Paediatric Abdominal Pain: a case of trials and tribulations mixed with phantoms of the operating theatre? Or maybe just a case of going back to the future!

CJ Beardsley

B.Comm (ANU)
M.B.B.S (ANU)

A thesis submitted in fulfillment of the requirements of the degree of Master of Philosophy (Surgery), Australian National University.

Advanced Trainee-General Surgery

Department of Surgery,
Canberra Hospital, Canberra (2012-2014)
Royal Prince Alfred Hospital, Sydney (2015- present)
Australia

January, 2017

Declaration

I hereby certify that the work contained within this document is the result of original research and is not being submitted for a higher degree at another university or institution. All research was principally carried out by the author, with some assistance with data collection and statistical analysis, as noted in acknowledgements on page 4

…….
……

Date

Word count: 27993

Ethics Clearance

The study conducted was approved by the Australian Capital Territory Health ethics committee and was conducted in line with the National Health and Medical Research Council and Australian Health Ethics Committee guidelines. All involved participants gave informed consent for their participation in the studies. Where minors were involved, consent was sought from the parent or guardian.

Dedication:

To my mother and father who have always been my vanguard.

Acknowledgements:

Dr Mimi Chiu- for help with data collection for the demographic component (For data collected for the PAIN study on November and December 2005).

Professor Croaker- for help with study design, thesis preparation and for being a mentor both as a surgeon and as a researcher.

Dr Alex Dillon-for help with statistical analysis, data collection (October 2005) and advice on data analysis.

Dr Florence Nguyen-for help with data collection (Ultrasound data 2011 and 2012).

Ms Gloria Spiropoulos-for being an exceptional aide to data collection by promptly enabling access to medical records and for her support.

Thesis Abstract

Background:

Paediatric abdominal pain has long been a diagnostic dilemma facing the emergency physician and surgeon alike. The majority of childhood abdominal complaints are benign. However, appendicitis represents the most common surgical emergency of childhood and if excessive delay in diagnosis and management occurs, serious complications and death can result. Expensive tests such as biochemical investigations and ultrasonography are often over-stated in their true value to the clinician.

Aim and Methods:

This thesis hopes to enhance the management of paediatric abdominal pain in three ways:

- By analyzing the epidemiology and presentation patterns in paediatric abdominal pain. This is discussed in chapter 3 and was conducted via a year's review of paediatric abdominal pain for the calendar year 2005.
- By investigating the role of biomarkers such as white cell count, neutrophil count, C-reactive protein and *radiological investigations such as* ultrasound in the management of paediatric abdominal pain. This study extrapolates some of the findings discussed in chapter 3 and examines them in greater detail. This is discussed in chapter 4 and was conducted through a ten year review of patients referred by Emergency physicians and surgeons for further work up of their abdominal pain between 1st of January 2002 and 31st December 2012.
- By investigating the role of socioeconomic factors, heritable conditions and extra-abdominal conditions in paediatric abdominal pain. This is discussed in chapter 5 and was conducted via a prospective review conducted between 2012 and 2013.

Results:

1) Appendicitis represented 6% of all presentations

2) Historical findings of most use included worsening pain, associated with nausea or vomiting which yielded moderate sensitivities and specificities (combined values over 70%).

3) Localised tenderness and percussion-tenderness were the only useful abdominal examination findings with sensitivities and specificities over 90%, respectively, when associated with moderate tenderness.

4) White Cell Count and CRP yielded sensitivities and specificities below 80%

5) Ultrasonography yielded high *sensitivity (>95%) when only ultrasounds which visualise the appendix are analysed but, as the appendix is often not visualised, the actual sensitivity is only 70%. Ultrasound has a greater diagnostic yield for females than males.*

6) Functional abdominal pain is the most common cause for presentation, followed by mesenteric adenitis and appendicitis. Children with Functional Abdominal Pain were more likely to have regular bowel habits and present in winter than those with other medical conditions. Of note, both groups had higher rates of parental smoking, atopic conditions and migraine than is usually seen in the general population.

Conclusion:

Paediatric abdominal pain is a common yet challenging scenario for clinicians. However, the most useful tools are an accurate history, thorough examination and sensible use of biomarkers and radiological investigations. Other factors affecting children should be taken into account, e.g. the family medical history, though they should not significantly alter the child's workup. Biomarkers and radiological investigations should only be used where doubt exists as to the diagnosis, and we suggest ultrasonography only in those children in whom significant diagnostic uncertainty exists and where the clinical picture clashes with the prior mentioned investigations.

Publications and Presentations arising directly from this review:

- Beardsley CJ, Dillon A, Chiu M, Shah R, Croaker GDH. Paediatric Abdominal Pain: Diagnostic nihilism rules? Royal Australian College of Surgeons Annual Scientific Meeting (Canberra, A.C.T). 5th November 2011. *Oral presentation.*

- Beardsley CJ, Dillon A, Chiu M, Shah R, Croaker GDH. Paediatric Abdominal Pain in Emergency Medicine. Convention of European Academy of Paediatric Societies (EAPS), Istanbul, Turkey. 5th October 2012. *Oral presentation.*

- Beardsley CJ, Nguyen F, Croaker GDH. Ultrasonography in paediatric abdominal pain: a case of trials and tribulations? 4th World Congress of Pediatric Surgeons. 13th-16th October, Berlin.

- Beardsley CJ, Dillon A, Nguyen F, Croaker GDH. Ultrasonography and paediatric appendicitis: A story of great expectations and the phantom appendix. Presented at the Convention of European Academy of Paediatric Societies (EAPS), Barcelona, Spain. 21st October 2014. *Oral presentation.*

- Beardsley CJ, Dillon A, Chiu M, Florence N, Croaker GDH. A case of back to the future: paediatric abdominal pain. Thorough history, clinical examination and senior clinician involvement remain imperative for successful management. Poster presentation at the Convention of European Academy of Paediatric Societies (EAPS), Barcelona, Spain. 21st October 2014. *Poster presentation.*

- Beardsley CJ, Melino J, Croaker GDH. External influences on paediatric abdominal pain: a holistic view may help. Poster presentation at the Convention of European Academy of Paediatric Societies (EAPS), Barcelona, Spain. 21st October 2014. *Poster presentation.*

Publications and presentations arising indirectly from this review:

- Dillon A, Beardsley CJ, Croaker GDH. Paediatric abdominal investigations: are all the tests useless? Royal Australian College of Surgeons Annual Scientific Meeting (Canberra, A.C.T). 5th November 2011. *Oral presentation.*
- Chiu M, Beardsley CJ, Dillon A, Croaker GDH. Paediatric abdominal investigations: epidemiology of casualty presentation. Royal Australian College of Surgeons Annual Scientific Meeting (Canberra, A.C.T). 5th November 2011. *Oral presentation.*
- F Nguyen, CJ Beardsley, GDH Croaker. "The Appendix is not visualised: how useful is ultrasound in the evaluation of possible appendicitis in children presenting to The Canberra hospital?" Royal Australian College of Surgeons Annual Scientific Meeting (Canberra, A.C.T). November 2012. *Oral presentation.*

Outline

Chapter 1. Aim of the thesis

To investigate the underlying aetiologies behind paediatric abdominal pain presentations, including both intrinsic and extrinsic factors, and the utility of investigations such as laboratory tests and ultrasound in aiding the diagnostic acumen of the clinician.

1.1 Hypothesis

That simple clinical parameters and tools are equal or superior to more advanced investigations in the management of paediatric abdominal pain, and that extrinsic factors may play a role in the aetiology of paediatric abdominal pain.

1.2 Specific predictions

1.2.1 That the majority of conditions underlying paediatric abdominal pain investigations are benign and that simple clinical tools (history & examination) fare no worse than more advanced investigations in helping to manage paediatric abdominal pain.

1.2.2 That there are extrinsic factors at play in the child who presents with paediatric abdominal pain and that factors including socio-economic parameters, familial conditions and extra-abdominal conditions that may influence paediatric abdominal pain.

1.2.3 That the sensitivity and specificity of abdominal ultrasound for abdominal pain is not significantly better than clinical examination.

1.3.4 That the non visualisation rate in abdominal ultrasonography significantly hampers the diagnostic utility of ultrasonography

1.3.5 That the rate of true appendicitis varies with not only age and sex but also (as a proportion of presentations) according to the patients social and genetic background.

Chapter 2. Literature Review

2.1 Background

Paediatric abdominal pain has long posed a problem for emergency physicians and surgeons alike. Whilst the vast majority of children with abdominal pain will have benign causes for their pain, a minority will have serious or life threatening illness underlying their presentations. Appendicitis, Pancreatitis, Cholecystitis, Meckel's diverticulum, Testicular torsion and Malignancy are some of the more common serious causes. The prospect of missing a life threatening condition in a child has led many practitioners to look towards laboratory and imaging tests to rule out such conditions. However, whilst some laboratory tests (e.g. Lipase for pancreatitis) are sensitive and specific, for many conditions there is no one test that is specific for the diagnosis.

This thesis primarily investigates appendicitis as a major diagnostic dilemma of paediatric abdominal pain. Despite major advances in surgery, medicine and radiology this condition continues to be an enigma in both adult and paediatric populations. Across the Pacific driven by medical litigation fears, many practitioners in the United States have relied upon Computed Tomography to confirm or rule out a differential diagnosis (1, 2). Whilst computed tomography offers the benefit of an operator independent imaging modality and in many cases contributes substantially to a patient's management, it does carry a substantial risk of malignancy in the future (3). Whilst the radiation dose is significant in adults, from an actuarial point of view, the years left to

develop neoplasia are far less than in children. Given that the driving ethos behind medicine is first to do no harm, it does seem illogical to be attempting to delay harm in the present time (i.e. to rule out appendicitis) for a trade-off of a future malignancy.

Relevant literature will now be presented relating to the individual chapters and their results.

2.2 Basic epidemiology and underlying causes of paediatric abdominal pain

Abdominal pain is a common presenting complaint of children in the emergency department, with between 5-10% of emergency presentations being related to abdominal pain in children (4-6). The majority of children with abdominal pain have benign causes for their presentation (4,7). The most common benign causes include non-specific abdominal pain, gastroenteritis and constipation (4,5). The most common surgical conditions are appendicitis, incarcerated inguinal hernias and intussusception (4). Other serious conditions include malrotation with volvulus, cholecystitis and acute pancreatitis. Serious extra-intestinal conditions, such as Pneumonia, occasionally manifest with abdominal pain thus mandating a thorough examination of the child's oropharynx, neck, chest, abdomen and groin (6). Other causes of extra-intestinal conditions causing abdominal pain include abdominal epilepsy, abdominal migraine, red back spider bite, diabetic keto-acidosis, haemolytic-uraemic syndrome, Henoch-Schönlein purpura, toxic ingestions and pharyngitis (8). In the female population, gynaecological conditions such as ectopic pregnancy, ovarian torsion and ovarian cyst accident should be considered. Furthermore, whilst rare, primary peritonitis may mimic

appendicitis.

Common causes of non-surgical abdominal pain presentations include viral gastroenteritis and urinary tract infections. Rotavirus and Campylobacter appear to be the most common causes of viral and bacterial gastroenteritis respectively (8). Constipation is a common precursor to a presentation with abdominal pain, and whilst in infancy it may be associated with several serious conditions (Hirschsprung's disease and hypothyroidism to list a few), in older children it is usually due to dietary changes and reduced fluid inputs (9).

2.3 Appendicitis in children, and diagnostic clues

The diagnosis of appendicitis in children has never been simple. Yet with the advances of time and technology, the management of paediatric abdominal pain has not advanced as much as we would like to believe. The underlying pathophysiology of this condition remains to be fully elucidated, with some authors implicating the western diet in the pathogenesis (10).

Faecolith impaction, lymphoid hyperplasia and parasites have all been implicated in this disease process, leading to obstruction of the appendiceal lumen (11). Addiss et al demonstrated seasonal variation of appendicitis and postulated that this could be due to enteric infections (12). They noted an 11% increase in cases occurring from May to August compared with November to February. The classical presentation of appendicitis is pain originating in the umbilical region and migrating to the right iliac fossa, and the associated symptoms of nausea, vomiting and anorexia.

Unfortunately children are less likely to conform to this typical presentation pattern, and this is especially true with the younger child (8). Furthermore, history taking from children can be challenging, and the abdominal examination can be misleading at best. This is especially so in very young children which results in appendiceal perforation being the rule rather than the exception in that group. Symptomatology varies according to age, with infants tending to present with vomiting and pain, whereas older children may present with a more 'classical picture' of appendicitis (11). Diarrhoea has been associated as an important symptom for appendicitis in children under the age of three (13). Whilst several studies have attempted to determine the sensitivity of history and exam findings *in adults*, the evidence base is not strong when applied to children. Bundy et al conducted a meta-analysis of studies on all children under the age of 18, with abdominal pain (14). Whilst it was found that a history of fever and vomiting accompanying RLQ pain generally was predictive of appendicitis, a significant likelihood ratio was not found across all studies. However, when studying examination findings, they found that isolated right lower quadrant tenderness was inferior to rebound tenderness in the right lower quadrant, which almost tripled the odds of the child having appendicitis. A limitation of this study is the age limit for the population being up to 18, with many surgeons considering an individual over 16 to be effectively an adult. Gendel et al, assessed 686 children who underwent appendicectomy and found that history and examination contributed very little when compared to laboratory investigations and ultrasonography (15). They found that 83% of children with appendicitis had peritoneal signs versus 76% of those with a normal appendix. Caution

must be taken when interpreting this study as the sample of children without appendicitis represented only 5% of the total study population. Alteration in vital signs and index temperature on admission are only useful if the child has had symptoms for a prolonged duration, however, they are useful for assessing the fluid balance and requirement for resuscitation (16). Reynolds and Jaffe found that 97% of children with appendicitis had 2 of 4 specific features (vomiting, right lower quadrant pain, abdominal tenderness or guarding) compared to 28% of control children (5). It should be noted though that this study suffered from small sample sizes.

Much contention exists with regard to inflammatory biomarkers, with some emergency practitioners advocating their use and others completely disregarding them (17-19). Ultrasonography, whilst theoretically attractive has faired poorly in several studies, primarily due to the great variation in operator ability and body habitus (20-22). Computed tomography remains the radiological investigation with the best all round sensitivity and specificity but with the major drawback being the significant radiation doses involved (3,21,23).

2.4 The concept of the acceptable negative appendicectomy rate in children

Currently there is great variation in the negative appendicectomy rate. Rates of 5%-15% have been described in the literature, with a markedly higher rate seen in pubescent females (14,24,25). Some authors have argued adamantly that computed tomography has the power to reduce this rate but this is hotly debated (23,24). In some centres negative appendicectomy rates of up to 30% are tolerated. This is especially so when it

comes to females. *Why* is this so? Because the underlying medical ethos is that early diagnosis will reduce the rate of appendiceal perforation and hence reduce death and complications from this disease. Perforation rates are highest in young children (up to 90%) and taper down to 15% in the adolescent age group (11). When perforation does ensue, intra-abdominal infection with *Eschericha Coli, Bactereoides Fragilis, Peptostreptococcus and Pseudomonas species* mandates a thorough washout and intensive treatment with intravenous antibiotics. The current philosophy in our hospital is to rely on clinical judgement, with the selective use of blood tests and ultrasonography. A study performed in 2002 in our hospital questioned the validity of ultrasonography in appendicitis and advocated the selective use of this tool (22). However this study looked at both children and adults. Whilst there has been a sway away from using ultrasonography in adults and towards computed tomography, in children the practice is still widespread. A major aim of this thesis is to identify whether the use of more complex tests such as blood tests and ultrasonography are justified in their use as an adjunct to clinical evaluation of the child with abdominal pain.

2.5 Functional disorders manifesting as abdominal pain

Whilst many *known* organic causes underlie paediatric abdominal pain presentations, a substantial number of children have no organic disease found after investigation. Furthermore, a significant *number* of children with abdominal pain go onto develop chronic or recurrent abdominal pain. In 1957, Apley and Naish (26), defined the concept of recurrent abdominal pain as children who had three episodes of abdominal pain,

severe enough to affect their activities over a period greater than 3 months and with the attacks continuing over to the preceding year.

Differentiating children who suffer from recurrent abdominal pain, and functional abdominal pain syndromes from those with an acute abdomen can be difficult due to the overlap of symptoms and the relative frequency of the latter conditions. One cannot be reassured by a past history of recurrent abdominal pain alone that there is no sinister cause behind their latest re-presentation.

Several authors have thus attempted to further describe the characteristics and pattern of children presenting with recurrent abdominal pain and functional abdominal pain syndromes. Chitkara et al performed a systematic review on recurrent abdominal pain (27). They reported; a prevalence from 0.3-19%; a female predilection; bimodal age peaks (4-6 years, and pre-adolescence) and a link with extra-intestinal symptoms (headache in particular). The ROME III convention on Gastroenterology was instrumental in this field, in that it set out to clearly define diagnostic criteria for Functional Abdominal Pain (28). In 2016, the recently updated ROME IV convention on gastroenterology has departed from ROME III by changing the nomenclature from functional abdominal pain syndrome to centrally mediated abdominal pain syndrome. The ROME IV committee believes this updated nomenclature more appropriately address the disorder's pathogenesis, minimize the stigma of the term functional, and is in keeping with the evolving concept of the brain–gut interaction (29).

ROME IV provides the following key diagnostic criteria for diagnosing *the Centrally Mediated Abdominal Pain syndrome:*

1) *Continuous or near continuous abdominal pain*
2) *No, or only occasional relationship of pain with physiological events (e.g. defaecation, menses, eating…etc)*
3) *The pain is not feigned*
4) *The pain is not explained by another structural or functional gastrointestinal disorder or other medical condition*

The criteria have been fulfilled if the symptoms have persisted for the last 3 months with symptom onset for at least 6 months before diagnosis (30).

The pain is often constant or frequently recurring, with the main differentiation between it and Irritable Bowel Syndrome being a lack of relation to food intake or defaecation. ROME IV also mentions that these patients are more likely to report other somatic symptoms of discomfort, including chronic pain thought to be related to the gynaecologic or urinary systems and a possible association with psychological disturbances when the pain is persistent over a long period of time. For the purpose of clarity within the thesis and the multiple references from other sources which refer to the term 'functional', the term functional abdominal pain is retained in this thesis. Ramchandani et al, in their population cohort study of 13,971 children found that

Recurrent Abdominal Pain (RAP) diagnosed at an age of under 6 was associated with RAP in older years of childhood and that these children also suffered from multi-system complaints (31). They also found an association between both parental and child anxiety and RAP. Fitzpatrick et al investigated the link between coeliac disease and recurrent abdominal pain and found there to be no significant link between the two conditions (32).

Whilst many studies on recurrent abdominal pain have looked at children from western nations, Boey and Goh, looked at Malaysian children with recurrent abdominal pain (33). They found that in children with RAP; lower socio-economic status; the presence of other somatic complaints and a family history of abdominal pain were all associated with this condition. Huang et al looked specifically at Australian children from a primary care perspective and conducted a review on paediatric abdominal pain (34). They found that nearly 44% of children may experience abdominal pain, and that in 12% this is experienced monthly. They also found that children who had suffered from abdominal pain in the last 12 months were also more likely to have suffered from anxiety and/or a sleep disturbance in the past. In addition, only 34% of respondent's sought medical advice with the majority either seeking alternative therapies or using over the counter medications. They did not find any associations with Helicobacter Pylori, Inflammatory Bowel Disease, or lactose intolerance.

An interesting concept in medicine has been the interlinking between childhood conditions and their later development in adulthood. Whilst for many organic disorders

(such as diabetes) it is obviously logical that this will continue, but what about functional disorders? Walker et al conducted a cohort study with follow up over 15 years and found that children with RAP and functional abdominal pain are at increased risk for chronic pain and headache (35). They found that up to one third of children who suffered from unresolved RAP as a child now suffered from headache and chronic *non-abdominal pain* compared to under 5% in control populations. Thus not only did they find that there was an overlap into adulthood with abdominal pain but that they manifested other chronic pain syndromes as they grew older. From the above it is obvious that in children with RAP there is an association with the development of functional conditions in the future, many of which have strong relationships with psychological and social well being states. This association was made formal in the ROME III treatise on the functional abdominal pain syndrome (see above). Gulewitsch et al found that recurrent abdominal pain in childhood was highly predictive of a diagnosis of Irritable Bowel Syndrome (IBS) with an Odds Ratio of 2.01 (36). Chitkara et al conducted a second systematic review assessing the link between childhood disorders and adult irritable bowel syndrome (37). They found that childhood trauma was associated with irritable bowel syndrome but interestingly found that coming from an affluent background was predictive of IBS in adulthood.

2.6 Systemic conditions and extra-intestinal causes of paediatric abdominal pain

Coeliac disease can be a serious cause of abdominal pain in childhood however its role in recurrent abdominal pain has been disputed. Fitzpatrick et al investigated the link

between coeliac disease *and* recurrent abdominal pain and found there to be no significant link between the two conditions (32). Gastro-oesophageal reflux disease, a common problem in adults, may also manifest as abdominal pain in the older child (38). Thakkar et al conducted a prospective study of children undergoing esophagogastroduodenoscopy for chronic abdominal pain and found a significant diagnostic yield from this procedure (39). 38% of children were diagnosed with a gastrointestinal condition after the procedure. This included Esophagitis (21%), Oesinophilic gastroenteritis (4.1%), Helicobacter Pylori infection (2.0%) and Coeliac disease (0.6%). Hence although many children with recurrent abdominal pain will not have a primary medical condition, it is important that the clinician be wary of other potential gastrointestinal conditions that may mimic RAP.

Whether extra-intestinal conditions such as asthma have an influence on abdominal pain is debatable. Remedios et al have linked asthma and other atopic disorders with oesinophilic oesophagitis, although the causal link here is obvious (40). Nation et al argue that children suffering from chronic rhinosinusitis may indeed have underlying gastro-oesophageal reflux contributing to their upper respiratory tract symptoms (41). Carson et al determined that up to 4% of children with recurrent abdominal pain may have previously undiagnosed abdominal migraine, the implication being that triggers can be identified and hence episodes avoided as much as possible(42) . Acutely children can present with abdominal pain which mimics a surgical abdomen, yet with an underlying medical cause. Diabetic Keto-Acidosis, Haemolytic Uraemic Syndrome, Endocarditis, to name only a few medical causes, can manifest as a potential surgical

abdomen (16). With accurate history and examination, clinical cues can be elucidated which steers the clinician away from surgical diagnoses in these patients, but these findings may be subtle. As such it can be demonstrated that there are medical conditions which whilst being primarily extra-intestinal may have gastrointestinal manifestations, and vice versa.

2.7 The role of investigations such as biomarkers and radiology in appendicitis

Abdominal pain is a common presenting complaint in children presenting to the emergency department. 10-30% of childhood emergency presentations can be attributed to a presenting complaint of abdominal pain. As such this condition places a significant cost burden on public hospitals (14, 43). Only a small, but significant number of children will have appendicitis, the most common surgical disease of childhood (14, 19). Differentiating these children from those with benign causes for their pain can be difficult even for an experienced paediatric surgeon. History can be unreliable and physical examination can be both operator and temporally dependent. Haematological and biochemical adjuncts such as the full blood count and C-reactive protein are relatively sensitive but not specific (14,18,43). Radiological investigations such as plain X ray, ultrasonography and computed tomography (CT) have been utilized, but in practice

only ultrasonography and CT remain useful adjuncts. Plain X ray's ability is limited to the detection of a localized ileus or the rare pick up of a faecolith and has been superseded by the latter two investigations (19).

In 1986 Julien Pulyaert described the use of graded compression ultrasonography to diagnose appendicitis (44). Ultrasonography steadily advanced into paediatrics with its ease of applicability and lack of ionizing radiation. Initial studies into its efficacy were positive and lead many clinicians to rely on this investigation even when there was a strong clinical suspicion of appendicitis (23, 45). However, as further studies were conducted it soon became obvious that the ability of ultrasonography to detect appendicitis was dependent on two variables: (1) the operator, and (2) the operating environment (21, 46). Many European studies reported high sensitivities and specificities of ultrasonography, however these were conducted in centres where experienced paediatric radiologists were performing the study, and in large hospitals where the prevalence of appendicitis in abdominal pain referrals was high (21,45,46-47). Hence ultrasonography initially appeared as a very attractive tool with the promise of a radiological investigation without ionizing radiation and with the ability to reliably detect not only appendicitis but its mimickers. However, many *European* clinicians were soon brought back to reality by the dismal visualisation rates seen in practice (21). Across the Atlantic, their counter parts were also reporting dismal results with ultrasonography and began to lean upon computed tomography to provide more acceptable sensitivities and specificities in clinical practice (48, 49).

Computed tomography is an excellent tool for ruling out appendicitis in the equivocal presentation but is limited by the significant radiation exposure associated with its use. Furthermore, some authors argue that computed tomography is limited in children by the fact that anatomically children possess less adipose tissue and hence 'fat stranding', a key finding in the diagnosis of acute appendicitis, is less likely to be present (50). However, the author would argue that with sky-rocketing rates of obesity in the western world, this is unlikely to be a significant problem *with* at least 25% of the paediatric population being overweight or obese (51)

The utility and popularity of biomarkers in the scientific literature for diagnosing appendicitis varies considerably between clinicians. This is especially so when it comes to the use of these biomarkers in paediatric appendicitis. Commonly used markers are the White cell count (WCC), Neutrophil count (NC) and C-Reactive Protein (CRP). Bilirubin has also been purported to be linked with perforation but this is uncommonly used in clinical practice (52). Procalcitonin has largely been relegated to experimental studies (53).

