion of malignancy.

Out of a total of 324 patients that underwent surgery, 306 (94.4%) underwent surgery after index presentation. Only 18 patients underwent surgery after recurrences, representing only 5.9% of all surgery. There were 238 recurrences, therefore, about 8% of patients with recurrence disease underwent elective surgery. Patients with recurrent disease were no more likely to undergo elective surgery than patients at index presentation.

The results for emergency surgery are interesting. Out of a total of 1299 patients, 209 (16.1%) underwent emergency surgery. On analysis of patients undergoing emergency surgery, Obese
patients were significantly less likely to undergo emergency surgery. Obese patients were also significantly more likely to be managed conservatively.

This finding has implications for practice. The cause of this is not clear, and could be either a different behaviour of the disease in obese patients, or reluctance for surgeons to operate on these patients. As discussed earlier, obesity results in relative immunosuppression. Obese patients are also clinically more difficult to examine, and standard abdominal signs may be masked in them due to a thick body wall masking peritoneal signs. It is possible that because of these factors, obese patients have a lower grade of disease, and may not progress the same as non-obese patients.

Surgery in obese patients represents serious challenges for surgeons. Surgery in the obese is associated with increased technical difficulty, and increased morbidity and mortality[292, 357]. Because of these reasons, it is possible that surgeons utilize a higher threshold when deciding to operate on these patients. There may be desire to persist with medical management and there may be a reluctance to operate for fear of causing harm to patients. This effect was only noted in patients at index admission. There was no difference in proportion of emergency surgery at recurrent episodes.

**Role of NSAIDS, Corticosteroid and Other Immunosuppressive medications**

Non-steroidal Anti-inflammatory medications are ubiquitous in the community. They are amongst the commonest pain relief medications taken in the world. NSAIDS have recognised side effects including loss of gastric mucosal barrier and peptic ulceration due to inhibition of cyclooxygenase mediated prostaglandin synthesis pathways. They also have extra gastric effects, including small bowel and colonic ulcers [336]. Previous studies have causally linked use of regular Non Steroidalals with an increased risk of diverticulitis [208, 266]. The mechanism for this is not clear. It is possible that NSAIDS impair the host immune acute inflammatory response, allowing for an infection to advance and thus make it more likely to get diverticulitis. It is also theoretically possible that NSAIDS damage mucosal barriers, allowing for translocation of bacteria and infection resulting in diverticulitis. NSAIDS have been associated with increased risk of perforated diverticulitis [267, 268].

Our results on NSAIDS are somewhat conflicting. In our study, about 34% of all patients were on a regular NSAID. It is estimated that 26% of the American population used an NSAID regularly in 2004 [265]. The use of NSAIDS was significantly higher in obese patients, patients over 60 years of age and women. It would seem that our dataset is comparable to this. We could not demonstrate a significant increased risk of complicated disease at index presentation. This finding is significant, and is contrary to previous published findings. The cause of this is not clear and is an area for future study. We did, however, find that patients on regular NSAIDS were significantly more likely to have recurrent disease.
A total of 44% of patients with recurrence were regular users of NSAIDS. Again, we could not demonstrate a higher incidence of complicated disease at recurrence. NSAIDS did not have a significant effect on emergency surgery or type of surgery performed.

Our results suggest that there may be an effect of NSAIDS in the establishment of acute diverticulitis, without specifically increasing the risk of perforation.

When looking at corticosteroid and other immunosuppressant use, we could not demonstrate a significant increased risk of complicated disease, surgery or recurrence. We attempted to divide patients into high dose and low dose users, and again, we could not demonstrate a statistically significant difference.

This does seem counterintuitive. There is some overlap between diverticulitis and inflammatory bowel disease, and there is some evidence that acute diverticulitis may be a low grade inflammatory autoimmune colitis[358, 359]. This is the rationale for management of acute uncomplicated diverticulitis without antibiotics [360]. There is emerging evidence that uncomplicated diverticulitis can be safely managed without antibiotics[310, 361]. It is possible that steroids do not affect the natural history of acute diverticulitis, or if anything, treat it. Steroids work at a cellular transcription level, and have more pronounced effects on chronic inflammation rather than acute inflammation. This may also be a potential reason as to why there is no increased risk of acute diverticulitis or increased risk of complicated disease.

