THE SPECTRUM, OUTCOMES AND COSTS OF ACUTE APPENDICITIS AT EDENDALE HOSPITAL AND ITS RELATED CATCHMENT AREAS

By

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As the candidate's supervisor I have approved this thesis for submission.

Dr. Colleen ALDOUS **Date: 09 September 2014**

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Dr. Damian CLARKE **Date: 09 September 2014**

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Dedication

This thesis is dedicated to the almighty God who has given me wisdom, guidance, strength and the perseverance to complete this work.

Declaration

I, **Victor Kong**, declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Signed: **Date: 09 September 2014**

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Dr. Colleen Aldous, my supervisor, for her patience and support throughout my thesis.

Dr. Damian Clarke, my greatest mentor, who never stop believing in me.

Abstract

Acute appendicitis is the most common abdominal surgical emergency worldwide. In the developing world however, the spectrum of this disease is markedly different from the developed world. It is a surgical disease typified by late presentation and prolonged delay to definitive care that translates into preventable morbidity and even mortality. In paper 1 (Acute appendicitis in a developing country), we described the spectrum of the disease seen at Edendale Hospital, a large regional hospital in western Kwa-Zulu Natal, South Africa and highlighted the current scale of the problem. We found that acute appendicitis is a much more sinister disease compared with the developed world.

The primary health care approach in the developing world often emphasises preventative strategies rather than curative services, but acute appendicitis is not amenable to primary preventative strategies. Secondary prevention is aimed at limiting the complications of the disease process, but this relies upon early recognition and early surgery. It would appear that improving access to appropriate curative surgical services would be a cost effective intervention in the management of acute appendicitis in order to limit the morbidity currently associated with the disease. However, very little research data currently exists which attempts to quantify these costs. In paper 2, (The cost effectiveness of the early management of acute appendicitis underlies the importance of curative surgical services to a primary health care programme) we constructed a cost model to quantify the actual cost in the management of acute appendicitis at our institution. This disease in our environment required over three million US dollars to manage.

It is well known that substantial disparities exist in access to surgical services between countries, between different regions within countries, and between groups of patients within countries, across the world. These disparities of care often translate into major differences in clinical outcomes for patients. South African series in the past decade highlighted a relatively high rate of perforation, often in excess of 50%, with the equivalent perforation rate in the developed world being less than half of that in South Africa. Geographic variations in outcomes for surgical patients are well known in the developed world, but very little data is available that illustrates the situation in South Africa. South Africa is home to a large, economically deprived rural population, and poor access to

appropriate surgical services is often considered to be implicated in poor clinical outcome. In paper 3 (Quantifying the disparity in outcome between urban and rural patients with acute appendicitis in South Africa), we compared rural and urban patients and identified that rural origin was an independent risk factor for poor clinical outcome from acute appendicitis.

Delayed source control has repeatedly been shown as the variable most closely associated with poor outcomes from intra-abdominal sepsis. Therefore, strategies designed to reduce the morbidity associated with acute appendicitis must attempt to reduce the delay to definitive care. If the treatment of appendicitis is thought of as a process of care, then there are a number of distinct areas within the process where delay can be experienced. There is currently no local literature that quantifies factors which contribute to the delay to definitive surgical care of acute appendicitis in our healthcare system. In paper 4 (Understanding the reasons for delay to definitive surgical care of patients with acute appendicitis in rural South Africa), we identified that there were separate domains acting synergistically to contribute to overall delay. The most noteworthy factor was health seeking behaviour, compounded by failure of healthcare staff to diagnose the condition and delay in referral.

In order for early surgical intervention to be effective, accurate diagnosis must be made early, with swift referral to a surgical centre. The clinical diagnosis of acute appendicitis is challenging because numerous other conditions can mimic its presentation. Its diagnosis is especially problematic in the developing world because HIV and other tropical diseases result in a much wider diagnostic differential. The situation is further compounded by limited access to advanced diagnostic imaging. Various clinical prediction scores have been advocated to facilitate clinical decision making in the diagnosis of acute appendicitis; the Alvarado score is the most commonly used. International literature generally supports the use of Alvarado score as an accurate clinical predictive tool. However, there is a paucity of literature which examines its applicability to the Black South African population. In paper 5 (The accuracy of Alvarado score in predicting acute appendicitis in the Black South African population needs to be validated), we identified that the Alvarado score has limited application in the Black South African population. Further concerns exist as those patients with the disease would potentially have been missed and inappropriately discharged if such score was to be widely adapted in the rural hospitals.

Acute appendicitis in South Africa remains a serious disease associated with late presentation and advanced pathology. Consequently, surgeons are frequently required to manage complex intra-abdominal sepsis. Owing to the associated morbidity and mortality, aggressive surgical management is essential, as early source control remains the cornerstone of therapy. Achieving adequate source control frequently requires one or more repeat operations, but decision making relating to the need for re-operation and the optimal timing of re-operation is often highly subjective. The decision to re-operate is often challenging when presented with critically ill patients with non-specific signs and symptoms of partially treated sepsis. There is a lack of general consensus about which patients should be subjected to re-operation or not, and in this respect two approaches are generally taken:

a) the planned approach sends all patients with complex sepsis back to the operating room at regular forty-eight hour intervals until adequate source control has been achieved, and

b) the on-demand approach deems that all patients are treated expectantly; only patients who manifest signs of unresolved intra-abdominal sepsis are subjected to re-operation.

In paper 6 (Developing a clinical model to predict the need for re-operation for severe intra-abdominal sepsis secondary to complicated appendicitis), we constructed a simple clinical model to aid this decision making process, utilising both pre-operative and intra-operative factors that accurately predicts the need for re-laparotomy. Our model identified four key clinical factors that allowed a 90% accuracy of predicting the need for a re-operation.

Acute appendicitis in our environment is a sinister disease associated with major adverse outcome, which translates to significant financial cost. Rural patients fare worst and multiple delays within the health system contributed to late presentation. The Alvarado score has limited applicability in the Black South African population, and with established advanced pathology, a simple clinical prediction score allows accurate prediction of the need for re-operation in these patients.

List of Abbreviations

BREC	Biomedical Research Ethics Committee
CPR	Clinical Prediction Rules
EDH	Edendale Hospital
GBP	Great British Pound
HR	Heart Rate
ICU	Intensive Care Unit
KZN	KwaZulu Natal
LC	Local Contamination
4QC	Four Quadrant Contamination
OD	On Demand Relaparotomy
PMB	Pietermaritzburg
PR	Planned Relaparotomy
ROC	Receiver Operator Characteristics
SA	South Africa
SHD	Sisonke Health District
TAC	Temporary Abdominal Closure
UHERB	Umgungundlovu Health Ethics Review Board
USD	United States Dollars
WCC	White Cell Count
ZAR	South African Rand

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Study Development and Rationale

This study commenced in 2010 when I was first employed as a resident surgical officer in the Department of Surgery at Edendale Hospital, Pietermaritzburg, South Africa. It initially began as a quality improvement programme designed to determine the number of complicated cases of acute appendicitis seen at our institution. The clinical impression was that in our setting, acute appendicitis was a disease that presented late, with significant morbidity and mortality. At the time, Dr. Bojana Bulajic and I informed the head of department of our thinking and began to collate data for our own departmental audit, as part of a quality improvement initiative.

As the extent of the problem emerged, the need to share the data through scientific publication became apparent and we applied to the Umgungundlovu Health Ethics Review Board (UHERB) for permission to publish some of the initial data accumulated. This resulted in the first publication (Chapter 2) presented in this thesis documenting our experience with the first 200 cases of acute appendicitis at our institution [1]. The data in this publication revealed a picture of acute appendicitis vastly different from that seen in the developed world. Our patients with acute appendicitis presented with advanced disease and suffered a great deal of morbidity and even mortality. At the time we wrote the initial paper, literature published in the developed world was increasingly filled with reports documenting the successful conservative non-operative treatment of early acute appendicitis. What we were encountering was a completely different spectrum of disease, yet we found a relative dearth of literature on the topic of acute appendicitis throughout sub-Saharan Africa.

As we realised the many research questions that could potentially be asked, the idea of registering for a PhD degree at the University of KwaZulu Natal emerged. This lead to the development of a formal concept sheet and a study protocol. Ethics approval for the study was further formalised by direct application to the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu Natal.

This research project dovetailed with an existing research project undertaken by one of my supervisors, Dr. Damian Clarke, looking at the development of a multifaceted quality improvement programme to uplift rural trauma care at Edendale Hospital and Sisonke

Health District [2,3]. A copy of this paper can be seen as Appendix 1. Many of the concepts Dr. Clarke elaborates on could also be applied to the study of acute appendicitis. These concepts and constructs include the use of a strategic planning health system model as well as modern error theory and the development of appropriate quality metrics [3,4].

The concept behind the research project for this thesis was to collect as much data as possible on acute appendicitis at our institution both prospectively and retrospectively, in order to gain a complete overview or situational analysis of the problem. Once this broad overview had been established, we decided to cost the problem and tried to establish a monetary value for the morbidity we were encountering.

Using ideas in the structured strategic planning system that Dr. Clarke had developed looking at rural trauma care, we investigated the possible reasons for late presentations we were seeing, and this resulted in the formulation of further research questions. Firstly, we were interested in knowing what the barriers to accessing care were. We achieved this by comparing outcomes in rural and urban patients to see which group was more likely to have a poor clinical outcome. We then interviewed the patients (the prospective cohort) to determine the narrative story of what had actually happened to them from the onset of illness. We identified that there were pre-hospital barriers to accessing care, but that once care had been accessed, there was a delay associated with failure to establish the diagnosis. This implied a failure of medical education, and we were interested in examining the reason for this.

It was postulated that diagnostic delay may be the result of a different clinical presentation of the disease to that described in standard text books. We explored this by reviewing the accuracy of the Alvarado score for the diagnosis of acute appendicitis among the local Black South African population. Furthermore, we focused on the unique surgical aspects of the disease as seen in our environment. In contrast to the developed world, acute appendicitis in our institution is a late disease, with severe intra-abdominal sepsis that frequently required multiple aggressive relaparotomy to control sepsis. Such encounters are rare in the developed world and there is a scarcity of data in this specific situation. We therefore looked to develop a simple clinical tool which would assist clinicians with decision making when considering re-laparotomy for patients with complicated acute appendicitis.

Study aims

The aims of this research project were:

- To assess the clinical spectrum and outcome of acute appendicitis at Edendale Hospital.
- To quantify the financial cost of management of acute appendicitis at our institution.
- To investigate the difference in clinical outcome of patients from rural and urban areas who present with acute appendicitis.
- To identify the possible reasons for late presentation and contributing factors to poor outcome.
- To assess the applicability of the Alvarado score for diagnosis of acute appendicitis in our local Black South African population.
- To develop a clinical tool in assisting with clinical decision making in the surgical management of patients with complicated acute appendicitis.

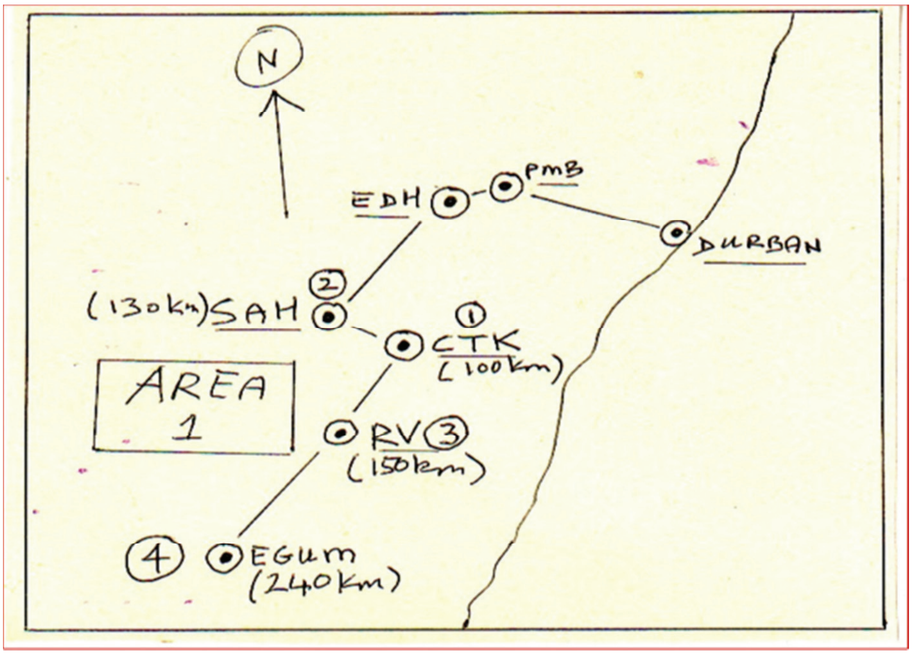
The Study Setting

The city of Pietermaritzburg is the capital of KwaZulu-Natal and is the largest city in the western part of the province. It has a population of one million people, and is served by a tertiary hospital (Grey's Hospital), a regional hospital (Edendale Hospital) and a district hospital (Northdale Hospital). Western KwaZulu-Natal is a predominantly rural province and is made up of four health districts with a population of two million people. There are 2 other regional hospitals in western KwaZulu-Natal and 19 district hospitals.

Sisonke District is a rural area in south western Kwa-Zulu Natal with a population of half a million people and has four district hospitals. These are: Usher Memorial Hospital in Kokstad, Christ the King Hospital in Ixopo, Saint Apollinaris Hospital in Creighton and Rietvlei Hospital, which is half way between Kokstad and Harding. Taylor Bequest Hospital in Matatiele has now been incorporated into the Eastern Cape Province and is no longer part of the official drainage area. However, it still refers many patients through to the regional hospitals.

Edendale Hospital is an 800 bed regional hospital located just outside the city of Pietermaritzburg. It is the referral hospital for Sisonke District and hence Sisonke and Edendale Hospital together form a health system. The hand-drawn map created by Dr. Jonathan Handley (shown below), my anaesthetic companion on many of the visits to these district hospitals over the last five years, shows the four hospitals in geographical relationship to Edendale Hospital in Pietermaritzburg and Durban.

Figure 1: Schematic map of Sisonke District and the four district hospitals



Courtesy of Dr. Jonathan Handley, FCA(SA)

Key:

EDH: Edendale Hospital, Regional Hospital, Pietermaritzburg

PMB: Pietermaritzburg City, Capital of KwaZulu Natal Province

CTK: Christ the King District Hospital, Ixopo. [100km]

SAH: St. Apollinaris District Hospital, Centocow. [130km]

RV: Rietvlei District Hospital, Umzinkhulu. [150 km]

EGUM: East Griqualand and Usher Memorial District Hospital, Kokstad. [240 km]

The Structure of this Thesis

This is a thesis by publication and comprises three parts. Each part contains two chapters, which correspond to the publications. The publications have either been published, are in press, or are currently under review.

- **Part one** consists of an introduction to the problem of acute appendicitis in rural South Africa and provides a situational analysis of the current scale of the problem in a section of the province of Kwa-Zulu Natal. It also provides an overview of the burden of disease, the quality of the process of care, and attempts to objectively cost the management of acute appendicitis to the health service in our setting.
- **Part two** reviews the outcome of patients from rural and urban areas and attempts to identify reasons for the late presentation seen in our institution. It examines barriers to care, delays in diagnosis, and other factors contributing to the late presentation of advanced disease.
- **Part three** determines the applicability of Alvarado score in diagnosing acute appendicitis in our local Black South African population. It further examines the unique surgical management of complex intra-abdominal sepsis in acute appendicitis leading to the development a clinical tool for determining which patient requires re-laparotomy to control severe sepsis.
- **The Conclusions and Recommendations** chapter provides a summary of the entire thesis and points the way forward for possible improvement strategies.

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Chapter 1: Introduction

Acute appendicitis is the most common abdominal surgical emergency worldwide [1], with an estimated incidence of approximately 52 cases per 100 000 head of population [2,3]. South African series from the last quarter of the twentieth century showed that less than one per cent of the Black African population underwent appendicectomy [4,5,6,7]. The estimated incidence of appendicitis amongst Black Africans was in the order of 10 per 100 000 head of population [2]. Later studies suggested a progressive increase in the incidence of disease, approaching that of the developed world [7,8,9]. While the reason for this is unclear, it is usually ascribed to rapid westernisation and changes in dietary habits [2]. Although appendicitis in South Africa is comparatively less common than in the developed world, it is a far more serious surgical disease, frequently associated with significant morbidity and even mortality [5,6,7].

The spectrum of disease described in the most of the literature from the developed world is remarkably different from that seen in the developing world [13,14]. Furthermore, most of the local series from South Africa were undertaken over a decade ago, and they do not reflect the true spectrum of disease in the twenty-first century [4,5,6,7]. Therefore, there is a need for an accurate descriptive study in order to define the current spectrum and outcome of the disease in our locality. Edendale Hospital is a major regional hospital located in Pietermaritzburg, western KwaZulu Natal, South Africa. It is government hospital that provides definitive surgical services to two health districts, namely the rural Sisonke district, and the urban Umgungundlovu district. It has a combined catchment population of over three million. Within this region, it also serves as the surgical referral centre for four other peripheral rural hospitals, and numerous other primary care polyclinics.

The aetiology of appendicitis remains elusive and the general consensus of management is one of clinical diagnosis and early definitive surgical treatment [1]. It is generally accepted that acute appendicitis is a progressive disease in the majority of cases [10]. Once the pathology begins, it pursues a relentless course until definitive surgical management is instituted [11]. There is, however, an increasing trend in the developed world for conservative management in selected cases, but this relies on early patient presentation, early diagnosis with advanced radiological imaging, and appropriate resources for perioperative management [12]. This is in stark contrast to the situation in most parts of the developing world, where late presentation with multiple barriers to access for definitive management is the norm [13].