White cell count has been argued by some authors to be both non-specific and non-sensitive for the detection of appendicitis in children, with neutrophil count being slightly better (11, 53). Although authors often state that this is because many other extra-intestinal and gastrointestinal conditions present with a leucocytosis or neutrophilia it should be mentioned that many of these can be sorted out via clinical

examination (e.g. oropharyngeal examination in tonsillitis or auscultation in pneumonia) or other simple bed side tests (e.g. urinalysis for urinary tract infections). Arguing for WCC, Wang (54), believes that the presence of an increased WCC or left shift carries with it a high sensitivity (79%), and that the presence of both high WCC and left shift has the highest specificity (94%). They go onto argue that these values are helpful in the diagnosis and specifically the *exclusion* of appendicitis. Neutrophil count has been reported to have higher sensitivities than white cell count (11). C-reactive protein is a biochemical marker for non-specific inflammation and also possesses a mixed popularity with clinicians. Kwan et al (55), argue that when combined with a WCC over 12 x 10^9 /L, a CRP value over 3mg/l carries an adjusted odds ratio of 7.75. It should be noted that the same authors also concluded that a child with the 'hopping pain' sign had an adjusted odds ratio of 2.69. Yu et al (53), in their systematic review of biochemical markers in appendicitis however found neither Pro-calicitonin, White Cell Count or CRP to be useful. Whilst Pro-calcitonin did have a pooled specificity of 89% its sensitivity was a meagre 33%. Another potential application of biomarkers is through serial levels (repeat biochemical tests over several hours or days) combined with serial examinations (56). Gendel et al, conducted a large scale retrospective review of children with suspected appendicitis and argue that the utility of white cell count, neutrophil count and ultrasound far outstrip that of history and clinical examination (15). However, it must be noted that in Gendel's analysis when comparing history and exam findings between populations, the control sample (those without appendicitis) made up only 5% of the total population. Hence, any recommendations from this study that are made are

more applicable to a population of children with a very high pre-test probability of appendicitis (i.e. not the population presenting to an emergency department).

2.8 Scoring systems: a brief review

Paediatric appendicitis scores attempt to calculate a child's risk of appendicitis based on history, examination and haematological parameters. Whilst scoring systems were first popularized in the mid-80s, their uptake amongst primary care physicians is variable, and many have only recently been introduced to the concept of appendicitis scoring systems (57). The Alverado score remains the most recognized of appendicitis scoring systems but other models do exist, for example the Pediatric Appendicitis Score (58).

The Alverado score calculates a projected risk of appendicitis and then stratifies the patient into suggested management strategies, namely discharge, observation or surgery (59). The total score consists of ten points, with one point awarded to the presence of migration, nausea, elevated temperature, rebound pain, and left shift. Two points were awarded for tenderness in the right iliac fossa and a leukocytosis. A score greater than 5 warrants admission, and greater than 7 warranted surgery. Ohle et al, conducted a systematic review to determine diagnostic accuracy and appropriate calibration of the Alvorado score for the diagnosis of appendicitis in men, women and children (60). Their analysis demonstrated that as a rule out tool, a score of < 5 had excellent sensitivities (>95%) and could be relied upon across all three groups. However, they found that the Alverado score was likely to over predict the diagnosis of

appendicitis in children and women. This is a significant finding, given that these are the exact patient groups which pose diagnostic challenges to the clinician. As mentioned previously, other scoring systems do exist, with the Paediatric Appendicitis Score (PAS) being another major scoring system in use. Significant contention exists with regards to the superiority between scoring systems with Ebell et al, arguing for the Alverado score, whilst Pogorelic et al, found both scoring systems to be of benefit although the PAS performed marginally worse (58, 61). Ebell et al, concluded that the Alverado scoring system was useful for excluding appendicitis for those populations with a pre-test probably of under 60%, and where the Alverado score was under 4 (58). They also found that for ruling in the diagnosis, the PAS was useful but that it was inferior to the Alverado score for excluding the diagnosis. Pogorelic et al (61), found that both scoring systems had moderately high sensitivities (89% and 86%, respectively for the Alverado score and PAS) but poor specificities (59% and 50% respectively). Modified scoring systems have been developed which do not include blood tests, with Khanafer et al, demonstrating that these tests were not significantly inferior when performed without haematological criteria (62).

2.9 Summary and the Canberra Hospital paediatric surgical group's approach

Appendicitis in children poses a significant dilemma for clinicians due to the great variation in its presentation, the difficulty of history and examination in younger children, and the fact that there is no perfect non-invasive test for children. The differential diagnosis for paediatric abdominal pain includes surgical diagnoses, medical diagnoses and functional conditions. A history of migratory pain and vomiting are mentioned as the most useful history parameters, and the presence of rebound tenderness in the right iliac fossa is also specific for appendicitis. It should be noted that much of the current evidence for the accuracy of history and examination is based upon meta-analyses, much of which include studies which have older paediatric populations and in studies which are now over thirty years old. Hematological tests such as white cell count and neutrophil count may be of use by helping to rule in a diagnosis of appendicitis, but a negative result does not exclude the possibility of a diagnosis. Ultrasonography is inherently operator dependent, and many initial studies validating its use involved radiologist performed ultrasounds. Computed tomography is an excellent diagnostic tool but has the major caveat of ionizing radiation. Paediatric appendicitis scores may of use in helping the clinician to exclude a diagnosis in that they provide a systematic and somewhat objective tool, with the Alverado scores and PAS being the most popular. In the Canberra Hospital, our preference is to primarily rely on clinical judgement with biomarkers and radiological investigations as adjuncts. Ultrasonography is our main radiological tool in the management of paediatric appendicitis, however poor appendix visualisation rates was a prompt for the author to conduct a review into

the diagnostic accuracy of ultrasound. Computed tomography of the abdomen is not used in routine acute abdominal pain presentations. Finally, for any child in whom the diagnosis cannot be confidently excluded by either clinical or radiological mean is admitted for observation and a low threshold for diagnostic laparoscopy is held if their symptoms do not resolve. This thesis hopes to add to the available scientific literature by providing an up to date and comprehensive assessment of the epidemiology of paediatric abdominal pain and the diagnostic accuracy of history, examination and clinical adjuncts when assessing children with abdominal pain.

Chapter 3. Epidemiology of Paedatric Abdominal Pain and the utility of clinical examination with investigations in the assessment of the child with abdominal pain.

3.1 Chapter background

Paediatric abdominal pain poses a diagnostic dilemma to emergency physicians and surgeons alike. The majority of presentations represent underlying benign causes but differentiating serious aetiologies can be difficult due to the specific challenges imposed by our young patients. Understanding the epidemiology of paediatric abdominal pain, and how clinical assessment and clinical adjuncts perform in this population is a necessary for all clinicians involved in the care of the child with abdominal pain.

3.2 Chapter Aim

1) To analyze the epidemiology and clinical features of children presenting to our casualty with abdominal pain

2) To analyze the utility of the clinical examination, as compared with selected laboratory and radiological tests. This will allow comparison with data described in chapter 4.

3.3 Methods

Retrospective review of children between 0-16 years of age, presenting with abdominal pain to the casualty department for the calendar year of 2005, specifically between the dates of 1st of January 2005 and the 31st of December 2005. International Classification of Disease (ICD) coding system was utilized by medical records staff to ascertain patients. Any patient with a code of abdominal pain regardless of the type, who presented to the emergency department, was included into the study. In addition, for the full calendar years 2005-2010, simple demographic data such as sex, presentation date and time was collected by the medical records department and analysed. Data was stored and simple statistics calculated via Microsoft excel. Statistical significance and P values were computed using Microsoft excel's data analysis package for continuous quantitative data. For discrete quantitative data, the chi square test was utilized to determine statistical significance.

3.4 Results

1007 patient records were provided for data extraction of which 962 were included. The 45 other patient records did not relate to abdominal pain presentations. 505 females, and 457 males were in the study. Mean age was 9 for the total population. For girls, mean age was 9, with a peak in incidence in the late teens. For boys, mean age was 8 with the peak incidence at seven years. 44% of children had a blood test and 15% underwent ultrasonography. The most common diagnoses in descending order were:

non specific abdominal pain, gastroenteritis, constipation, appendicitis, urinary tract infection and menstrual related disorders.

3.4.1 Demographics

There was a female predominance with 505 females, and 457 males. The mean age was 9. For girls, a peak in abdominal pain presentations was noted in the teenage period (i.e a peak post 12 years of age). For boys mean age was 8 with a peak incidence of abdominal pain around the 7 year mark. Overall there was a bimodal peak in abdominal pain with a peak at 7 years and another during the teenage period. By gender, presentation is equal up until the teenage years where the female sex dominates (See figures 3.1 and 3.2).

Figure 3.1 Abdominal pain presentations versus age for the year 2005.

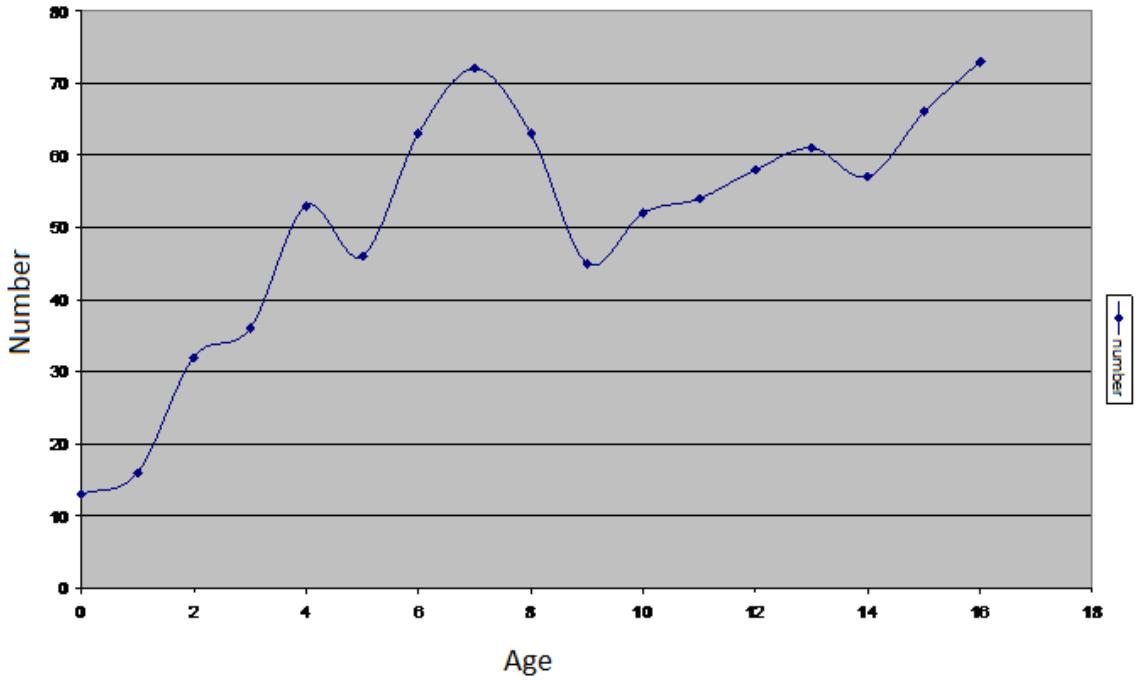


Figure 3.1: A bimodal distribution observed with peaks at 7 years of age and during the late teens (age fifteen and upwards). In this age group, female presentations rise which is most likely associated with gynaecological maturation (see below).

Figure 3.2 The association between sex and abdominal pain presentations.

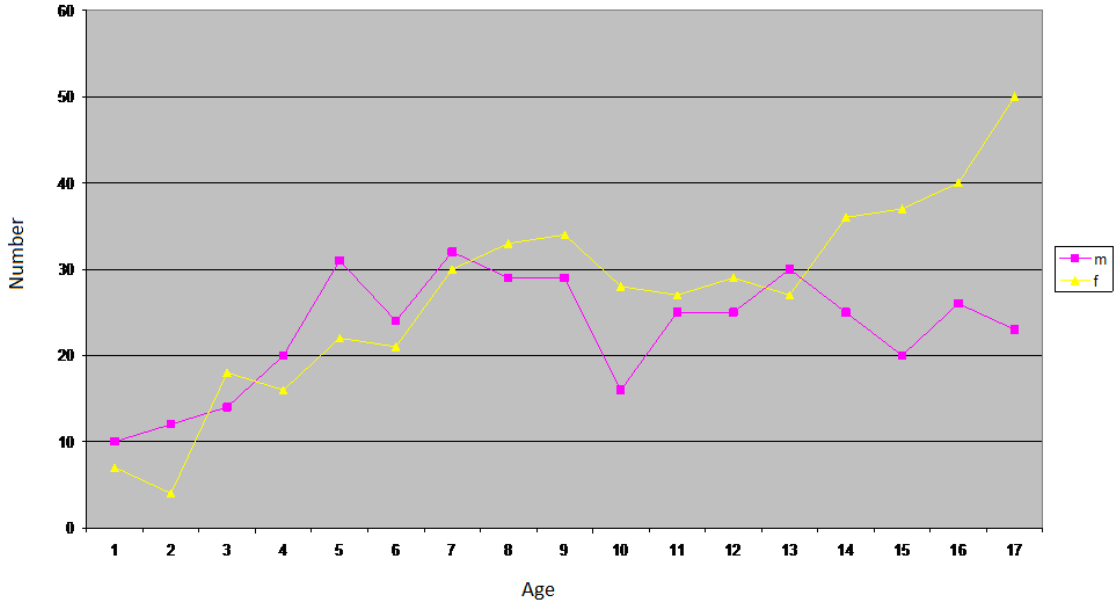


Figure 3.2: Abdominal pain presentations remain fairly equal up until the teenage years, where the female gender presentation rate exceeds the male presentation rate.

As described in the literature review, several authors had drawn association between

abdominal conditions and seasonality. In our study we were unable to find any seasonal linkages within appendicitis, but for all abdominal pain presentations there was a peak in the late winter months (July-August).

Figure 3.3 Abdominal pain incidence by month between 2005 and 2010.

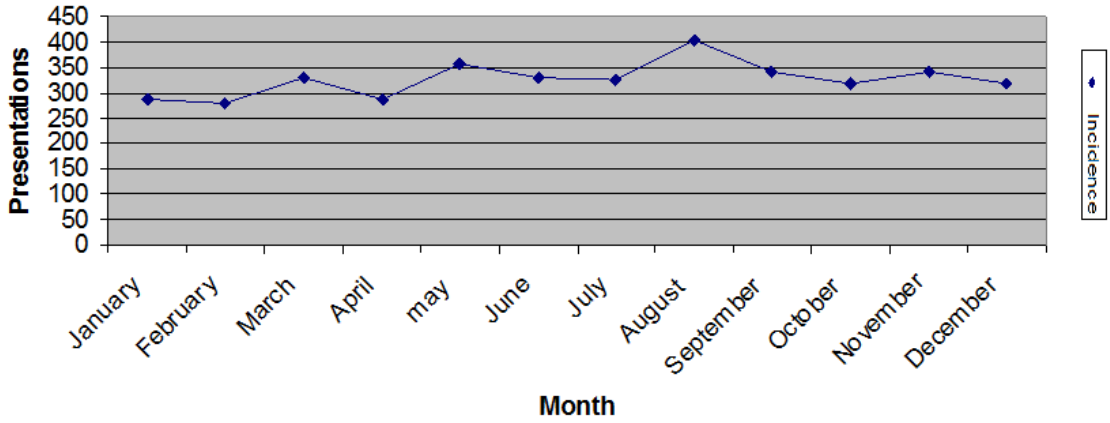


Figure 3.3: There is a slight winter peak in presentation by ~25% (about 2 standard deviations above monthly mean), consistent with seasonal infective effect, but no seasonal trends with appendicitis were observed.

Whilst the incidence of appendicitis appears to remain constant over the months, the pain incidence varies diurnally and seasonally as well as being influenced by age and sex. Peaks were noted in the late winter months (see figure 3.3) and incidence is significantly higher in the evening / after midday (see figure 3.4). By contrast, for appendicitis presentations there is no association and presentation is equally spread out through the

day.

Figure 3.4 Abdominal pain versus appendicitis presentations by time of day

	All abdominal pain (2005 – 2010)	Appendicitis (2005 – 2006)
Arrive ED **before** midday	36.3%	50.7%
Arrive ED **after** midday	63.6%	49.3%

P = 0.01

Figure 3.4: Children with non-specific abdominal pain were more likely to present to the emergency department after midday whilst those with appendicitis presented throughout the day.

3.4.2 Underlying causes

Please refer to Figure 3.5 which graphically displays the general causes of paediatric abdominal pain for the study population and table 3.1 which details the specific

conditions and their numerical representation within the study population. The majority of presentations were due to so called non-specific abdominal pain. Despite thorough clinical evaluation no specific cause is found for the child's pain. Mesenteric adenitis and functional abdominal pain are often grouped into this diagnosis, although mesenteric adenitis is a true clinical entity in itself. The next most common cause was gastroenteritis. Specific infectious agents included in order of frequency include: Campylobacter; C Dificile; Salmonella; Epstein Barr Virus; Cryptosporidium and Giardia. The third most common cause in our population was appendicitis which accounted for 6% of all presentations. 80 patients were diagnosed with appendicitis and taken to theatre, and 61 patients were proven to have histological appendicitis. Thus in our patient cohort the overall negative appendicectomy rate was 24%, but in females the rate was 30%. As predicted, the majority of presentations were in the pubescent age group of the female cohort. The fourth most common diagnosis was mesenteric adenitis, a benign (likely viral) infection of the lymph nodes of the small bowel. Non specific viral illness, the fifth most common cause of abdominal pain can also present with fever and abdominal pain, although children often have other viral symptoms (rash, and typical coryzal symptoms…etc).

As can be seen from the above the majority of the most common causes are benign. However, aside from appendicitis, several other serious surgical entities were also encountered in the study population. These included acute pancreatitis, small bowel obstructions, intussusception, acute cholecystitis and obstructing renal calculi. Female genitourinary causes represent only 4% of female presentations, however,

serious conditions such as ovarian torsion represented 10% of gynaecological pathology. By contrast only 1% of presentations in males related specifically to the male gonads, but it is important to note that two testicular torsions were present in this group, and that like ovarian torsion this is a true surgical emergency. All in all over 9% of presentations may be due to an underlying surgical emergency.

Whilst the author is primarily concerned with surgical emergencies it is important to highlight that a small but significant amount of presentations are also made up of medical emergencies. Please refer to table 3.1 and the discussion section for further details. Primarily extra intestinal causes make up about 2% of pain presentations, and of importance is the fact that the majority of these patients will have readily treatable conditions such as Pneumonia or tonsillitis. Urinary tract infections are also worthy of a mention because they make up nearly 5% of all presentations with abdominal pain. Of considerable importance is the fact that nearly 10% of patients did not wait for a medical review. These children were triaged and basic vital signs taken to exclude any immediate life threatening conditions and then placed back into the emergency department to await review.

Figure 3.5 Aetiology of paediatric abdominal pain presentations for the year 2005.

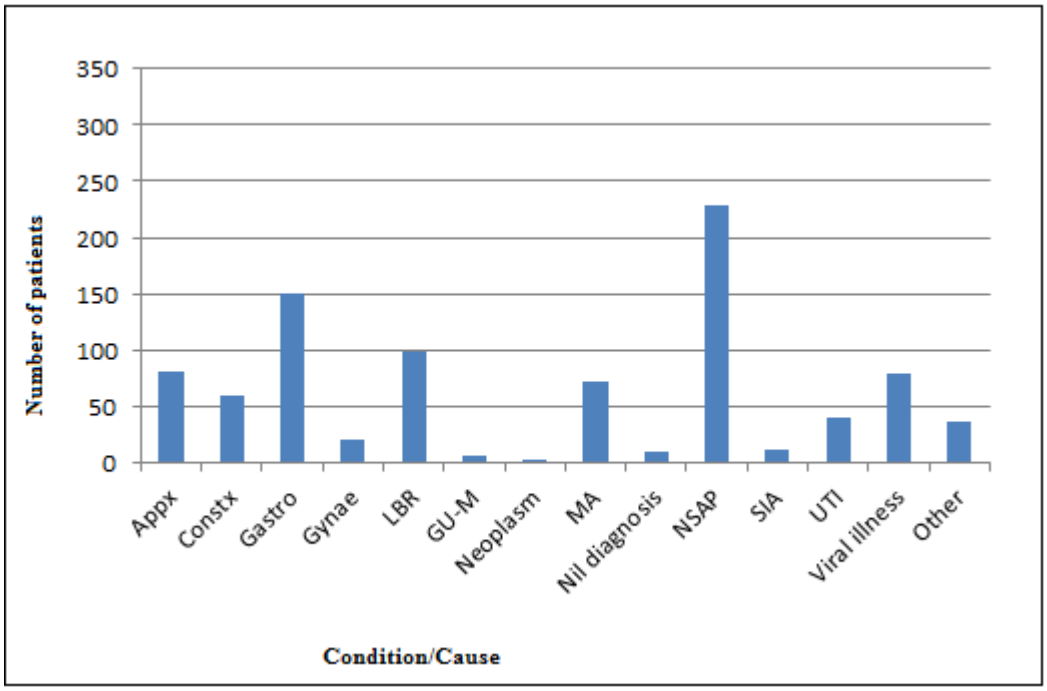


Figure 3.5: The majority of conditions are non-life threatening, with the most common condition being non-specific abdominal pain which along with mesenteric adenitis and viral illnesses made up nearly half of all presentations. However serious causes are prevalent with the 3rd most common cause being a surgical condition: appendicitis.

LBR-Left before Revew; GU-M- Male urogenital disorders, MA-mesenteric adenitis, SIA-Specific infectious agents, UTI-Urinary tract infetion.

Table 3.1: Causes of abdominal pain

Cause	**Number**
Appendicitis	
Preoperative diagnosis	80
(Positive by pathology relative to total appendicectomy count)	(61/80)
Constipation	60
Gastroenteritis	151
Gynaecological	
Dysmenorrhea	4
Endometriosis	1
Mittelschmerz	6
Ovarian cyst	6
Ovarian Torsion	2
Pregnancy related	1
Left before review	99
Male genito-urinary tract	
Benign testicular pain	2
Torsion of testicular appendix	1
Torsion of Testes	2
Malignancy	

Carcinoid tumour of the appendix	1
Small round cell desmoplastic tumour	1
Mesenteric Adenitis	72
Nil diagnosis recorded	9
Non-specific abdominal pain	230
Specific infectious agents	
Campylobacter	4
Clostridium Dificile	3
Cryptosporidium	1
Epstein-Barr Virus	1
Giardia	1
Salmonella	1
Streptococcus Pharyngitis	1
Urinary tract pathology	
Acute Pelvi-ureteric obstruction	1
Renal and/ or Bladder calculi	2
Urinary Tract infection	40
Tubulointerstitial nephritis	1
Urinary Retention	1
Viral illness	78
Other	
Abdominal migraine	1

Acute Pancreatitis	5
Anal fissure	1
Acute cholecystitis	1
Anxiety	1
Biliary colic	5
Burn	2
Bulimia	1
Child abuse	1
Collagenous Colitis	1
Crohns disease	3
Dehydration	1
Diabetic ketoacidosis	3
Familial Mediterranean Fever	1
Foreign Body	4
Gastro-Oesophageal Reflux	7
Gilbert's syndrome	1
Henoch Schonlein Purpura	1
Inguinal hernia	4
Intussusception	2
Megaloblastic anaemia	1
Migraine	1
Musculoskeletal injury	14

Peptic ulcer	2
Pneumonia	7
Post op infection/pain	2
Pyloric stenosis	1
Small Bowel Obstruction (adhesive)	5
Trauma related	16
Tonsillitis	3
Tooth ache	1
Total	962

Table 3.1: Appendicitis includes both preoperative and pathological diagnoses (see breakdown In table). The most common causes were non-specific abdominal pain, gastroenteritis and appendicitis. Interestingly nearly 10% of the population left before a medical review could be performed. Other conditions represented a small variety of miscellaneous conditions.

3.4.3 Age and Sex as predictors of appendicitis and other conditions

There was a slight female preponderance to non specific abdominal pain and gastroenteritis whilst males were more likely to be diagnosed with Mesenteric adenitis, viral illness and appendicitis. Girls were more likely to have a normal appendix removed ($p<0.05$) (see *appendicectomy* later in chapter). Mean age was 9. With a convincing

history and examination, age can be utilized as a predictor of appendicitis ($p<0.05$). There is a slight female predominance with 505 females and 457 males although this is not statistically significant. With consistent history, and physical examination findings age over 6 years was associated with a sensitivity of 0.94 and specificity of 0.36. Sex was a reasonable indicator in males over 6 with a predictive sensitivity of 65% and specificity of 74%. In girls, however, it was a poor indicator with a sensitivity of 29% and specificity of 62%. Whilst pain was rare in children younger than 5, an age under 2 years was almost always associated with specific diagnosis, for example; intussusception and incarcerated hernias.

3.4.4 Symptomatology

Table 3.2 displays the sensitivity and specificities of individual history and examination findings for the diagnosis of appendicitis in children presenting with abdominal pain. No history finding had excellent sensitivity, but several had excellent specificity. Anorexia was the most sensitive history question, with a sensitivity of 70%. The presence of nausea, anorexia and vomiting was highly specific for appendicitis with a specificity of 90%. Progression of symptoms (worsening pain, migration of pain) and painful movement was also highly specific. However, of note these signs had only moderate sensitivity. The presence of vomiting and anorexia had reasonable sensitivities and specificities. Nausea alone was not a useful symptom. See table 3.2 for a comparative analysis of sensitivities and specificities of history and examination findings. The most

common presenting pain complaint was that of diffuse generalized abdominal pain (see figure 3.5). Whilst this can be associated with perforated appendicitis, the over-whelming majority of these patients had benign abdominal pain. The next most common pain types were Right Iliac Fossa pain (RIF), periumbilical pain, hypogastric pain, right sided and left sided pain presentations.

3.4.5 Examination findings

Table 3.2 provides sensitivities and specificities for specific examination findings. Pulse was not a useful predictor of appendicitis. The presence of a temperature (>37.6 degrees celcius) had sensitivity and specificity of 70% and 59% respectively. Localized tenderness was the most sensitive test, with children who were lacking right iliac fossa tenderness having a very low likelihood of appendicitis. Rebound tenderness and guarding were highly specific (>90%), but with moderate sensitivities (70%). A positive cough/jump test was also highly specific, again limited by average sensitivities. In our study cohort, other signs such as Rovsing's and the Psoas sign were so infrequently performed that reliable sensitivities and specificities could not be calculated.