**Role of Chronic Autoimmune Disease and Diabetes**

Chronic autoimmune diseases include collagen vascular disease, systemic vasculitidies and other syndromes. These have well recognised effects on the gastrointestinal tract [362]. Rheumatoid arthritis, and other vasculitic arthritides has been associated with a collagenous colitis, and sometimes mimics inflammatory bowel disease [363]. Autoimmune diseases have also been associated with increased risk of bowel perforation [362] [193].

We could not demonstrate a significantly increased risk of autoimmune diseases at index presentation in patients with Acute Diverticulitis. There was however, a significantly higher proportion of patients with autoimmune disease with recurrent diverticulitis (4.6% vs 1.1%). Patients with autoimmune diseases are at higher risk of recurrence.
Diabetes is also a condition that is prevalent in our community. Diabetes has well documented effect on infections. We hypothesized that diabetics were at increased risk of acute diverticulitis and recurrence. On review of the data, we could not demonstrate a significant difference in proportion of patients with diabetes in uncomplicated and complicated disease, surgery and recurrence.

**Role of Routine Colonoscopy after Diverticulitis**

Traditionally, diverticulitis has been diagnosed clinically. There is a wide differential for diverticulitis, and it is known that up to 37% of diagnoses change with cross sectional imaging[230]. Prior to availability of CT scanning, Barium enema tests were used to confirm diverticular disease. This is technically difficult, operator dependent and can miss up to half of all cancers [314, 321]. This resulted in the practice of performing routine colonoscopy after diverticulitis to exclude a malignancy.

Initial Single Slice CT scanning technology resulted in grainy images with thick slices, and while an improvement over existing barium enema technology, were still not up to par, and the practice of colonoscopy continued [364]. Technology has improved significantly since then. Most institutions now have multi-slice, multi-detector CT Scanners, which allow for thinner slices at greater resolution[323, 365]. This allows for better evaluation of the colon.

There is also recognition that uncomplicated diverticulitis may not have the same natural history as complicated disease. Uncomplicated diverticulitis is defined as the presence of colonic diverticular disease with localised wall thickening and/or stranding of pericolic fat on CT. Complicated diverticulitis is defined as; the presence of abscess, perforation (including any pericolic or extraluminal gas), obstruction or fistula formation, protracted disease with symptoms, or an associated mass lesion.

Previous studies looking at uncomplicated diverticulitis showed a low rate of malignancy[309, 310]. We performed a Systematic Review and Meta-analysis of all studies with radiologically confirmed diverticulitis and attempted to quantify the risk. This was published in Annals of Surgery [366]. We found that the risk of malignancy after uncomplicated disease was 1.6% and the risk after complicated disease was 10.8%. Comparing this to a large screening study on a asymptomatic individuals, we showed that the risk of malignancy after uncomplicated diverticulitis was not different to that of the general population [316].

Since the publication of our study in 2014, the finding of a low risk in uncomplicated diverticulitis equivalent to that of the general population, and a much higher risk in complicated diverticulitis has been shown in multiple studies, confirming our findings[367-370]. There have been at least 2 large
studies confirming our findings [371, 372]. This study has been included in evidence for recent guidelines [373].

Our study has resulted in a change in practice at our institution (Christchurch Public Hospital), and has also resulted in change in practice in Helsinki University Central Hospital [374]. There may be a wider change in practice which has not been published in literature. A recent Delphi study tried to find consensus amongst experts around the world for management of diverticulitis [341]. On most aspects, there was more non-consensus than consensus on issues to do with management of diverticulitis. On the issue of colonoscopy, however, there was consensus that colonoscopy was not needed for every patient, and a selective approach can be employed. Our study was cited as high level evidence supporting this practice[375].