In the developing world, the primary healthcare approach often emphasises preventative strategies rather than curative services. Acute appendicitis however, is not amenable to any primary preventative strategies [15]. Secondary prevention of the disease aims at limiting complications and other adverse outcomes from the disease process itself, but this approach relies upon early recognition and early definitive surgery [10,15]. This represents a major challenge in the developing world with limited resources, poor infrastructure, and often poorly organised healthcare systems [15]. With increasing pressure and restrictions being placed on healthcare resources in this setting, an understanding of the cost factors associated with the management of acute appendicitis is essential [16,17]. Implementing strategies aimed at improving access to curative surgical services should be a cost effective intervention, as this would reduce the morbidity and mortality associated with advanced disease [16]. Accurate costing is therefore, important for policy makers and administrators [16,17,18]. There is currently a shortage of literature quantifying the costs associated with the late presentation of acute appendicitis and this study addresses this deficit by costing the surgical management of acute appendicitis in our local setting.

Substantial disparities exist in access to surgical services between countries, between different regions within countries, and between groups of patients within countries, across the world [19]. Although this in itself is not unique to South Africa, a multitude of factors, such as health seeking behaviour, inadequate access to healthcare facilities, failure to recognise and refer acute appendicitis, and logistical difficulties all together conspire together to contribute to poor outcomes amongst patients in the developing world with an inherently weak healthcare system [19]. In reality, these disparities of care often translate into differences in clinical outcomes. Geographic variations in outcomes for surgical patients are well known mostly in the developed world [20]. Previous South African series highlighted a relatively high rate of perforation, usually in excess of 50%, compared with rate in the developed world of less than half of that experienced in South Africa [4,5,6,7]. South Africa also has a large population who reside in rural areas, and these areas remain some of the most economically deprived areas in the world [21]. It is unclear how geography contributes to the high rate of adverse clinical outcome from acute appendicitis, as there is currently no literature from South Africa addressing this issue.

Delayed source control of severe intra-abdominal sepsis has repeatedly been shown to be the single most important variable associated with poor clinical outcomes [22]. Therefore, any strategy to reduce the morbidity associated with acute appendicitis must attempt to eliminate delays to definitive surgical care [23]. If the management of acute appendicitis is considered as a process of care, then a number of distinct domains exist within the process where delay can be experienced. There is currently no local literature to quantify the factors involved in the process which contribute to the delay to definitive surgical care of acute appendicitis in our healthcare system. Gaining this information may allow for the development of targeted quality improvement programmes.

Early surgical intervention requires an early diagnosis [11]. However, the diagnosis of acute appendicitis is often challenging because numerous other conditions can mimic its presentation [24]. This diagnostic dilemma is especially acute in the developing world, because the high incidence of HIV and other tropical diseases result in a much wider diagnostic differential [25]. This situation is further complicated by medical staff who have little surgical experience working at hospitals in rural areas, and limited access to advanced diagnostic imaging [26]. Numerous clinical predictive scoring systems have been advocated to facilitate this clinical decision making process of diagnosing appendicitis [27]. The Alvarado score is the best known and most widely used clinical scoring system in this context [28]. International literature supports the use of the Alvarado score, and it has shown to be an accurate clinical predictive tool in the developed world setting [27]. However, literature from other developing countries on the applicability of the Alvarado score have generated mixed and inconsistent results, with some authors advocating modification of the original scores to suit the local populations [29,30]. There is very little literature that specifically examines the applicability of any scoring system to the Black South African population.

As acute appendicitis in South Africa is associated with delayed presentation and much more advanced pathology compared to the developed world, surgeons in South Africa are frequently required to manage complex intra-abdominal sepsis [8,9]. Early aggressive source control remains the cornerstone to ensure patient survival and improved outcomes [22]. However, with advanced disease adequate, source control frequently requires one or more repeat operations [31]. The decision on the need for re-operation, and the optimal timing, is often highly subjective and challenging in the setting of critically ill patients with non-specific signs and symptoms of partially treated sepsis. [32]. Currently, there are two broad approaches to the surgical management of severe intra-abdominal sepsis:

- The 'planned' approach sends all patients with complex sepsis back to the operating room at regular forty-eight hour intervals until adequate source control has been achieved.
- The 'on-demand' approach deems that all patients are treated expectantly with only patients who manifest signs of unresolved intra-abdominal sepsis being subjected to re-operation [33].

This decision making process remains a controversial area, and the available literature does not resolve the issue [34]. This lack of evidence is especially noticeable in the specific subgroup of patients with complicated appendicitis, which is infrequently seen in the developed world [35,36]. Consequently, there is an urgent need to devise a simple clinical model that will aid this decision making process and ensure only selected patients who are likely to benefit should undergo such procedure. There is no literature that currently addresses this issue specifically in the context of complicated appendicitis.

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Part ONE: Situational analysis

Acute appendicitis is the commonest surgical emergency worldwide. Previous South African studies over a decade ago suggested a relatively low incidence, but it appears to be increasing steadily. In contrast to the developed world, acute appendicitis is a completely different spectrum of disease, which is typified by advanced pathology with major morbidity and mortality. My initial interest as a Resident Surgical Officer at Edendale Hospital was triggered by the frequent encounter of critically ill patients with severe intra-abdominal sepsis from appendicitis, which was rarely seen in the developed world. This was an evolving project that began as a prospective study of patients managed at our institution. This lead to the first publication of our experience with the initial cohort of 200 cases. The project continued to evolve, and the prospective cohort eventually reached 500, with a further 500 cases reviewed retrospectively from medical records. A total of 1000 patients were collected which spanned over a 5 year period, which forms the basis of this part of the thesis.

Of the 1000 patients with acute appendicitis confirmed intra-operatively during the five-year period from January 2008 to December 2012, male comprised 54.1% and female 46.9%, with a median age of 21 years (12 - 26). Medical care was sought 4.2 days (mean) after the onset of symptoms. Half of all patients (50%) presented from the rural areas, and the other half from the urban areas. The most common symptoms were nausea and or vomiting (70.7%), anorexia (58%), and non-migratory generalised abdominal pain (68%). Only 32.4% of patients described the classic migratory abdominal pain described in standard textbooks. Diarrhoea was reported in 46%, constipation in 41% and dysuria in 22%. Mean temperature on admission was 37.5 ^{o}C; mean heart rate 103/min, and mean White Cell Count (WCC) was 14.8 x 10^{9}/L. A total of 490 patients were assessed as having generalised peritonitis at presentation and the remaining 510 patients presented with localised peritonitis. Local incision was performed on 39.4%, while 60.6% required a laparotomy. Intra-operative findings were as follows: Inflamed, non-perforated appendices: 40% (405/1000), perforated appendices: 60% (595/1000). Of the cohort with perforated appendices, 30% (177/595) had perforation associated localised intra-abdominal sepsis, and 70% (418/595) had perforation associated with generalised intra-abdominal sepsis.

Temporary abdominal closure was required by 23% (234/1000) of all patients, and 41% (406/1000) of patients required relaparotomy for residual sepsis. Just under ten per cent (9.5%) of all patients required post-operative intensive care admission, all of which were associated with perforation and generalised intra-abdominal sepsis. The mean length of stay in intensive care was 6 days. The remaining 90% of case were managed in the general surgical wards. Overall complications were as follows: hospital acquired pneumonia: 8.2% (82/1000), acute kidney injury 5.7% (57/1000), wound sepsis: 14.2% (142/1000) and others: 2% (20/1000). The overall mortality was 1.3%.

As there is a high volume of patients with acute appendicitis during the study period, frequently associated with severe intra-abdominal sepsis, the financial implication of their management became increasing apparent. Using our initial cohort of 200 cases, a cost model was constructed based on a micro-costing approach. The total cost of management of the 200 cases was calculated and a separate cost was derived for patients at each stage of the disease. The cost per patient based on the above cohort was found to be exponential as the disease progressed (See Figure 2 below). The final cohort of 1000 cases was used to describe the actual cost involved in the management of all these patients over the 5 year period (See Table 1 below).

Figure 2: Graph depicting the cost per patient (in ZAR) according to stage of the disease

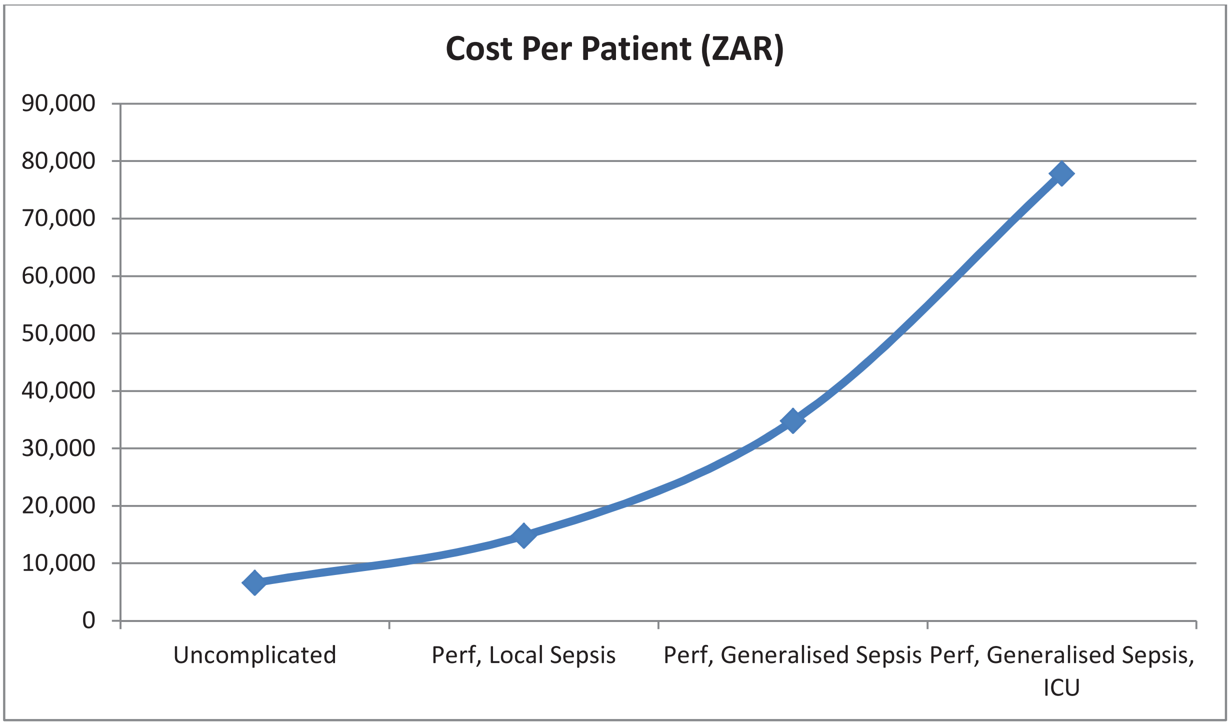

Table 1: summarising the cost of managing all 1000 cases of appendicitis by disease stage

Disease Stage	Early, Uncomplicated	Perf, Local Sepsis	Perf Gen. Sepsis No ICU	Perf, Gen. Sepsis ICU
Number of Patients	405	177	324	94
Mean Cost Per Patient (ZAR)	6,578	14,791	34,773	77,816
Total Cost of Management (ZAR)	2,664,090	2,618,007	11,266,452	7,314,704

Based on the initial cohort of 200 cases, the mean cost of treating acute appendicitis per patient when it was early and uncomplicated, was 6,578 ZAR (908 USD). As the disease progressed, then the cost increased. For a patient with perforated appendices with localised intra-abdominal sepsis, the cost increased to 14,791 ZAR (2,041 USD). Once the disease progressed to perforation with generalised intra-abdominal sepsis without the need for ICU, the cost was 34,773 ZAR (4,799 USD). When ICU support was required, the cost further escalated to 77,816 ZAR (10,739 USD). This was over 10 times the cost of treating early uncomplicated cases. When the final cohort of 1000 cases was considered, the total cost of managing these patients over the 5 year study period was 23,863,253 ZAR (3,293,129 USD).

Chapter 2: Acute appendicitis in a developing country

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Acute Appendicitis in a Developing Country

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Abstract

Background This prospective audit of appendicitis at a busy regional hospital reviews the spectrum and outcome of acute appendicitis in rural and peri-urban South Africa.

Method We conducted a prospective audit from September 2010 to September 2011 at Edendale Hospital in Pietermaritzburg, South Africa.

Results Over the year under review, a total of 200 patients with a provisional diagnosis of acute appendicitis were operated on at Edendale Hospital. There were 128 males (64 %) in this cohort. The mean duration of illness prior to seeking medical attention was 3.7 days. Surgical access was by a midline laparotomy in 62.5 % and by a Lanz incision in 35.5 %. Two percent of patients underwent a laparoscopic appendicectomy. The operative findings were as follows: macroscopic inflammation of the appendix without perforation in 35.5 % (71/200) and perforation of the appendix in 57 % (114/200). Of the perforated appendices, 44 % (51/114) were associated with localised intra-abdominal contamination and 55 % (63/114) had generalised four-quadrant soiling. Thirty percent (60/200) required temporary abdominal closure (TAC) with planned repeat operation. Major complications included hospital-acquired pneumonia in 12.5 % (25/200), wound dehiscence in 7 % (14/200), and renal failure in 3 % (6/200). Postoperatively 89.5 % (179/200) were admitted directly to the general wards, while 11 % (21/200) required admission to the intensive care unit. The overall mortality rate was 2 % (4/200).

Conclusions The incidence of acute appendicitis amongst African patients seems to be increasing. Although it is still lower than the reported incidence amongst patients in the developed world, it is a common emergency that places a significant burden on the South African health service. The disease presents late and is associated with a high incidence of perforation which translates into significant morbidity and even mortality.

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Introduction

Appendicitis remains the commonest abdominal surgical emergency in the developed world, with an estimated incidence of about 52 cases per 100,000 head of population [1–3]. South African series from the last quarter of the 20th century estimated that 10 % of the white population had undergone appendicectomy, whereas <1 % of the African population required the operation [4–7]. The estimated incidence of appendicitis amongst Africans was on the order of 10 per 100,000 head of population. This difference in incidence is usually ascribed to different dietary habits, with people from the developing world consuming a diet low in fat and high in fibre [8, 9].

In the developed world the management of appendicitis has come to rely heavily on advanced radiological imaging [10]. This has led to earlier diagnosis and a number of reports of the successful nonoperative management of acute appendicitis [11–13]. In the developing world, however, appendicitis remains a surgical disease with late presentation and delayed definitive care [14]. This translates into major morbidity and even mortality [15]. This prospective audit of appendicitis at a busy regional hospital reviews the spectrum and outcome of acute appendicitis in rural and peri-urban South Africa.

Method

This was a prospective study conducted from September 2010 to September 2011 at Edendale Hospital in Pietermaritzburg, South Africa. All patients who were operated on for suspected acute appendicitis were included in the study. Consent to take part in this audit was obtained from all the patients. Data were collected by patient interview, as well as from hospital records and entered into a spreadsheet. Basic demographic data included the mode of presentation of each patient. There were four modes of presentation, namely, direct self-referral to the hospital emergency department, referral from a general practitioner, referral from the local community health clinic, or referral from one of the four rural district hospitals that feed to Edendale Hospital. Patients were specifically asked about their health-care-seeking behaviour. They were asked about the onset and duration of symptoms prior to seeking contact with the health-care system. The clinical symptoms, physical examination findings, baseline vital signs, and laboratory results were recorded. Clinical details noted included the type of incision, macroscopic appearance of the appendix, the presence of appendiceal perforation, the degree of abdominal contamination, the need for temporary abdomen containment, and the need for repeat operation. The clinical course of each patient was closely followed up until discharge. This included the type and nature of any major complication, the need for repeat operation, and admission to the intensive care unit (ICU). The total length of ICU stay and hospital stay were recorded. The need for repeat operation was classified as planned or unplanned.

Results

Over the year under review, a total of 200 patients with a provisional diagnosis of acute appendicitis were operated on at Edendale Hospital. There were 128 males (64 %) and 72 females (36 %) in this cohort. The mean age of presentation was 21.5 years for males and 22.2 years for females. Most patients, 43.5 % (87/200), were self-referrals who presented directly to the emergency department. A further 19 % (38) were referred from the surrounding primary health-care clinics and 2.5 % (5/200) were referred from local general practitioners. Referrals from the four rural referral hospitals constituted 35 % (70/200) of all admissions.

Clinical presentation

The mean duration of illness prior to seeking medical attention was 3.7 days. The most common symptoms were nausea and or vomiting (81 %), anorexia (68.5 %), and nonmigratory generalised abdominal pain (68 %). Only 33 % of patients described the classic migratory abdominal pain described in standard textbooks. Diarrhoea was reported in 12 % of patients, constipation in 6 %, and dysuria in 4 %. On presentation, 39 % had tenderness localised to the right iliac fossa, 21 % had localised peritonitis, and 40 % had generalised peritonitis. Mean temperature on admission was 37.5 °C, mean heart rate was 102 beats/min, and mean white cell count was 15.1.

Management and operative findings

Surgical access was by a midline laparotomy in 62.5 % and by a Lanz incision in 35.5 %. Two percent of patients underwent a laparoscopic appendicectomy. The operative findings were as follows: macroscopic inflammation of the appendix without perforation in 35.5 % (71/200) and perforation of the appendix in 57 % (114/200). Of the perforated appendices, 44 % (51/114) were associated with localised intra-abdominal contamination and 55 % (63/114) had generalised four-quadrant soiling. In 7.5 % (15/200), pathologies other appendicitis were identified, including pelvic inflammatory disease (10), perforated Meckel's diverticulum (1), perforated duodenal ulcer (1), perforated gastric ulcer (1), perforated jejunum of unknown aetiology (1), and perforated terminal ileum secondary to tuberculosis (1).