Table 3.2. Comparative sensitivity and specificity of History, Examination and Investigations for the diagnosis of appendicitis in children presenting to emergency department with abdominal pain.

		Sensitivity			
		Excellent (0.9-1.0)	Good (0.7-0.9)	Moderate (0.5-0.7)	Poor (0.1-0.5)
Specificity	Excellent (0.9-1.0)		Rebound Tenderness Guarding	N+A+V Symptoms progressing Painful to move	Diarrhoea Migration of pain Ultrasound
	Good (0.7-0.9)	Localized Tenderness	Vomiting Neutrophil Count White Cell Count		Unwell looking
	Moderate (0.5-0.7)		Anorexia	Nausea Index Temp	
	Poor (0.1-0.5)				Pulse on admission

Table 3.2: No one symptom complex, exam finding or investigation offered excellent sensitivity and specificity. Nausea and index temperature was a particularly poor predictor of appendicitis.

3.4.6 Use of investigations

The majority of children will undergo some form of investigation prior to a formal diagnosis being made. In our study, nearly 50% of children underwent haematological testing and 19% had some form of radiological investigation performed.

Whilst the sensitivity and specificity of investigations will be dealt with in full in chapter 3, a brief discussion will be included later in this chapter. It can be seen from Figure 3.6 that for simple haematological investigations a substantial amount of patients have a "positive" test.

Table 3.3 describes the normal ranges of white cell counts by population.

Table 3.3: Normal range of white cell counts by age group

	Cord blood	7 days	3 months	5 years	12 years	Adult
WCC	8.0 – 32.5	6.0 – 21.0	6.0 – 12.0	6.0 – 11.0	5.5 – 11.0	4.0 – 11.0
Neutrophils	5.6 – 22.6	1.7 – 12.6	1.0 – 6.1	1.2 – 5.0	1.5 – 7.0	1.8 – 7.5
Lymphocytes	1.6 – 11.4	2.5 – 14.5	2.1 – 8.3	2.0 – 7.8	1.5 – 7.0	1.0 – 3.5
Monocytes	0.5 – 2.9	0.3 – 2.4	0.1 – 1.0	0.2 – 0.8	0.2 – 0.8	0.2 – 0.8
Eosinophils	0.10 – 2.50	0.02 – 0.20	0.05 – 0.17	0.04 – 0.40	0.04 – 0.40	0.02 – 0.50
Basophils	0.04 – 0.10	0.01 – 0.10	0.01 – 0.10	0.01 – 0.10	0.01 – 0.10	0.00 – 0.10

Table 3.3: Normal values vary between the age groups.

Source: South Australia Pathology

http://www.imvs.sa.gov.au/wps/wcm/connect/SA+Pathology+Internet+Content/Content/Home

Figure 3.6 describes the individual proportions of haematological and biochemical tests which turn up normal and abnormal results. As can be seen nearly 50 % of White Cell Counts came back as positive.

Figure 3.6: Percentage of haematological investigations ordered which are above the reference range

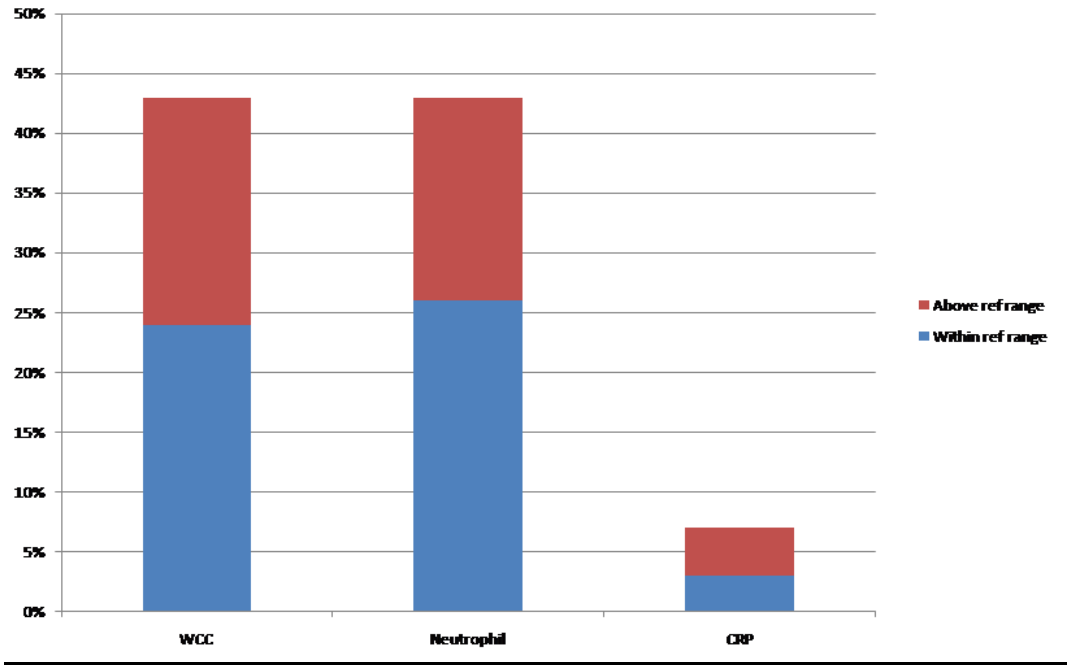


Figure 3.6: As can be seen a significant number of patients with abdominal pain will have raised inflammatory markers despite the fact that less than 10% have surgically or medically significant conditions.

Only 7% of patients had a C-reactive protein (CRP), and in half of these children the test was positive. In our study a normal value was taken at under 5mg/L and for high sensitivity assays, a value under 0.5 mg/L.

With regards to WCC and NC, mean values for children with histologically proven appendicitis were 14.0 x 10^9 /L and 11.1 x 10^9 /L respectively. For those children with benign abdominal pain it was 9.5 x 10^9 /L, and 6.3 x 10^9 /L respectively. At laparoscopy,

27% of patients who had appendicitis had perforated appendicitis. For those children, the mean WCC was 16.0 x 10^9 /L and NC was 13.0 x 10^9 /L. For the overall population, the sensitivity and specificity of WCC and NC was 79% and 85%, and 78% and 88%. Positive predictive value and Negative predictive value was 26% and 96% for WCC, and 32% and 96% for NC count. When a sub-analysis was performed with regards to sex, higher cut-offs were needed in females suspected of having appendicitis. A WCC cut off over 12 x 10^9 /L was necessary for acceptable sensitivities and specificities in females. CRP was insufficiently ordered to generate sufficient numbers for analysis.

Figure 3.7 shows the breakdown of radiological investigations ordered for the study population.

Figure 3.7: Breakdown of radiological investigations.

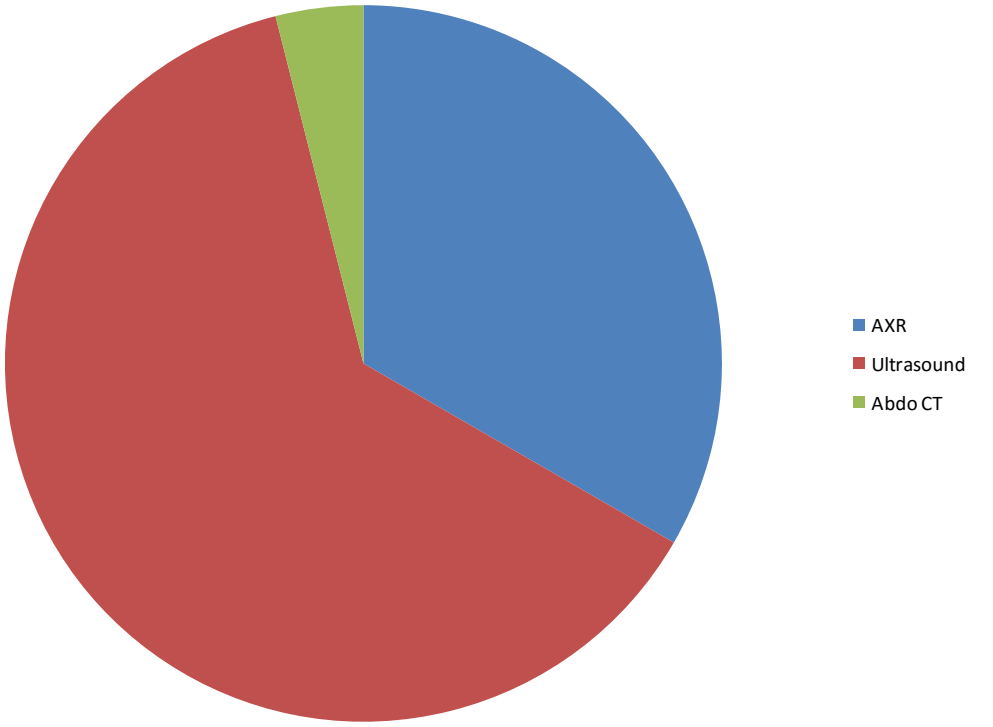


Figure 3.7: Overall, 19% of presentations had imaging – ultrasound being the imagine modality of choice followed by AXR. 135 Ultrasounds were ordered for abdominal pain, 35 abdominal X-rays and 8 CT scans. Of note compared to abroad, the rate of CT imaging was just under 1%.

In only 15% of all ultrasounds ordered (n=143), was the appendix visualized. Of note this visualisation rate is in patients with *undifferentiated* abdominal pain. The sensitivity of ultrasonography was poor, at only 48% but the specificity was over 90%. The positive and negative predictive value were 89% and 36% respectively.

3.4.7 Appendicectomy and other operations.

80 patients were diagnosed with appendicitis and underwent appendicectomy. 61 were found to have a true diagnosis of appendicitis, 1 was found to have a Carcinoid tumour and 19 did not have the condition. Thus in total, the negative appendicectomy rate was

24%. In males the positive appendicectomy rate approached 90% whereas in females this rate was 70%. Females were twice as likely to have their normal appendix removed as males ($p<0.05$) and the mean age of females with normal appendicectomies was 13. Figure 3.8 shows that the rate of operation increases by age group as does the rate of surgical pathology such as appendicitis.

Figure 3.8: Count of operation by age

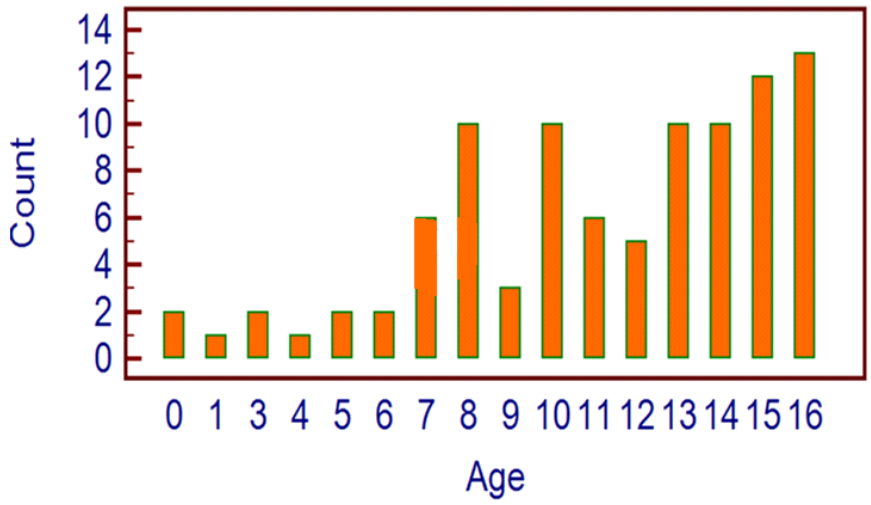


Figure 3.8: The rate of operations increases with age, as does the incidence of appendicitis.

3.5 Discussion

Abdominal pain is a common presenting complaint for children coming to the emergency department. Yet despite its frequency, the rate of over investigation and negative appendicectomy remain high, and often for good reason for the complications of a missed appendicitis are not to be dismissed (14,19).

Simple demographic features of a child's presentation are important when assessing children. There was a female preponderance in this study population, and this is most likely due to maturation of the female urogenital system in the later years and conditions associated with the menstrual cycle. Age and sex can be helpful predictors of appendicitis in children with abdominal pain, with male children over the age of six being moderately predictive of appendicitis. Children with non-specific abdominal pain were found to be more likely to present after mid-day then children with appendicitis who presented at all times throughout the day. It was also noted that there was a peak in abdominal pain presentations during the winter, although this did not apply to children with appendicitis.

Overall in terms of aetiological causes, appendicitis was the third most common cause of paediatric abdominal pain, highlighting the importance of thorough clinical examination and the use of selected investigations. Appendicitis was a leading cause of mortality in the pre-antibiotic era but mortality rates have now dropped significantly

due to antibiotics and early surgery. However, this reduction in mortality often comes at a cost of a greater negative appendicectomy rate. This is seen more commonly in females due to the intra-abdominal location of the female reproductive organs and potential co-existing pathologies. Other causes of abdominal pain must be taken into account, including easily diagnosable urinary tract infections and extra-abdominal causes (14,16). Over 1% of children who present with abdominal pain may have a serious underlying medical condition. These include but are not limited to Pneumonia, Diabetic ketoacidosis and Inflammatory bowel disease. This study population had seven cases of pneumonia where abdominal pain was a presenting feature. Whilst triple intravenous antibiotic therapy treats pneumonia, significant embarrassment is associated with the removal of an appendix when in fact it is the patient's right lower lobe pneumonia which was causing their abdominal pain, not to mention the risk of anesthetic and surgical complications.

Children often suffer from Rotavirus infections and less so from bacterial causes (such as Shigella and Campylobacter). More serious causes such as Salmonella are rare but do occasionally present. Whilst vomiting and diarrohea are often the main hallmarks of these conditions, children occasionally present with abdominal pain as a major symptom complaint. There were two cases of malignancy which presented with abdominal pain. A Carcinoid tumour was diagnosed retrospectively by the pathologist whilst a child with a small round cell desmoplastic tumour presented with abdominal pain and an abdominal mass. Child abuse can be a significant cause of abdominal pain

presentations due to physical, psychological and/or emotional abuse. In the year 2001-2002, 30,500 cases of substantiated child abuse or neglect occurred (Source Australian Bureau of Statistics). This is a national figure, and it is interesting to note that in this series, 1 child presented with abdominal pain due to known underlying physical abuse. This represents a 0.1% prevalence.

Of note, 10% of children were not able to be reviewed by an emergency doctor and in these children, one suspects that the likely cause for the departure was long waiting times in the emergency department, during which the child's pain resolved; the parents decided upon a general practitioners review or they did not seek medical review. This is line with the findings from Huang et al (34).

History and examination findings have long been the main stay of assessment. However, various studies have demonstrated significant variances in the sensitivity and specificity of this tool (7,15). Yet, this must be balanced by the ease and cost with which these tools can be utilized. Our study cites reasonable sensitivities and specificities for key history and physical examination findings. History can yield conflicting results, and is for obvious reasons, unreliable in younger children. For example, a young child with acute testicular torsion may not provide a history of scrotal pain despite ongoing ischaemia. In young, or pre verbal children, a collateral history from parents is often a necessity and the presentation for serious conditions like appendicitis is often not in keeping with classical teachings (14). Examination of the child with abdominal pain can also be

challenging, and techniques of distraction may need to be employed to help calm the child. To add to these challenges, the increasing prevalence of child hood obesity is making examination findings even less accurate. Kutasy et al, in their study showed that the negative appendicectomy rate was 24.6 vs 9.9% for obese and non-obese individuals (63). This has led some authors to conclude that the high rate of negative appendicectomy in obese children rates justifies the use of computed tomography for obese children with abdominal pain, despite the risk of ionizing radiation (64). Yet despite its limitations, the major advantage of history and examination is that in a well trained and experienced clinician, a tailored history and examination may be more diagnostic than more expensive and costly examinations. A history finding of anorexia or vomiting coupled with a consistent pain history demonstrated good sensitivities. Migratory pain, pain worse with movement and the constellation of anorexia, nausea and vomiting had good specificities but poor sensitivities. Whilst rebound tenderness and guarding provided good sensitivities, the examination finding of localized tenderness or rebound guarding was highly sensitive for a diagnosis of appendicitis. Thorough history taking and clinical examination also increases the likelihood that extra-intestinal causes of abdominal pain will be diagnosed prior to any surgical review or intervention.

There is much contention regarding the use of biomarkers, particularly in children. Many authors have cited that a substantial number of children with appendicitis have normal biomarkers (19,20). They also argue that in the presence of a convincing history and

physical examination there is no need to perform markers. There is also a marked variation between age groups which needs to be taken into account. As demonstrated, a significant amount of haematological tests that are ordered come back with positive results despite their being no serious surgical or medical cause underlying the result. This is typified by a child with mesenteric adenitis or a viral illness, who frequently presents with fevers and leukocytosis thereby negating the discriminatory value of this test. However, our study also demonstrates that for use in the diagnosis of appendicitis these tests offer reasonable sensitivities and specificities with minimal cost. In our cohort, in those children with appendicitis only 13% had normal white cell count. Sensitivities and specificities of these tests are useful, especially in the child with a discrepancy in the history or examination findings. CRP as a test is less popular with clinicians, due to its expense and the fact that this test may take over 72 hours to result in a positive value. Many clinicians do not see the value in this test. The fact that over 50% of CRPs ordered were positive may reflect the fact that this investigation is only ordered *or allowed to be ordered* when a clinician is particularly concerned about a child.

Ultrasonography in our population was not useful due to the low visualisation rates with only 15% of appendixes being visualized, making this test simply impractical. The true utility of ultrasonography is the ability to visualize an inflamed appendix or a normal appendix, a test where the appendix is not visualized is not helpful (20,46-,48,49). However, a major caveat exists in our study. That is our ultrasounds are performed by

sonographers and not senior radiologists or paediatric radiology specialists. Subsequently the test suffered from poor sensitivities, and at our centre where the rates of normal appendiceal visualisation were sparse, subsequent visualisation meant that the child was very likely to have appendicitis. The specificity was over 90% when the appendix was seen, however, given the high non visualization rate, this study is effectively as useful as flipping a coin for ruling out appendicitis.

3.6 Limitations

Our study is a retrospective review and is as such only as good as the data that was collected by the physician of the day. We included children in this study who presented to Canberra hospital with abdominal pain and were coded as such. Hence if a child's primary complaint was vomiting or nausea they may not have been included. With regards to our ultrasound analysis, it should be mentioned that the studies in our centre our performed by sonographers and reported by the radiologist after the scan has been performed. Furthermore, in this study children could have been referred for ultrasounds where the primary differential diagnosis is a condition other than appendicitis. This would hence distract the radiologist and sonographer from detecting the appendix. The use of ultrasonography will be discussed in detail in chapter 3.

3.7 Conclusion

Abdominal pain is a common presenting complaint, yet the majority of causes are

benign. However, from our study 10% of all presentations will have a serious cause behind their presentation. Whilst appendicitis is the most common emergency condition per se in this group (and the most common surgical emergency), serious conditions such as acute pancreatitis, pneumonia and diabetic ketoacidosis can also cause abdominal pain. The history and examination of a child in distress can be challenging, but with experience and adequate follow up examinations, this simple tool can yield better diagnostic accuracy than more complex and costly investigations. However, it is one tool that suffers from extreme operator dependence. White cell count and Neutrophil count are appealing investigations because of their relative simplicity, uniformity and cheap cost. However they yield only moderate sensitivities and specificities due to the fact that many children with relatively benign medical conditions (such as tonsillitis or gastroenteritis) will have raised inflammatory markers. This issue will be further addressed in chapter 3. Ultrasonography is the most commonly ordered radiological investigation for paediatric abdominal pain yet the additional value of ultrasonography was hard to demonstrate given that in only 15% of our cohort was the appendix visualized. However, this test is not cheap, both in terms of financial and opportunity costs. Computed tomography is not used in our centre due to the unacceptable risk of radiation induced malignancies. Thus from this preliminary results in this chapter it is suggested that history and examination with supplementary biomarkers remain the gold standard for the safe diagnosis of appendicitis in children with abdominal pain. Thorough history and examination, and the use of bed-side tests are essential for the diagnosis of both serious intra-abdominal and extra-abdominal

conditions. If there is any discrepancy between a clinician's assessment, biomarkers and ultrasonography, active observation overnight is recommended.

Chapter 4. Investigations in Paediatric Abdominal Pain

4.1 Chapter outline

Chapter 4 further explores the use of investigations in paediatric abdominal pain. Four investigations are discussed in specific detail. The use of biomarkers such as White Cell Count (WCC), Neutrophil Count (NC), C-Reactive Protein (CRP) and radiological investigations such as ultrasonography are discussed. The appeal of biomarkers is their relative simplicity and low cost. The ultimate biomarker would be one that is specifically associated with a disease condition. Unfortunately a biomarker for appendicitis continues to elude researchers and clinicians alike. The use of abdominal ultrasonography in paediatric abdominal pain is discussed. Ultrasonography is not only important for the diagnosis of appendicitis, but also for the diagnosis or exclusion of the differential diagnosis.

An important caveat should be discussed when referring to the analysis of ultrasound in paediatric abdominal pain. In chapter 3, visualisation rates, sensitivities and specificities were obtained for ultrasonography and biomarkers. However, these tests were ordered in children with unspecified *abdominal pain*. Thus many of these children (as outlined in table 1 of the chapter) have a variety of extra and intra-abdominal causes for their pain.

In chapter 4, analyses are based on patients who presented with either RIF, Right sided or Peri-umbilical pain. Thus it is more plausible that in this group, the rate of appendicitis will be higher than the 6% observed in Chapter 3's population. Furthermore, when applied to ultrasonography it is likely that this will have a significant impact on visualisation rates and hence sensitivity and specificity. Thus this chapter looks specifically at the utility of these investigations in diagnosing and/or ruling out appendicitis as a differential. First a brief discussion on biomarkers, ultrasonography and a brief review of the relevant statistics in this chapter is discussed. This is followed by an analysis of the effectiveness of biomarkers and ultrasonography at the Canberra hospital.

4.2 Literature review of Biomarkers and Ultrasonography

4.2.1 Biomarkers (WCC, NC & CRP)

These tests are utilised in clinical practice as discriminators between sick and healthy patients. These tests are non-specific and any condition which can cause inflammation can raise the value of either test. This includes entities such as Pneumonia, and even a volunteer study patient who is vomiting.

Whilst they are not specific for any condition per se, their main advantages are:

1) Cost
2) Accessibility

From a cost point of view, it costs $16.95 (AUD) to order a WCC/NC, and $9.70 for a CRP (65). Whilst these tests appear cheap at first glance, when applied to our population in chapter 3 of 962 children, if both tests were ordered this would equal $25,637. One of the major benefits of biomarkers is their ready availability to a large group of clinicians. These tests are easily obtainable to a general practitioner in suburban Sydney as they are to a clinician in rural Queensland. Tests results are also rapidly available, especially in major centres, where results are often generated within an hour of being received.

However, their major limitations are their non-specificity and the fact that these tests cause considerable distress to children whilst being potentially dubious in their clinical applications. Whilst their overall value seems low, in a health system which is struggling to provide for an ageing and growing population, any cost savings are always beneficial.

4.2.2 Ultrasound

Being a relatively new investigation, Ultrasound (US) has become the gold standard for many conditions. Its role in obstetrics, vascular, musculoskeletal and biliary conditions is firmly cemented. In 1986 Julien Pulyaert described the use of ultrasonography (US) for the detection of appendicitis (44). Much interest soon spawned from these results, in

perhaps the notion that for once an investigation would be able to pin down this surgical enigma.

US signs of acute appendicitis include visualization of a blind-ending tubular structure, which is noncompressible, with a diameter of 7 mm or greater (66). In addition, an appendicolith may be seen as a hyperechoic focus casting an acoustic shadow, and the surrounding inflammatory mass, which consists mainly of fat, is hyperechoeic (66,67). In addition, the appendix may be hyperemic (increased blood flow), surrounding free fluid may be present and the patient should be maximally tender over the suspected structure. Sensitivities and specificities range from 78-98, and 85-98% respectively (66). The test is, unfortunately notoriously operator dependent (see figures 4.1a and 4.1b).

Figure 4.1 Ultrasound images of an inflamed appendix, and a normal appendix

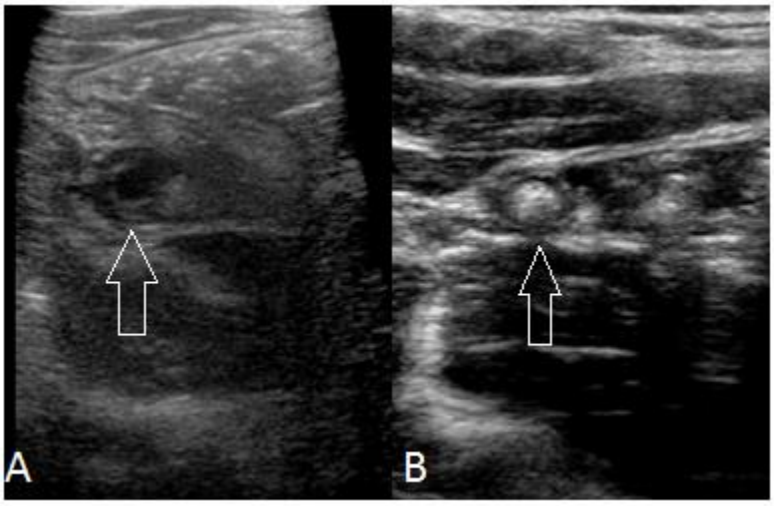


Figure 4.1:

A. Transverse Ultrasound image of an inflamed appendix (Arrow: Appendix with thickened wall, non compressible). B. Is this a normal appendix? Transverse image of an apparently normal appendix (Arrow: thin walled, normal appendix like structure). Note the difficult nature of this examination and its interpretation, especially in static form.

Yet the routine abdominal ultrasound has a cost over five times that of a simple biomarker such as WCC. The average abdominal ultrasound costs $109.10, and hence the limited use of this investigation (65). Although as noted in chapter, 14% of the study population underwent ultrasound investigation. The benefits of this investigation are its lack of ionising radiation, and widespread access to ultrasound devices. It is also far cheaper than a computed tomography scan of the abdomen which costs $ 480.05 per patient and emits significant amounts of radiation (65).