Summary

Obese patients are significantly overrepresented in patients with diverticulitis and recurrence. Obese patient were significantly more likely to be managed conservatively and were significantly less likely to undergo emergency surgery. Male patients were significantly more likely to be obese at index presentation.

Factors not associated with an increased risk of complicated diverticulitis at index presentation include obesity, NSAIDS, Corticosteroid and immunosuppressive medications, Chronic autoimmune diseases, diabetes, age and gender.

Factors associated with an increased risk of recurrent diverticulitis include regular NSAID use, Autoimmune disease, and uncomplicated disease at index presentation. Obesity was not associated with an increased risk of recurrence.

The only factor associated with a decreased risk of recurrent diverticulitis was surgery. There was no difference whether the surgery was emergency or elective surgery. The risk of recurrent diverticulitis decreased with each recurrence. Greater than 3 recurrences are rare. Surgery cannot be justified based on the presumption of increased risk of recurrence after 2 attacks.

References


95. Prilepskaia SI, Baryshnikov EN, Kosacheva TA et al. [Prevalence of diverticulosis and colon tumors among adult population of Moscow with constipation and symptoms of anxiety (according to population-based study MUSA)]. Eksp Klin Gastroenterol 2011; 22-26.
810.1097/1001.sla.0000219682.000298158.000219611.


<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>253. Katz LH, Guy DD, Lahat A et al. Diverticulitis in the young is not more aggressive than in the elderly, but it tends to recur more often: systematic review and meta-analysis. J Gastroenterol Hepatol 2013; 28: 1274-1281.</td>
</tr>
</tbody>
</table>
341. Leary DP, Noel Lynch, MCh; Cillian Clancy, MB; Desmond C. Winter, MD; Eddie Myers, MD. International, Expert-Based, Consensus Statement Regarding the Management of Acute Diverticulitis. JAMA surgery 2015; 150: 899.
342. Organization WH. Obesity and Overweight Fact Sheet.
357. !!! INVALID CITATION !!!
12. Author’s Declaration

THE UNIVERSITY LIBRARY

DECLARATION CONCERNING THESIS

Author’s full name and year of birth:
(for cataloguing purposes)

Title of thesis:

Degree:

Department:

Permanent Address:

I agree that this thesis may be consulted for research and study purposes and that reasonable quotation may be made from it, provided that proper acknowledgement of its use is made.

I consent to this thesis being copied in part or in whole for:

i) a library

ii) an individual

at the discretion of the Librarian of the University of Otago.

Signature: ..............................................................

Date: .................................................................

Note: This is the standard Library Declaration Form used by the University of Otago for all theses. Any restriction on access to a thesis may be permitted only with the approval of:

(i) the appropriate Pro-Vice-Chancellor in the case of a Master’s thesis;

(ii) the Deputy Vice-Chancellor (Research), in consultation with the appropriate Pro-Vice-Chancellor, in the case of a PhD thesis.

Where appropriate, the Director of the Enterprise Office may also be consulted.

The form is designed to protect the work of the candidate, by requiring proper acknowledgement of any quotations from it. At the same time the declaration preserves the University philosophy that the purpose of research is to seek the truth and to extend the frontiers of knowledge and that the results of such research which have been written up in thesis form should be made available to others for scrutiny.

The normal protection of copyright law applies to theses.

June 2008

20
DECLARATION CONCERNING THE THESIS PRESENTED FOR THE DEGREE OF

Programme Name ____________________________________________

________________________________________________________ (full name)

Student ID ________________________________________________

declare in relation to the thesis entitled:

________________________________________________________________________

________________________________________________________________________

____ That the work was done by me, personally
or
____ That the thesis contains co-authored work
and
____ The material has not previously been accepted in whole, or in part, for any other degree or diploma
and
____ The thesis has been checked for plagiarism

Signature: ___________________________________________ Date: ____________________________

Please present this separate hand-signed form when you present your soft-bound copies for marking

Doctoral theses should be submitted to the Graduate Research School, or Christchurch/Wellington School of Medicine (if appropriate). Masters theses should be submitted to your primary Department.

Authorised by: Research Management Governance Group Date Revised: 20/02/2016