Clinical course

Thirty percent (60/200) required temporary abdominal closure (TAC) with planned repeat operation. Of the 60 patients who required TAC, 58 (96.7 %) underwent the planned repeat operation and 2 died before the surgery. Of the 140 patients who underwent primary abdominal wall closure, 13 (9 %) required an unplanned repeat operation due to on-going sepsis. Major complications included hospital-acquired pneumonia in 12.5 % (25/200), wound dehiscence in 7 % (14/200), and renal failure in 3 % (6/200). One patient developed an enterocutaneous fistula and two patients developed adult respiratory distress syndrome in the ICU. Postoperatively, 89.5 % (179/200) were admitted directly to the general wards, while 11 % (21/200) required admission to the ICU. The overall mortality rate was 2 % (4/200). All four patients who died had four-quadrant intra-abdominal contamination and all required initial ICU admission. Overall mean length of hospital stay for all patients was 6.1 days (median = 5 days).

Subgroup analysis

The 185 patients with confirmed appendicitis were further subdivided into two groups based on the presence or absence of perforation. In those without perforation, the mean duration of illness prior to seeking medical attention was 2.7 days, while the mean duration of illness for those with perforation was 4.4 days. All 21 patients who were admitted to the CU had perforation associated with four-quadrant soiling. Mortality was confined to this group. The mean length of hospital stay was 2.5 days for patients without perforation and 8.5 days for patients with perforation.

Estimations of incidence

Edendale Hospital drains two health districts, namely, the rural Sisonke district and the urban and peri-rural Umgungundlovu district. According to the South Africa census data of 2001, the Sisonke district has 300,000 inhabitants and the Umgungundlovu district has 1,000,000 inhabitants. No other hospitals in our drainage area perform appendicectomy. This allowed an incidence of acute appendicitis per 100,000 of the population to be estimated based on the census data. Using the 2001 census data, we estimate a population incidence of acute appendicitis of 15 per 100,000 of the population in our drainage area.

Discussion

Acute appendicitis remains the commonest general surgical emergency in the developed world [1]. However, in the developing world the incidence is lower [2]. The reported incidence in the UK is 52 cases per 100,00 head of population [2]. The incidence amongst African patients in South Africa was previously reported to be approximately 9 per 100,000 head of population. Walker and Segal [2] stated that appendicitis was rare amongst rural Africans in South Africa. According to them, in 1986 at Murchison Hospital, in southern KwaZulu-Natal (KZN), there were only seven cases of acute appendicitis out of 8,000 admissions and a potential population draining to the hospital of 200,000 people. At the same time, at Baragwanath Hospital in Soweto, a large urban conurbation, there were only 210 patients with appendicitis out of a total of 24,000 surgical admissions [16]. The population of Soweto at the time was estimated to be 2.5 million people. Walker and Segal [2] estimated a rate of 8.2 cases per 100,000 of population in the mid-1980s. By 1994, they estimated the rate of appendicitis in Soweto to be about 9.5 cases per 100,000. This was still one-tenth the rate in Sweden. A study from the Eastern Cape Province of South Africa in 2006 [17] estimated an incidence of 15 cases per 100,000. This is similar to our own estimate and would support the contention that the incidence amongst African patients is increasing. It is now believed that the change in diet of the population is well established and that we will begin to see a much more Western pattern of disease [8, 9].

Despite the relatively lower incidence of the disease in South Africa, there is a significant burden on hospitals that deal with the pathology. In Frere Hospital [17] in East London, there are a total of 17 cases of acute appendicitis a month. The average at our institution is also 17 a month. The reported average number of cases a month from KEVIII hospital in Durban [7] was lower at slightly over 10 a month. However, that study was a retrospective review over 5 years and was undertaken more than a decade ago.

Although appendicitis in Africa has a lower incidence than in the developed world, it generally has a far more serious clinical course [15, 18, 19]. The vast majority of patients in this audit waited at least 72 h before seeking any form of medical attention. In an earlier retrospective series from Durban [20], the average delay in presentation was 3.6 ± 5.6 days. This was similar to the audit from East London [17], which also demonstrated long delays. In the developed world the average duration of symptoms prior to presentation to the emergency department is 15 h or less [21]. The reasons for late presentation in our setting are multifactorial and include cultural factors as well as difficulty in accessing health-care services. Our study has also demonstrated a perforation rate of 54 %. Other South African audits report similar rates ranging from 43 to 51 % [3, 7, 17, 20]. Table 1 provides the comparative South African data. Table 2 is adapted from Rogers et al. [17] and shows the equivalent data from the developed world [22–26]. The perforation rate in the developed world is less than half of that in South Africa.

It was thought that the risk of perforation was relatively low during the first 36 h following the onset of symptoms [27] but increased dramatically by 5 % for each 12-h period thereafter [28]. The early administration of

Table 1 The sub-Saharan African experience with acute appendicitis (adapted from [17])

City/Country	Year	Perforation rate (%)	Normal appendicectomy rate (%)	No. per month
Kumasi, Ghana [18]	1996	39	26	NA
Johannesburg [3]	1997	22	21	NA
Durban (KEVIII) [7]	1998	43	9	10
Durban (PMH) [20]	2009	34	17	15
East London [17]	2009	51	21	17
Pietermaritzburg	2012	57	10	17

Table 2 The developed world's experience with acute appendicitis (adapted from [17])

City/Country	Year	Perforation rate (%)	Normal appendicectomy rate (%)
Reading, UK [24]	1993	18	15
Calgary, Canada [26]	1995	16	14
Los Angeles, USA [25]	1997	28	9
Washington, USA [23]	1997	21	13
Wellington, NZ [22]	2006	14	21

intravenous fluid and antibiotic therapy may in select cases avert the need for surgical intervention. It has been shown that children in hospital where operation was deferred for up to 12 h had no increase in adverse outcomes [29]. A similar study from the US demonstrated that in-hospital deferral of appendicectomy between 12 and 24 h after presentation does not significantly affect the clinical outcome [30]. However, other authors have shown that the incidence of perforation may start increasing significantly at even less than 12 h following the onset of symptoms [31]. Generally, most clinicians would be guided by their clinical findings. Early uncomplicated appendicitis may well benefit from a 12–24-h period of medical therapy and repeated observation [32]. Clinical deterioration would prompt surgery but an improvement may allow for successful nonoperative therapy [33]. However, these data cannot easily be extrapolated to our environment. Our patient cohort experienced a cumulative delay far longer than any described in the literature from the developing world, and it is doubtful whether the algorithms from the developed world can be applied to our situation.

Only a small proportion of our patients presented with the classic migratory abdominal pain. The most common symptoms encountered were all nonspecific, with generalised peritonitis frequently present. These findings were similar to those previously reported from Durban [7, 20]. The nonspecific nature of these symptoms has implications for the clinical assessment of African patients. The negative appendicectomy rate of 10 % in our study was comparable to that of other studies from South Africa, as was the incidence of pathology other than appendicitis as a cause for abdominal pain. The majority of these cases were females who had peritonitis associated with severe pelvic inflammatory disease, which were difficult to differentiate from complicated appendicitis. Female patients between the ages of 13–40 tend to have the highest diagnostic error rate [34]. Gynaecological assessment and the appropriate use of imaging may help to define the pathology better and avoid unnecessary surgery. The high incidence of infective diseases such as abdominal tuberculosis, worm infestation, amoebiasis, schistosomiasis, and typhoid that present with nonspecific abdominal pain makes it difficult to establish a firm clinical diagnosis of acute appendicitis. The differential diagnosis of abdominal pain in our environment is much broader than in the developed world [35]. In two patients in our series there was a small bowel perforation due to tuberculosis and one of uncertain aetiology, possibly either tuberculosis or trauma. In some cases of abdominal tuberculosis, operative intervention is unnecessary or even contraindicated, making it even more important to make the distinction [35].

Although Madiba et al. [7] did not feel that delay was associated with perforation, our findings suggest the opposite. We found that long delay to definitive therapy is associated with perforation, which is in turn associated with the need for reoperation and for ICU admission. Four-quadrant soiling was associated with mortality. Patients with perforation had a significantly longer hospital stay than those without perforation.

Surgical access was predominantly via a midline laparotomy, whereas only 2 % of patients underwent laparoscopic appendicectomy. Table 3 summarizes the South African data. The use of midline laparotomy reflects the fact that these patients presented with established diffuse peritonitis. Temporary abdominal containment (TAC) is seldom required in series from the developed world. However, in our experience TAC was necessary in just under one third of our patients. We find that the use of a plastic fluid bag sutured to the skin is the most reliable method of TAC as the bowel is often grossly distended [36]. The sutureless approach of the so-called "Opsite sandwich" preserves the skin edges but cannot contain the grossly distended bowel and needs to be replaced within 48 h. All of the patients in the TAC group were subjected to planned repeat operation. Of the group that underwent primary abdominal closure, 6 % required one or more unplanned repeat operations, which tends to support our aggressive approach with planned repeat operation. However, evidence supporting planned repeat operation or "on-demand" repeat operation remains conflicting. A previous meta-analysis [37] suggested a reduction in mortality in the on-demand laparotomy group, but a recent meta-analysis [38] demonstrated no difference in mortality. The only difference appeared to be related only to the reduced

Table 3 Comparative data for surgical access in South Africa

Study	Year	Lanz	Laparotomy	Laparoscopy
KEVIII [7]	1998	NA	NA	NA
Frere [17]	2006	82 %	18 %	Nil
PMH [20]	2009	NA	47 %	Nil
Edendale	2012	36 %	60 %	2.7 %

Table 4 Comparative data between the US Department of Defense [23] and the current study

Comparative data	US Department of Defense	Edendale
Year	1997	2010–2011
Patients	4950	200
Centres	197	1
Number per centre per year	25	200
Mortality	0.08 %	2 %
ICU	NA	11 %
Reoperation rate	27(0.5 %)	29 %
Temporary abdominal containment	NA	30 %

number of relaparotomies required and the associated health-care cost.

Our approach to the management of abdominal sepsis can be summarised by the adage that we have a low threshold for surgical re-exploration. We tend to invert the thinking process surrounding this decision by saying that the patient needs to earn the right not to have a repeat operation rather than earn the right to have one. Four-quadrant soiling, extensive faecal soiling, ischaemic bowel, and TAC remain our major indications for planned repeat operation. In all other patients we would be prepared to observe the patient and have a low threshold for a return to theatre. TAC, reoperation, and ICU admission must be considered major morbidity in the management of acute appendicitis. Table 4 compares our data with pooled data from the US Department of Defense [23] from a decade earlier. Reoperation, ICU admission, and the use of TAC is uncommon in the developed world and reflects the fact that our patients experience long delays in definitive treatment.

There is a growing realization that surgical care is an integral part of primary health care, and a variety of tools have been developed with the intention of improving surgical care in developing countries. Many of these tools measure inputs into the health-care system but do not measure outputs. There is a need to develop tools to monitor system outputs. Maternal and child health-care services use crude statistics to assess the quality of output of a system. Acute appendicitis is a disease that may allow for the development of a qualitative measure of output of a surgical system. It is a common disease that is treatable by a relatively straightforward surgical intervention and definitive treatment is curative. A number of outcomes of acute appendicitis may be useful as markers of quality of surgical care. These potential metrics include delay to definitive treatment, perforation rates, laparotomy rates, reoperation rates, ICU admission rates, and open abdomen rates. The routine collection of data on acute appendicitis may be a useful measure of the quality of surgical care across a rural health district.

Conclusion

The incidence of acute appendicitis amongst African patients seems to be increasing. Although it is still lower than the reported incidence amongst patients in the developed world, it is a common emergency that places a significant burden on the South African health-care service. The disease presents late and is associated with a high incidence of perforation which translates into significant morbidity and even mortality. Identifying and addressing the reasons for these long delays may help reduce the burden of preventable morbidity that is currently associated with acute appendicitis in South Africa. We suggest that the routine collection of basic data about acute appendicitis may well provide managers with a tool to measure the output of a surgical system.

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Chapter 3: The cost effectiveness of the early management of acute appendicitis underlies the importance of curative surgical services to a primary health care program

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The cost effectiveness of early management of acute appendicitis underlies the importance of curative surgical services to a primary healthcare programme

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ABSTRACT

INTRODUCTION Appendicitis in the developing world is a cause of significant preventable morbidity. This prospective study from a regional hospital in South Africa constructs a robust cost model that demonstrates the cost effectiveness of an efficient curative surgical service in a primary healthcare-orientated system.

METHODS A prospective audit of all patients with acute appendicitis admitted to Edendale Hospital was undertaken from September 2010 to September 2011. A microcosting approach was used to construct a cost model based on the estimated cost of operative and perioperative interventions together with the associated hospital stay. For cost analysis, patients were divided into the following cohorts: uncomplicated appendicitis, complicated appendicitis with localised intra-abdominal sepsis, complicated appendicitis with generalised intra-abdominal sepsis, with and without intensive care unit admission.

RESULTS Two hundred patients were operated on for acute appendicitis. Of these, 36% (71/200) had uncomplicated appendicitis and 57% (114/200) had perforation. Pathologies other than appendicitis were present in 8% (15/200) and these patients were excluded. Of the perforated appendices, 45% (51/114) had intra-abdominal contamination that was localised while 55% (63/114) generalised sepsis. The mean cost for each patient was: 6,578 ZAR (£566) for uncomplicated appendicitis; 14,791 ZAR (£1,272) for perforation with localised intra-abdominal sepsis and 34,773 ZAR (£2,990) for perforation with generalised intra-abdominal sepsis without intensive care admission. With intensive care admission it was 77,816 ZAR (£6,692). The total cost of managing acute appendicitis was 4,272,871 ZAR (£367,467). Almost 90% of this total cost was owing to advanced disease with abdominal sepsis and therefore potentially preventable.

CONCLUSIONS Early uncomplicated appendicitis treated appropriately carries little morbidity and is relatively inexpensive to treat. As the pathology progresses, the cost rises exponentially. An efficient curative surgical service must be regarded as a cost effective component of a primary healthcare orientated system.

KEYWORDS

Appendicitis – Complications – Cost – Model

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Previously, it was reported that acute appendicitis was relatively uncommon in Southern Africa. More recent studies have suggested that the incidence of the disease in the region is increasing.[1–5] These studies also suggest that in Southern Africa, acute appendicitis presents late and is associated with significant morbidity.[1] In Southern Africa, the reported perforation rate of acute appendicitis ranges from 22% to 54%.[1–5] This is much higher than that reported in the developed world, which ranges from 14% to 22%.[1–5] This translates into considerable morbidity due to abdominal sepsis, which places a major burden on already limited resources.[6] The primary healthcare approach that has been advocated in the developing world emphasises preventative strategies rather than curative services.[7–10] However, acute appendicitis is not amenable to primary preventative strategies. Secondary prevention aims at limiting the complications of the disease process, and this depends on early recognition and early surgery.[11]

Traditionally, the public health approach has not focused on surgical services, which have been perceived as expensive curative services that benefit individuals rather than communities.[12] Despite this, there is a growing realisation that basic curative surgical care is an integral part of a comprehensive and efficient primary healthcare system.[7–9,13] The provision of appropriate curative surgical services should be an extremely cost-effective healthcare interven-

Table 1 Cost formulas

Cost of operation	Cost per minute (108 ZAR) x time (mins) x number of patients
Cost of analgesia	Cost per day (50 ZAR) x number of days x number of patients
Cost of antibiotics	
Amoxicillin/clavulanic acid	100 ZAR per day x number of days x number of patients
Gentamicin	60 ZAR per day x number of days x number of patients
Piperacillin/tazobactam	650 ZAR per day x number of days x number of patients
Fluconazole	750 ZAR per day x number of days x number of patients
Cost of hospital stay	
Cost of ICU stay	8,000 ZAR per day x mean number of days x number of patients
Cost of ward stay	1,245 ZAR per day x mean number of days x number of patients
Cost of hospital stay (ICU cases)	Cost of ICU stay + cost of ward stay

ICU = intensive care unit

tion in the management of acute appendicitis.[7,10] It would limit the morbidity associated with the disease in the region currently.[7] There is a paucity of published research focusing on the cost of acute appendicitis in developing countries. Our study from a regional hospital in South Africa attempts to construct a robust cost model of acute appendicitis with the intention of demonstrating the cost effectiveness of early surgical intervention in this disease compared with the cost of managing delayed advanced disease.

Methods

From September 2010 to September 2011, a prospective audit of acute appendicitis was undertaken at Edendale Hospital in Pietermaritzburg, South Africa. Patients were divided into two broad groups for analysis: uncomplicated non-perforated acute appendicitis and complicated acute appendicitis. Furthermore, the complicated appendicitis cohort was subdivided into those patients in whom perforation was associated with localised intra-abdominal contamination and those in whom it was associated with generalised four-quadrant soiling. Patients requiring intensive care unit (ICU) admission were analysed separately.

Four cost drivers were considered: cost of operative time, cost of analgesia, cost of antimicrobials and cost of hospital stay. A cost formula was constructed for each individual cost driver. Costs of consumables (antibiotics and analgesia) were obtained from the pharmacy manager, and cost of operating room and ward costs were obtained from the hospital financial manager. The sum of each individual cost drives was used to generate a total cost. The individual cost formulas are depicted in Table 1. The total cost was calculated by summation of all the individual costs.