4.3 A review of this chapter's relevant statistics: Diagnostic yield, Sensitivity & Specificity and Receiver Operator Curves.

A detailed discussion is now provided for ultrasound specifically, so that the reader has a comprehensive understanding of the results presented below. For Ultrasound specifically, diagnostic yield was measured. Diagnostic yield measures the proportion of test results which yielded or confirmed a diagnosis which was only capable by as a result of that specific test. For example, an ultrasound ordered to specifically confirm a clinician's suspicion of ovarian cyst related abdominal pain. Conversely, diagnoses not specifically associated with the test themselves tend to lower the diagnostic yield because their suspicion can be confirmed without the un-necessary expense of the test (e.g. diagnosing type 1 diabetes does not need an ultrasound). Conditions which did not necessarily require an ultrasound like mesenteric adenitis were not included as positive results for diagnostic yield.

A brief review of Sensitivity and Specificity is now discussed, because it is especially relevant to Ultrasonography, given its specific limitations. Broadly speaking, Sensitivity and specific assess the ability of a test to accurately identify a patient with a disease and accurately identify a patient without the disease, respectively.

Mathematically, this corresponds to:

***Sensitivity*= TP/TP+FN**

***Specificity*= TN/TN + FP**

Where TP is true positive, TN is true negative and FP and FN are False positives and False negatives respectively. Thus from the above, the limiting factor in sensitivity and specificity is the false negative rate and false positive respectively. From this one can infer that a test with high sensitivity will have a very low rate of false negatives and one with specificity will have very low false positive rates. Thus a test with a high sensitivity is effective at *ruling out* a disease or condition, whereas one with a high specificity is effective at *ruling in* a disease or condition (68). With regards to Ultrasound in paediatric abdominal pain, appendicitis is the condition of major interest, and this is often the main reason a physician sends a patient for ultrasonographic analysis. That is the test is ordered to *rule out* appendicitis rather than *rule in*, otherwise one has wasted large amounts of money and time on an un-necessary investigation, as appendicitis remains primarily a clinical diagnosis! Sensitivity and Specificity analyses for appendicitis, however are complicated by the classification of positive and negative. To remain pure to statistical philosophy, and indeed the gold standard of ultrasonographic diagnosis, the appendix must be visualised and must either appear abnormal (thickened, non-compressive, hyperemic…etc) or normal.

Finally, this chapter utilises Receiver operator curves (ROC) in its statistical analysis, and a brief explanation of their use follows. ROC were originally used to discriminate a radar operators ability to detect an aircraft versus signal noise. Their use has now been extended in medicine to determining the optimal cut-off value for diagnostic tests, to assess the diagnostic accuracy of a test, and to compare the usefulness of different tests (69). As seen in the below ROC figures, the curve plots sensitivity versus 1- specificity.

An ideal cut off value would provide a test with Area Under the Curve (AUC) values of 1.0 (perfect sensitivity and perfect specificity), and a test with no diagnostic utility would represent an AUC value of 0.5, represented by the purple straight line in the following ROC figures. Thus these curves allow the 'operator' to determine the optimal test value in terms of sensitivities and specificities. This of course will depend on the nature of the disease and whether the test is being utilised to rule in or rule out a diagnosis.

4.4 Study Aim

To determine the relative clinical utility of commonly ordered investigations in children with localized periumbilical or right iliac fossa pain. The commonly ordered biomarkers (White Cell Count, Neutrophil Count, C-Reactive Protein) were assessed, as well as Ultrasonography, for their ability to diagnose and exclude appendicitis accurately.

4.5 Methods

10 year retrospective review, between 1st January 2002 and 31st December 2012, for all children referred to the department of imaging at Canberra hospital, for further work-up to exclude appendicitis as a differential for their presentation with abdominal pain.

Inclusion criteria:

1) Age 0-16

2) Presented with right iliac fossa pain, peri-umbilical pain or right sided abdominal pain

3) The ultrasound was specifically ordered for diagnosing or ruling out appendicitis

Exclusion criteria:

1) Non-specific requests: e.g. a request stating patient has abdominal pain without further clarification

2) Ultrasounds ordered for other pathologies (e.g. Renal tract ultrasounds).

Data was extracted from the above patients who met the inclusion criteria, namely their age, gender, results of the ultrasound and associated biomarker results (if performed). A final diagnosis of appendicitis was only accepted if the histology result demonstrated acute appendicitis, acute suppuratives appendicitis, gangrenous and/or perforated appendicitis. Clinical diagnoses of appendicitis (e.g. an injected appendix without pus) operation with normal pathology were treated as normal appendixes. Data analysis was conducted through Microsoft excel and Microsoft SPS for generation of ROC curve analysis. To determine whether differences were statistically significant amongst continuous quantitative data (e.g age, white cell count…etc.), the student's T test was utilized. Chi square analysis was used for discrete quantitative comparisons. For analysis of haematological and biochemical tests, the following values were utilized for the determination of abnormal results: WCC > 11.0 x 10^9/L , NC >7.0 x 10^9/L and CRP > 5.0 mg/L.

For the Sensitivity and Specificity analysis on ultrasound specifically, two scenarios were utilized to determine the results:

1) *"The ideal world" where* the appendix has been visualised, and is either normal of abnormal.

2) *"The real world"* where the appendix has not necessarily been visualised, hence the negative results include tests where the appendix was not visualised.

This has been performed because as previously discussed, a significant amount of ultrasounds fail to visualize the appendix. The two scenarios thus allow the reader to discriminate between the utility of a test when the appendix has been visualized and when it has not.

4.6 Results

2530 Ultrasounds were reviewed, and 737 ultrasounds met the inclusion criteria.

4.6.1 Demographics of the population and underlying aetiologies

Mean age was 10, and there was a male predominance with 430 males and 307 females.

Mean age for females was 11, and for males it was 10 (p= NS).

Visualisation rate for the total population was 28%. Between the genders, it was 21% in female cohort, versus 34% in males (Chi square test=P < 0.001).

The prevalence of histologically proven appendicitis was 21% in the study population.

For females and males, the prevalence of appendicitis was 18% and 24% respectively.

The prevalence of histologically proven appendicitis was 21% in the study population.

For females and males, the prevalence of appendicitis was 18% and 24% respectively.

In those whose appendix was not visualised, the prevalence of appendicitis was 8%.

Tables 4.1 and 4.2 provide a list of the aetiologies behind male and female populations.

Table 4.1-Aetiological makeup of the female population

Cause	Number
Appendicitis	
Histologically negative	11
Histologically positive	54

Non –specific abdominal pain	85
Mesenteric Adenitis	62
Ovarian cyst	33
Viral illness	25
Urinary Tract Infection	12
Gastroenteritis	8
Constipation	8
Ovarian mass Benign Malignant terratoma	 1 1
Other *coeliac disease* *conservatively managed appendicitis* *Septic arthritis (hip)* *Small bowel obstruction* *Tonsillitis*	 1 1 1 1 1

Table 4.1: The top 4 diagnoses in females were non-specific abdominal pain, appendicitis, mesenteric adenitis and gynaecological disease.

Table 4.2 Aetiological makeup of the male population

Cause	Number
Appendicitis	
Histologically negative	23
Histologically positive	104
Mesenteric adenitis	136
Non-specific abdominal pain	106
Viral illness	20
Gastroenteritis	10
Other	
Acute cholecystitis	1
*Conservatively managed appendicitis**	1
Constipation	3
Hydronephrosis	1
Inflammatory Bowel Disease	2
Intussception	1
Iliac Fossa abscess	1

Pneumonia	6
Reactive arthritis	1
Septic arthritis (R hip)	1
Type 1 Diabetic Ketoacidosis	1
Tonsillitis	3
Torsion of hydatid of morgani	1
Urinary Tract Infection	3

*This child had an ultrasonographic diagnosis of appendicitis which was inconsistent with the clinical impression, hence the child was treated with observation, and subsequently improved.

Table 4.2: The top 4 diagnoses were mesenteric adenitis, appendicitis, non-specific abdominal pain and viral illnesses.

4.6.2 Ultrasound

1) Diagnostic Yields of Ultrasound:

28% of all ultrasounds ordered provided ultrasound specific diagnoses. In females, the yield was higher at 30%, whereas it was 26% in males. The female urogenital tract accounts for the difference in diagnostic yield rates, due to the extra diagnoses of ovarian cysts and ovarian masses.

2) Sensitivities and Specificities of Ultrasound

As discussed in section 4.3, there are two possible scenarios when a clinician receives a ultrasound report, either the appendix is visualized (the ideal world scenario) or it is not seen (the real world scenario).

Scenario 1: The Ideal world report

Below are the sensitivities and specificities (table 4.3), please refer to appendix 1 for specific calculations.

Table 4.3: Sensitivities and Specificities for Ultrasound in the ideal world scenario

Analysis:	Value
Sensitivity:	0.96
Specificity:	0.54

PPV (where prevalence = 21.3%):	0.73
NPV (where prevalence = 21.3%):	0.91

Table 4.3: Sensitivities and specificities for ultrasounds where both positive and negative results visualized an appendix. Note the excellent sensitivity of the test in this scenario.

Scenario 2: *The Real World Report*

In this scenario, the appendix is not necessarily visualised. Hence, the clinician is forced to either utilise the non-visualized result as a negative test or disregard the test and re-evaluate the patient. See table 4.4.

Table 4.4: Sensitivity and Specificity of Ultrasound in the Real World

Analysis:	Value
Sensitivity:	0.71
Specificity:	0.93
PPV (where prevalence = 21.3%):	0.73
NPV (where prevalence = 21.3%):	0.92

Table 4.4: In this analysis, negative results included tests where the appendix was not necessarily visualized. Note the drop in sensitivity when compared to Table 4.3.

In this scenario, the value of the negative result has decreased due to non-visualisation of the appendix and hence the correspondingly low sensitivity. The specificity however has increased because the large number of true negative test results dilutes the false positive rate.

3) Sex differences in Ultrasonography

Given the higher rate of negative appendicectomy in females, ultrasonography is theoretically appealing to reduce this volume. Unfortunately sensitivities are similar to those quoted above. As before, these analyses are divided into two scenarios, where in scenario 1 a negative test means the appendix is seen and is normal, and in scenario 2 where a negative test means the appendix was not necessarily seen (the negative value is equivocal at best). See tables 4.5 and 4.6 respectively.

Table 4.5: Analysis for Scenario 1 comparing the difference between sexes

Analysis:	Females	Males	P value
Sensitivity:	0.97	0.94	P < 0.01
Specificity:	0.59	0.53	P < 0.05
PPV	0.70	0.75	P < 0.01
NPV	0.95	0.86	P= NS

Table 4.5: Results from the previous analyses are applicable, with the test having excellent sensitivities when negative tests are reported on the basis of appendix visualisation.

Table 4.6: Analysis for Scenario 2 comparing the difference between sexes

Analysis:	Females	Males	P value
Sensitivity:	0.54	0.83	P < 0.001
Specificity:	0.94	0.91	P= NS
PPV	0.70	0.75	P < 0.01
NPV	0.91	0.94	P = NS

Table 4.6: Note the drop in sensitivities, and in particular the significant differences in sensitivity and positive predictive value between the male and female genders.

4) Factors predicting visualisation:

The visualisation rate was 28% for the total population. Visualisation was increased in males (34% vs 21%, rate for males and females respectively $p < 0.001$), and in those with elevated white cell counts or CRP. Mean age group was 10 for both populations. Mean WCC was higher in ultrasound with and without visualised appendixes, 12 versus 10 at $P < 0.001$. Mean Neutrophil count was also predictive of visualising an appendix, with NC 9 versus 7 at $P < 0.001$. Mean CRP in the visualised group was 36 versus 24 in the non-visualized group.

The below ROC analyses are utilised to determine what levels of WCC, NC and CRP could be utilised to determine whether an ultrasound will detect appendicitis (see figure 4.3).

Figure 4.3 Receiver Operator Curve For appendix visualisation:

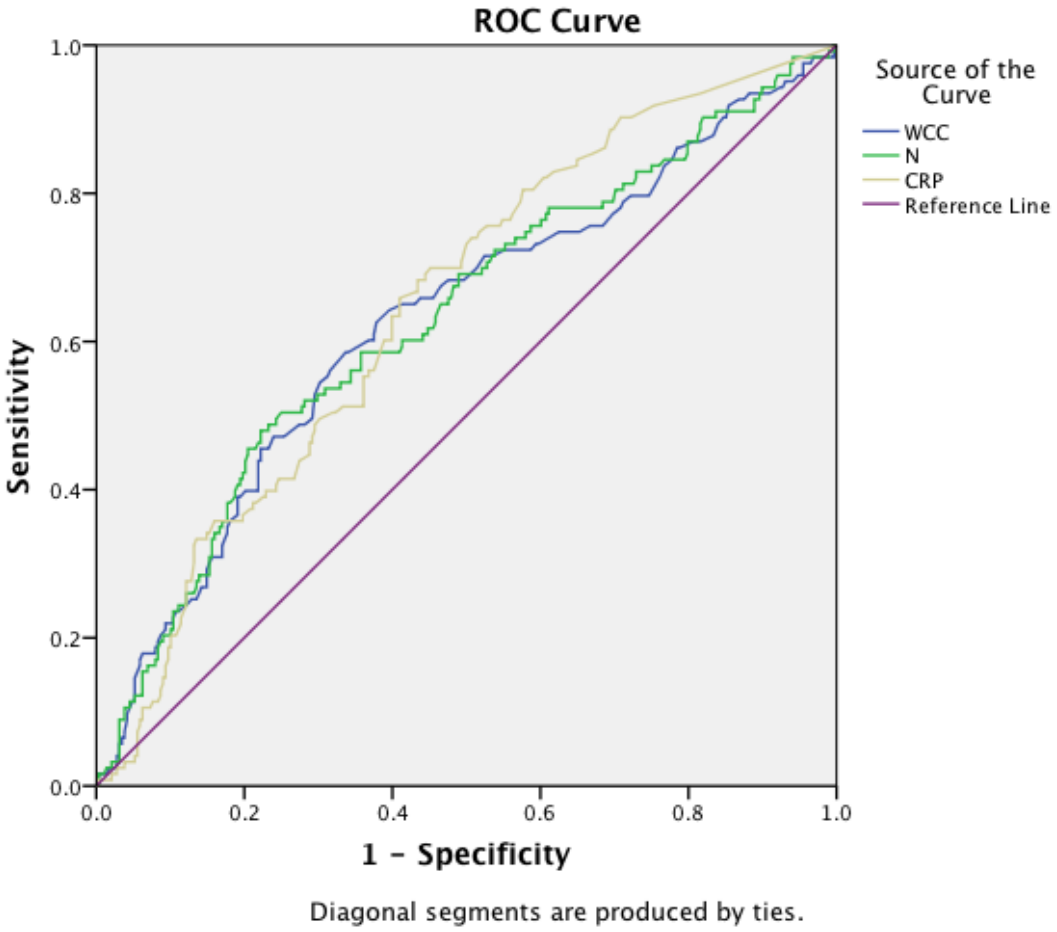


Figure 4.3: CRP is the biomarker of most utility in predicting appendix visualisation, closely followed by neutrophil count and white cell count. Values over 60mg/L, 16.0 x 10^9/L, and 12.5 x 10^9 /L represent useful threshold levels for visualising an appendix on an ultrasound. Thus children with values below these are less likely to have their appendixes visualised. Please see the appendix for individual data tabulations.

Perforation was present in 15% of those whose appendix was visualised and only 3% in those where the appendix was not visualised (chi square test, $p < 0.001$).

5) Are Appendix visualisation rates falling?

Anecdotally many clinicians had noted that less appendixes were being visualised and hence the value of the test was declining but was this simply a clinical impression or does truth lie behind this assertion? Figure 4.4 demonstrates that unfortunately visualisation rates were higher 10 years ago than they are now for the ultrasound ordered for "*query appendicitis".* Figures 4.5-4.7 also demonstrates that the incidence of appendicitis in the scanning population has been declining since 2002, and that this appears to be related to the decline in the visualisation rate. However, the correlation coefficient is a modest 0.37, thus highlighting that this is not a *strong* association.

Figure 4. 4 Appendix visualisation rate over 10 years:

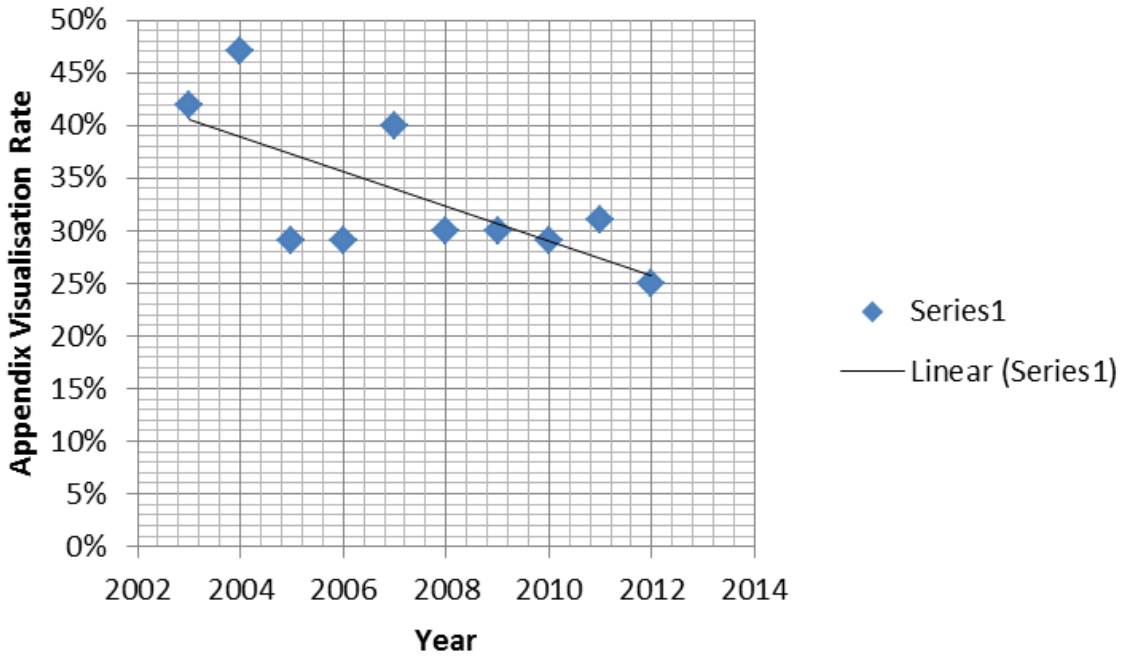


Figure 4.4 : A decline in visualisation is demonstrated over the study period.

Figure 4.5 Number of scans ordered over the past 10 years

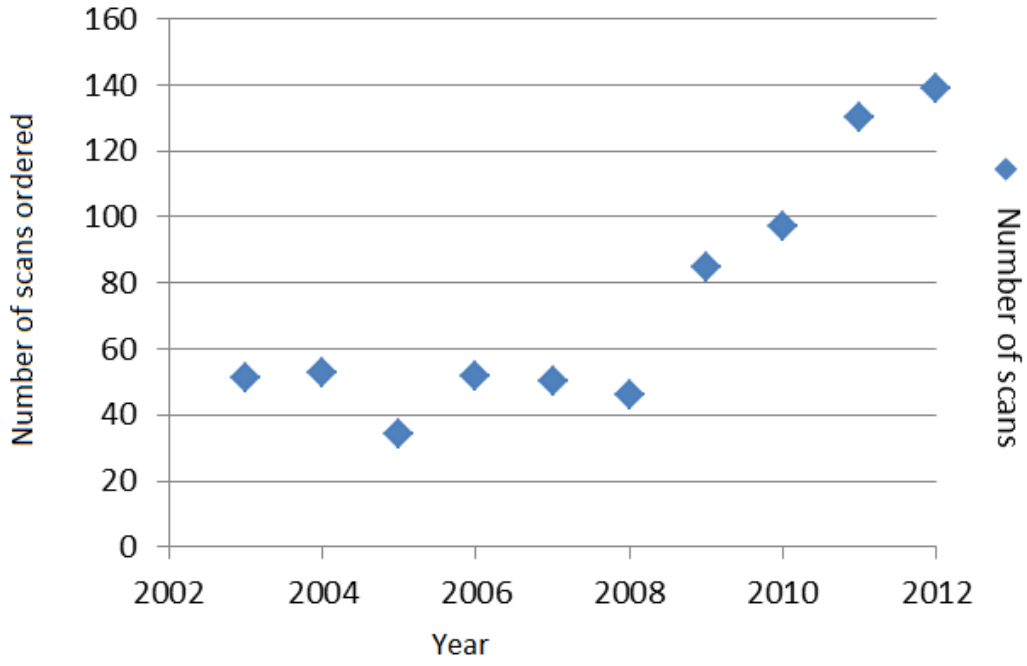


Figure 4.5: Since 2002 the rate of Ultrasounds performed for assessment of RIF pain/appendicitis has more than doubled

Figure 4.6 Incidence of appendicitis in those patients whose ultrasound did not visualise their appendix

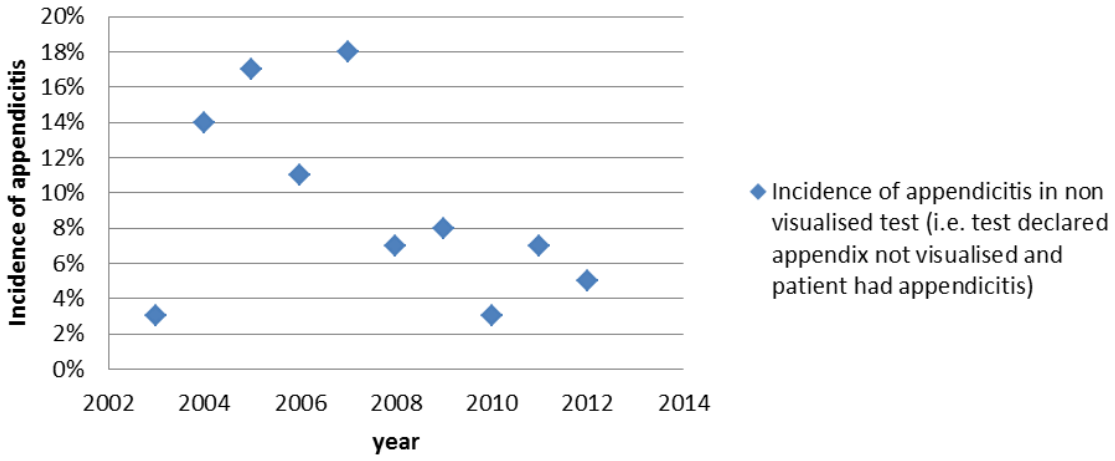


Figure 4.6: The incidence of appendicitis in the non-visualised group has dropped substantially during the 10 year period.

Figure 4.7 Incidence of appendicitis versus Visualisation rate plotted by year

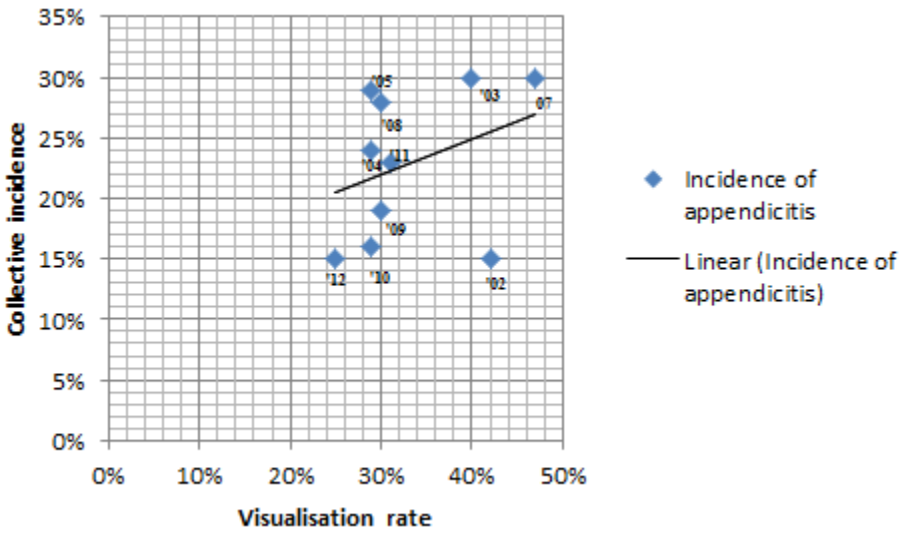


Figure 4.7: There is a linear association between visualisation rate and incidence.

4.6.3 Biomarkers- White Cell Count, Neutrophil Count and CRP.

Two analyses have computed, due to the influence of age on cut-off thresholds for biomarker tests.

Analysis 1 utilises an age standardized value of WCC > 11.0 x 10^9/L , NC >7.0 x 10^9/L and CRP > 5.0 mg/L. Many non-specialists will look at the absolute value, rather than age specific methods, and indeed these values represent the cut-offs for those over the age of 5.0 mg/L (which represents 93% of the total population). See figure 4.8.

Figure 4.8 Receiver-Operator Curve for biomarkers in predicting appendicitis

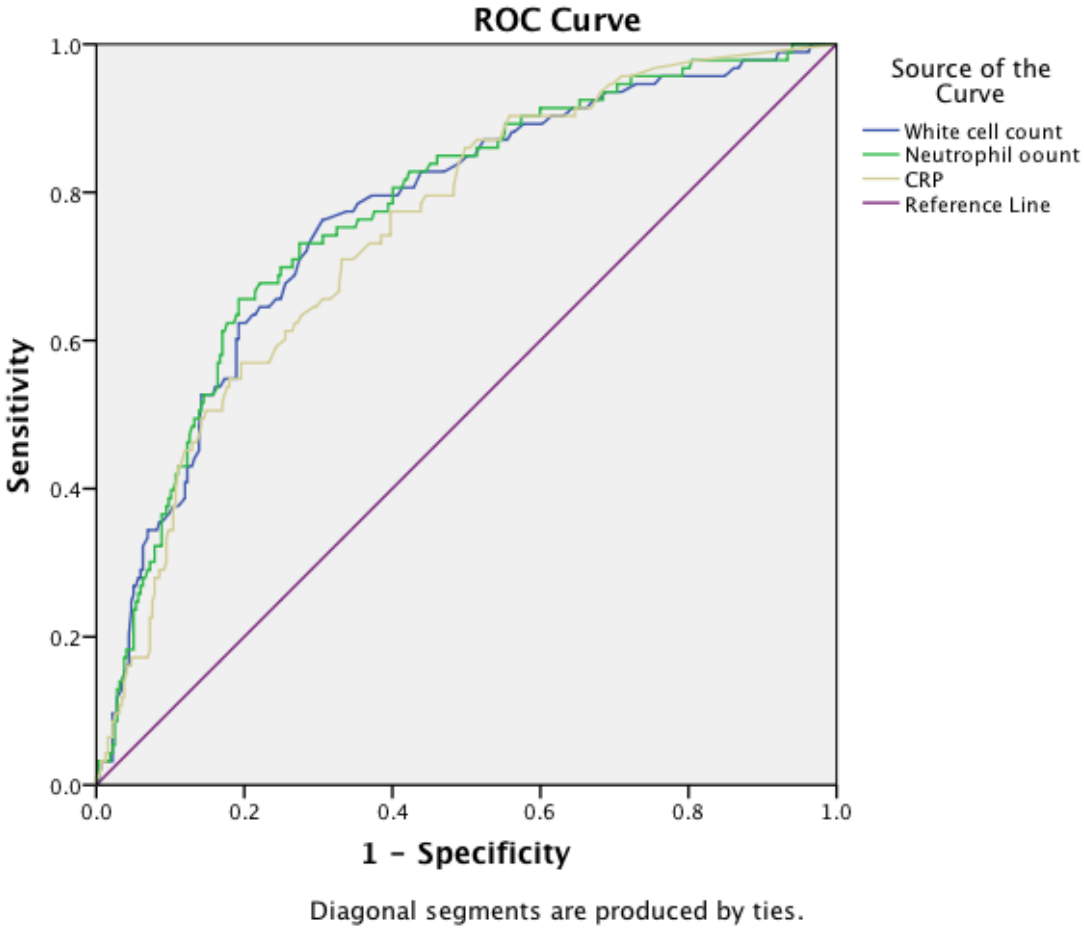


Figure 4.8: All biomarkers provide some clinical utility in managing paediatric abdominal pain, however none offers perfect sensitivities or specificities. ROC values are provided in the appendix to aide in choosing an acceptable cut-off value.

With regards to sensitivity and specificity calculations, normal cut-offs were as in table 2.3. However, whilst these cut-offs have been utilised for calculating *total* sensitivity and specificity these may not be as clinically useful as choosing the optimal value from the ROC analysis. If one were to accept a test value with sensitivities over 80% and specificities of 90%, then a WCC > 17 x 10^9/L, NCC>14 x 10^9/L, and CRP>75 mg/L would deliver the aforementioned sensitivities. Note that all of these values are markedly higher than the elevated range for most tests of 11 x 10^9, 7 x 10^9/ Land 5mg/L respectively. Tables 4.5-4.8 describe the results of clinical utility analyses of white cell count, neutrophil count, CRP and pooled (combined) values.

Table 4.5 White Cell count: Sensitivities and Specificities

Analysis	Total population	Female	Male	M vs F, P value
Sensitivity	71	73	69	NS
Specificity	68	66	75	P <0.05
Positive Predictive Value	39	32	41	P < 0.05
Negative Predictive Value	89	92	90	P = NS

Table 4.5: A break-down of the sensitivity and specificity for WCC for the total population and sub-group analysis for the respective genders is provided.

Table 4.6 Neutrophil cell count: Sensitivities and Specificities

Analysis	Total population	Female	Male	M vs F
Sensitivity	78	81	78	P = NS
Specificity	61	63	60	P = NS
Positive Predictive Value	37	33	40	P= NS
Negative Predictive Value	91	93	88	P= NS

Table 4.6: A break-down of the sensitivity and specificity for NC for the total population and sub-group analysis for the respective genders is provided.

Table 4.7 CRP : Sensitivities and Specificities

Analysis	Total population	Female	Male	M vs F
Sensitivity	77	77	77	P = NS
Specificity	58	66	52	P= NS
Positive Predictive Value	35	33	36	P= NS
Negative Predictive Value	89	92	87	P = NS

Table 4.7: A break-down of the sensitivity and specificity for CRP for the total population and sub-group analysis for the respective genders is provided.

Table 4.8 Value of combined biomarkers for appendicitis

Analysis	Pooled Invx	WCC	CI vs WCC
Sensitivity	87	71	P= <0.05
Specificity	49	68	P= NS
Positive Predictive Value	51	39	P= NS

Negative Predictive Value	93	89	P= NS

Table 4.8: A break-down of the sensitivity and specificity for the combined investigations versus a single investigation (WCC), note the superior sensitivity for the pooled investigation group.

Analysis 2 Calculates sensitivity of WCC and NC for the specific under 5 year group due to the higher cut-offs for diagnoses. This is also the age group where the diagnosis is most difficult due to the complexities in undertaking the clinical history and examination (See table 4.9).

Table 4.9: Sensitivity and Specificity of WCC and NC in children under the age of 5

Analysis	WCC	NC
Sensitivity	50	83
Specificity	48	30
Positive Predictive Value	12	14
Negative Predictive Value	86	93

Table 4.9: Neutrophil count is more sensitive than WCC in those under age 5.

Analysis 3 is an analysis of the utility of WCC, CRP and combined power tests for ALL serious medical conditions, I.E this includes medical conditions as well as appendicitis. Please see table 4.10 for results.

Table 4.10 WCC, CRP and combined analysis for serious medical conditions:

Analysis	WCC	CRP	Pooled Invx
Sensitivity	65	75	93
Specificity	70	48	58
Positive Predictive Value	45	70	55
Negative Predictive Value	85	54	91

Table 4.10: Pooled investigations again provide the highest sensitivity amongst the investigations.

4.7 Discussion:

4.7.1 Ultrasonography

Ultrasonography was first described for appendicitis by Julien Pulyaert in 1986. He specifically described graded compression ultrasonography performed by a *radiologist* to diagnose acute appendicitis (44). This preceded the advent of computed tomography for the diagnosis of appendicitis, and hence ultrasonography steadily advanced into paediatric surgery with its ease of applicability and lack of ionizing radiation. Initial studies into its efficacy proved positive and lead many clinicians to rely on this investigation even when there was a strong clinical suspicion of appendicitis (12,44). However, as time progressed and further studies conducted it became evident that the ability of ultrasonography to detect appendicitis was dependent on two variables: (1) the operator, and (2) the operating environment (20,21). Over in Europe, many authors were reporting high sensitivities and specificities of ultrasonography, however these studies were conducted in centres where experienced paediatric radiologists were performing the study, and in large hospitals where the prevalence of appendicitis in abdominal pain referrals was high (21,44, 46-48). Across the Atlantic Ocean, however, many American authors were reporting dismal results with ultrasonography and began to lean upon computed tomography to provide a more acceptable range of sensitivities and specificities in clinical practice (48-50).

Our results demonstrate that when the appendix is visualized, ultrasonography is a useful adjunct in the management of abdominal pain because it can differentiate those children with benign causes from more serious aetiologies. A high sensitivity and negative predictive values allows some confidence for the clinician to exclude appendicitis based on a normal ultrasound. In real clinical practice, calculating ultrasound efficacy on the above is inaccurate because in only 28% of cases can you see the appendix, and visualisation of the normal appendix is what gives ultrasonography its diagnostic power (21, 44, 67). Visualisation rates have been quoted to range from 23% to 83% (21,44,46,47,49,). In our population this figure was closer to the former. Visualisation itself is dependent on the operator, childhood BMI and the prevalence of appendicitis in the study population (20,64,70). In Chapter 4, the prevalence of histologically proven appendicitis was 21% in the study population. Note how this is significantly greater than the prevalence of appendicitis in the general population and also in chapter 3's study population (approximately 6%). This is because Chapter 4's study population has highly localized abdominal pain, i.e. RIF, Right sided or periumbilical, which is more likely to be associated with a diagnosis of appendicitis then left iliac or left upper quadrant pain would be. Thus this cohort has a higher rate of appendicitis due to the clinical presentation of the child, and this must be taken into account when comparing analyses of ultrasound. Of considerable concern is the fact that in the population where the appendix was not visualized, the prevalence of appendicitis was 8%, which is greater than that seen in the general population.

When the appendix is not visualized and this is treated as a negative test, sensitivity drops significantly from 96% to 71%. In our population, an appendix was more likely to be visualised in the male sex than the females. When an appendix was visualised in the female population, the test added significant clinical utility a sensitivity approaching 97% and a NPV of 95%. Unfortunately, the visualisation rate was 21% and a sub-analysis revealed that the sensitivity was reduced to mediocre levels, and the NPV reduced to 91%. This higher prevalence of appendicitis in the male population (24% versus 18%) likely corresponds with the higher positive predictive value of the test.

Thus when comparing between the sexes, AND when the appendix is visualised, ultrasonography would appear to be more useful in females in ruling out appendicitis with its higher sensitivities and negative predictive values. Unfortunately, this only applies to the ideal world (scenario one), and in real life (scenario two), when the appendix is not visualized this actually provides more clinical utility if the patient is a male.

Ultrasonography is therefore a *theoretically* appealing test because it offers the hope of reasonable sensitivities and specificities coupled with the lack of ionizing radiation but in real world practice its relatively mediocre sensitivity is no better than a simple full blood count (18,43,69,71). This is only a problem when the appendix is not visualized of course, but unfortunately in our centre this is the rule rather than the exception. Furthermore, it has also been demonstrated that the visualisation rate appears to have dropped over the 10 year study period (refer to figure 4.6). There is appears to be a

modest association between the incidence of appendicitis and the visualisation rate. One explanation for the decline in visualisation rate could be that more and more patients are being inappropriately sent for ultrasounds hence diluting the prevalence of this condition in the study population. As it is easier for a sonographer to detect an inflamed appendix this could explain why visualisation rates appear to be declining. This could be due to the clinicians responding to a more litigious environment and also to the emergence of the 4-hour emergency assessment rule which puts pressure on clinicians to come up with a diagnosis rather than encouraging diagnostic accuracy.

Ultrasonography is useful for females, because it may help to diagnose several ovarian conditions which can mimic appendicitis. The overall diagnostic yield was 30% in females versus 26% in males, thus there is some benefit (albeit a moderate benefit) seen. Computed tomography versus ultrasonography is ever the rage in the great trans-Atlantic debate but the potential for oncological development in children is significant. In the end, the complication of an iatrogenically induced malignancy (especially so for recurrent presenters) would appear to outweigh the risk of delay in appendicitis treatment. Indeed doubt still exists as to whether even this investigation adds significant value to the management of children with equivocal presentations (49,50,70-72).

4.7.2 Biomarkers

From the results one can see that neither WCC, NCC, or CRP provide a perfect investigation for either ruling out or ruling in appendicitis. As mentioned previously, the most important aspect of management is not missing the child with appendicitis. Thus the negative value of the test is most important, as clinicians do not diagnose appendicitis based upon a blood test value. From this point of view, the test which performs the best across genders and age groups is by far the NC. This is perhaps because it is more likely for the white cell count to be raised by more benign pathologies whereas the neutrophil count is usually associated with bacterial infections and/or inflammation. This test is especially useful for the clinician in children where the history and examination may be more unreliable, i.e. those under 5, with the caveat of the distress that they cause (see table 4.9). However, just as with other blood tests, the NC suffers from poor positive predictive value and specificity are the result of many other conditions. Children with severe pneumonia will have a raised NC but at the same time so can a child with mesenteric adenitis.

CRP is a contentious biomarker, with a great variability of use amongst clinicians. Many claim that the potential 72 hour delay associated with CRP, and its added cost to the work-up provides all most no added value. Indeed, this biomarker appears to offer little over the standard white cell count but it is inferior to the neutrophil count (see table 4.7). Thus it would appear that if a clinician was faced with ordering a WCC or a CRP, they should simply order a WCC. However, what about the value of combined investigations, i.e. when a physician orders a WCC and a CRP?

What happens when a clinician utilizes a combination of biomarkers to help him or her assess a child with abdominal pain? A positive test is then one in which either the WCC, NC, or CRP was raised and a negative test one where no such level was raised (see table 4.8). It can be seen that this actually offers the best sensitivities and negative predictive values compared to any one single test. The downside is that the specificity and positive predictive value are at their lowest. However, the above analysis challenges the attitudes of many physicians who state that CRP is a waste of time. Yes, CRP can be a waste of time and money if ordered alone, but in combination with a WCC and NCC it does add value as demonstrated.

How do these tests perform when used as a marker for a broad range of serious medical conditions? These tests once again show moderate sensitivities and negative predictive values (except for CRP's NPV), but once again the combination of WCC and CRP is the most effective at ruling out serious conditions. It should be noted however that even with the combination test, 9% of children with serious medical conditions such as appendicitis and pneumonia would be missed if reliance was placed solely on a normal CRP or WCC (see 4.10 for further details).

As demonstrated from the above, none of these tests provide excellent sensitivities and specificities and commonly quoted reference ranges provide mediocre sensitivity and specificity to exclude appendicitis. Cut-off values of 17 $x10^9$/L, 14 x 10^9/L, and 75 mg/L

for WCC, NCC and CRP respectively offer acceptable sensitivities and specificities for ruling out or ruling in appendicitis. In summary, neutrophil count offers the most utility to the clinician being the most sensitive and specific. CRP should not be ordered alone, as it provides sub-standard performance when compared to a NC (which is a component of the WCC). However, it does provide added sensitivity and specificity when combined with WCC to exclude appendicitis. Thus the most appropriate recommendation is that if a clinician is considering ordering blood tests, they should order either a WCC alone, WCC and CRP, or no test at all.

4.7.3 How these results apply to the current literature

To conclude the discussion, several important points that were raised by the literature warrant further reflection given our results. Firstly ultrasonography is an operator dependent technique, and in centres (predominantly in Europe) where radiologists are utilized for ultrasonographic examination, there is clearly more enthusiasm for this technique (21,45,46,50,70-72). Our results showed comparatively lower visualisation rates than some other authors, and it should be noted this study's population it was the ultrasonographer that performed the scan. This is not to say that an ultrasonographer is worse at sonographic examination than a radiologist but perhaps the real time experience of scanning is essential in enhancing the interpretation of this test. For in the end it is the reading radiologist that makes the call as to whether the scan was positive or negative. Secondly, this test is dependent on the location, study population and the referral base of the hospital. With decreasing BMIs the chance that a normal

appendix will be visualized is greater (20,47,64). Furthermore, in major referral centres where many of the children have been referred specifically for the possibility of appendicitis, the prevalence of appendicitis will be greater and hence the probability of appendiceal visualisation (72). Whilst the Canberra hospital does have a large paediatric service, it is not a paediatrics only hospital. Thirdly, there is no randomized control trial which has validated the utility of this intervention in paediatric surgery and as such the evidence for its actual use remains controversial (48,70,72). This is further reinforced when one looks at the opportunity cost involved. Whilst ultrasonography appears to be a mediocre test for appendicitis, it is a reliable and useful test in many other areas of clinical practice. Ultrasound has many evidence based application and contributes significantly to the diagnosis of acute cholecystitis, deep vein thrombosis and as a guidance tool during medical procedures. Although the absence of ionizing radiation makes this an appealing test, it's clinical performance in our study raises the question of whether hospitals and patients alike would be better off if this service was diverted to more useful applications. Finally, there is much contention regarding the use of laboratory markers, particularly in children. Many authors have cited that a substantial number of children with appendicitis have normal inflammatory markers (18,19). They also argue that in the presence of a convincing history and physical examination there is no need to perform markers. However, from our results these tests offer reasonable sensitivities and specificities with minimal cost. In our cohort, in those children with appendicitis only 13% had normal biomarkers. Sensitivities and specificities of these

tests are useful, especially in the child with a discrepancy in the history or examination findings.

4.8 Limitations

The limitations of this study included its retrospective nature, and the fact that BMI was unavailable in our study cohort.

4.9 Conclusion

Ultrasonography in paediatric abdominal pain is a useful test, when and only when, the appendix is visualized. If it is not visualized the test becomes only marginally better than a far cheaper blood test. The visualisation rate at the Canberra hospital was a meagre 28%. From the literature review, visualisation of the appendix appears to be enhanced by the presence of a radiologist performing the test, and in hospitals where children's BMIs are lower and the prevalence of appendicitis is high due to referral bias. Ultrasonography may provide added clinical utility to the female patient due to the extra diagnostic yield from ovarian related conditions. However whether it adds clinical utility for the equivocal population is contentious and for our centre, at present this test is attractive only in a theoretical sense, and it may well be that for ailing public healthy systems this scarce resource would be better off in areas where there is solid evidence for its use. Unfortunately an ultrasound which is blinded to the appendix offers little diagnostic evidence to the practitioner facing a child with an undifferentiated abdomen.

Ultrasonography may provide clinical utility if ordered for a female patient and a male patient where another abdominal differential is likely (e.g. cholecystitis). For the remainder of the population, those in who the diagnosis is in question may benefit from a combined WCC and CRP, and if the clinician is still suspicious regarding the diagnosis, admission with observation with either discharge if the symptoms resolve or laparoscopy if symptoms persist.

Chapter 5 Background factors in paediatric abdominal pain: A holistic view may help

5.1 Chapter background

Abdominal pain should always be treated as a serious complaint by the clinician due to potentially serious medical and surgical conditions which can present with abdominal pain. However, both in adults and children, a large proportion of patients will not have any significant disease processes underway. In adults (and now children), Irritable Bowel Syndrome (IBS) is one of the major benign abdominal processes behind abdominal complaints, including abdominal pain. Abdominal pain can be a manifestation of other non-abdominal complaints as demonstrated in prior chapters, but importantly it can also be a manifestation of anxiety disorders other extrinsic psychological factors. This *prospective* study focuses on extraneous factors which may be associated with abdominal pain presentations. For example, is there a link between family history, family background and abdominal pain presentation? Do children from families with markers for lower socio-economic status (e.g. criminal records, smoking and public housing residency) affect presentation pattern?

5.2 Aim

To determine the link between background factors such as, social and family history factors, and abdominal pain presentations and their underlying aetiologies.

5.3 Methods

Prospective study of children presenting to the emergency department with abdominal pain was conducted between June 2012 and December 2013. Participants and their parents were consented for an 18 question survey (please refer to Appendix 4 for details). The survey was predominantly performed by the main author and Dr J Melino, a surgical registrar at Canberra Hospital. Patients were principally recruited from the Canberra hospital and Calvary hospital Emergency departments whenever Dr Melino or the author was referred potential surgical patients. In addition, patients were also recruited on an adhoc basis when the opportunity presented itself (i.e. when reviewing another patient), thus not all surveys were performed on patients referred for surgical review. Records were de-identified with the patient's medical record number being the sole form of identification. Data analysis was conducted through Microsoft excel and Microsoft SPS. To determine whether differences were statistically significant amongst continuous data the student's T test was utilized. Chi square analysis was used for discrete quantitative comparisons. For statistical analysis, the population was divided into two groups based on *initial* discharge diagnosis. Those children who presented with abdominal pain and were subsequently diagnosed with a functional abdominal pain (FAP) syndrome were included in the FAP group. All children who presented with medical conditions other than FAP (e.g. appendicitis, mesenteric adenitis, gastroenteritis…etc) were included in the *A*ll *M*edical *O*ther than FAP *C*onditions (AMOC).

5.4 General Results

97 patients surveys were obtained but 89 were included for analysis. The remainder were excluded due to incompletion. The study comprised 41 females, and 48 males. Mean age was 11. There was no difference in mean age between males and females. The three most common diagnoses were of Functional Abdominal Pain (FAP), and within the AMOC group: Mesenteric adenitis and appendicitis (see table 5.1).

5.4.1 Survey Results

Table 5.2 summarizes the survey questionnaire that was handed out to patients. Appendix 4 includes the survey and consent statement for your perusal.

Between groups the only significant difference observed appeared to be related to the child's bowel habit, with those in FAP often having more regular bowel habits and those in the AMOC group having less regular bowel motions. 92% of children in the FAP group had a regular bowel habit compared to 56% in the AMOC group ($p<0.05$).

For the other questions, there were differences between the AMOC group and FAP group but no statistically significant differences were found. As such, in the following text, the majority of results are presented for the total population and specific numbers can be viewed in table 5.1. Between the two groups, there was a greater female sex proportion in the FAP group than the AMOC group, but mean ages were similar between the two groups.

15% of children had a history of influenza in the home at time of presentation. 74% of

the group's parents were both engaged in full time work. 76% of children had parents who had obtained higher educational qualifications, again no significant differences were observed. Most of the children were first time presenters without a history of abdominal pain and this applied to both groups. 26% of parents smoked and 19% consumed over two standard drinks a day. 34% of children had a family history of migraine, 9% had a history of IBS and Coeliac disease. Please see table 2 for further details.

A sub-analysis of the female population showed that 7% had a family history of endometriosis and 30% had a family history of irregular periods. There were no significant differences between the AMOC group and the FAP group.

Presentation patterns:

Children with benign abdominal pain were more likely to present in the winter months than those with other medical conditions (see Figures 1 and 2). This is in line with findings from Chapter 3. Children with all other medical conditions had a peak in presentation during the spring months.

Table 5. 1 Aetiologies of study population

Condition	Number
Functional Abdominal Pain	48

Mesenteric adenitis	18
Appendicitis	7
Constipation	3
Gastroenteritis	3
Normal appendix removed	2
Other diagnoses Mittelschmerz Ovarian Cyst Pancreatitis Pharyngitis Post-appendicectomy sepsis Pseudo-obstruction Ulcerative Colitis UTI	 1 1 1 1 1 1 1 1

Table 5.1: Benign Abdominal Pain, Mesenteric Adenitis and Appendicitis were the three most common diagnoses. Of note one child who presented with abdominal pain initially and was discharged with a diagnosis of FAP, presented 1 week later with a perforated appendix.

Table 5. 2 Summary of the Survey findings

Parameter	**FAP** (n=48)	**AMOC** (n=41)	**Chi square p**
Sex			
m	24	24	NS
f	24	17	NS
Influenza at home	7	6	NS
Immunisation status			
Fully immunized	43	38	NS
Employment status of parents			
both parents working	37	29	NS
one parent working	11	10	NS
Both unemployed		2	NS
Parental education			
Tertiary	29	26	NS
Vocational	8	5	NS
Year 12	10	9	NS
Primary	1	1	NS

Parental status			
Married	35	30	NS
Defacto	5	8	NS
Sole parent	6	3	NS
Bowel habits			
Regular bowel habit	44	23	P <0.05
Constipated	1	6	NS
Other-smooth muscle		1	
myopathy			NS
Prior history of			
abdominal pain			
Yes	9	14	NS
No	33	24	NS
Smoking in the family?			
yes	13	10	NS
No	35	41	NS
Alcohol intake over 2			
s.d?			
Y	8	9	NS
N	40	32	NS

Siblings Only child One sibling Two or more	 3 22 23	 4 13 24	 NS NS
Reside in Public housing	1	2	NS
Criminal record	2	1	NS
Migraine	17	13	NS
Hx of GORD in family	7	3	NS
Hx of IBS	5	3	NS
Hx of Asthma	19	15	NS
Familial mediteranean fever	0	1	NS
Eczema	15	10	NS
Coeliac disease	2	6	NS

Table 5. 2: Summary of responses from the 18 question survey conducted. Whilst there were differences between the two populations, due to sample size most of the differences were not statistically significant. Of note, children with FAP are more likely to have a regular bowel habit than those without the diagnosis.

Figure 5.1 Functional abdominal pain presentations by month

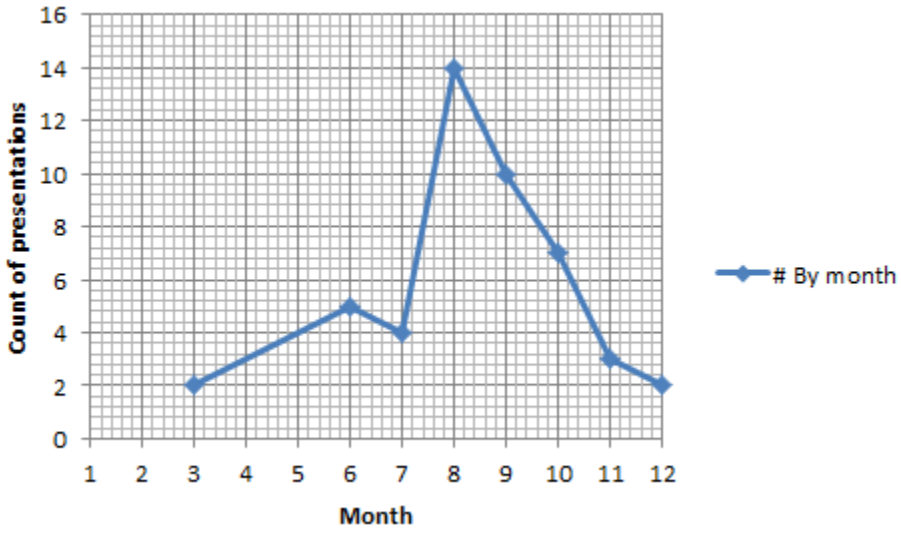


Figure 5. 1: There was a peak in winter presentations for those with FAP.