Results

A total of 200 patients (128 male [64%], 72 female [36%]) were operated on for suspected acute appendicitis. The mean age was 22.8 years (median: 19.5 years). Of this group, 15 patients (8%) had pathologies other than appendicitis. These were excluded from our costing. Macroscopic inflammation of the appendix without perforation was found in 36% (71/200) and perforation in 57% (114/200). Of the perforated appendices, 45% (51/114) were associated with localised intra-abdominal contamination and 55% (63/114) had generalised four-quadrant soiling. The patients were divided into four groups for analysis: macroscopic inflammation without perforation (n=71), perforation with local contamination (n=51), perforation with four-quadrant contamination not requiring ICU admission (n=43), and perforation and four-quadrant contamination requiring ICU admission (n=20).

Strict antibiotic guidelines are enforced at our institution and these were used as a basis for our cost estimations. Patients with an inflamed appendix receive 24 hours of amoxicillin/clavulanic acid, a total of 3 doses of 1.2g each. Patients with perforated appendicitis receive 5 days of amoxicillin/clavulanic acid (1.2g 3 times per day for 5 days) together with gentamicin (240mg once daily for 5 days). Patients with four-quadrant sepsis who do not respond to the above regimen are converted to extended spectrum antibiotics (piperacillin/tazobactam) and an antifungal agent (fluconazole).

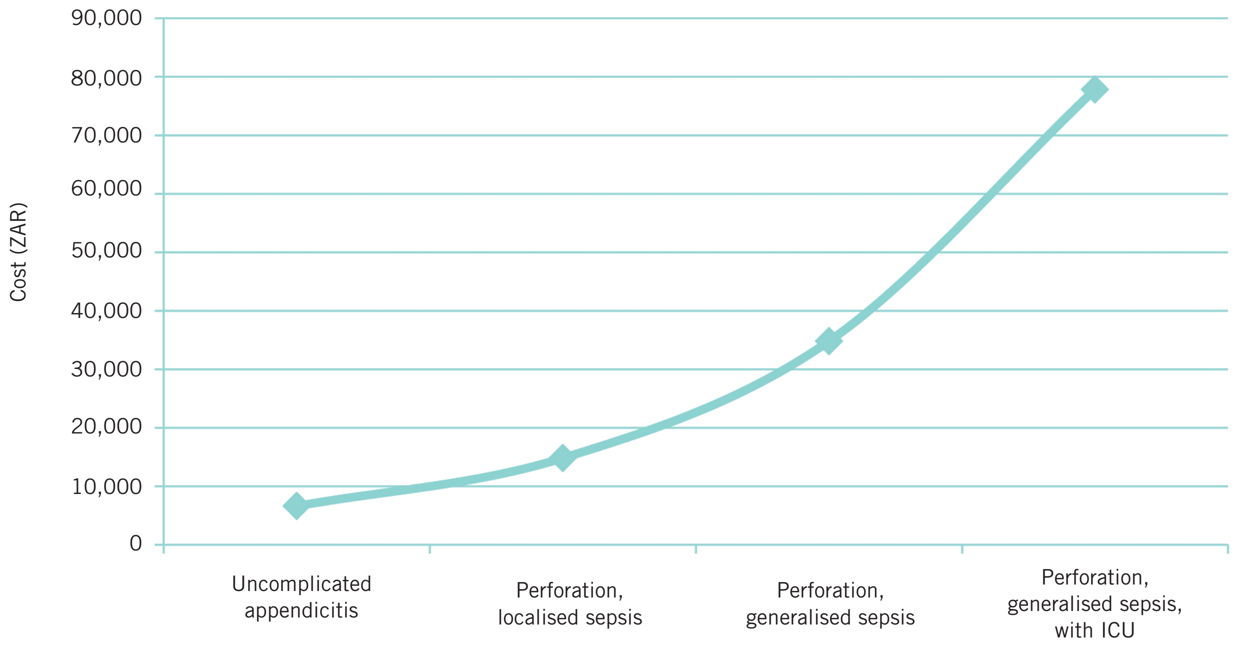
The cost of operating theatre time was 108 ZAR per minute. The cost of analgesia for an average patient was approximately 50 ZAR per day. For the uncomplicated group, the mean operating time was 30 minutes. All these patients received a mean of 24 hours of antibiotics and had a mean length of hospital stay of 2.5 days.

A total of 51 patients had perforation associated with localised intra-abdominal contamination. The mean operating time in this cohort was 60 minutes. All these patients received a mean of 5 days of antibiotics and the mean length of hospital stay was 5.8 days.

There were 63 patients with perforation associated with four-quadrant contamination. Twenty required ICU admission while forty-three were admitted to the general ward. The mean operating time required for each case was 90 minutes. Of the 43 patients who did not require ICU admission, the mean length of hospital stay was 9.5 days. In the cohort of 20 patients who required ICU admission, the mean length of stay in the ICU was 4.8 days. Following discharge from the ICU, the mean length of stay in the general ward was 12.9 days.

The total cost of antimicrobial therapy for the ICU was calculated based on the combination of agents used, with the mean duration of therapy derived from all patients in the group. The cost to stay in the ward was 1,245 ZAR per day and in the ICU it was 8,000 ZAR per day. The ICU daily cost included the use of the ventilator, oxygen therapy and sedation.

Table 2 summarises all the costs. The total cost for all 185 patients with acute appendicitis over the 12-month period was 4,272,871 ZAR. As severity of the illness increased, so costs increased exponentially (Fig 1).



ICU = intensive care unit; ZAR = South African rands

Figure 1 Cost per patient in South African rands for different patient cohorts

Table 2 Summary of costs

Cost driver	Uncomplicated appendicitis (*n*=71)	Perforation, localised sepsis (*n*=51)	Perforation, generalised sepsis (*n*=43)	Perforation, generalised sepsis, with ICU (*n*=20)	Total cost
Operating time	230,040	330,480	417,960	194,400	**1,172,880**
Analgesia	8,875	14,790	20,425	17,700	**61,790**
Antibiotics	7,100	40,800	548,250	255,000	**851,150**
Hospital stay	220,988	368,271	508,583	1,089,210	**2,187,051**
Total cost	**467,003**	**754,341**	**1,495,218**	**1,556,310**	**4,272,871**
Mean cost for each patient (ZAR)	**6,578**	**14,791**	**34,773**	**77,816**	
Mean cost for each patient (GBP)*	**566**	**1,272**	**2,990**	**6,692**	
Mean cost for each patient (USD)*	**908**	**2,041**	**4,799**	**10,739**	

*Based on yearly average exchange rate in 2011: 1 ZAR = 0.086 GBP

**Based on yearly average exchange rate in 2011: 1 ZAR = 0.138 USD

Discussion

Acute appendicitis represents a significant workload for the surgical services in our environment.[1,2,14,15] As in other developing countries, a multitude of factors (eg health-seeking behaviour, inadequate access to healthcare facilities, failure to recognise and refer acute appendicitis and logistical difficulties) conspire to cause delay, resulting in significant morbidity.[1,16–18] Preventable morbidity translates into significant consumption of already limited resources.[7–9]

While the primary prevention of acute appendicitis is not possible, the secondary prevention of morbidity is potentially achievable. Public health measures must focus on ensuring adequate access to facilities capable of recognising and treating acute appendicitis and early operative intervention.[19,20] It is important that secondary prevention of the complications of acute appendicitis is prioritised.

Accurate costing is important for administrators and policy makers.[21] The methods of estimating the direct cost of healthcare have traditionally been classified into two broad groups:[22–24] the bottom-up approach (microcosting) and the top-down approach (macrocosting). The bottom-up approach identifies and assesses the cost of each individual factor that contributes to the total cost to the healthcare system. The top-down approach uses global measures such as overall hospital stay to assign the total costs of a pathology to the healthcare system. This overall cost is then divided by the total number of patients treated to derive an estimate of average individual cost per patient. There are variations in the estimated cost using these different approaches.[25] In general, the bottom-up approach usually results in a higher but more accurate estimate.[26]

A study on the cost of orthopaedic trauma in KwaZulu Natal province compared the two methods and showed a difference of approximately 10%.[25] Other studies have demonstrated that the difference can be as high as 20%.[27] The bottom-up approach is more accurate because it allocates costs based on the actual consumption of specific resources, especially those relating to administrative and other services that support patient care. These represent a significant proportion of total direct costs.[27] In general, three types of costs need to be considered: direct costs, which include hospitalisation costs, physicians costs and medication costs; indirect costs, which are those borne by the patient (eg as time off work, time of travel and productivity losses); and opportunity costs.[28,29] An opportunity cost is the cost incurred because a limited resource is being used to treat a preventable pathology.[30,31] This resource cannot therefore be used to treat another deserving pathology.

Our study confined itself to assessing the direct costs of acute appendicitis and demonstrated that the total direct cost to the service was over four million ZAR. For a patient presenting with uncomplicated appendicitis, the total direct cost was 6,578 ZAR. In other words, for less than £600 the disease is cured, morbidity is negligible and the patients (who are usually young) experience minimal disruption and loss of income.[12]

Once the patient develops a perforation associated with localised intra-abdominal contamination, the direct cost doubles to 14,791 ZAR. Perforation with four-quadrant contamination that does not require ICU support sees a further doubling of direct costs to 34,773 ZAR. Once ICU support is required, the direct cost doubles again to 77,816 ZAR. This is over ten times that of an uncomplicated case. The treatment of advanced and complicated acute appendicitis accounted for 90% of the total expenditure. This implies that earlier recognition and treatment would have resulted in significant savings.

What was not considered in this study was the opportunity costs incurred in treating advanced disease, and the indirect costs borne by the patient and society in terms of lost economic activity. Consuming operating time and ICU resources for this preventable disease means that these resources cannot be used for the treatment of other pathologies. This costing is important as it shows the centrality of providing appropriate curative surgical services to a developing world health system. If secondary prevention fails, costs and morbidity rise exponentially.

Failure of secondary prevention of the complications of acute appendicitis results in major preventable cost and morbidity. In order to reduce cost and morbidity, the efforts of public health planners must be directed towards the secondary prevention of advanced abdominal sepsis. This involves a multifaceted approach that includes patient education programmes as well as efforts to increase access to healthcare facilities in rural areas and to improve the capacity of primary healthcare facilities in recognising acute appendicitis and to refer accordingly. There must be an improvement in the logistics to transfer these patients to surgical facilities.

An efficient and robust healthcare system is of the utmost importance if savings are to be achieved and morbidity is to be avoided. This costing provides convincing evidence to support the contention that efficient surgical services are a vital component of an integrated, comprehensive and cost-effective developing world healthcare service. Neglected benign surgical disease results in preventable morbidity as well as dramatically increased direct costs and opportunity costs.

Conclusions

Acute appendicitis is a common surgical pathology in our environment. If treated appropriately, early uncomplicated appendicitis has little morbidity and is relatively inexpensive to treat. As the pathology progresses from localised perforation to generalised perforation with sepsis, the cost of treating the disease rises exponentially. Improvements in so-called secondary prevention of this disease process will reduce morbidity and provide major cost savings. This study shows the importance and potential cost effectiveness of appropriate surgical services in a primary healthcare system. Without appropriate efficient surgical services, actual costs and preventable morbidity from this common disease escalate exponentially.

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Part TWO: Understanding the reasons behind adverse clinical outcome

In light of the findings from Part One, it is clear that acute appendicitis at our institution is a severe disease that cannot be considered equivalent to that described in the developed world. It is a serious disease associated with high rate of perforation, major morbidity and even mortality. It is also expensive to treat, and this contributes to a substantial financial burden on our already under-resourced healthcare system.

If patients manage to reach definitive surgical care at an early stage of the disease, it is logical then that associated morbidity, and, hence, the cost of treatment will be substantially reduced. Geographical variation is well known to play a major role in contributing to difference in clinical outcome of surgical patients across the world. South Africa remains a developing country that has a large, economically deprived rural population. Our institution covers a vast area in the western part of the province with large rural population, as well as the urban districts surrounding the city of Pietermaritzburg. We sought to identify if there was any noteworthy difference in clinical outcomes for those from rural and urban areas in our catchment population. Continuing from the initial cohort, a total of 500 prospective cases were collected and included in this part of the study. There were 200 patients from the rural areas and 300 from the urban areas.

We identified that rural origin is the most significant independent risk factor for poor clinical outcome for all patients with acute appendicitis. This is in keeping with the findings of international literature, and partly it reflects the accessibility of a surgical service within a healthcare system. The rural patient's journey from onset of illness through to definitive surgery was substantially longer than an urban patient's journey with identical illness. Rural patients fared substantially worse than their urban counterparts in every aspect of clinical outcome; clinical presentations were much more severe, perforation rates significantly higher, and these patients were associated with more frequent complications and the need for intensive care support. The mortality rate of patients from rural areas was over 10 times that of urban patients.

Having identified a considerable discrepancy in outcome for rural patients, we set out to identify the possible contributing factors that may be involved. The narrative of these patients' journeys from onset of illness to definitive surgery was sought. The two most important domains contributing to late presentation were pre-hospital delay and a further in-hospital delay. By and large, pre-hospital delay reflects heath seeking behaviour, in that patients seldom seek medical attention until the disease is advanced. This is most likely related to complex sociological dimensions encompassing issues such as gender, culture, beliefs, and education etc. Of significant concern was the further in-hospital delay in referral for definitive surgical management. A sizeable proportion of patients who made contact with the healthcare system (whether early or late) were either inappropriately discharged home initially, or admitted inappropriately to rural hospitals. This failure of recognition of the disease contributed to further delay to definitive surgery and, ultimately, worse clinical outcome.

Chapter 4: Quantifying the disparity in outcome between urban and rural patients with acute appendicitis in South Africa

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Quantifying the disparity in outcome between urban and rural patients with acute appendicitis in South Africa

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Background. Acute appendicitis in South Africa is associated with higher morbidity than in the developed world.
Objective. To compare outcomes of urban and rural patients in KwaZulu-Natal and to determine whether there are disparities in outcome.
Methods. We conducted a prospective study from September 2010 to September 2012 at Edendale Hospital in Pietermaritzburg, South Africa. All patients who presented with acute appendicitis were included. The operative and clinical course of urban and rural patients was compared.
Results. A total of 500 patients were included, with 200 patients in the rural group and 300 in the urban group. Those from the rural group had a significantly longer duration of symptoms prior to presentation. All septic parameters were significantly worse in the rural group. Significantly more patients from the rural group required a laparotomy (77% v. 51% urban; $p<0.001$). Inflamed, non-perforated appendicitis was more commonly seen in the urban group (52.3% v. 21% rural; $p<0.001$), while perforated appendicitis was much more common in the rural group (79% v. 47.7% urban; $p<0.001$). Perforation associated with generalised, four-quadrant intra-abdominal contamination was significantly higher in the rural group than the urban group (60.5% v. 21%, respectively; $p<0.05$). Significantly more patients from the rural group required an open abdomen (46% v. 12% urban; $p<0.001$) and ≥1 re-laparotomies to control severe intra-abdominal sepsis (60.5% v. 23.3% urban; $p<0.001$).
Conclusion. We have identified rural origin as an independent indicator of poor outcome. Possible reasons may include difficulty in accessing the health system or delay in transfer to a regional hospital. These need to be investigated further.

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There are significant disparities in access to surgical care across countries in the world, as well as between regions within countries and between groups of patients.[1] These disparities in access to care often translate into differences in outcome.[2] We have previously published our experience with acute appendicitis in South Africa (SA) and have shown that there are significant delays in accessing care with an associated perforation rate of 54%.[3] This is in keeping with other SA audits, which report similar rates ranging from 43% to 51%.[4] The equivalent perforation rate in the developed world is less than half of that in SA.[3]

Objective

To determine whether disparities in outcome between SA and the developed world were reflected in both urban- and rural-based patients in SA.

Methods

We conducted a prospective study from September 2010 to September 2012 at Edendale Hospital in Pietermaritzburg, KwaZulu-Natal (KZN). Edendale Hospital drains 2 health districts, namely the rural Sisonke District and the urban uMgungundlovu District. Patients who presented from uMgungundlovu District were classified as urban-based patients. Those who presented from 1 of the 4 rural hospitals in Sisonke District were classified as rural-based patients. All patients who presented with a clinical diagnosis and intraoperative confirmation of acute appendicitis were included. Assessment of the diagnosis was made on purely clinical grounds; advance imaging was not utilised. All patients with an alternative intraoperative diagnosis were excluded. Basic demographic data were collected. Each patient was specifically asked about his/her health-seeking behaviour, including the duration of symptoms prior to contact with the healthcare system. Clinical symptoms, physical examination findings, baseline vital signs and results of laboratory tests were recorded. Details of operative findings were obtained from the operative records. The clinical course of each patient to discharge (or death) was followed. Admission to the intensive care unit (ICU), the need for 're-look' laparotomy, major complications and death were recorded. Patients in the rural-based group were then compared with the urban-based cohort.

Ethics approval was obtained from the uMgungundlovu Health Review Board.

Statistical analysis

The Pearson χ^2 test was used when the sample size assumption was adhered to. Fischer's exact test was utilised in cases where the χ^2 assumption was not fulfilled and Mann-Whitney *U* tests were performed to identify any significant difference between the 2 patient cohorts after the data distributions were proved to be asymmetrical. Non-parametric (asymmetrical) data were described in terms of median and interquartile range (IQR). Statistical significance was considered when $p<0.05$. All statistical analysis was performed using SPSS version 19.

Results

During the study period, a total of 500 patients presented with acute appendicitis. There were 200 patients in the rural and 300 in the urban cohorts. Results are summarised in Table 1.

Basic demographics

The mean age of patients in the rural v. urban groups was not statistically significantly different (18 v. 19 years, respectively; $p=0.8$). Of the 200 patients in the rural group, males comprised 57% (114/200) and females 43% (86/200). Of the 300 urban patients, there were more males 73% (202/300) and fewer females 33% (98/300) (rural v. urban for both males and females, $p=0.02$).