Figure 5.2 All other presentations by month

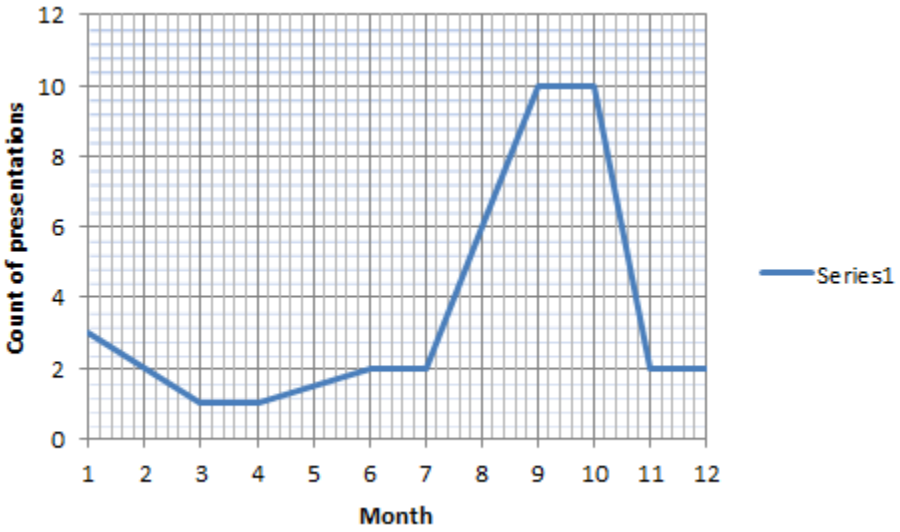


Figure 5.2: By contrast, there was a peak in presentations during for the AMOC group during the later months of the year, predominantly during the spring season.

5.4.2 Subgroup analysis of Female populations

With regards to the female gender a specific sub-group analysis was carried out for any observable differences with regards to endometriosis, irregular periods or migraine. Please see table 5.3 for further details.

Table 5. 3-specific comparative characteristics of the female population

Number	FAP (n=24)	All other (n=17)	P
Hx of endometriosis	1	5	NS
Hx of Irregular periods	5	7	NS
Hx of Migraine	8	7	NS

Table 5.3: Whilst rates of endometriosis and irregular periods were greater in the AMOC group, there was no overall significant difference in the presentation patterns.

5.5 Discussion

This study has demonstrated that children presenting with benign abdominal pain syndromes and those with other medical conditions, represent a very similar patient population. Mean age group and the gender make-up of both populations were similar.

Children with FAP syndromes tended to have a more regular bowel habit than those with other medical conditions.

However, when one looks at the total population there are some interesting points. Firstly, by and large the cohort of children came from a relatively well educated background, with over 75% of parents having completed a vocational or tertiary qualification. Unfortunately, 26% of parents in the population smoked. This is greater than the 14.5% for the total Australian population over 18 years of age in the ABS survey from 2014-2015 (73). Of interest, inflammatory conditions such as eczema and asthma seemed to be represented in greater proportions than in the general population. For example, there was a family history of asthma in 38% of this patient population compared to 10.2% in the general population as per the ABS (74). Whilst there were no significant differences between both the AMOC and FAP groups, the high prevalence of asthma and eczema could point to a potential inflammatory related cause for abdominal pain syndromes. The prevalence of migraine was also high in this group, with 34% of patients having a family history of migraine compared to an expected prevalence of 11% (75).

Appendicitis was the third most common cause after benign abdominal pain and mesenteric adenitis. This is different to what is seen in earlier chapters, and this is primarily due to the study design as discussed in the limitations section. However, even in this population, the incidence of surgical conditions is not low in the paediatric abdominal pain presentations thus strengthening arguments for diagnostic vigilance.

One child was originally diagnosed with FAP and subsequently presented with a perforated appendix. It is important to note the high family prevalence of eczema, asthma and migraine because it has been postulated that some abdominal pain presentations actually represent manifestations of other conditions. For example, as discussed in the literature review, abdominal migraine is a condition that is suspected to be underdiagnosed in the paediatric population.

This study also demonstrated that there is a seasonal presentation pattern with benign abdominal pain groups and those patients with medical conditions. There was a peak in winter presentations for those with FAP. Possible reasons could be due to the greater burden of viral illnesses sustained during winter. This is in keeping with findings from the previous chapters of this thesis which demonstrated a peak of pain presentations in the winter period.

5.6 Limitations

The study was limited by a small sample size and selection bias. Whilst 97 surveys were collected, only 89 were used for this thesis due to incomplete data. Whilst 89 patients is a reasonable sample size, this provides limitations when it comes to the calculations of statistical significance. Hence much of the differences seen between populations have not yielded statistical significance.

The study is also potentially limited by selection bias. This is because the surveys were conducted by members of the paediatric surgical team and as such there is an inherent

bias towards patients with a ‘surgical’ presentation. Also one of the main data collectors (CJB) collected surveys at different rates depending on his medical placement, i.e. more surveys were collected in his emergency term, and this may influence seasonality findings.

5.7 Conclusion

Whilst Children with FAP were more likely to present during winter months but the vast majority of children with abdominal pain have similar social, demographic and family history factors regardless of the ultimate aetiology. Thus unfortunately, this does not help the clinician in separating between the two patient populations. However, this study has demonstrated that appendicitis is a very common diagnosis in this patient population thus warranting a thorough work-up so to exclude this diagnosis before a diagnosis of a FAP syndrome is made. It is interesting to note however, that in those children presenting to hospital with abdominal pain a higher prevalence of parental smoking, eczema, asthma and migraine was noted.

Chapter 6. Thesis Summary and Conclusions

6.1 Thesis summary

Paediatric abdominal pain poses a diagnostic challenge for general practitioners, emergency physicians and surgeons alike. Up to 5% of paediatric consults for primary care physicians are due to paediatric abdominal pain complaints. Similar rates of presentation are seen by emergency departments across Australia. Thus this particular presenting complaint makes up a significant proportion of paediatric medicine. The main goal for the clinician is to exclude serious medical conditions, such as appendicitis, which may be the underlying cause for the presentation. Unfortunately, appendicitis has been known to be one of the most deceptive diseases in medical history. Whilst this condition now has a mortality rate under 2%, a perforated appendix can still have significant ramifications as well as the threat of sepsis.

In addition, the diagnosis can often be obscured by the inherent difficulties of dealing with children. History and examination are particularly challenging, and an examination by different clinicians may yield entirely different results. Basic haematological and biochemical tests have been lauded by many physicians but their real life application is often far less practical and often only leads to further confusion. For example, a child with a non-surgical abdomen may be referred to a surgical registrar simply because the white cell count was elevated! Yet, sending home a child with right iliac fossa pain and a

negative white cell count would amount to great negligence on behalf of the treating clinician.

In adults the situation is made far easier by the fact that radiological investigations such as Computed Tomography pose *less* of a threat to the adult's remaining years of life left. Many adult surgeons routinely order CTs for adults over the age of forty years with RIF pain to exclude malignancy prior to an appendicectomy. However, when one thinks that a forty year old may have forty years to develop a malignancy from this investigation, whilst a ten year old has seventy years to develop a malignancy it becomes obvious that this investigation should not be utilised in children except when absolutely necessary. Thus ultrasonography was hailed as the investigation which could provide the key to the diagnosis of appendicitis. Lauded as an investigation without damaging radiation, it soon became one of the key tools in the clinician's diagnostic armentarium towards the child with the undifferentiated abdomen.

Ultrasonography relies on the major principle of appendix visualisation *to rule in or rule out* the diagnosis. One can be reasonably certain that a child has appendicitis if a dilated, thickened and blind ended tube is seen in the right iliac fossa. Unfortunately, there is often not a clear cut result, and the clinician is left wondering about the value of the scan she has in front of her, with the radiologist's statement "*the exam appears normal, although the appendix was not visualized and hence appendicitis cannot be excluded".* This leaves the clinician stranded in a sea of diagnostic nihilism. And herein

was the primary motivating factor for this thesis, that is to determine the true added value of investigations to the clinical impression.

Chapter 3 discussed the epidemiology of paediatric abdominal pain, and the utility of history and examination. It determined that appendicitis was the third most common cause of paediatric abdominal pain. Thus this is not a complaint that should be treated lightly. Children over the age of six years are more likely to develop appendicitis than the younger child where other surgical conditions predominate (for example intussusception). The female gender was also strongly associated with a negative appendicectomy. Index parameters such as pulse rate and temperature are of no use in the initial diagnosis of appendicitis, but serial parameters may be more useful (although this study did not examine this hypothesis). The presence of the symptom complex Nausea, Anorexia, Vomiting and Abdominal pain had a moderate sensitivity and specificity for appendicitis. The presence of isolated nausea with pain was of no diagnostic help at all. The finding of localized tenderness appeared to be the most useful examination finding, with rebound tenderness being highly specific but poorly sensitive. White cell count, Neutrophil count and CRP underwent a basic analysis in chapter 3, and it was shown that these tests had moderate sensitivities. Ultrasound was also assessed in this population and a very poor visualisation rate of 15% was obtained. It must be noted that this rate is significantly lower than that seen in Chapter 4. However, this is explained simply by the factor that in Chapter 3, the population who underwent ultrasounds had relatively undifferentiated abdominal pain whereas those in Chapter 4

had right iliac fossa pain or right sided abdominal pain. Thus this difference in visualisation rate is not unexpected and the quotation of Chapter 3's visualisation rate for assessment of ultrasound would be unfair.

Chapter 4 looked in detail at the utility of commonly ordered clinical investigations namely White cell count, neutrophil count and ultrasonography. Neutrophil count was superior to all of the investigations in terms of overall practicality and utility and in terms of diagnostic accuracy. However, it is seldom ordered alone and often comes with a full white cell panel. CRP was not useful alone, but its addition with the white cell panel does add diagnostic value compared to either WCC or CRP alone. The main value of these tests appears to be in excluding appendicitis. A positive test means nothing because a child with tonsillitis is just as likely to have a raised WCC as a child with appendicitis. However, a negative CRP and negative WCC do have value in that their negative predictive value is 93%. Thus only 7% of children with a negative test will have appendicitis. Whilst this is not an insignificant percentage, it is far less than when a single blood test is relied upon.

The utility of ultrasonography was also assessed, as was the visualisation rate. It was demonstrated that when the appendix is visualised, ultrasonography is an incredibly useful test with a higher sensitivity and negative predictive value than any other haematological test. When the appendix is not visualised, however, the test falls into

diagnostic mediocrity. Importantly though, the specificity and positive predictive value is higher when a negative test includes tests which don't visualise the appendix. Whilst the sensitivity and specificity of ultrasound is no better with females, the *diagnostic yield* of ultrasound is greater in females due to the extra diagnoses of ovary related issues. It has also been demonstrated that the appendix visualisation rate has declined significantly since 2002. This could be due to a poorer standard of patient referral than when ultrasound first became main stream for appendicitis. Here lies a potential use of CRP and WCC, in that a raised WCC or CRP is moderately sensitive for visualising an appendix on an ultrasound. This could help enhance visualisation rates by referring only those children with deranged blood parameters in which the diagnosis still remains in question.

Chapter 5 looked at some of the background factors behind paediatric abdominal pain presentations, mainly the impact of social, demographic and family history factors on aetiology. It is important to note the high prevalence of inflammatory conditions such as eczema, asthma and coeliac disease in this population. It is also important to note the high rate of smoking in the parents of children. Whether or not there is a link between these factors and paediatric abdominal pain presentations is difficult to say. However, there did not appear to be any significant differences in social, demographic and family history factors between children with functional abdominal pain and those with other medical syndromes.

6.2 Thesis conclusion

At the conclusion of this thesis, it remains obvious that appendicitis remains the phantom in the opera, the opera here being the emergency department. However, it is also clear that a good history and examination can add equally as much value as costly tests such as an ultrasound. With the judicious use of these investigations, some benefit from their cost can be obtained. Clinicians should order either a full panel of blood tests or none at all. This way diagnostic accuracy is maximized. If one or more test is positive, and the child has non-distractible abdominal tenderness than the child should be further worked up. If both tests are negative then if the clinician is confident that the child does not have a surgical abdomen he or she should be discharged. However, if the blood tests are normal but the child is tender in the right iliac fossa, the blood test result should be disregarded and a surgical opinion promptly sought. Ultrasound may be useful in the female population and in those who have a raised white cell count or CRP, in whom the diagnosis remains uncertain. It is however, limited by poor visualisation rates. If the appendix is not seen, the chance that this child has appendicitis is as great as any child in the casualty department (that is the prevalence of appendicitis in the general population). Hence such a negative result cannot be relied upon to exclude the diagnosis. But what of the child who has normal blood markers but a positive examination? For this child, surgical opinion should be sought and the surgeon contacted. If the history, examination and investigation findings are conflicting the child should be admitted as this is the third most common cause of pain in children with abdominal pain. Whilst this thesis does not decode the enigma which is appendicitis, it

does demonstrate that the best tools in the clinician's armentarium are her brain and hands in which she formulates the clinical diagnosis.

APPENDIX 1: Calculations

Sensitivity and specificity calculation for Ultrasound:

Table 1, Cross table utilised for sensitivity, specificity, positive predictive value and negative predictive value calculations.

APX? * HISTO Crosstabulation

Count

		HISTO		
		0	1	Total
APX?	NV	489	40	529
	N	49	5	54
	Y	42	112	154
Total		580	157	737

Where N= negative test, Y= positive test. NV= appendix not visualized.

Table 2: Scenario 1 calculations.

	Histologically appendicitis	Histologically not appendicitis
US findings indicative of appendicitis	112	42
US findings not indicative of appendicitis	5	49
Sensitivity:	0.96	
Specificity:	0.54	
PPV (where prevalence = 21.3%):	0.73	
NPV (where prevalence = 21.3%):	0.91	

In this scenario, for a negative test to be included the appendix must have been visualized.

Table 3: Scenario 2 Calculations

	Histologically appendicitis	Histologically not appendicitis		
US findings indicative of appendicitis	112	42		
US findings not indicative of appendicitis	45	538		
Sensitivity:	0.71			
Specificity:	0.93			
PPV (where prevalence = 21.3%):	0.73			
NPV (where prevalence = 21.3%):	0.92			

APPENDIX 2: Receiver Operator Curves for US visualization of the appendix

Table 4 Receiver operator curve inputs for visualization of the appendix based on bloods.

Note to reader:
Please see Chapter 4 for a discussion on receiver operator curves. Note that the below table describes the White Cell Counts, Neutrophil counts and CRP levels which provide a balance between visualizing the appendix on the ultrasound. Also note that the far right column is 1-specificity, not specificity. Thus a WCC of 1, results in a very low likelihood of an appendix being visualized on an ultrasound. Conversely a WCC of 36 provides optimal specificity for appendiceal visualisation.

Coordinates of the Curve			
Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
WCC	1.000	1.000	1.000
	2.100	1.000	0.997
	2.750	0.992	0.997
	3.400	0.984	0.997
	3.550	0.984	0.993
	3.650	0.984	0.990
	3.750	0.984	0.983
	3.850	0.984	0.979
	3.950	0.984	0.969
	4.050	0.976	0.965
	4.150	0.976	0.958
	4.300	0.976	0.955
	4.450	0.959	0.955
	4.550	0.959	0.948
	4.650	0.951	0.941
	4.750	0.951	0.931
	4.850	0.943	0.927
	4.950	0.943	0.924
	5.050	0.935	0.910
	5.150	0.935	0.899
	5.250	0.935	0.896

	5.350	0.935	0.882
	5.500	0.927	0.875
	5.650	0.927	0.868
	5.750	0.919	0.854
	5.850	0.902	0.851
	5.950	0.902	0.847
	6.050	0.894	0.840
	6.150	0.878	0.833
	6.250	0.870	0.816
	6.350	0.870	0.806
	6.420	0.862	0.788
	6.470	0.862	0.785
	6.550	0.846	0.778
	6.650	0.837	0.767
	6.750	0.821	0.760
	6.850	0.797	0.747
	6.950	0.797	0.736
	7.050	0.797	0.729
	7.150	0.797	0.722
	7.250	0.789	0.712
	7.350	0.780	0.708
	7.450	0.772	0.698
	7.550	0.756	0.684
	7.650	0.756	0.667
	7.750	0.748	0.653
	7.850	0.748	0.635
	7.950	0.748	0.625
	8.050	0.740	0.611
	8.130	0.732	0.597
	8.180	0.732	0.594
	8.250	0.724	0.587
	8.325	0.724	0.580
	8.375	0.724	0.576
	8.450	0.724	0.559
	8.550	0.724	0.552
	8.650	0.715	0.535
	8.750	0.715	0.524
	8.850	0.699	0.514

	8.950	0.683	0.497
	9.050	0.683	0.476
	9.150	0.675	0.465
	9.250	0.659	0.455
	9.350	0.659	0.438
	9.450	0.650	0.431
	9.550	0.650	0.420
	9.650	0.650	0.417
	9.750	0.650	0.413
	9.850	0.642	0.396
	9.950	0.626	0.378
	10.050	0.610	0.375
	10.150	0.602	0.375
	10.300	0.602	0.368
	10.450	0.585	0.340
	10.550	0.585	0.337
	10.650	0.561	0.316
	10.750	0.553	0.313
	10.850	0.545	0.302
	10.950	0.537	0.299
	11.050	0.528	0.295
	11.150	0.496	0.292
	11.250	0.488	0.281
	11.350	0.488	0.274
	11.500	0.480	0.264
	11.650	0.472	0.253
	11.750	0.472	0.243
	11.850	0.472	0.240
	12.000	0.455	0.233
	12.150	0.455	0.222
	12.250	0.439	0.222
	12.350	0.439	0.219
	12.435	0.407	0.219
	12.485	0.398	0.219
	12.550	0.398	0.201
	12.650	0.390	0.194
	12.750	0.390	0.191
	12.850	0.382	0.191

	12.950	0.366	0.191
	13.050	0.358	0.181
	13.150	0.350	0.177
	13.250	0.341	0.177
	13.350	0.325	0.170
	13.450	0.309	0.170
	13.550	0.309	0.167
	13.650	0.309	0.156
	13.750	0.301	0.153
	13.850	0.293	0.149
	13.950	0.285	0.149
	14.050	0.276	0.149
	14.150	0.268	0.149
	14.250	0.268	0.142
	14.350	0.252	0.135
	14.500	0.252	0.132
	14.700	0.252	0.128
	14.900	0.244	0.122
	15.050	0.236	0.111
	15.150	0.236	0.108
	15.250	0.228	0.104
	15.350	0.220	0.104
	15.450	0.220	0.101
	15.650	0.220	0.097
	15.850	0.220	0.094
	15.950	0.211	0.094
	16.150	0.203	0.087
	16.350	0.195	0.083
	16.450	0.187	0.083
	16.550	0.187	0.080
	16.700	0.179	0.080
	16.850	0.179	0.076
	16.950	0.179	0.069
	17.050	0.179	0.066
	17.200	0.179	0.063
	17.350	0.171	0.059
	17.450	0.163	0.059
	17.550	0.146	0.052

	17.700	0.138	0.052
	17.900	0.130	0.052
	18.050	0.122	0.052
	18.250	0.114	0.052
	18.600	0.114	0.049
	18.900	0.106	0.045
	19.200	0.098	0.042
	19.450	0.089	0.042
	19.850	0.073	0.038
	20.250	0.065	0.038
	20.350	0.065	0.035
	20.700	0.057	0.035
	21.150	0.057	0.031
	21.350	0.049	0.031
	21.450	0.041	0.031
	22.250	0.041	0.028
	23.400	0.033	0.028
	23.900	0.024	0.028
	24.100	0.024	0.024
	24.550	0.024	0.021
	25.400	0.024	0.017
	26.450	0.016	0.014
	27.250	0.016	0.010
	28.600	0.016	0.007
	30.100	0.016	0.003
	32.900	0.000	0.003
	36.300	0.000	0.000
Neutrophil count			
	0.9350	1.000	0.997
	1.3300	0.992	0.997
	1.5050	0.992	0.990
	1.6000	0.984	0.990
	1.6600	0.984	0.986
	1.7150	0.984	0.983
	1.7650	0.984	0.979
	1.8450	0.984	0.976
	1.8950	0.984	0.972
	1.9350	0.984	0.965

	1.9750	0.984	0.958
	1.9900	0.984	0.955
	2.0100	0.984	0.951
	2.0400	0.984	0.944
	2.0650	0.984	0.941
	2.0750	0.976	0.941
	2.0850	0.976	0.938
	2.1000	0.967	0.938
	2.1300	0.959	0.938
	2.1550	0.959	0.934
	2.1750	0.959	0.931
	2.2300	0.959	0.924
	2.2850	0.959	0.920
	2.3100	0.951	0.917
	2.3250	0.943	0.917
	2.3400	0.943	0.910
	2.3850	0.943	0.903
	2.4400	0.943	0.899
	2.4750	0.935	0.899
	2.5000	0.935	0.896
	2.5200	0.927	0.896
	2.5450	0.927	0.892
	2.5650	0.927	0.889
	2.5850	0.919	0.889
	2.6150	0.911	0.889
	2.6350	0.911	0.885
	2.6700	0.911	0.882
	2.7150	0.911	0.875
	2.7450	0.911	0.872
	2.7650	0.911	0.868
	2.7850	0.911	0.861
	2.8100	0.911	0.854
	2.8350	0.911	0.851
	2.8550	0.911	0.847
	2.8650	0.911	0.837
	2.8900	0.902	0.837
	2.9300	0.902	0.833
	2.9600	0.902	0.826

	2.9900	0.902	0.823
	3.0150	0.902	0.819
	3.0300	0.894	0.816
	3.0600	0.886	0.816
	3.0850	0.878	0.813
	3.0950	0.870	0.813
	3.1050	0.870	0.809
	3.1150	0.870	0.806
	3.1250	0.870	0.799
	3.1400	0.862	0.799
	3.1650	0.854	0.799
	3.1850	0.846	0.795
	3.2150	0.846	0.792
	3.2550	0.846	0.788
	3.2800	0.846	0.781
	3.3050	0.846	0.774
	3.3400	0.846	0.771
	3.3800	0.846	0.767
	3.4100	0.837	0.760
	3.4300	0.837	0.757
	3.4550	0.837	0.753
	3.4750	0.837	0.750
	3.4850	0.829	0.750
	3.5150	0.829	0.747
	3.5500	0.829	0.740
	3.5650	0.829	0.729
	3.5850	0.821	0.729
	3.6150	0.813	0.726
	3.6450	0.813	0.722
	3.6700	0.813	0.719
	3.6850	0.813	0.715
	3.7000	0.813	0.712
	3.7500	0.805	0.712
	3.8150	0.805	0.708
	3.8450	0.805	0.701
	3.8600	0.789	0.698
	3.8950	0.789	0.694
	3.9450	0.789	0.691

	3.9750	0.789	0.684
	3.9900	0.780	0.684
	4.0400	0.780	0.681
	4.0950	0.780	0.677
	4.1250	0.780	0.674
	4.1450	0.780	0.667
	4.1550	0.780	0.663
	4.1650	0.780	0.660
	4.1950	0.780	0.656
	4.2550	0.780	0.653
	4.2950	0.780	0.649
	4.3400	0.780	0.642
	4.3900	0.780	0.639
	4.4250	0.780	0.632
	4.4750	0.780	0.628
	4.5100	0.780	0.625
	4.5300	0.780	0.622
	4.5550	0.780	0.618
	4.5800	0.780	0.611
	4.6050	0.772	0.611
	4.6250	0.772	0.608
	4.6350	0.764	0.608
	4.6750	0.764	0.601
	4.7200	0.756	0.601
	4.7400	0.756	0.597
	4.7600	0.756	0.587
	4.7750	0.748	0.587
	4.7950	0.748	0.583
	4.8200	0.748	0.580
	4.8350	0.740	0.580
	4.8550	0.740	0.573
	4.8850	0.740	0.569
	4.9150	0.740	0.566
	4.9350	0.732	0.566
	4.9550	0.732	0.563
	4.9750	0.732	0.556
	4.9950	0.732	0.552
	5.0300	0.724	0.552

	5.0600	0.724	0.549
	5.0900	0.724	0.545
	5.1200	0.724	0.542
	5.1650	0.724	0.538
	5.2100	0.715	0.538
	5.2300	0.715	0.535
	5.2450	0.707	0.531
	5.2550	0.707	0.528
	5.2900	0.699	0.528
	5.3300	0.699	0.524
	5.3450	0.699	0.521
	5.3550	0.691	0.521
	5.3650	0.691	0.517
	5.3850	0.691	0.514
	5.4100	0.691	0.510
	5.4500	0.691	0.507
	5.4900	0.691	0.500
	5.5100	0.691	0.497
	5.5450	0.691	0.493
	5.5750	0.691	0.490
	5.5900	0.683	0.490
	5.6100	0.675	0.490
	5.6350	0.675	0.486
	5.6550	0.675	0.483
	5.6900	0.659	0.479
	5.7750	0.659	0.476
	5.8450	0.650	0.476
	5.8750	0.650	0.472
	5.8950	0.650	0.469
	5.9100	0.650	0.465
	5.9400	0.642	0.462
	6.0400	0.634	0.458
	6.1300	0.626	0.458
	6.1500	0.618	0.455
	6.1700	0.618	0.451
	6.2550	0.618	0.448
	6.3400	0.610	0.448
	6.3800	0.610	0.444

	6.4150	0.610	0.441
	6.4250	0.602	0.441
	6.4350	0.602	0.438
	6.4550	0.602	0.434
	6.4950	0.602	0.431
	6.5350	0.602	0.427
	6.5750	0.602	0.420
	6.6300	0.602	0.417
	6.6800	0.602	0.413
	6.7050	0.593	0.413
	6.7200	0.585	0.410
	6.7350	0.585	0.406
	6.7550	0.585	0.403
	6.7800	0.585	0.399
	6.8050	0.585	0.396
	6.8400	0.585	0.392
	6.8800	0.585	0.389
	6.9450	0.585	0.382
	7.0100	0.585	0.378
	7.0400	0.585	0.375
	7.0800	0.585	0.372
	7.1350	0.585	0.368
	7.1900	0.585	0.365
	7.2350	0.585	0.361
	7.2700	0.585	0.358
	7.3100	0.577	0.358
	7.3400	0.569	0.358
	7.3550	0.561	0.358
	7.4200	0.561	0.354
	7.4850	0.561	0.351
	7.5650	0.561	0.347
	7.6450	0.561	0.344
	7.7650	0.553	0.344
	7.8850	0.545	0.344
	7.8950	0.545	0.340
	7.9100	0.545	0.337
	7.9350	0.545	0.333
	7.9750	0.545	0.330

	8.0150	0.537	0.330
	8.0850	0.537	0.326
	8.1450	0.537	0.323
	8.1600	0.537	0.316
	8.1750	0.537	0.313
	8.1950	0.537	0.309
	8.2250	0.528	0.309
	8.2700	0.528	0.306
	8.3200	0.528	0.302
	8.3600	0.528	0.299
	8.4000	0.520	0.299
	8.4300	0.520	0.295
	8.4450	0.520	0.292
	8.4550	0.520	0.288
	8.4750	0.520	0.285
	8.4950	0.520	0.281
	8.5050	0.512	0.281
	8.5150	0.512	0.278
	8.5300	0.504	0.278
	8.5550	0.504	0.274
	8.5800	0.504	0.271
	8.5950	0.504	0.267
	8.6050	0.504	0.264
	8.6200	0.504	0.260
	8.6450	0.504	0.257
	8.7250	0.504	0.253
	8.8100	0.504	0.250
	8.8600	0.496	0.243
	8.8950	0.488	0.243
	8.9150	0.488	0.240
	8.9350	0.488	0.236
	8.9650	0.488	0.233
	8.9950	0.480	0.233
	9.0050	0.480	0.229
	9.0250	0.480	0.222
	9.0700	0.472	0.222
	9.1200	0.463	0.222
	9.1650	0.463	0.219

	9.2000	0.455	0.215
	9.2250	0.455	0.212
	9.2900	0.455	0.208
	9.3850	0.455	0.205
	9.4350	0.447	0.205
	9.4700	0.439	0.201
	9.5050	0.431	0.201
	9.5200	0.423	0.201
	9.6650	0.423	0.198
	9.8450	0.415	0.198
	9.9400	0.415	0.194
	10.0300	0.407	0.194
	10.0850	0.407	0.191
	10.1400	0.398	0.188
	10.1950	0.390	0.188
	10.2250	0.382	0.181
	10.2500	0.382	0.177
	10.2700	0.374	0.177
	10.2900	0.366	0.177
	10.3650	0.358	0.177
	10.4750	0.358	0.174
	10.5900	0.358	0.170
	10.6850	0.350	0.170
	10.7350	0.350	0.167
	10.7650	0.341	0.167
	10.7850	0.341	0.163
	10.8050	0.341	0.160
	10.8650	0.333	0.160
	10.9350	0.333	0.156
	10.9850	0.317	0.156
	11.0800	0.309	0.156
	11.1500	0.309	0.153
	11.1650	0.301	0.153
	11.1950	0.293	0.153
	11.2250	0.285	0.153
	11.2700	0.285	0.149
	11.3150	0.285	0.142
	11.3350	0.285	0.139

	11.3950	0.276	0.139
	11.4750	0.276	0.135
	11.5350	0.268	0.135
	11.5800	0.260	0.132
	11.6500	0.260	0.128
	11.7150	0.260	0.125
	11.7400	0.260	0.122
	11.7850	0.252	0.122
	11.8600	0.244	0.122
	11.9500	0.244	0.118
	12.0950	0.244	0.115
	12.2250	0.244	0.111
	12.2800	0.236	0.111
	12.3150	0.236	0.108
	12.3500	0.236	0.104
	12.3900	0.228	0.104
	12.4200	0.220	0.104
	12.4650	0.211	0.104
	12.5050	0.211	0.101
	12.5750	0.203	0.101
	12.7650	0.203	0.097
	12.8950	0.203	0.094
	12.9300	0.203	0.090
	13.0150	0.195	0.090
	13.0850	0.195	0.087
	13.1300	0.187	0.083
	13.1650	0.179	0.083
	13.2650	0.171	0.083
	13.3900	0.171	0.080
	13.4500	0.163	0.080
	13.5650	0.163	0.076
	13.6900	0.163	0.073
	13.7800	0.163	0.069
	13.9050	0.154	0.069
	14.0050	0.154	0.066
	14.2500	0.154	0.063
	14.5450	0.146	0.063
	14.6600	0.138	0.063

	14.7300	0.130	0.063
	14.8100	0.122	0.063
	14.9100	0.122	0.059
	14.9800	0.122	0.056
	15.0200	0.122	0.052
	15.0550	0.114	0.052
	15.0900	0.114	0.049
	15.4750	0.114	0.045
	16.0900	0.106	0.045
	16.3800	0.106	0.038
	16.5550	0.098	0.038
	16.7000	0.089	0.038
	16.8550	0.089	0.035
	17.0850	0.089	0.031
	17.3250	0.081	0.031
	17.5750	0.073	0.031
	18.0250	0.065	0.031
	18.5000	0.057	0.031
	18.6800	0.049	0.031
	19.0000	0.041	0.031
	19.3550	0.033	0.031
	19.4800	0.033	0.028
	19.8000	0.033	0.024
	20.8950	0.033	0.021
	21.8500	0.024	0.021
	22.5800	0.024	0.017
	23.8850	0.024	0.014
	25.0900	0.016	0.010
	25.5750	0.016	0.007
	26.1950	0.016	0.003
	27.4550	0.000	0.003
	29.1000	0.000	0.000
CRP	0.10	1.000	1.000
	0.25	0.935	0.816
	0.35	0.919	0.753
	0.45	0.902	0.722
	0.55	0.902	0.708

	0.65	0.886	0.698
	0.75	0.886	0.694
	0.85	0.862	0.688
	0.95	0.854	0.670
	1.05	0.846	0.649
	1.15	0.837	0.649
	1.25	0.829	0.618
	1.33	0.821	0.608
	1.38	0.821	0.604
	1.45	0.805	0.590
	1.55	0.805	0.576
	1.65	0.789	0.573
	1.75	0.772	0.563
	1.85	0.764	0.559
	1.95	0.764	0.549
	2.05	0.756	0.545
	2.15	0.756	0.535
	2.30	0.756	0.531
	2.45	0.756	0.528
	2.55	0.748	0.517
	2.65	0.740	0.514
	2.75	0.740	0.507
	2.90	0.732	0.500
	3.05	0.707	0.493
	3.15	0.699	0.493
	3.25	0.699	0.486
	3.35	0.699	0.483
	3.45	0.699	0.479
	3.55	0.699	0.476
	3.70	0.699	0.472
	3.90	0.699	0.465
	4.10	0.699	0.451
	4.25	0.691	0.444
	4.40	0.683	0.444
	4.55	0.683	0.441
	4.65	0.683	0.434
	4.75	0.667	0.434
	4.90	0.667	0.431

	5.15	0.659	0.410
	5.35	0.650	0.410
	5.45	0.634	0.410
	5.60	0.634	0.406
	5.85	0.634	0.403
	6.05	0.634	0.399
	6.15	0.626	0.399
	6.30	0.618	0.399
	6.45	0.610	0.399
	6.60	0.602	0.399
	6.75	0.602	0.396
	6.90	0.602	0.389
	7.10	0.561	0.375
	7.25	0.561	0.372
	7.40	0.561	0.368
	7.55	0.553	0.368
	7.65	0.553	0.365
	7.75	0.553	0.361
	7.90	0.545	0.361
	8.20	0.520	0.361
	8.70	0.512	0.361
	9.30	0.512	0.344
	9.65	0.512	0.337
	9.85	0.512	0.333
	10.30	0.504	0.323
	10.80	0.504	0.319
	11.50	0.496	0.302
	12.20	0.488	0.295
	12.50	0.480	0.295
	12.80	0.472	0.292
	13.05	0.463	0.292
	13.20	0.463	0.288
	13.60	0.455	0.288
	13.95	0.447	0.288
	14.50	0.439	0.274
	15.50	0.415	0.267
	16.50	0.415	0.257
	17.50	0.415	0.247

	18.00	0.407	0.243
	19.00	0.398	0.243
	20.65	0.398	0.229
	21.65	0.390	0.229
	22.50	0.390	0.226
	23.05	0.382	0.215
	23.25	0.382	0.212
	23.45	0.374	0.212
	23.75	0.374	0.208
	25.00	0.366	0.198
	26.15	0.358	0.198
	27.15	0.358	0.194
	28.55	0.358	0.184
	29.45	0.358	0.181
	29.90	0.358	0.177
	31.00	0.358	0.174
	32.50	0.358	0.167
	33.50	0.358	0.163
	34.50	0.358	0.160
	35.50	0.341	0.153
	36.05	0.341	0.149
	37.05	0.333	0.149
	38.05	0.333	0.146
	38.55	0.333	0.142
	39.50	0.333	0.139
	41.00	0.333	0.135
	42.50	0.325	0.132
	43.40	0.309	0.132
	43.90	0.301	0.132
	45.00	0.276	0.128
	46.50	0.276	0.122
	48.00	0.268	0.122
	49.50	0.260	0.122
	50.50	0.252	0.122
	52.00	0.244	0.122
	53.50	0.236	0.118
	54.50	0.228	0.115
	55.50	0.220	0.115

	56.50	0.211	0.111
	58.50	0.203	0.108
	60.50	0.203	0.104
	61.55	0.203	0.101
	62.55	0.195	0.101
	64.50	0.187	0.101
	66.50	0.187	0.097
	67.50	0.171	0.097
	68.50	0.163	0.094
	69.50	0.154	0.094
	71.00	0.146	0.094
	72.50	0.146	0.090
	75.00	0.138	0.090
	77.50	0.130	0.087
	79.50	0.122	0.087
	83.50	0.114	0.083
	90.50	0.114	0.080
	96.00	0.114	0.076
	99.50	0.106	0.073
	105.00	0.106	0.069
	109.00	0.106	0.066
	113.00	0.106	0.063
	118.00	0.098	0.063
	120.50	0.089	0.063
	123.00	0.089	0.059
	132.50	0.081	0.059
	142.00	0.073	0.056
	146.50	0.065	0.056
	152.00	0.057	0.056
	155.50	0.049	0.056
	158.00	0.041	0.056
	163.00	0.041	0.052
	167.50	0.033	0.052
	170.00	0.033	0.049
	172.00	0.033	0.045
	175.00	0.033	0.042
	178.00	0.033	0.038
	179.50	0.024	0.038

	182.00	0.024	0.035
	185.00	0.024	0.031
	197.00	0.024	0.028
	215.50	0.016	0.028
	223.50	0.016	0.024
	225.00	0.016	0.021
	238.00	0.008	0.021
	253.00	0.008	0.017
	258.00	0.008	0.014
	263.50	0.008	0.010
	289.00	0.008	0.003
	337.00	0.000	0.003
	364.00	0.000	0.000
The test result variable(s): WCC, N, CRP has at least one tie between the positive actual state group and the negative actual state group.			
a The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.			

Appendix 3 Receiver Operator Values for biomarkers in appendicitis

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
White cell count	0.768	0.028	0.000	0.713	0.822
Neutrophil oount	0.774	0.027	0.000	0.720	0.827
CRP	0.749	0.028	0.000	0.695	0.803
The test result variable(s): White cell count, Neutrophil oount, CRP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

Coordinates of the Curve			
Test Result Variable(s)	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
White cell count	1.000	1.000	1.000
	2.100	1.000	0.997
	2.750	1.000	0.994

	3.400	1.000	0.991
	3.550	1.000	0.987
	3.650	1.000	0.984
	3.750	1.000	0.978
	3.850	1.000	0.975
	3.950	1.000	0.965
	4.050	0.989	0.962
	4.150	0.989	0.956
	4.300	0.989	0.953
	4.450	0.989	0.946
	4.550	0.989	0.940
	4.650	0.989	0.931
	4.750	0.989	0.921
	4.850	0.978	0.918
	4.950	0.978	0.915
	5.050	0.978	0.899
	5.150	0.978	0.890
	5.250	0.978	0.886
	5.350	0.978	0.874
	5.500	0.968	0.868
	5.650	0.968	0.861
	5.750	0.957	0.849
	5.850	0.957	0.839
	5.950	0.957	0.836
	6.050	0.957	0.826
	6.150	0.957	0.814
	6.250	0.957	0.795
	6.350	0.957	0.785
	6.420	0.957	0.767

	6.470	0.957	0.763
	6.550	0.946	0.754
	6.650	0.946	0.741
	6.750	0.946	0.729
	6.850	0.935	0.710
	6.950	0.935	0.700
	7.050	0.935	0.694
	7.150	0.935	0.688
	7.250	0.925	0.678
	7.350	0.925	0.672
	7.450	0.914	0.662
	7.550	0.914	0.644
	7.650	0.903	0.631
	7.750	0.903	0.615
	7.850	0.892	0.603
	7.950	0.892	0.593
	8.050	0.892	0.577
	8.130	0.882	0.565
	8.180	0.882	0.562
	8.250	0.871	0.555
	8.325	0.871	0.549
	8.375	0.871	0.546
	8.450	0.871	0.530
	8.550	0.871	0.524
	8.650	0.849	0.511
	8.750	0.849	0.502
	8.850	0.839	0.489
	8.950	0.828	0.470
	9.050	0.828	0.451

	9.150	0.828	0.438
	9.250	0.806	0.429
	9.350	0.806	0.413
	9.450	0.796	0.407
	9.550	0.796	0.397
	9.650	0.796	0.394
	9.750	0.796	0.391
	9.850	0.796	0.372
	9.950	0.785	0.353
	10.050	0.774	0.347
	10.150	0.774	0.344
	10.300	0.774	0.338
	10.450	0.763	0.309
	10.550	0.763	0.306
	10.650	0.731	0.287
	10.750	0.720	0.284
	10.850	0.710	0.274
	10.950	0.699	0.271
	11.050	0.688	0.268
	11.150	0.677	0.256
	11.250	0.656	0.249
	11.350	0.656	0.243
	11.500	0.645	0.233
	11.650	0.645	0.221
	11.750	0.634	0.215
	11.850	0.634	0.211
	12.000	0.624	0.202
	12.150	0.624	0.192
	12.250	0.602	0.192

	12.350	0.602	0.189
	12.435	0.559	0.189
	12.485	0.548	0.189
	12.550	0.548	0.174
	12.650	0.538	0.167
	12.750	0.538	0.164
	12.850	0.538	0.161
	12.950	0.527	0.158
	13.050	0.527	0.148
	13.150	0.527	0.142
	13.250	0.516	0.142
	13.350	0.484	0.139
	13.450	0.462	0.139
	13.550	0.452	0.139
	13.650	0.441	0.132
	13.750	0.430	0.129
	13.850	0.430	0.123
	13.950	0.419	0.123
	14.050	0.409	0.123
	14.150	0.409	0.120
	14.250	0.387	0.120
	14.350	0.376	0.110
	14.500	0.376	0.107
	14.700	0.376	0.104
	14.900	0.366	0.098
	15.050	0.355	0.088
	15.150	0.355	0.085
	15.250	0.344	0.082
	15.350	0.344	0.079

	15.450	0.344	0.076
	15.650	0.344	0.073
	15.850	0.344	0.069
	15.950	0.333	0.069
	16.150	0.323	0.063
	16.350	0.301	0.063
	16.450	0.290	0.063
	16.550	0.290	0.060
	16.700	0.280	0.060
	16.850	0.280	0.057
	16.950	0.269	0.054
	17.050	0.269	0.050
	17.200	0.258	0.050
	17.350	0.247	0.047
	17.450	0.237	0.047
	17.550	0.204	0.044
	17.700	0.194	0.044
	17.900	0.183	0.044
	18.050	0.172	0.044
	18.250	0.161	0.044
	18.600	0.161	0.041
	18.900	0.151	0.038
	19.200	0.140	0.035
	19.450	0.129	0.035
	19.850	0.118	0.028
	20.250	0.108	0.028
	20.350	0.097	0.028
	20.700	0.097	0.025
	21.150	0.097	0.022

	21.350	0.086	0.022
	21.450	0.075	0.022
	22.250	0.065	0.022
	23.400	0.054	0.022
	23.900	0.043	0.022
	24.100	0.032	0.022
	24.550	0.032	0.019
	25.400	0.032	0.016
	26.450	0.032	0.009
	27.250	0.032	0.006
	28.600	0.022	0.006
	30.100	0.022	0.003
	32.900	0.000	0.003
	36.300	0.000	0.000
Neutrophil count	0.3600	1.000	1.000
	0.9350	1.000	0.997
	1.3300	1.000	0.994
	1.5050	1.000	0.987
	1.6000	1.000	0.984
	1.6600	1.000	0.981
	1.7150	1.000	0.978
	1.7650	1.000	0.975
	1.8450	1.000	0.972
	1.8950	1.000	0.968
	1.9350	1.000	0.962
	1.9750	1.000	0.956
	1.9900	1.000	0.953
	2.0100	1.000	0.950
	2.0400	1.000	0.943

	2.0650	1.000	0.940
	2.0750	0.989	0.940
	2.0850	0.989	0.937
	2.1000	0.989	0.934
	2.1300	0.978	0.934
	2.1550	0.978	0.931
	2.1750	0.978	0.927
	2.2300	0.978	0.921
	2.2850	0.978	0.918
	2.3100	0.978	0.912
	2.3250	0.978	0.909
	2.3400	0.978	0.902
	2.3850	0.978	0.896
	2.4400	0.978	0.893
	2.4750	0.978	0.890
	2.5000	0.978	0.886
	2.5200	0.978	0.883
	2.5450	0.978	0.880
	2.5650	0.978	0.877
	2.5850	0.978	0.874
	2.6150	0.978	0.871
	2.6350	0.978	0.868
	2.6700	0.978	0.864
	2.7150	0.978	0.858
	2.7450	0.978	0.855
	2.7650	0.978	0.852
	2.7850	0.978	0.845
	2.8100	0.978	0.839
	2.8350	0.978	0.836

	2.8550	0.978	0.833
	2.8650	0.978	0.823
	2.8900	0.978	0.820
	2.9300	0.978	0.817
	2.9600	0.978	0.811
	2.9900	0.978	0.808
	3.0150	0.978	0.804
	3.0300	0.968	0.801
	3.0600	0.968	0.798
	3.0850	0.968	0.792
	3.0950	0.957	0.792
	3.1050	0.957	0.789
	3.1150	0.957	0.785
	3.1250	0.957	0.779
	3.1400	0.957	0.776
	3.1650	0.957	0.773
	3.1850	0.957	0.767
	3.2150	0.957	0.763
	3.2550	0.957	0.760
	3.2800	0.957	0.754
	3.3050	0.957	0.748
	3.3400	0.957	0.744
	3.3800	0.957	0.741
	3.4100	0.957	0.732
	3.4300	0.957	0.729
	3.4550	0.957	0.726
	3.4750	0.957	0.722
	3.4850	0.946	0.722
	3.5150	0.946	0.719

	3.5500	0.946	0.713
	3.5650	0.946	0.703
	3.5850	0.935	0.703
	3.6150	0.935	0.697
	3.6450	0.935	0.694
	3.6700	0.935	0.691
	3.6850	0.935	0.688
	3.7000	0.935	0.685
	3.7500	0.925	0.685
	3.8150	0.925	0.681
	3.8450	0.925	0.675
	3.8600	0.925	0.666
	3.8950	0.925	0.662
	3.9450	0.925	0.659
	3.9750	0.925	0.653
	3.9900	0.914	0.653
	4.0400	0.914	0.650
	4.0950	0.914	0.647
	4.1250	0.914	0.644
	4.1450	0.914	0.637
	4.1550	0.914	0.634
	4.1650	0.914	0.631
	4.1950	0.914	0.628
	4.2550	0.914	0.625
	4.2950	0.914	0.621
	4.3400	0.914	0.615
	4.3900	0.914	0.612
	4.4250	0.914	0.606
	4.4750	0.914	0.603

	4.5100	0.914	0.599
	4.5300	0.903	0.599
	4.5550	0.903	0.596
	4.5800	0.903	0.590
	4.6050	0.903	0.587
	4.6250	0.903	0.584
	4.6350	0.903	0.580
	4.6750	0.903	0.574
	4.7200	0.892	0.574
	4.7400	0.892	0.571
	4.7600	0.892	0.562
	4.7750	0.892	0.558
	4.7950	0.892	0.555
	4.8200	0.892	0.552
	4.8350	0.882	0.552
	4.8550	0.871	0.549
	4.8850	0.871	0.546
	4.9150	0.871	0.543
	4.9350	0.860	0.543
	4.9550	0.860	0.539
	4.9750	0.860	0.533
	4.9950	0.860	0.530
	5.0300	0.860	0.527
	5.0600	0.860	0.524
	5.0900	0.860	0.521
	5.1200	0.860	0.517
	5.1650	0.860	0.514
	5.2100	0.849	0.514
	5.2300	0.849	0.511

	5.2450	0.849	0.505
	5.2550	0.849	0.502
	5.2900	0.849	0.498
	5.3300	0.849	0.495
	5.3450	0.849	0.492
	5.3550	0.849	0.489
	5.3650	0.849	0.486
	5.3850	0.849	0.483
	5.4100	0.849	0.479
	5.4500	0.849	0.476
	5.4900	0.849	0.470
	5.5100	0.849	0.467
	5.5450	0.849	0.464
	5.5750	0.849	0.461
	5.5900	0.839	0.461
	5.6100	0.839	0.457
	5.6350	0.839	0.454
	5.6550	0.839	0.451
	5.6900	0.828	0.445
	5.7750	0.828	0.442
	5.8450	0.828	0.438
	5.8750	0.828	0.435
	5.8950	0.828	0.432
	5.9100	0.828	0.429
	5.9400	0.828	0.423
	6.0400	0.817	0.420
	6.1300	0.817	0.416
	6.1500	0.806	0.413
	6.1700	0.806	0.410

	6.2550	0.806	0.407
	6.3400	0.806	0.404
	6.3800	0.806	0.401
	6.4150	0.796	0.401
	6.4250	0.785	0.401
	6.4350	0.785	0.397
	6.4550	0.785	0.394
	6.4950	0.774	0.394
	6.5350	0.774	0.391
	6.5750	0.774	0.385
	6.6300	0.774	0.382
	6.6800	0.774	0.379
	6.7050	0.774	0.375
	6.7200	0.763	0.372
	6.7350	0.763	0.369
	6.7550	0.763	0.366
	6.7800	0.763	0.363
	6.8050	0.763	0.360
	6.8400	0.763	0.356
	6.8800	0.763	0.353
	6.9450	0.753	0.350
	7.0100	0.753	0.347
	7.0400	0.753	0.344
	7.0800	0.753	0.341
	7.1350	0.753	0.338
	7.1900	0.753	0.334
	7.2350	0.753	0.331
	7.2700	0.753	0.328
	7.3100	0.753	0.325

	7.3400	0.742	0.325
	7.3550	0.742	0.322
	7.4200	0.742	0.319
	7.4850	0.742	0.315
	7.5650	0.742	0.312
	7.6450	0.742	0.309
	7.7650	0.742	0.306
	7.8850	0.731	0.306
	7.8950	0.731	0.303
	7.9100	0.731	0.300
	7.9350	0.731	0.297
	7.9750	0.731	0.293
	8.0150	0.731	0.290
	8.0850	0.731	0.287
	8.1450	0.731	0.284
	8.1600	0.731	0.278
	8.1750	0.731	0.274
	8.1950	0.720	0.274
	8.2250	0.710	0.274
	8.2700	0.710	0.271
	8.3200	0.710	0.268
	8.3600	0.710	0.265
	8.4000	0.699	0.265
	8.4300	0.699	0.262
	8.4450	0.699	0.259
	8.4550	0.699	0.256
	8.4750	0.699	0.252
	8.4950	0.699	0.249
	8.5050	0.688	0.249

	8.5150	0.688	0.246
	8.5300	0.677	0.246
	8.5550	0.677	0.243
	8.5800	0.677	0.240
	8.5950	0.677	0.237
	8.6050	0.677	0.233
	8.6200	0.677	0.230
	8.6450	0.677	0.227
	8.7250	0.677	0.224
	8.8100	0.677	0.221
	8.8600	0.667	0.215
	8.8950	0.656	0.215
	8.9150	0.656	0.211
	8.9350	0.656	0.208
	8.9650	0.656	0.205
	8.9950	0.656	0.202
	9.0050	0.656	0.199
	9.0250	0.656	0.192
	9.0700	0.645	0.192
	9.1200	0.634	0.192
	9.1650	0.634	0.189
	9.2000	0.624	0.186
	9.2250	0.624	0.183
	9.2900	0.624	0.180
	9.3900	0.624	0.177
	9.4700	0.613	0.174
	9.5050	0.613	0.170
	9.5200	0.602	0.170
	9.6650	0.591	0.170

	9.8450	0.581	0.170
	9.9400	0.581	0.167
	10.0300	0.570	0.167
	10.0850	0.570	0.164
	10.1400	0.548	0.164
	10.1950	0.538	0.164
	10.2250	0.527	0.158
	10.2500	0.527	0.155
	10.2700	0.527	0.151
	10.2900	0.527	0.148
	10.3650	0.527	0.145
	10.4750	0.516	0.145
	10.5900	0.516	0.142
	10.6850	0.505	0.142
	10.7350	0.505	0.139
	10.7650	0.495	0.139
	10.7850	0.495	0.136
	10.8050	0.495	0.132
	10.8650	0.484	0.132
	10.9350	0.484	0.129
	10.9850	0.473	0.126
	11.0800	0.462	0.126
	11.1500	0.462	0.123
	11.1650	0.452	0.123
	11.1950	0.441	0.123
	11.2250	0.430	0.123
	11.2700	0.430	0.120
	11.3150	0.430	0.114
	11.3350	0.430	0.110

	11.3950	0.419	0.110
	11.4750	0.419	0.107
	11.5350	0.409	0.107
	11.5800	0.398	0.104
	11.6500	0.398	0.101
	11.7150	0.387	0.101
	11.7400	0.387	0.098
	11.7850	0.376	0.098
	11.8600	0.376	0.095
	11.9500	0.366	0.095
	12.0950	0.366	0.091
	12.2250	0.366	0.088
	12.2800	0.355	0.088
	12.3150	0.344	0.088
	12.3500	0.333	0.088
	12.3900	0.323	0.088
	12.4200	0.323	0.085
	12.4650	0.323	0.082
	12.5050	0.323	0.079
	12.5750	0.312	0.079
	12.7650	0.301	0.079
	12.8950	0.301	0.076
	12.9300	0.301	0.073
	13.0150	0.290	0.073
	13.0850	0.290	0.069
	13.1300	0.280	0.066
	13.1650	0.280	0.063
	13.2650	0.269	0.063
	13.3900	0.269	0.060