Clinical presentations

Rural-based patients had a significantly longer duration of symptoms with a median of 6 days (IQR 3 - 9) prior to presentation when compared with the median duration of 3 days in urban patients (IQR 2 - 4; rural v. urban; $p<0.001$). Comparison of clinical features present on admission was as follows (rural v. urban patients, respectively): anorexia 70.5% v. 69%; nausea and vomiting 80.5% v. 79%; migratory abdominal pain 28% v. 32.3%; non-migratory abdominal pain 71.5% v. 67.7%; dysuria 2% v. 3.3%; diarrhoea 4.5% v. 8.8%; and constipation 7% v. 5.3%. Differences were not statistically significant. However, significantly more patients in the rural group had generalised peritonitis on presentation (59%, 118/200 v. 20%, 60/300 urban; $p<0.001$); significantly more patients in the urban group had localised peritonitis (80%, 240/300 v. 41%, 82/200 rural; $p<0.001$). Other clinical parameters (rural v. urban, respectively) including the median temperature (37.9°C, IQR 37 - 38.4 v. 37.2°C, IQR 36.9 - 38; $p<0.001$), heart rate (103 bpm, IQR 90.5 - 120 v. 99 bpm, IQR 88 - 109; $p<0.001$) and total leukocyte counts (15.6 x 10^9/l, IQR 12 - 20 v. 13.9 x 10^9/l, IQR 11 - 15.5; $p<0.001$) were significantly higher in the rural group.

Operative findings

Significantly more patients from the rural group required a laparotomy (77% v. 51% urban; $p<0.001$) as the initial choice of surgical access, while relatively more patients from the urban group required a local incision (49% v. 23% rural; $p<0.001$). Highly significant differences were found at operation. An inflamed, non-perforated appendix was more commonly found intraoperatively in the urban group (52.3% v. 21% rural; $p<0.001$). A perforated appendix was much more common in the rural group (79% v. 47.7% urban; $p<0.001$). Of those patients in whom the appendix had perforated, intra-abdominal contamination was more frequently localised in the urban group (26.7% v. 18.5% rural; $p=0.04$), in contrast to the rural group where significantly higher perforation (60.5% v. 21% urban; $p<0.001$) associated with generalised, four-quadrant intra-abdominal contamination was observed.

Clinical course

The majority of patients in the urban group were managed in the general ward (97.7% v. 77% rural; $p<0.001$). The need for ICU admission was 10 times higher in the rural group (23% v. 2.3% urban; $p<0.001$). The median overall length of hospital stay was also significantly longer in the rural group (8 days, IQR 3 - 15 v. 4 days, IQR 2 - 7 urban; $p<0.001$). Significantly more patients in the rural group required an open abdomen (46% v. 12% urban; $p<0.001$) and required ≥1 re-laparotomies to control severe intra-abdominal sepsis (60.5% v. 23.3% urban; $p<0.001$).

Complications

The overall complication rate was significantly higher in the rural group (35% v. 11% urban; $p<0.001$). Considered separately, each of the following was significantly higher in the rural group (rural v. urban, respectively): hospital-acquired pneumonia (21.5% v. 5%; $p<0.001$), renal failure (14% v. 0.7%; $p<0.001$), wound sepsis (22.5% v. 6.7%; $p<0.001$) and other miscellaneous conditions (5.5% v. 0.3%; $p<0.001$). The overall mortality was significantly higher among rural-based patients than urban-based patients (3.5% v. 0.3%, respectively; $p=0.008$).

Table 1. Outcomes of rural v. urban patients with acute appendicitis in South Africa

Characteristics	Rural (*N*=200)	Urban (*N*=300)	*p*-value
Demographics			
Male, *n* (%)	114 (57)	202 (67.3)	0.02
Female, *n* (%)	86 (43)	98 (32.7)	0.02
Age (years), median (range)	18 (12 - 29)	19 (13 - 27)	0.8
Duration (days), median (range)	6 (3 - 9)	3 (2 - 4)	<0.001
Clinical features, *n* (%)			
Anorexia	141 (70.5)	207 (69)	0.72
Nausea, vomiting	161 (80.5)	237 (79)	0.68
Migratory pain	56 (28)	97 (32.3)	0.3
Non-migratory pain	143 (71.5)	203 (67.7)	0.36
Dysuria	4 (2)	10 (3.3)	0.38
Diarrhoea	9 (4.5)	24 (8)	0.12
Constipation	14 (7)	16 (5.3)	0.44
Localised peritonitis	82 (41)	240 (80)	<0.001
Generalised peritonitis	118 (59)	60 (20)	<0.001
Baseline vital signs, mean (range)			
Temperature (^{o}C)	37.9 (37 - 38.4)	37.2 (36.9 - 38)	<0.001
Heart rate (bpm)	103 (91 - 120)	99 (88 - 109)	<0.001
Leukocyte count ($\times 10^9$)	15.6 (12 - 20)	13.9 (11 - 15.5)	<0.001
Surgical access, *n* (%)			
Local incision	46 (23)	147 (49)	<0.001
Laparotomy	154 (77)	153 (51)	<0.001
Operative findings, *n* (%)			
Inflamed appendix	42 (21)	157 (52.3)	<0.001
Perforated appendix	158 (79)	143 (47.7)	<0.001
Localised contamination	37 (18.5)	80 (26.7)	0.04
Generalised contamination	121 (60.5)	63 (21)	<0.001
Clinical course			
Ward admission, *n* (%)	154 (77)	293 (97.7)	<0.001
ICU admission, *n* (%)	46 (23)	7 (2.3)	<0.001
Total hospital stay (days), mean (range)	8 (3 - 13)	4 (2 - 7)	<0.001
Open abdomen, *n* (%)	92 (46)	36 (12)	<0.001
Re-laparotomy, *n* (%)	121 (60.5)	70 (23.3)	<0.001
Complications, *n* (%)			
Pneumonia	43 (21.5)	15 (5)	<0.001
Renal failure	28 (14)	2 (0.7)	<0.001
Wound sepsis	45 (22.5)	20 (6.7)	<0.001
Other	11 (5.5)	1 (0.3)	<0.001
Death	7 (3.5)	1 (0.3)	0.008

ICU = intensive care unit.

Discussion

Acute appendicitis is the most common surgical emergency worldwide. The natural history of appendicitis is one of progression from inflammation to perforation and on to diffuse abdominal sepsis.[5]

With early recognition and appropriate surgery, it is typically associated with low morbidity and negligible mortality.[6] However, it is a disease that is associated with disparate outcomes. Several studies from SA have reported much higher rates of appendicular rupture, and subsequently much more problematic clinical outcomes than in the developed world.[3,4] Generally, costs and length of hospital stay are all significantly longer in patients who experience appendicular rupture.[7] Appendicular rupture is associated with the need for re-laparotomy, temporary abdominal closure and ICU admission.[3] Our previous work demonstrated a significant disparity in outcome between patients in SA and those in the developed world.[3] Our current study extends this insight by demonstrating a disparity in outcome between urban- and rural-based patients within SA. Rural patients had a much longer delay between the onset of symptoms and seeking healthcare than urban patients. Consequently, when they did arrive at the regional hospital they were more ill and more likely to have diffuse peritonitis. In turn, they were more likely to require a laparotomy and ICU admission postoperatively. Rural patients were disproportionately more likely to be managed with temporary abdominal closure and re-laparotomy. They were more likely to develop acute renal failure.

Acute appendicitis is a time-sensitive pathology.[5] Once the disease process commences, progression to end-stage disease is relentless unless there is appropriate surgical intervention.[7] A number of mile-stones in each patient's narrative are important, including the onset of abdominal pain, parental or patient recognition of the potential urgency of the illness and timely health-seeking behaviour followed by clinical recognition of potential acute appendicitis, appropriate referral and surgical intervention. Variations in these milestones account for the disparate outcomes. SA reports on appendicitis have almost exclusively focused on black patients.[3] However, within the developed world, there are disparities in the outcome of acute appendicitis. Studies from the USA have demonstrated several associations between increased rates of appendicular rupture and variables such as method of payment, access to primary care, source of referral and ethnicity.[8,9] Higher rupture rates have been reported in ethnic minority children, younger children, children with addresses from socioeconomically poorer ZIP codes, children who lack private insurance and children referred from somewhere other than a dedicated emergency department.[10] In our study cohorts, rural patients fared significantly worse than their urban counterparts. Both groups were black, thus eliminating issues of ethnicity or cultural practices as an explanation for disparate outcomes. Rural origin of the patient emerges as an independent risk factor for appendicular rupture. The most striking underlying difference between the urban- and rural-based groups is the prolonged delay between onset of symptoms and accessing the healthcare system on the part of the latter. The risk of appendicular perforation and subsequent complications is proportional to the time between onset of symptoms and surgical intervention.

The rural communities in SA remain some of the most impoverished areas in the world.[11] However, poor health outcome in rural areas is not solely confined to SA. A significant body of literature demonstrates disparity in outcomes between urban and rural patients in developed countries with sizable rural populations such as Australia, Canada and the USA.[12] Reasons for this disparity are multifaceted. There are several common problems faced by rural areas throughout the world. They are plagued with chronic understaffing of hospitals and high staff turnover and lack specialist and radiological imaging and laboratory services. The remoteness of rural areas means that there are long delays in accessing healthcare and further delays may be associated with the transfer of these patients to higher levels.[13] Moreover, there is a shortage of basic general surgical services for rural communities throughout the world.[14]

Patients from the rural areas remote from surgical centres may experience difficulties in accessing appropriate services.[15] These difficulties are referred to as 'barriers to care' and authors have suggested various systems to classify these.[16] The classification scheme described by Grimes *et al.*[16] defines 3 categories: cultural (acceptability), financial (affordability) and structural (accessibility). For pragmatic and quality-improvement reasons it is useful to divide barriers to care into pre-contact (with the health system) and post-contact factors. Pre-contact factors include health-seeking behaviour, cultural factors and issues of access and affordability, while post-contact factors include delays in the recognition of the disease and delays in transfer and referral.

Health-seeking behaviour is influenced by gender, education and socioeconomic status.[17] Patients may expect spontaneous resolution of symptoms and hence delay seeking healthcare.[18] Although access to primary care is free, the perceived potential for hospital admission and subsequent loss of ability to work or missed school days potentially prevented many patients from seeking medical attention. Children may experience further delays due to lack of responsible carers.[17] KZN Province covers a vast area and has a large rural population. Within the rural Sisonke District and the urban uMgungundlovu District covered by our surgical unit, there are series of local polyclinics and 4 peripheral hospitals serving the local population. There are still significant problems with access to the local polyclinics, as substantial travelling is usually required.

Of concern is the issue of delayed recognition of the disease once the patient has presented to the health system. Rural facilities in Sisonke District have staff of varied levels of experience.[19] Almost no abdominal general surgery[20] is undertaken at these rural district hospitals; all patients with acute appendicitis are referred to the regional hospital for further assessment, thus creating two further potential delays – in diagnosis/recognition (it is not uncommon for patients to be sent home from a healthcare institution on several occasions with an incorrect diagnosis (authors' personal observations)) and in transportation from a district to a regional hospital for surgery.

Conclusion

This survey identifies rural origin as an independent risk factor for appendicular rupture and a poor clinical course. Rural patients have major delays between the onset of symptoms and definitive surgery compared with urban patients. The exact reasons for these delays require further investigation. Health-seeking behaviour is complex and is influenced by rural poverty and remoteness as well as cultural issues such as the reliance on traditional healers as a primary source of care and health advice.

However, failure of clinical recognition once contact with the health system has been made followed by delays in transfer for surgery to the regional hospital are failings of the health system. Intervention is urgently needed to improve the outcomes of acute appendicitis among rural patients, following further research aimed at quantifying the relative contributions of patient behaviour and the failings of the health system.

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Chapter 5: Understanding the reasons for delay to definitive surgical care of patients with acute appendicitis in rural South Africa

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Understanding the reasons for delay to definitive surgical care of patients with acute appendicitis in rural South Africa

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Background. Acute appendicitis in rural South Africa is associated with significant morbidity due to prolonged delays before definitive surgical care.
Objective. This audit aimed to quantify the delay in our healthcare system.
Methods. From September 2010 to September 2012, all patients with confirmed acute appendicitis were interviewed and asked about the onset of symptoms and subsequent events in the disease process. Events before and after contact with the healthcare system were referred to as the pre-hospital or behavioural domain and the in-hospital or assessment domain, respectively.
Results. Of the 500 patients, 350 (70.0%) experienced a delay of >48 hours from onset of symptoms to definitive surgical care. The mean time before treatment for this group was 5 days (range 3 - 7), while the mean for the group without delay was 1.6 days (range 1 - 2) ($p<0.0001$). Of 463 delays, 291 were in the behavioural domain and 172 in the assessment domain; 178 patients (50.9%) experienced delay in the behavioural domain only, 59 (16.9%) in the assessment domain only, and 113 (32.2%) in both domains. The mean ambulance transport time from the district hospital to the regional hospital was 4.9 hours.
Conclusion. There are barriers that prevent patients with acute appendicitis from accessing care. There are also prolonged delays within the system once care has been accessed. Both these sources of delay need to be addressed by quality improvement programmes.

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Acute appendicitis in South Africa is associated with prolonged delays to definitive surgical care and significant morbidity due to intra-abdominal sepsis.[1-3] This is a directly causal relationship, as delayed source control has repeatedly been shown to be the variable most closely associated with poor outcomes from intra-abdominal sepsis.[4,5] Strategies and quality improvement interventions designed to reduce the morbidity associated with acute appendicitis must attempt to reduce delays to definitive care.[2] However, there is a paucity of research on the reasons for these delays. If the treatment of appendicitis is thought of as a process of care, there are a number of distinct areas or domains within the process where delay can be experienced.[6] There may be a significant delay between the onset of symptoms and the patient making contact with the healthcare system. Once the patient has made contact with the system, further delays can be experienced. These include delayed recognition of the need for surgical care and subsequent logistical delays in transferring the patient to the regional hospital. This audit quantifies the delay to definitive surgical care of acute appendicitis in our system and attempts to increase our understanding of where in the process of care the delay was experienced and the factors that contributed to delay in each area or domain. It is hoped that this information may allow for the development of targeted quality improvement programmes.

Methods

Ethics approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, and the Umgungundlovu Health Review Board. It was conducted from September 2010 to September 2012 at Edendale Hospital in Pietermaritzburg, South Africa. Edendale Hospital receives patients from the city of Pietermaritzburg and surrounding peri-urban settlements and is the regional hospital for the four rural hospitals in Sisonke district. None of the rural hospitals performs appendectomy. All patients with acute appendicitis confirmed at operation were eligible for inclusion. Basic demographic data were collected, and each patient was interviewed by the principal author and specifically asked about the onset of symptoms and subsequent events in their disease process. All events before the patient made contact with the healthcare system were referred to as the pre-hospital or behavioural domain, while events from making contact up to recognition of the need for definitive surgical care were referred to as the in-hospital or assessment domain. We asked the patients whether they had been sent home after making initial contact with the healthcare system. All such cases were classified as inappropriate discharges. Fig. 1 schematically demonstrates the timeline of the disease process. Detailed questioning was used to classify the reasons for any delay in the assessment domain, e.g. whether patients were discharged home, or admitted to hospital for inappropriate management. A significant delay was defined as >48 h from the onset of symptoms to definitive surgery.

Statistical analysis

Pearson's χ^2 test was used when the sample size assumption was adhered to, Fisher's exact test was used in cases where the χ^2 assumption was not fulfilled, and the Mann-Whitney *U* test was performed to identify any significant difference between the two groups after data distributions were proven to be asymmetrical. Non-parametric (asymmetrical) data were described in terms of a median and interquartile range (IQR Q1 - Q3). Statistical significance was set at $p<0.05$. All statistical analysis was performed using SPSS version 19.

Results

A total of 500 patients presented to our unit with acute appendicitis during the 2 years of the study. The mean age was 22 years (standard deviation (SD) ±6.1), and 316 (63.2%) were male and 184 (36.8%) female. Of all patients, 70% (350/500) experienced a delay of >48 h from onset of symptoms to definitive surgical care.

In the delay group, 64% were males (224/350) and 36% females (126/350), and the mean age was 22.4 years (range 12 - 29). The mean time from onset of symptoms to definitive surgical care for this group was 5 days (SD ±1.6), while the mean for the group without delay was 1.6 days (SD ±0.5) ($p<0.0001$). Table 1 summarises the demographics of these patients.

There were 463 delays in total, of which 291 were in the behavioural domain and 172 in the assessment domain; 178/350 patients (50.9%) experienced delay in the behavioural domain only, 59 (16.9%) in the assessment domain only, and 113 (32.2%) in both domains. The mean duration of illness from the onset of symptoms to first contact with the healthcare system in the behavioural domain group was 4.4 days (SD ±1.5). Tables 2 and 3 provide a summary of the above. Fig. 1 provides a narrative of the reasons for delay from onset of symptoms to definitive surgery.

Of the 172 patients with delay in the assessment domain, 71% (122/172) were inappropriately discharged from the hospital, and 29% (50/172) were admitted prior to referral for definitive surgical care. For the 122 who were inappropriately discharged, a mean of 2.5 days (SD ±1.0) elapsed between discharge and re-presentation at the hospital. For the 50 who were admitted to hospital for observation, the mean duration of stay prior to referral was 2.3 days (SD ±1.0). The mean ambulance transport time from the district hospital to the regional hospital was 4.9 h (SD ±2.1). Of the total of 500 patients, 49 (9.8%) had taken traditional medicine at some point during the course of the illness; of the 172 patients who experienced delay in the assessment domain, 20.4% (n=35) used traditional medicines, while the figure for the 328 without a delay in assessment was 4.3% (n=14) ($p<0.0001$).