	13.4500	0.258	0.060
	13.5650	0.258	0.057
	13.6900	0.247	0.057
	13.7800	0.247	0.054
	13.9050	0.237	0.054
	14.0050	0.237	0.050
	14.2500	0.226	0.050
	14.5450	0.215	0.050
	14.6600	0.204	0.050
	14.7300	0.194	0.050
	14.8100	0.183	0.050
	14.9100	0.183	0.047
	14.9800	0.183	0.044
	15.0200	0.183	0.041
	15.0550	0.172	0.041
	15.0900	0.172	0.038
	15.4750	0.161	0.038
	16.0900	0.151	0.038
	16.3800	0.140	0.035
	16.5550	0.140	0.032
	16.7000	0.129	0.032
	16.8550	0.129	0.028
	17.0850	0.118	0.028
	17.3250	0.108	0.028
	17.5750	0.097	0.028
	18.0250	0.086	0.028
	18.5000	0.086	0.025
	18.6800	0.075	0.025
	19.0000	0.065	0.025

	19.3550	0.054	0.025
	19.4800	0.054	0.022
	19.8000	0.043	0.022
	20.8950	0.043	0.019
	21.8500	0.032	0.019
	22.5800	0.032	0.016
	23.8850	0.032	0.013
	25.0900	0.032	0.006
	25.5750	0.032	0.003
	26.1950	0.022	0.003
	27.4550	0.000	0.003
	29.1000	0.000	0.000
CRP	0.10	1.000	1.000
	0.25	0.978	0.814
	0.35	0.968	0.754
	0.45	0.957	0.722
	0.55	0.957	0.710
	0.65	0.946	0.697
	0.75	0.946	0.694
	0.85	0.935	0.681
	0.95	0.914	0.669
	1.05	0.914	0.647
	1.15	0.903	0.647
	1.25	0.903	0.615
	1.33	0.903	0.603
	1.38	0.903	0.599
	1.45	0.903	0.580
	1.55	0.903	0.568
	1.65	0.903	0.558

	1.75	0.882	0.549
	1.85	0.871	0.546
	1.95	0.871	0.536
	2.05	0.871	0.530
	2.15	0.871	0.521
	2.30	0.871	0.517
	2.45	0.871	0.514
	2.55	0.860	0.505
	2.65	0.860	0.498
	2.75	0.849	0.495
	2.90	0.839	0.489
	3.05	0.806	0.483
	3.15	0.796	0.483
	3.25	0.796	0.476
	3.35	0.796	0.473
	3.45	0.796	0.470
	3.55	0.796	0.467
	3.70	0.796	0.464
	3.90	0.796	0.457
	4.10	0.796	0.445
	4.25	0.785	0.438
	4.40	0.774	0.438
	4.55	0.774	0.435
	4.65	0.774	0.429
	4.75	0.774	0.423
	4.90	0.774	0.420
	5.15	0.774	0.397
	5.35	0.763	0.397
	5.45	0.742	0.397

	5.60	0.742	0.394
	5.85	0.742	0.391
	6.05	0.742	0.388
	6.15	0.742	0.385
	6.30	0.731	0.385
	6.45	0.731	0.382
	6.60	0.731	0.379
	6.75	0.731	0.375
	6.90	0.731	0.369
	7.10	0.710	0.347
	7.25	0.710	0.344
	7.40	0.710	0.341
	7.55	0.710	0.338
	7.65	0.710	0.334
	7.75	0.710	0.331
	7.90	0.699	0.331
	8.20	0.677	0.328
	8.70	0.667	0.328
	9.30	0.656	0.315
	9.65	0.656	0.309
	9.85	0.656	0.306
	10.30	0.645	0.297
	10.80	0.645	0.293
	11.50	0.634	0.278
	12.20	0.624	0.271
	12.50	0.624	0.268
	12.80	0.613	0.265
	13.05	0.613	0.262
	13.20	0.613	0.259

	13.60	0.613	0.256
	13.95	0.602	0.256
	14.50	0.591	0.243
	15.50	0.570	0.233
	16.50	0.570	0.224
	17.50	0.570	0.215
	19.00	0.570	0.208
	20.65	0.570	0.196
	21.65	0.559	0.196
	22.50	0.548	0.196
	23.05	0.548	0.183
	23.25	0.548	0.180
	23.45	0.538	0.180
	23.75	0.538	0.177
	25.00	0.516	0.170
	26.15	0.505	0.170
	27.15	0.505	0.167
	28.55	0.505	0.158
	29.45	0.505	0.155
	29.90	0.505	0.151
	31.00	0.505	0.148
	32.50	0.495	0.145
	33.50	0.495	0.142
	34.50	0.484	0.142
	35.50	0.462	0.136
	36.05	0.462	0.132
	37.05	0.462	0.129
	38.05	0.452	0.129
	38.55	0.452	0.126

	39.50	0.452	0.123
	41.00	0.452	0.120
	42.50	0.441	0.117
	43.40	0.430	0.114
	43.90	0.430	0.110
	45.00	0.398	0.107
	46.50	0.376	0.107
	48.00	0.376	0.104
	49.50	0.366	0.104
	50.50	0.355	0.104
	52.00	0.344	0.104
	53.50	0.344	0.098
	54.50	0.333	0.095
	55.50	0.323	0.095
	56.50	0.301	0.095
	58.50	0.290	0.091
	60.50	0.290	0.088
	61.55	0.290	0.085
	62.55	0.280	0.085
	64.50	0.280	0.082
	66.50	0.280	0.079
	67.50	0.258	0.079
	68.50	0.247	0.076
	69.50	0.237	0.076
	71.00	0.226	0.076
	72.50	0.226	0.073
	75.00	0.215	0.073
	77.50	0.194	0.073
	79.50	0.183	0.073

	83.50	0.172	0.069
	90.50	0.172	0.066
	96.00	0.172	0.063
	99.50	0.172	0.057
	105.00	0.172	0.054
	109.00	0.172	0.050
	113.00	0.172	0.047
	118.00	0.161	0.047
	120.50	0.161	0.044
	123.00	0.161	0.041
	132.50	0.151	0.041
	142.00	0.140	0.038
	146.50	0.129	0.038
	152.00	0.118	0.038
	155.50	0.118	0.035
	158.00	0.108	0.035
	163.00	0.108	0.032
	167.50	0.097	0.032
	170.00	0.097	0.028
	172.00	0.097	0.025
	175.00	0.086	0.025
	178.00	0.086	0.022
	179.50	0.075	0.022
	182.00	0.065	0.022
	185.00	0.065	0.019
	197.00	0.065	0.016
	215.50	0.054	0.016
	223.50	0.043	0.016
	225.00	0.043	0.013

	238.00	0.032	0.013
	253.00	0.032	0.009
	258.00	0.032	0.006
	263.50	0.022	0.006
	289.00	0.011	0.003
	337.00	0.011	0.000
	364.00	0.000	0.000
The test result variable(s): White cell count, Neutrophil count, CRP has at least one tie between the positive actual state group and the negative actual state group.			
a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.			

Appendix 4 – Copy of Questionnaire used in survey.

Demystifying Abdominal Pain in Children

What familial and social factors have an impact on the presentation of the child with abdominal pain?

We are asking you to help us with a project to look at the effect of social and familial factors on the presentation and final diagnosis of children presenting with abdominal pain. This is a common presenting problem, yet the majority of children with abdominal pain do not have a serious underlying cause. However, differentiating between the child with benign causes for their pain and those with more serious causes can be challenging as history and examination findings in children can be conflicting. We are studying social and familial factors that may help identify those children with benign causes for their pain, thereby sparing unnecessary investigations and hospital admissions.

We are asking two main questions.

1) Do medical conditions that run in the family influence the ultimate diagnosis of children with abdominal pain?

2) Do social factors influence how and why children present with abdominal pain.

To do this we will need to ask you several personal questions about the medical conditions that run in your family, and some basic questions about the structure of your family and its social dynamics. It is entirely at your discretion to take part in the study. There is no perceived risk to the patient or researcher in this study. All material that is collected is kept under confidential constraints, and the only identifying record is the patient's medical record number. That is the name, and dates of birth of your child are not included in any database.

This study has been approved by the ACT Health Directorate Human Research Ethics Committee (or sub-committee). If you have any concerns or complaints about the conduct of this study, and do not feel comfortable discussing this with study staff, you may contact the Committee secretariat who is nominated to receive complaints about research projects. You should contact the secretariat on 6174 7968 or acthealth-hrec@act.gov.au

We would be happy to answer any questions that you may have, and we can be contacted via the phone number below.

Yours faithfully,

Christian Beardsley and David Croaker
Dr CJ Beardsley, BComm MBBS,
A/Prof. GDH Croaker MB BS FRACS FRCS PhD,
Dept Paediatric Surgery
The Canberra Hospital,
Yamba Dr.,
Garran . ACT 2605 Australia
***Telephone*: 02 6244 3259**

CONSENT FORM

[To be used in conjunction with the Subject Information Sheet "*Demystifying abdominal pain in children:* What familial and social factors have an impact on the presentation of the child with abdominal pain? "]

1. I,..... of ...., aged .....years, agree to be interviewed as a subject in the study described in the information statement attached to this form.
2. I acknowledge that I have read the information statement, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.
3. Before signing this consent form, I have been given the opportunity of asking any questions relating to my participation and I have received satisfactory answers.
4. I understand that I can withdraw from the study at any time without prejudice to my relationship to the Canberra Hospital.
5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
6. I understand that if I have any questions relating to my participation in this research, I may contact Dr Beardsley and Prof Croaker on telephone 02 6244 3259 who will be happy to answer them.
7. I am aware that this study has been approved by the ACT Health Directorate Human Research Ethics Committee (or sub-committee). If you have any concerns or complaints about the conduct of this study, and do not feel comfortable discussing this with study staff, you may contact the Committee secretariat who is nominated to receive complaints about research projects. You should contact the secretariat on 6174 7968 or acthealth-hrec@act.gov.au
8. I acknowledge receipt of a copy of this Consent Form and the Subject Information Statement.

Signature of subject Signature of witness

Please PRINT name Please PRINT name

Date Nature of Witness

Demystifying Paediatric Abdominal Pain Survey
UR: (or attach sticker)

Please circle the most appropriate answer

1) *Is anyone ill with the flu at home? Y or N*

2) *What is the immunisation status of the parents and children?*
   a. immunizatons up to date for all family members
   b. immunizations up to date for some family members
   c. no one in the is family immunized

3) *What is the employment status of you, and your partner:*
   a. both parents working,
   b. one parent,
   c. both unemployed

4) *What are the educational qualifications of you and your partner?*
   a. Primary school certificate
   b. Year 12 certificate
   c. Vocational qualification
   c. Tertiary qualification

5) *What is your marital status;*
   a. Married,
   b. Defacto
   c. sole parent;

6) *What is your child's bowel habit like?*
   a) Is it regular?
   b) How many times a day or week does your child pass a bowel motion?
   c) What is it's consistency (using the Bristol Stool chart)?
   d) Is there a history of abdominal pain?
   e) Does your child ever soil themselves?

7) *Is there a Smoker in family; Y or N*

8) *Do you or your partner drink over two standard drinks a day? Y or N*

9) *How many people live in the house;*

10) *How many siblings?*

11) *Do you reside in public housing? Y or N*

12) *Does anyone suffer from a psychiatric disorder in family? Y or N*

13) *Does anyone have a criminal record in the family? Y or N*

14) *) Is there a history of endometriosis in the family? Y or N*

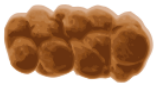
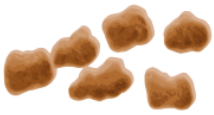
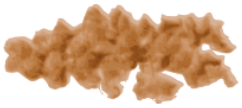
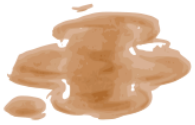
15) *Is there a history of irregular periods in the family? Y or N*

16) *Is there a history of migraine in the family? Y or N*

17) *Please circle any of the relevant conditions that run in the family:*
    a. *Gastro-Oesophageal Reflux Disease,*
    b. *Irritable Bowel Syndrome,*
    c. *Eczema,*
    d. *Asthma?*
    e. *If so what was the age at onset?*

18) *Is there a history of Familial Mediterranean Fever, Haemochromatosis, Coeliac Disease?*

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

References

1) Fahimi J, Herring A, Harries A, Gonzales R, Alter H. Computed tomography use among children presenting to emergency departments with abdominal pain. Pediatrics. 2012 Nov;130(5):e1069-75.

2) Harswick C, Uyeneshi AA, Kordick MF, Chan SB. Clinical guidelines, computed tomography scan, and negative appendectomies: a case series. Am J Emerg Med. 2006 Jan;24(1):68-72.

3) Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, Feigelson HS, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 Aug 1;167(8):700-7.

4) Mason JD. The evaluation of acute abdominal pain in children. Emerg Med Clin North Am 1996 Aug;14(3):629–44.

5) Reynolds SL, Jaffe DM. Diagnosing abdominal pain in a pediatric emergency department. Pediatr Emerg Care. 1992 Jan; 8(3):126-128.

6) Tsalkidis A, Gardikis S, Cassimos D, Kambouri K et al. Acute abdomen in children due to extra-abdominal causes. Pediatr Intnl. 2008 Jun;50 (3):315-318.

7) Marin JR. Abdominal pain in children. Emerg Med Clin N Am. 2011 May; 29 (2): 401–428

8) McCollough M, Sharieff G. Abdominal pain in children. Pediatr Clin N Am 53 (2006) 107 -137.

9) Afzak N, Tighe M, & Thomson, M. Constipation in Children. Ital J Pediatr. 2011 Jun; 37(28): 1-10.

10) Burkitt DP, Walker ARP, Painter NS. Dietary fiber and disease. JAMA. 1974 Aug;229 (8):1068-1074.

11) Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000 Jul;36(1):39 –51

12) Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990 Nov;132(5):910-924

13) Horwitz JR, Gursoy M, Jaksic T, Lally KP. Importance of diarrhea as a presenting symptom of appendicitis in very young children. Am J Surg. 1997 Feb;173(2):80-2.

14) Bundy D, Byerley J, Liles A, Perrin E et al. Does this child have appendicitis? JAMA. 2007 Jul;298 (4): 438-451.

15) Gendel I, Gutermacher M, Buklan G, Lazar L, Kidron D, Paran H, et al. Relative value of clinical, laboratory and imaging tools in diagnosing pediatric acute appendicitis. Eur J Pediatr Surg. 2011 Aug;21(4):229-33.

16) Kim JS. Acute Abdominal Pain in Children. Pediatr Gastroenterol Hepatol Nutr. 2013 Dec; 16(4): 219–224.

17) Wang LT, Prentiss KA, Simon JZ, Doody DP et al. The use of white blood cell count and left shift in the diagnosis of appendicitis in children. Pediatr Emerg Care. 2007 Feb; 23(2):69-76.

18) Cardall T, Glasser J, Guss DA. Clinical value of total white blood cell count and temperature in the evaluation of patients with suspected appendicitis. Acad Emerg Med. 2004 Oct; 11(10): 1021-1027

19) Acheson J, Banerjee J. Management of suspected appendicitis in children. Arch Dis Child Educ Pract Ed. 2010 Feb; 95(1):9-13.

20) Emil S, Mikhail P, Laberge JM, Flageole H et al. Clinical versus sonographic evaluation of acute appendicitis in children: a comparison of patient characteristics and outcomes. J Pediatr Surg. 2001 May;36 (5):780-783.

21) Puig S, Staudenherz A, Felder-Puig R, Paya K. Imaging of appendicitis in children and adolescents: useful or useless? A comparison of imaging techniques and a critical review of the current literature. Semin Roentgenol. 2008 Jan; 43:22-28.

22) Fergusson J, Hitos K, Simpson E. Utility of white cell count and ultrasonography in the diagnosis of acute appendicitis. ANZ J. Surg. 2002 Nov;72(11):781-785.

23) Holscher H, Heij H. Imaging of acute appendicitis in children: EU versus US… or US versus CT? A European perspective. Pediatr Radiol. 2009 May; 39(5):497-499.

24) Kosloske A, Love L, Rohrer J, Goldthorn J, Lacey S. The Diagnosis of appendicitis in children: Outcomes of a strategy based on pediatric surgical evaluation.

Pediatrics. 2004 Jan;113 (1): 29-34.

25) Cavusoglu Y, Erdogan D, Karaman A, Aslan M et al. Do not rush into operating and just observe actively if you are not sure about the diagnosis of appendicitis. Pediatr Surg Int. 2009 Mar; 25(3):277-282.

26) Apley, J and Naish N. Recurrent Abdominal Pains: A Field Survey of 1,000 School Children. Arch Dis Child. 1958 Apr; 33(168): 165–170.

27) Chitkara D, Rawat D, Talley N. The epidemiology of childhood recurrent abdominal pain in Western countries: a Systematic review. American Journal of gastroenterology. 2005 Aug; 100 (8):1868-1875

28) Baber K, Anderson J, Puzanovova M, Walker LS. Rome II versus Rome III classification of functional gastrointestinal disorders in pediatric chronic abdominal pain. J Pediatr Gastroenterol Nutr. 2008 Sep;47(3):299-302.

29) Drosman D, Hasler W. Rome IV-functional GI disorders: Disorders of Gut-Brain interaction. Gastroenterology. 2016 May;150(6):127-1261

30) Keefer L, Drossman DA, Guthrie E, Simren M, Tillisch K, Olden K et al. Centrally Mediated Disorders of Gastrointestinal Pain. Gastroenterology 2016 May; 150 (6): 1408-1419.

31) Ramchandani PG, Hotopf M, Sandhu B, Stein A. The epidemiology of recurrent abdominal pain from 2 to 6 years of age: results of a large, population based study. Pediatrics 2005 Jul;116 (1):46-50.

32) Fitzpatrick K, Sherman P , Ipp M, Saunders N, Macarthur C. Screening for coeliac disease in children with recurrent abdominal pain. Journal of Paediatric Gastroenterology and Nutrition. 2001 Sep:33 (3):250-252

33) Boey CCM, Goh KL. Predictors of recurrent abdominal pain among 9-15 year old urban school-children in Malaysia. Acta Paediatrica. 2001 Mar; 90(3): 353-355. 2001.

34) Huang RC, Palmer LJ, Forbes DA. Prevalence and pattern of childhood abdominal pain in an Australian General Practice. J. Paediatr Health. 2000 Aug; 36 (4); 349-353.

35) Walker LS, Dengler-Crish CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. Pain.

2010 Sep; 150 (3):568-572.

36) Gulewitsch MD, Enck P, Hautzinger M, Schlarb AA. Irritable bowel syndrome symptoms among German students: prevalence, characteristics, and associations to somatic complaints, sleep, quality of life, and childhood abdominal pain. Eur J Gastroenterol Hepatol. 2011 Apr;23(4):311-6.

37) Chitkara DK, van Tilburg MA, Blois-Martin N, Whitehead WE Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol. 2008 Mar;103(3):765-74

38) Hassall E. Decisions in diagnosing and managing chronic gastroesophageal reflux disease in children. J Pediatr. 2005 Mar;146 (S3):S3-S12.

39) Thakkar K, Chen L, Tessier ME, Gilger MA. Outcomes of Children After Esophagogastroduodenoscopy for Chronic Abdominal Pain. Clin Gastroenterol Hepatol. 2014 Sep;12(6):963-9.

40) Remedios M, Jones D, Kerlin P. Eosinophilic oesophagitis: epidemiology, pathogenesis and management. Drugs. 2011 Mar 26;71(5):527-40.

41) Nation J[1], Kaufman M[2], Allen M[3], Sheyn A[4], Coticchia J[4]. Incidence of gastroesophageal reflux disease and positive maxillary antral cultures in children with symptoms of chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2014 Feb;78(2):218-22.

42) Carson L, Lewis D, Tsou M, McGuire E et al. Abdominal migraine: an under diagnosed cause of recurrent abdominal pain in children. Headache. 2011 May; 51(5):707-712.

43) Allister L, Bachur R, Glickman J, Horwitz B. Serum markers in acute appendicitis. J surg research. 2011 Jun;168 (1):70-75.

44) Pulyaert JBCM. Acute Appendicitis: US evaluation using graded compression. Radiology. 1986 Feb;158 (2);355-360.

45) Kao S, Smith , Abu-Yousef M, Franken E et al. Acute appendicitis in children: sonographic findings. AJR. 1989 Aug;152 (3):375-379.

46) Wiersma F, Toorenvliet B, Bloem J, Allema J et al. US examination of the appendix in children with suspected appendicitis: the additional value of secondary signs. Eur Radiol. 2009 Sep;19(2):455-461.

47) Wjersma F, Sramek A,, Holscher H. US features of the normal appendix and surrounding area in children. Radiology. 2005 Jun:235;1018-1022.

48) Frush D, Frush K, Oldham K. Imaging of acute appendicitis in children: EU versus U.S… or US vs CT? A north American perspective. Pediatr Radiol. 2009 May:39(5);500-505.

49) Newman B. Ultrasound body applications in children. Pediatr Radiol. 2011 Sep;41(s2):S555-S561.

50) Krishnamoorthi R, Ramarajan N, Wang N, Newman B et al. Effectiveness of a staged US and CT protocol for the diagnosis of pediatric appendicitis: reducing radiation exposure in the age of ALARA. Radiology. 2011 Apr;259(1):231-239.

51) Australian Bureau of Statistics. Obesity: Measures of Australia's Progress (internet). Canberra ACT. 2010 [updated 15/9/10, Cited 1/4/2017]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/1370.0~2010~Chapter~Obesity%20%284.1.6.6.3%29

52) McGowan D, Sims H, Zia K, Uheba M, and I Shaikh. The Value of biochemical markers in predicting a perforation in acute appendicitis. ANZ J Surg. 2013 Jan: 83(1-2); 79-83

53) Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC.Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg. 2013 Feb;100(3):322-9.

54) Wang LT, Prentiss KA, Simon JZ, Doody DP, Ryan DP. The use of white blood cell count and left shift in the diagnosis of appendicitis in children. . Pediatr Emerg Care. 2007 Feb;23(2):69-76.

55) Kwan KY, Nager AL . Diagnosing pediatric appendicitis: usefulness of laboratory markers. Am J Emerg Med. 2010 Nov;28(9):1009-15.

56) Li YC, Chen CY, Huang MY, Wu KH, Yang WC, Wu HP. Significant change between primary and repeated serum laboratory tests at different time points in pediatric appendicitis. Eur J Emerg Med. 2012 Dec;19(6):395-9.

57) Nogrady B. Check List Measures Appendicitis Risk. Australian doctor. [2016 Sep, cited 1/4/17]. Available from: http://www.australiandoctor.com.au/news/latest-news/check-list-measures-appendicitis-risk

58) Ebell MH & Shinholser J. What are the most clinically useful cutoffs for the Alvarado and Pediatric Appendicitis Scores? A systematic review.Ann Emerg Med. 2014 Oct;64(4):365-372

59) Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med.1986 May;15(5):557–564.

60) Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med. 2011 Dec;139(9):1-13.

61) Pogorelić Z, Rak S, Mrklić I, Jurić I. Prospective validation of Alvarado score and Pediatric Appendicitis Score for the diagnosis of acute appendicitis in children. Pediatr Emerg Care. 2015 Mar;31(3):164-8

62) Khanafer I, Dori-Ann M, Mitra T, Eccles R, Brindle M, Nettel-Aguirre A, Thompson G. Test characteristics of common appendicitis scores with and without laboratory investigations: a prospective observational study. BMC Pediatr. 2016 Aug; 16(1): 147.

63) Kutasy B[1], Hunziker M, Laxamanadass G, Puri P. Increased incidence of negative appendectomy in childhood obesity. Pediatr Surg Int. 2010 Oct;26(10):959-62.

64) Roy H, Burbridge B. To CT or not to CT? The influence of computed tomography on the diagnosis of appendicitis in obese pediatric patients. Canadian J Surg. 2015 Jun;58(3):181-7.

65) Department of Health (Australia). Medicare Benefits Schedule. Canberra, ACT: Dpt of Health. {Accessed 15/01/2014} http://www9.health.gov.au/mbs/search.cfm?q=65070&sopt=I

66) Adam: Grainger & Allison's Diagnostic Radiology, 5th ed. London: Churchill Livingstone; 2009

67) Lee J, Jeong Y, Park K, Park J et al. Operator dependent techniques for graded compression sonography to detect the appendix and diagnose acute appendicitis. AJR.2005 Jan;184(1):91-97.

68) Altman DG, Bland JM. Diagnostic test: Sensitivities and Specificities. BMJ 1994 Jun;308(6943):1552.

69) Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr. 2007 May;96(5):644-7

70) York D, Smith A, Phillips JD, Von Allmen D. The influence of advanced radiographic imaging on the treatment of pediatric appendicitis. J Pediatr Surg 2005 Dec;40(12):1908–11.

71) Wong M, Casey S, Leonidas J, Elkowitz SS, Becker J. Sonographic diagnosis of acute appendicitis in children. J Pediatr Surg. 1994 Oct; 29 (10): 1356-1360.

72) Dilley A, Wesson D, Munden M, Hicks J, Brandt M, Minifee P, Nuchtern J. The impact of ultrasound examinations on the management of children with suspected appendicitis: a 3 year analysis. J Pediatr Surg. 2001 Feb;36(2):303-308.

73) Australian Bureau Statistics. Smoking. Canberra, ACT; 2015 {Updated 8/12/15, accessed 20/12/16} http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.001~2014-15~Main%20Features~Smoking~24

74) Australian bureau of Statistics. Asthma. Canberra, ACT 2013. {Updated June 2013. Accessed 24/01/2014. } http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4338.0main+features152011-13

75) Lipton RB, Stewart WF, Scher A. Epidemiology and economic impact of migraine. Curr Med Res Opin. 2001: 17 Suppl: s4-12.