Discussion

Acute appendicitis in South Africa is associated with significant morbidity due

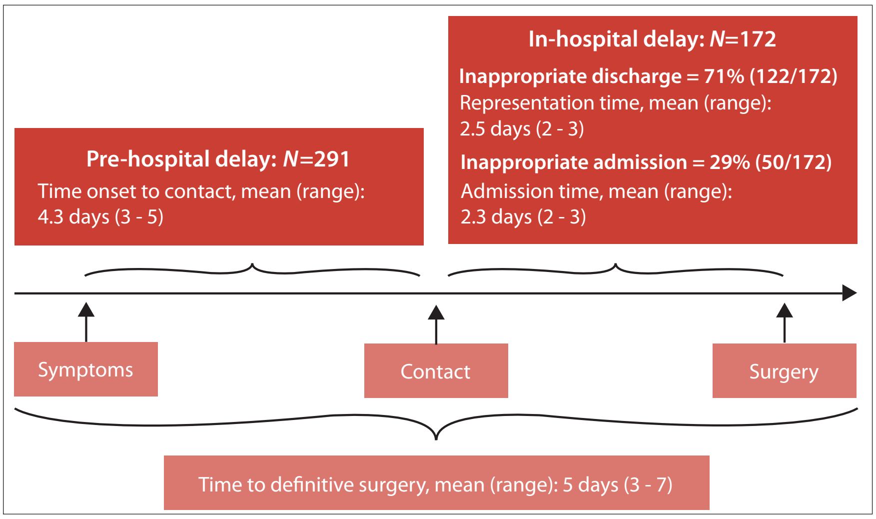

Fig. 1. Reasons for delay according to different domains.

Table 1. Basic demographics of the delay and non-delay groups

	Delay (*N*=350)	No delay (*N*=150)
Age (years), mean (±SD)	22.4 (±11.1)	21.3 (±13.2)
Males, *n* (%)	224 (64.0)	92 (61.3)
Females, *n* (%)	126 (36.0)	58 (38.7)
Duration (days), mean (±SD)	5 (±1.6)	1.6 (±0.5)

SD = standard deviation.

Table 2. Delay according to domain (*N*=350)

	n (%)
Behavioural domain	291 (83.1)
Assessment domain	172 (49.1)
Behavioural domain only	178 (50.9)
Assessment domain only	59 (16.9)
Combined delay	113 (32.3)

Table 3. Subgroups of patients with delay

	Behavioural domain only (*N*=178)	Assessment domain only (*N*=59)	Combined domains (*N*=113)
Age (years), mean (±SD)	18.6 (±8.9)	32 (±16.6)	23.2 (±14.3)
Males, *n* (%)	159 (88.8)	28 (47.5)	37 (32.7)
Females, *n* (%)	19 (10.7)	31 (52.5)	76 (67.3)
Time to surgery (days), mean (±SD)	4.4 (±1.5)	4.1 (±1.6)	6.4 (±0.9)
Delay time (days), mean (±SD)	2.4 (±1.5)	1.5 (±1.4)	4.1 (±0.9)

SD = standard deviation.

to intra-abdominal sepsis.[1] Intra-abdominal sepsis is a time-dependent condition, and delayed surgical source control is directly associated with adverse outcomes.[4,7] We demonstrated a significant delay from onset of symptoms to definitive care in our cohort. The reasons for this delay are almost certainly multifactorial. We broke down the process of care of acute appendicitis into two broad domains where delay may be experienced, and showed that each domain contributes to the overall delay to definitive care. This is a significant finding, because strategies and avenues of research to address deficits differ according to the domain in which the deficits occur.

The majority of patients in our series did not make contact with the healthcare system until long after the onset of abdominal symptoms. Making contact with the healthcare system is referred to as health-seeking behaviour and is influenced by a multitude of factors, such as gender inequalities, educational levels, awareness, inadequate infrastructure, endemic poverty and cultural factors.[8-10] Factors that deter health-seeking behaviour are collectively referred to as barriers to care and have been divided into cultural (acceptability), financial (affordability) and structural (accessibility) issues.[11] Dissecting out and understanding the barriers to care requires a nuanced methodology incorporating culturally appropriate qualitative techniques. It is doubtful that our methodology would be able to do this complex problem justice. We have, however, illustrated the point that there is a long delay between the onset of symptoms and seeking medical opinion. Further public health and sociological research is required to improve understanding of the reasons for late presentation following the onset of symptoms in our environment, and the barriers to care.

A significant number of the patients in our series sought advice from traditional healers, and this was directly associated with subsequent assessment failure. Developing a programme that integrates traditional healers into the healthcare system may be a potential intervention.[12] In Pietermaritzburg we run a course with local traditional healers, attempting to educate them on the warning signs of acute appendicitis and encouraging them to refer specific groups of patients to the healthcare system earlier.

Our findings indicate that patients with acute appendicitis are at risk for delayed diagnosis after they have made contact with the healthcare system. A significant number were discharged home inappropriately, and a further sub-group were admitted for excessive periods of observation. Acute appendicitis, although common, is a difficult clinical diagnosis, and the classic clinical features may only be present in a third of patients.[13] This is especially true among black Africans, many of whom present with nonspecific abdominal pain.[1,14] Female patients have a wider differential diagnosis, and gynaecological causes of abdominal pain and symptoms associated with pregnancy need to be excluded.[15] The situation is made still more complex by the high prevalence of infectious diseases, such as abdominal tuberculosis associated with HIV disease.[16] The relatively junior level of the staff at the rural hospitals in our drainage area exacerbates the clinical dilemma.[17] Addressing this deficit is complex and requires a multifaceted strategy that may include the use of educational initiatives, 'tick box'-type clerking sheets, and possible telemedicine support.

Conclusions

Patients with acute appendicitis experience significant delays between the onset of symptoms and definitive surgical treatment, resulting in major morbidity. The reasons for this situation are multifactorial and include barriers to healthcare, delays in assessment, and logistical problems with patient transfer. Understanding these reasons may help in developing targeted quality improvement interventions. There are delays associated with health-seeking behaviour and delays associated with failure of healthcare workers to recognise the need for surgery. Delay related to health-seeking behaviour is difficult to modify, and improvement initiatives must focus on improving access to care. Improving the diagnostic capability of healthcare workers in rural district hospitals must be addressed as a matter of urgency.

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Part THREE: Scoring systems to facilitate clinical decision making

In our locality, it is clear that acute appendicitis is a serious disease that continues to plague our under resourced healthcare system. Multiple factors act synergistically to contribute towards poor clinical outcomes for patients; rural origin is the major risk factor. Both pre-hospital and inter-hospital delays conspire together to contribute to late presentation and major morbidity. While the pre-hospital domain may be difficult to modify, interventions targeted at encouraging early referral to centres with surgical capacity may help to improve the situation. This relies on appropriately trained medical staff, particularly at rural hospitals, but levels of experience and training seen at these hospitals often varies considerably.

We were interested in the use of a simple tick box style triage tool incorporated into the initial assessment of patients to facilitate clinical decision making. The Alvarado score is the most widely scoring system aimed at assessing the clinical probability of patients with abdominal pain who are likely to have acute appendicitis. It is widely used in the developed world and current literature continues to support its use. In our locality however, HIV, abdominal tuberculosis and numerous other tropical diseases are common and can all present as abdominal pain causing further diagnostic difficulties. Furthermore, the applicability of the Alvarado Score to our local Black South African population is currently unknown.

Using our final cohort of 1000 cases with confirmed acute appendicitis, we retrospectively assigned the Alvarado Score and generated a clinical probability assessment of what the diagnosis would have been if this score was to be used as a front-line triage tool. We found that use of Alvarado score in our setting was much less accurate than those reported from literature in the developed world. Our greatest concern using this scoring system was that a high proportion of our patients who had the disease would have been assessed as having ‘low clinical probability’ of acute appendicitis, and, potentially, they would have been discharged home or managed inappropriately. At present, the use of the Alvarado score in our clinical setting is not recommended, and further prospective validation is urgently needed.

Acute appendicitis in our local setting remains a serious disease with grave outcomes from late presentation. The reality is that the early, aggressive management of complex intra-abdominal sepsis from acute appendicitis is the only way to ensure survival of these patients, wherever they come from. Surgical management frequently involves the use of temporary abdominal closure (TAC) and relaparotomy for source control. Two different approaches are available; either the 'on demand' approach, whereby relaparotomy is performed only in patients who continue to show signs of sepsis, or the 'mandatory' approach, whereby relaparotomy is planned at regular interval until sepsis subsides. The decision for the need for relaparotomy is often highly subjective, and there little guidance is provided in the literature to assist this decision making process, especially in the setting of acute appendicitis. This is a unique problem in our locality, because severe sepsis caused by acute appendicitis is rare in the developed world. As a result we pursued to develop a simple clinical scoring system in order to aid this decision making process.

Using our final cohort of 1000 cases, a mathematical model was constructed based on various pre-operative and intra-operative parameters. This was then simplified into a four item clinical score for use at the bedside. These parameters were: patient presentation from any rural centre within our catchment area, duration of illness of > 5 days, heart rate on presentation > 120 per minute and generalised intra-abdominal sepsis found intra-operatively. One point was assigned to each item. We have found that if any patient has all of the above four factors present, it accurately predicts that there is a 90% probability that a relaparotomy will be required. This has significant clinical implications because this means that these patients can be identified at the outset, and an early planned re-laparotomy for further source control can be instituted at an earlier stage without undue delay from indecisiveness or clinical uncertainty. It is hoped that this scoring system will improve outcomes for this unique group of patients. However, further research is needed to validate this model.

Chapter 6: The accuracy of Alvarado score in predicting acute appendicitis in the Black South African population needs to be validated

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The accuracy of the Alvarado score in predicting acute appendicitis in the black South African population needs to be validated

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Background: The Alvarado score is the most widely used clinical prediction tool to facilitate decision-making in patients with acute appendicitis, but it has not been validated in the black South African population, which has much wider differential diagnosis than developed world populations. We investigated the applicability of this score to our local population and sought to introduce a checklist for rural doctors to facilitate early referral.

Methods: We analyzed patients with proven appendicitis for the period January 2008 to December 2012. Alvarado scores were retrospectively assigned based on patients' admission charts. We generated a clinical probability score (1–4 = low, 5–6 = intermediate, 7–10 = high).

Results: We studied 1000 patients (54% male, median age 21 yr). Forty percent had inflamed, nonperforated appendices and 60% had perforated appendices. Alvarado scores were 1–4 in 20.9%, 5–6 in 35.7% and 7–10 in 43.4%, indicating low, intermediate and high clincial probability, respectively. In our subgroup analysis of 510 patients without generalized peritonitis, Alvarado scores were 1–4 in 5.5%, 5–6 in 18.1% and 7–10 in 76.4%, indicating low, intermediate and high clinical probability, respectively.

Conclusion: The widespread use of the Alvarado score has its merits, but its applicability in the black South African population is unclear, with a significant proportion of patients with the disease being potentially missed. Further prospective validation of the Alvarado score and possible modification is needed to increase its relevance in our setting.

Contexte : Le score d'Alvarado est l'outil de prédiction clinique le plus couramment utilisé pour faciliter la prise de décision chez les patients présentant une appendicite aiguë, mais il n'a pas été validé dans la population noire sud-africaine chez qui le diagnostic différentiel est beaucoup plus vaste que dans les populations des pays industrialisés. Nous avons exploré l'applicabilité de ce score à notre population locale et tenté de présenter une liste de vérification aux médecins ruraux pour accélérer les demandes de consultation.

Méthodes : Nous avons analysé les dossiers de patients atteints d'une appendicite avérée pendant la période allant de janvier 2008 à décembre 2012. Les scores d'Alvarado ont été assignés rétrospectivement selon les dossiers d'admission des patients. Nous avons généré un score de probabilité clinique (1–4 = faible, 5–6 = intermédiaire, 7–10 = élevé).

Résultats : Nous avons ainsi étudié 1000 patients (54 % de sexe masculin, âge médian 21 ans). Quarante pour cent présentaient des appendices enflammés non perforés et 60 % des appendices perforés. Les scores d'Alvarado se situaient à 1–4 chez 20,9 %, à 5–6 chez 35,7 % et à 7–10 chez 43,4 %, correspondant à une probabilité clinique faible, intermédiaire et élevée, respectivement. Dans notre analyse de sous-groupes sur 510 patients indemnes de péritonite généralisée, les scores d'Alvarado se situaient à 1–4 chez 5,5 %, à 5–6 chez 18,1 % et à 7–10 chez 76,4 %, correspondant à une probabilité clinique faible, intermédiaire et élevée, respectivement.

Conclusion : L'utilisation répandue du score d'Alvarado a ses mérites, mais son applicabilité dans la population noire d'Afrique du Sud est indéterminée, la maladie risquant de passer inaperçue chez une proportion significative de patients. Il faudra procéder à une validation prospective plus approfondie du score d'Alvarado et le modifier peut-être si l'on veut en accroître la pertinence dans notre contexte.

It is increasingly accepted that the omission of surgical care from the Millennium Development Goals was a serious oversight, and over the last decade there has been an increased awareness of the important role that surgery plays in global health.[1,2] Disparities in access to surgical care result in major discrepancies in the outcomes of patients with common surgical conditions, and our group has studied the outcomes of acute appendicitis in our setting.[3–5] We have demonstrated that acute appendicitis in rural South Africa has a very different disease profile to that seen in the developed world.[3] It is associated with prolonged delays to definitive surgical care and significant morbidity due to intra-abdominal sepsis.[4,5] We proceeded to investigate the reasons behind these lengthy delays in presentation and identified rural origin as an independent risk factor for poor outcome from this disease.[5] It would appear that rural patients in South Africa experience delays before presenting to district hospitals, and once they have presented to these district facilities they experience further delays owing to failure of staff to diagnose the condition and refer them through to regional centres with surgical capacity.[5] There is a causal relationship between delay to definitive surgery and poor outcome in the management of acute appendicitis, and strategies to reduce these delays are urgently required.[6]

One of the suggested strategies aimed at facilitating the diagnosis of acute appendicitis is the introduction of tick-box-style clerking sheets to facilitate clinical decision-making among junior doctors working in relatively unsupervised, resource-constrained environments. A number of authors have advocated the use of clinical prediction rules (CPRs) to assist with clinical decision-making in cases of acute appendicitis.[7,8] These CPRs attempt to quantify the possibility of a disease being present based on key symptoms, signs and the results of special investigations and to generate a score that predicts the probability of the disease being present.[8] We sought to generate a tick-box-style sheet with a CPR that would allow junior staff working in relatively unsupervised district hospitals to triage patients with abdominal pain into those who require urgent referral and those who can be discharged home.

The Alvarado score is the most widely used CPR for acute appendicitis and sums up 3 symptoms and 3 signs as well as the results of standard blood tests to give an overall score out of 10 (Box 1).[9] On the basis of this score, 3 groups of patients are identified.[9] Patients with a score of 1–4 can be discharged home, those with a score 5–6 should be admitted and those with a score of 7–10 should be considered candidates for surgery. A recent review of the published data on the Alvarado score reported that it is most useful in predicting the absence of appendicitis, and an Alvarado score below 5 has a sensitivity of 94%–99% for appendicitis not being present.[10] The authors concluded that a score of 5 or less rules out appendicitis.[10] When it comes to positively establishing the presence of acute appendicitis, the score is less reliable; the same review stated that "the pooled diagnostic accuracy in terms of 'ruling in' appendicitis at a cut-point of 7 points is not sufficiently specific in any patient group to proceed directly to surgery." The score is well calibrated in men, but tends to overpredict the presence of acute appendicitis in women.[10] In children, the score has also been shown to be inaccurate.[7] The applicability of the Alvarado score in South Africa is unclear, and there is evidence to suggest that the clinical presentation of acute appendicitis is different to that in the developed world.[3,11] Furthermore, the differential diagnosis of abdominal pain in South Africa is much broader than in the developed world. There is a high incidence of childhood diarrheal illness; HIV; and tropical diseases, such as amoebiasis, abdominal tuberculosis and typhoid, which may all present with acute abdominal symptoms.[12] Prior to designing a possible tick-box-style sheet for abdominal pain to be used in our rural hospitals, we set out to establish the validity of the Alvarado score at our institution.

Methods

We obtained ethics approval to audit acute appendicitis from the Umgungundlovu Health Ethics review board and from the Biomedical Research Committee of the University of KwaZulu-Natal. This study was conducted at Edendale Hospital, a large regional hospital in Pietermaritzburg, the capital city of KwaZulu-Natal, South Africa. Edendale Hospital drains a predominantly black African population from the urban areas around Pietermaritzburg and from the deep rural areas of Sisonke Health District (SHD), a rural area in southwestern KwaZulu-Natal with a population of half a million people and 4 district hospitals. This study was conducted from January 2008 to December 2012. For the period from January 2008 to December 2009, we retrospectively reviewed the records of all patients with acute appendicitis and entered the data into an Excel database. From January 2010 onwards, data from all patients with acute appendicitis were entered prospectively into the same database. Individual Alvarado scores were generated for all patients using data from their charts, and a score was

Box 1. The Alvarado score

Feature	Score
Migration of pain	1
Anorexia	1
Nausea	1
Right lower quadrant tenderness	2
Rebound pain	1
Elevated temperature > 37.5° C	1
Leucocytosis	2
Left shift of white cell count	1
Total	10

assigned to each patient. On the basis of each individual score a clinical probability score was generated, as previously described.[9]

Statistical analysis

We entered all data into an Excel spreadsheet for processing. All statistical analysis was performed using SPSS version 19 (IBM Corp).

Results

Our study sample comprised 1000 patients (54% male, 46% female, median age 21 [range 12–26] yr) with acute appendicitis confirmed both intraoperatively and with histology during the 5-year period from January 2008 to December 2012. Medical care was sought on average 4.2 days after the onset of symptoms. Half of the patients presented from rural areas and the other half from urban areas. A total of 490 patients were considered to have generalized peritonitis at presentation, and the remaining 510 patients presented with localized peritonitis or nonspecific abdominal pain. Intraoperative findings were as follows: 405 (40.5%) had inflamed, nonperforated appendices and 595 (59.5%) had perforated appendices. Of the cohort with perforated appendicitis 177 (29.7%) had perforation-associated localized intra-abdominal sepsis, and 418 (70.2%) had perforation-associated generalized intra-abdominal sepsis. In all, 234 (23.4%) patients required temporary abdominal closure, and 406 (40.6%) patients required revision laparotomy for residual sepsis. Ninety-five (9.5%) patients required postoperative intensive care admission owing to perforation and generalized sepsis. The mean length of stay in intensive care was 6 days. The remaining patients were admitted to the general surgical wards. Overall complications were as follows: 82 (8.2%) patients had hospital-acquired pneumonia, 57 (5.7%) had acute kidney injury, 142 (14.2%) had wound sepsis, and 20 (2.0%) experienced other complications. Overall mortality was 1.3%.

Table 1. Comparative data between the US Department of Defense and our institution

Comparative data	US Department of Defense	Edendale Hospital
Year	1997	2008–2012
Patients, no.	4950	1000
Centres, no.	147	1
Patients/centre/yr, no.	25	200
Perforation rate, %	24	60
Mortality, %	0.08	1
Intensive care unit, %	NA	10
Reoperation rate, %	0.5	23
Temporary abdominal closure, %	NA	41

NA = not available.

Table 1 compares the outcomes of acute appendicitis at our institution with those in institutions in the developed world.[11]

Alvarado score

For the entire cohort of 1000 patients, Alvarado scores were 1–4 in 20.9%, 5–6 in 35.7% and 7–10 in 43.4%, indicating low, intermediate and high clincial probability, respectively. The frequency of occurrence of each item on the Alvarado score and relative clinical probabilities are shown in Tables 2 and 3. Figure 1 provides a summary of the Alvarado scores for all patients with acute appendicitis.

Subgroup analysis

For the purpose of subgroup analysis, a total of 510 patients (65.5% male, 34.5% female, median age 19 [range 11–25] yr) who did not have generalized peritonitis on presentation were analyzed separately. A total of 393 of 510 (77.1%) patients had inflamed, nonperforated appendices and 117 (22.9%) had perforated appendices associated with localized intra-abdominal sepsis.

The Alvarado scores of all 510 patients were 1–4 in 5.5%, 5–6 in 18.1% and 7–10 in 76.4%, indicating low, intermediate and high clinical probability, respectively. The frequency of occurrence of each item on the Alvarado score and relative clinical probabilities are

Table 2. Alvarado score for all patients with acute appendicitis in, *n* = 1000

Alvarado score	No.	(%)
1	20	(2.0)
2	25	(2.5)
3	44	(4.4)
4	120	(12.0)
5	155	(15.5)
6	202	(20.2)
7	110	(11.0)
8	120	(12.0)
9	135	(13.5)
10	69	(6.9)

Table 3. Clinical probability according to Alvarado score, *n* = 1000

Score	Clinical probability	No.	(%)
1–4	Low	209	(20.9)
5–6	Intermediate	357	(35.7)
7–10	High	434	(43.4)

shown in Tables 4 and 5. Figure 1 provides a summary of the Alvarado score with separate subgroup analysis.

The Alvarado scores of the 393 patients with inflamed, nonperforated appendices were 1–4 in 6.9%, 5–6 in 21.9% and 7–10 in 71.2%, indicating low, intermediate and high clinical probability, respectively. The frequency of occurrence of each item on the Alvarado score and relative clinical probabilities are shown in Tables 6 and 7.

The Alvarado scores of the 117 patients with perforated appendices (localized sepsis) were 1–4 in 0.9%, 5–6 in 5.1% and 7–10 in 94.0%, indicating low, intermediate and high clinical probability, respectively. The frequency of occurrence of each item on the Alvarado score and relative clinical probabilities were shown in Tables 6 and 7.

Table 4. Alvarado score for all patients without generalized peritonitis on presentation, *n* = 510

Alvarado score	No.	(%)
1	0	(0)
2	0	(0)
3	9	(1.8)
4	19	(3.7)
5	31	(6.1)
6	61	(12.0)
7	87	(17.0)
8	114	(22.4)
9	124	(24.3)
10	65	(12.7)

Table 5. Clinical probability score according to Alvarado score, *n* = 510

Score	Clinical probability	No.	(%)
1–4	Low	28	(5.5)
5–6	Intermediate	92	(18.0)
7–10	High	390	(76.5)

Table 6. Alvarado score for subgroups of patients without generalized peritonitis

	Group; no. (%)	
Alvarado score	Inflamed *n* = 393	Perforation, local sepsis *n* = 117
1	0 (0)	0 (0)
2	0 (0)	0 (0)
3	9 (2.3)	0 (0)
4	18 (4.6)	1 (0.9)
5	29 (7.4)	2 (1.7)
6	57 (14.5)	4 (3.4)
7	69 (17.6)	18 (15.4)
8	81 (20.6)	33 (28.2)
9	85 (21.6)	39 (33.3)
10	45 (11.4)	20 (17.1)

Discussion

Acute appendicitis is an important clinical problem in South Africa, and the incidence appears to be increasing among the general population.[1,13] It is associated with long delays to definitive surgery, major morbidity and high cost.[3–5] While there is evidence to suggest that patients do not present early and that a great deal of the morbidity is related to the presence of barriers to care, there is a concern that even once contact with the health system has been made, clinical failure to recognize the condition exacerbates the delays.[5] There are a number of structural reasons for the high incidence of clinical failure that revolve around junior staff working in areas of limited resources with inadequate supervision.[14] However, it has been suggested that the clinical presentation of the disease in South Africa is also different to that in the developed world.[3,11] Abdominal tuberculosis; HIV; and other tropical diseases, such as typhoid, amoebiasis and pediatric diarrhea, may all mimic acute appendicitis.[12] In our previous study on acute appendicitis, only a small proportion of our patients presented with the classic migratory abdominal pain.[3] The most common symptoms encountered were all nonspecific, and these findings were similar to those previously reported in Durban, South Africa.[15] The nonspecific nature of these symptoms has implications for the clinical assessment of black African patients. The present results seem to support our suspicion that the presentation of acute appendicitis among the South African population is different to that in the developed world.[3,16]

Limitations

There are a number of limitations to our study. As the Alvarado score was applied retrospectively to patients already known to have the disease, there is a significant

Table 7. Clinical probability score, subgroup

		Group; no. (%)	
Score	Clinical probability	Inflamed, *n* = 393	Perforation, local sepsis, *n* = 117
1–4	Low	27 (6.9)	1 (0.9)
5–6	Intermediate	86 (21.9)	6 (5.1)
7–10	High	280 (71.2)	110 (94.0)

potential for selection bias, and it is quite possible that the average Alvarado score of patients in our study is higher than that of patients presenting to our institutions with nonspecific abdominal pain who did not receive surgery.

We are interested in developing a triage tool for rural hospitals. The concept would be to create tick-box-style clerking sheets in district hospitals that would enable junior doctors to score each patient presenting with abdominal pain. Patients meeting a specific score could then be triaged for urgent referral to a regional institution with surgical capacity. However, before the widespread introduction of the use of the Alvarado score in our setting, we need to prospectively investigate its applicability in our institutions. We have increasingly used tick-box-style clerking sheets to improve the quality of care in our setting. This is taken directly from the aviation industry, which makes frequent use of tick-box-style checklists to improve safety.[17] The assessment of abdominal pain may be amenable to such an intervention, and a major attractions of the Alvarado Score is that it can be tabulated into a routine clerking sheet.[18,19] However, our study has shown that using the Alvarado score, more than one-quarter of all patients with proven acute appendicitis would have been classified as having a low to intermediate probability of the disease being present and that slightly less than 5% of these patients would have been discharged home despite having the disease. The implications of this finding for staff in rural district hospitals are unclear. These individuals are usually busy generalists with limited access to advanced imaging who are unable to undertake the operation themselves.[14] There appear to be 3 options available to them: discharge, admit or transfer the patient. Our results suggest that approximately 20% of patients who have the disease may have been admitted to a district hospital for ongoing observations. Yet we know from our previous research that there is already a delay in transferring patients from district to regional hospitals, so this may simply exacerbate the problem.[5] A further 5% of patients with the disease would have been sent home. Similarly, we know that a substantial number of patients are in fact incorrectly sent home from a district-level facility despite the presence of the disease.[5] The concern with the Alvarado score remains that in our under-resourced hospitals its use may exacerbate rather than improve the current situation.

Conclusion

Acute appendicitis remains a common clinical diagnostic problem, and in our environment it is associated with significant delays and poor clinical outcomes. The widespread use of the Alvarado score as a clinical prediction tool has its merits, but its applicability in the black South African population is unclear, with a significant proportion of patients with the disease being potentially missed. This is likely to be related to a much wider range of pathologies and atypical clinical presentations. Future prospective research must be undertaken to validate the Alvarado score, with a possible modification, in order to improve its relevance in our environment.

Competing interests: None declared.

Contributors: All authors designed the study. V. Kong acquired the data, which V. Kong, S. van der Linde, J. Handley and D. Clarke analyzed. V. Kong and J. Handley wrote the article, which all authors reviewed and approved for publication.

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Chapter 7: Developing a clinical model to predict the need for re-operation for severe intra-abdominal sepsis secondary to complicated appendicitis

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Developing a clinical model to predict the need for re-operation for severe intra-abdominal sepsis secondary to complicated appendicitis

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Abstract:

Introduction: Complex intra-abdominal sepsis secondary to acute appendicitis is common in South Africa, and management frequently involves temporary abdominal closure and multiple re-laparotomies. The decision regarding selection of patients remains controversial. This study aimed to develop a clinical model to aid this decision making process.

Methodology: This study was conducted from January 2008 to December 2012 at Edendale Hospital, Pietermaritzburg. All patients with intra-operatively confirmed acute appendicitis and all patients within this group who underwent re-laparotomy were included. Their clinical course, intra-operative findings and outcome were followed until discharge (or death). Using a combination of pre-operative and intra-operative parameters, a clinical model was developed to predict the need for relaparotomy.

Results: 1000 patients with acute appendicitis were included. Male 54.1%, female 46.9%, median age 21 years (12 - 26). 406 patients ultimately required a re-laparotomy. 56% (227/406) underwent planned re-laparotomy and 40% (179/406) on demand. Of the re-laparotomy group, 90% (367/406) had positive findings at re-operation. Logistic regression analysis showed that the presence of the following 4 factors accurately predicts the need for subsequent re-laparotomy: Patients referred from any rural centre within our catchment population, Duration of illness > 5 days, Heart Rate > 120/min and Perforation associated with generalised intra-abdominal sepsis. This model had a predictive value of over 90%.

Conclusions: Using a simple clinical model based on a single disease, it may be possible to predict the need for subsequent relaparotomy from severe intra-abdominal sepsis at the initial laparotomy. Further study is needed to validate this model prior to integration into routine clinical practice.

Introduction:

In South Africa, acute appendicitis is often associated with late presentation and advanced pathology and consequently, surgeons are frequently required to manage complex intra-abdominal sepsis [1,2]. This condition is associated with serious morbidity and even mortality, and aggressive surgical management is essential because source control remains the corner stone of therapy [3,4]. Achieving source control frequently requires one or more repeat operations [4]. Deciding on the need for re-operation and the optimal timing is often highly subjective. The decision to re-operate is often challenging to make in the setting of dealing with critically ill patients with non-specific signs and symptoms of partially treated sepsis [5]. There is a lack of general consensus as to which patients should be subjected to re-operation [5,6,7]. There are essentially two approaches to the management of complex intra-abdominal sepsis. These are the so-called planned re-operation approach (PR) and the on demand re-operation (OD) approach [8]. The planned approach takes all patients with complex sepsis back to the operating room at regular forty-eight hour intervals until such a time as adequate source control has been achieved. With the on-demand approach, all patients are treated expectantly and only patients who manifest signs of unresolved intra-abdominal sepsis are subjected to re-operation [4]. The use of temporary abdominal closure (TAC) is generally reserved for patients with abdominal compartment syndrome or where technical issues preclude primary closure [8,9]. However, some authors advocate the elective use of temporary abdominal closure (TAC) for cases of abdominal sepsis in which source control is known to be inadequate, because it allows for better drainage of intra-abdominal sepsis [10].

For practical and ethical reasons, it is extremely difficult to compare these different options in a randomised study, and most of the evidence to support any of these approaches is at best level two [10,11]. Data that exists does not demonstrate any superior outcomes or survival advantage for either approach [12]. There is little data on this problem from the developing world where the spectrum of disease is very different from the developed world [1,5,13]. The objective of this study is to focus on a single disease process and use local data to identify pre-operative and intra-operative clinical factors that may predict the need for re-operation, and to construct a clinical model to assist clinicians in predicting the need for re-operation on patients with complex intra-abdominal sepsis following acute appendicitis.

Methodology:

The study was conducted from January 2008 to December 2012 at Edendale Hospital, Pietermaritzburg, South Africa. Edendale Hospital is a regional hospital in the city of Pietermaritzburg and is the referral hospital for the four rural district hospitals in Sisonke Health District. Currently, the management of abdominal sepsis following acute appendicitis is left to the discretion of the individual surgeon. All patients who require a TAC will undergo mandatory re-operation. In the OD group we have a very low threshold for re-operation and we tend to invert the thinking process somewhat by emphasising to staff that the patient must earn the right not to have a repeat operation rather than earn the right to have one.

Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of Kwa-Zulu Natal and the Umgungundlovu Health Ethics Review Board (UHERB). All patients with intra-operatively confirmed acute appendicitis were eligible for inclusion. Basic demographic data was collected. The clinical symptoms, physical examination findings, baseline vital signs and laboratory results were recorded. Intra-operative details were obtained and included the surgeon's assessment of the macroscopic appearance of the appendix and the presence of perforation. The severity of abdominal contamination was classified as either localised contamination or generalised four-quadrant contamination. The clinical progress of all patients was followed up until discharge (or death). All patients who had a TAC were subjected to PR. In the OD group, any clinical suggestion of persistent sepsis was an indication for re-operation. The findings at re-operation were classified as either positive or negative. Positive findings included turbid intra-abdominal fluid, purulent intra-abdominal fluid, appendix stump dehiscence, necrotising fasciitis and other pathologies, which included perforated stress ulcers or acalculous cholecystitis. Negative findings included serous fluid only in the abdomen with no other new findings.

Statistical Analysis:

Detailed statistical analysis was performed to compare the re-operation and the non re-operation groups. The Pearson Chi-Square test was used when the sample size assumption was adhered too; Fischer Exact test was utilised in cases where the Chi-square assumption was not fulfilled and the Mann Whitney U test were performed to identify any significant differences between the two groups after the data distributions were proven to be asymmetrical. Non-parametric (asymmetrical) data were descriptively described in terms of a median and a inter quartile range (IQR: Q1 – Q3). Finally a logistic regression was performed to investigate the prediction of the need for re-operation. A range of variables were considered and included based on clinical relevance. The final remaining variables in the model were reached via a backward stepwise regression. Statistical significance level was set at $p < 0.05$. All statistical analysis was performed using SPSS version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Statistical Model:

A logistic regression analysis (Backward Stepwise Conditional Method) was conducted to predict whether a re-operation would occur using specific pre-operative and intra-operative data as predictors (**Table 1**). This data was used to generate a Receiver Operating Curve (ROC) based on the number of true positives and false positives.

Results:

A total of 1000 patients with acute appendicitis confirmed intra-operatively were managed during the five-year period from January 2008 to December 2012. Male comprised 54.1% and female 46.9% of the cohort with a median age of 21 years (12 - 26). Medical care was sought on average 4.2 days after the onset of symptoms. 39.4% had a local incision, while 60.6% required a laparotomy. A total of 40% (405/1000) had inflamed non-perforated appendicitis whilst 60% (595/1000) had perforation. Of the 595 with a perforated appendix, 177 had localised intra-abdominal sepsis and 418 had generalised four-quadrant sepsis. A total of 406 patients ultimately required a re-operation. The two groups were compared and **Table 1** summarises the differences between the re-operation and the non re-operation groups. Of the 406 who required a re-operation, 56% (227/406) were PR and 44% (179/406) were OD. Of the re-operation group, 90% (367/406) had positive findings at re-operation. **Table 2** summarises the findings at re-operation.

Table 1: The differences between the re-operation and the non re-operation groups.

Characteristics	Re-operation (RL)		No Re-operation			
	N =	%	N =	%	p	Significance
Demographics						
Male	166	41.0%	375	63.0%	<0.001	S
Female	240	59.0%	219	37.0%		
Median Age (Years)	22	(13 - 29)	20	(11-25)	0.481	NS
Urban Patients	108	27	455	77	<0.001	S
Rural Patients	298	73	139	23		
Clinical Features						
Median Duration (Days)	5	(4 - 7)	3	(2 - 4)	<0.001	S
Anorexia	224	55.2%	353	59.4%	0.207	NS
Nausea Vomiting	274	67.5%	433	72.9%	0.065	NS
Migratory Pain	76	18.7%	248	41.8%	<0.001	S
Non Migratory Pain	330	81.3%	346	58.2%	<0.001	S
Dysuria	10	2.5%	12	2.0%	0.639	NS
Diarrhoea	20	4.9%	26	4.4%	0.684	NS
Constipation	25	6.2%	16	2.7%	0.007	S
Localised Peritonitis	51	12.6%	493	83.0%	<0.001	S
Generalised Peritonitis	355	87.4%	101	17.0%	<0.001	S
Baseline Vital Signs						
Mean Temperature (^{o}C)	37.8	(37.2 - 38.4)	37.2	(36.8 - 37.8)	<0.001	S
Mean Heart Rate (per min)	110	(99-121)	98	(88 - 109)	<0.001	S
Mean WCC (x10^6/L)	16.7	(13-20)	13.4	(11.9 - 15.5)	<0.001	S
Surgical Access						
Local Incision	396	98.0%	210	35.0%	<0.001	S
Laparotomy	10	2.0%	384	65.0%		
Operative Findings						
Inflamed Appendix	4	1.0%	401	67.5%	<0.001	S
Perforated Appendix	402	99.0%	193	32.5%	<0.001	S
Localised Contamination	36	8.9%	141	23.7%	<0.001	S
Generalised Contamination	366	90.1%	52	8.8%	<0.001	S

Table 2: Findings at re-operation

Positive Findings (N=367)	N	%
Purulent Fluid	166	45%
Turbid Fluid	159	43%
Necrotising Fasciitis	19	5%
Nonviable Bowel	11	3%
Stump Dehiscence	6	2%
Others	6	2%
	367	100%
Negative Findings (N=39)	**N**	**%**
Serous	39	100%

Mathematical Model:

Based on the differences between the re-operation and the non re-operation group, a number of parameters were considered for inclusion in a mathematical model to predict the need for re-operation. The criteria could either be categorical (yes or no) or a discrete number. The following five variables were selected:

Referral: Patients referred from any rural centre (Present = 1, Absent = 0)

Duration: Duration (days) of illness prior to contact with healthcare system

Heart Rate: Heart Rate on admission (beats/min)

Perforation was classified as: Inflam=0, LC or 4QC=1

Perforation with LC: Perforation with Localised contamination (Present = 1, Absent = 0)

Perforation with 4QC: Perforation with Generalised contamination (Present = 1, Absent = 0)

The Wald criterion demonstrated that the mode of referral (urban compared to rural) ($p = 0.019$) and perforation compared to non-perforation ($p < 0.001$) made a significant contribution to a confirmatory re-operation prediction.

The following mathematical model was generated incorporating the criteria listed above:

$LN(\hat{p}/1-\hat{p})$ = -6.116 + 0.566*(Referral: if Rural) + 0.075*(Duration) + 0.012*(HR) + 2.961*(Pref: if LC) + 5.933*(Pref: if 4QC)

Prediction success for this model overall was 90.8% (sensitivity is 90.1% and specificity is 91.2%). The Receiver Operating Characteristic (ROC) curve indicates: an area under the curve (AUC) of 0.948 (CI95%: 0.934 – 0.962) with p-value < 0.001, confirming good performance by the above model. An ROC curve, plots a predictor system as its threshold level to correctly classify re-operation is varied and is generated by plotting the true positives fraction against the false positives fraction at a range of different thresholds. The ROC compares the predictive value of a test against a random guess (diagonal 0.5 line on the ROC graph). If a test is towards the bottom right hand corner (below the random line) it is worse than a random guess, the closer it is to the top left hand corner the better it is than a random guess. ROC is a useful tool to select predictive models and the AUC is a single digit summary of the performance of true positives plotted against the false positives on the ROC graph. **Figure 1** shows the ROC curves for the five selected criteria and **Figure 2** shows the ROC curve for the combined formula. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between those whom required a re-operation compared to those who did not (chi square = 827.663, $p < 0.001$ with df = 5). The Hosmer-and-Lemeshow goodness of fit test indicated the data had a good fit to the predictive model (chi square = 7.442, $p = 0.490$ with df = 8). Nagelkerke's R2 of 0.760 indicated a good relationship between prediction and grouping.

Clinical Model:

A simplified clinical scoring system derived from the above model can be utilised. In the presence of the following four major predictive factors, there is a 90% probability that a re-operation is required.

Factors:

Referral from a rural centre

Duration of illness > 5 days

Heart Rate > 120/min

Perforation with associated generalised contamination

Figure 1: ROC curve analysis of the predictive model (individual predictors):

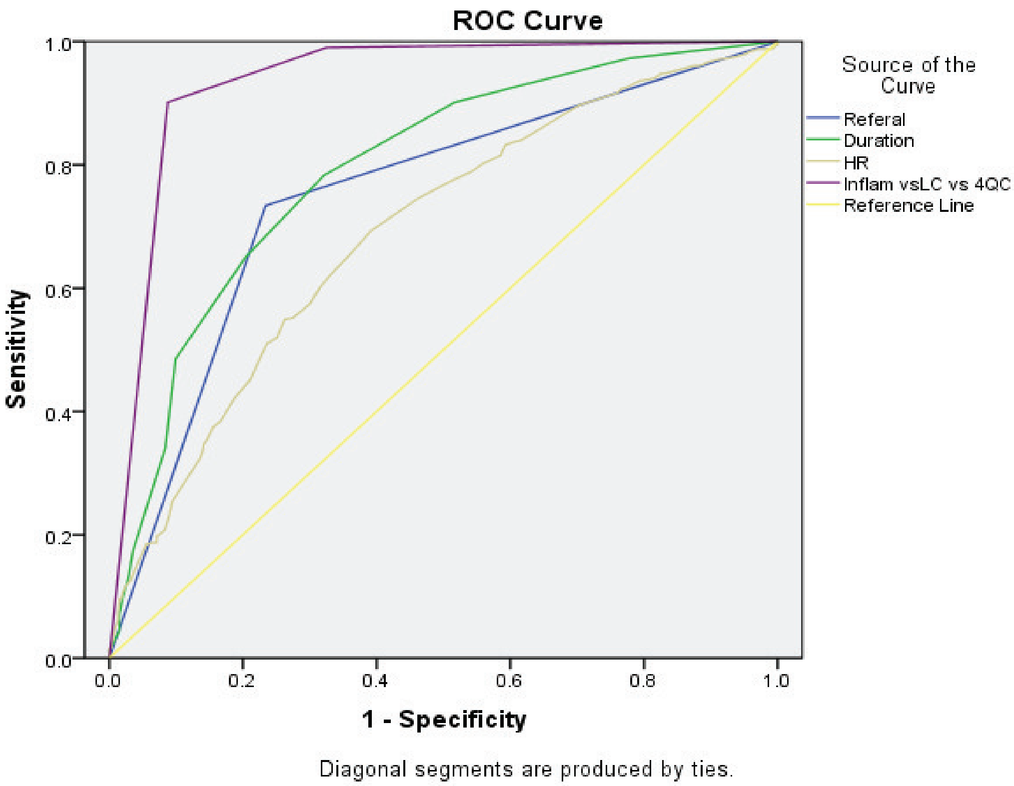
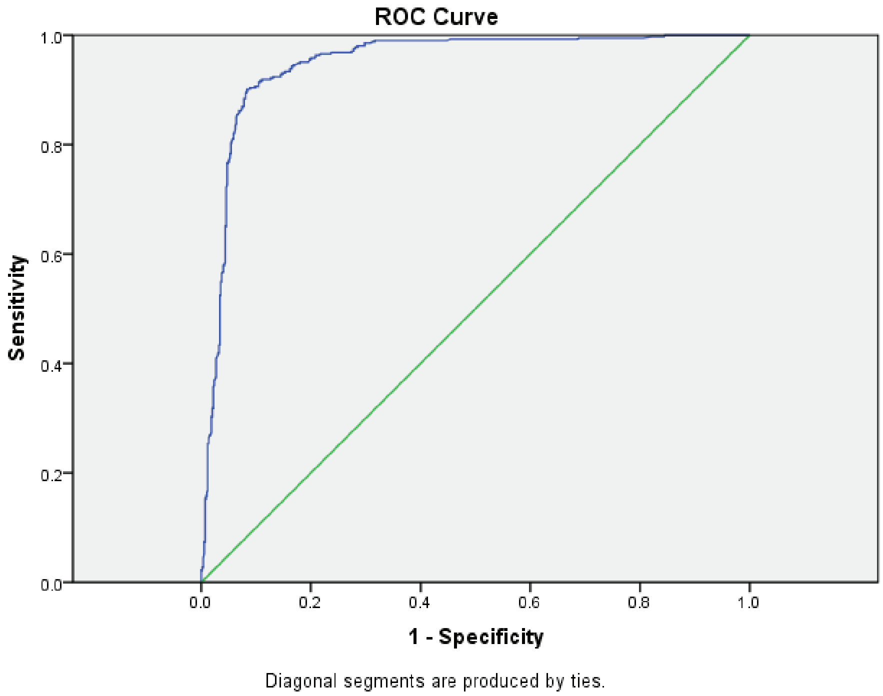


Figure 2: ROC curve analysis of the predictive model (combined):



Discussion:

In the developing world, acute appendicitis is associated with serious morbidity and even mortality due to late presentation and complex intra-abdominal sepsis [1,2]. The management of complex intra-abdominal sepsis is taxing and frequently requires re-operation to ensure adequate source control [4]. Although literature looking at predictors of the need for the re-operation exists, most have been undertaken in the developed world and have not focused on a specific disease process [5,13]. Of the methods currently employed for the management of complex intra-abdominal sepsis, it has been suggested that on-demand re-laparotomy is the most cost effective approach [10]. A randomised study was published by van Ruler et al in 2007 comparing PR and OD approaches for patients with complex intra-abdominal sepsis [12]. A total of 232 patients were randomised. In the PR group, re-operation was undertaken every 36 to 48 hours after the initial procedures until all intra-abdominal sepsis was cleared. In the OD group, re-operation was only performed for patients who either deteriorated clinically or failed to improve. Patients in the OD groups had shorter hospital stay and reduced need for ICU without any increased incidence on adverse events. This resulted in lower hospital costs. However, the general expert consensus is that if an OD approach is adopted, then early recognition of the need of further surgery is essential as delay in source control results in dramatically increased morbidity and mortality [3,4,14,15,16]. This makes a model to predict the need for re-operation important [8,14]. Our proposed model allows for a predictive value of over ninety per cent. For simplicity, this was modified into a clinical predictive score, which allows its use in a daily clinical practice. However, a further prospective study is required to validate this scoring system.

Conclusions:

Complicated appendicitis with severe intra-abdominal sepsis is a serious condition commonly seen in the developing world. The management of complex intra-abdominal sepsis is taxing, and its assessment has relied on clinical discretion. Our proposed scoring system may be able to accurately predict the need for re-operation in patients with acute appendicitis and it should be validated prospectively.

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Chapter 8: Conclusions and recommendations

Acute appendicitis remains the most commonly encountered surgical emergency worldwide. We have described the spectrum of disease in South Africa which is substantially different from that of the developed world, and it is typified by late presentation and advanced pathology. The perforation rate in our series was one of the highest reported in literature to date, and the disease is associated with disproportionally high morbidity and mortality. We have shown that acute appendicitis treated early carries little morbidity, and is relatively inexpensive to manage. However, as the pathology progresses, the cost of treating this diseases rises exponentially. The astronomical cost from this surgically curable disease unfortunately continues to plague our already under resourced healthcare system. Interventions for cost containment should focus on secondary prevention aimed at limiting the impact of the disease by early identification and early definitive surgery.

We have identified that rural origin is a major independent risk factor for adverse clinical outcome in acute appendicitis. Rural patients fare worse in every aspect of their clinical outcome compared with their urban counterparts. They experience major delays from the onset of illness through to definitive surgery. The reasons for the protracted delays were multi-factorial but centre on barriers to access to appropriate surgical services within the healthcare system. We have shown that the two major causes of delay were experienced in the pre-hospital domain, associated with health seeking behaviour, and in the in-hospital domain, associated with failure of healthcare workers to recognise the disease and the need for early referral for surgery. These factors often occur sequentially and conspire to the protracted delays frequently encountered at the receiving end. Health seeking behaviour represents one of the many facets of the complex sociological aspects of healthcare and further research in this area is needed.

We have shown that the Alvarado Score, contrary to literature from the developed world, is less applicable to the Black South African population, which may be related to much wider diagnostic differentials from HIV and tropical diseases. Of major concern was the significant proportion of patients who may be missed by the use of such a scoring system. Furthermore, prospective research in order to validate this scoring system is urgently needed, and possible modification might be needed before it can be considered as a potential triage tool to facilitate early referral for surgery in our setting.

The surgical management of complex intra-abdominal sepsis from acute appendicitis as the aetiology is unique to our locality. It is taxing for surgeons, the decision making process challenging and continues to be highly controversial. We have developed a simple, four item, clinical assistance tool, which utilises a combination of pre-operative and intra-operative parameters that accurately predict the need for subsequent re-laparotomy. However, this must be subjected to prospective validation prior to integration into routine clinical practice.

The main limitation of this project was the observational nature in a single centre, thus only provided a focused perspective of key aspects of acute appendicitis in a typical developing would environment. Further prospective and interventional studies may be helpful in increasing the generalisability of our work.

Appendices

Appendix 1: A concept paper: Using the outcomes of common surgical conditions as quality metrics to benchmark district surgical services in South Africa as part of a systematic quality improvement programme

A concept paper: Using the outcomes of common surgical conditions as quality metrics to benchmark district surgical services in South Africa as part of a systematic quality improvement programme

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The fourth, fifth and sixth Millennium Development Goals relate directly to improving global healthcare and health outcomes. The focus is to improve global health outcomes by reducing maternal and childhood mortality and the burden of infectious diseases such as HIV/AIDS, tuberculosis and malaria. Specific targets and timeframes have been set for these diseases. There is, however, no specific mention of surgically treated diseases in these goals, reflecting a bias that is slowly changing with emerging consensus that surgical care is an integral part of primary healthcare systems in the developing world. The disparities between the developed and developing world in terms of wealth and social indicators are reflected in disparities in access to surgical care. Health administrators must develop plans and strategies to reduce these disparities. However, any strategic plan that addresses deficits in healthcare must have a system of metrics, which benchmark the current quality of care so that specific improvement targets may be set.

This concept paper outlines the role of surgical services in a primary healthcare system, highlights the ongoing disparities in access to surgical care and outcomes of surgical care, discusses the importance of a systems-based approach to healthcare and quality improvement, and reviews the current state of surgical care at district hospitals in South Africa. Finally, it proposes that the results from a recently published study on acute appendicitis, as well as data from a number of other common surgical conditions, can provide measurable outcomes across a healthcare system and so act as an indicator for judging improvements in surgical care. This would provide a framework for the introduction of collection of these outcomes as a routine epidemiological health policy tool.

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Over the three-and-a-half decades since the Declaration of Alma Ata, healthcare systems have tended to become increasingly inequitable and cost-ineffective, implying that the traditional model of primary healthcare conceptualised at Alma Ata has to a large extent been unsuccessful.[1-7] This has necessitated a re-imagining of the model of primary healthcare. The new model views primary healthcare as a central hub, which focuses on strengthening the individual components of the health system beneath the overarching umbrella of primary healthcare. Traditionally the public health approach perceived surgical services as expensive curative services that benefited individuals rather than communities.[1-3] Since Nordberg first drew attention to the fact that much morbidity and mortality occurs in remote rural African villages because of common surgical conditions,[1-3] there has emerged a consensus that surgical care is an integral component of primary healthcare and that common surgical conditions such as trauma, hernias, appendicitis, obstetric emergencies and congenital anomalies are important public health problems.[1-7]

There are major disparities in access to surgical care across the world, and this disproportionately affects rural and marginal groups in low-income countries.[5-7] The World Health Organization (WHO) classifies countries as high, middle or low income based on the amount of money annually spent on healthcare per head of population, middle- to high-income countries spending between US$400 and US$1 000 per head of population. Only a third of the world's population lives in middle- to high-income countries, yet two-thirds of all surgical procedures are performed there, and the poorest third of the world's population undergoes less than 4% of all surgical procedures. It has been estimated that the global volume of major surgery in 2004 was between 187 million and 281 million cases, which equates to one operation for every 25 human beings.[7] Major morbidity complicates 3 - 16% of all surgical procedures, and there is an associated death or permanent disability rate from 0.5% to just under 1% in the developed world. The mortality rate of major surgery in the developing world is significantly higher, however, and has been estimated to be in the range of 5 - 10%. This means that approximately 7 million people a year experience a major complication, and 1 million people a year die, following surgery.[7] In view of the large numbers involved, improving outcomes for surgery is a public health priority, and the provision of adequate surgical services has been shown to be an extremely cost-effective healthcare intervention in the developing world.[7-10] Most of the strategies designed to address the disparities in access to surgical care focus on building the surgical capacity of district hospitals.[7-10]

Current resources and initiatives

Effective surgical services tend to bolster the entire health system and impact positively on other non-surgical services.[7-10] The WHO has responded to this new understanding of the importance of effective surgical systems by developing a number of resources and programmes. In 2005 the Global Initiative for Emergency and Essential Surgery Care was established to increase the capacity of low- and middle-income countries to provide effective surgical services. The Emergency and Essential Surgical Care Project, the Integrated Management of Emergency and Essential Surgical Care toolkit and the textbook *Surgical Care at the District Hospital* are designed to help resource-constrained institutions establish effective educational and service packages based on the WHO's prescribed minimum standards and technologies for emergency and essential surgical care.[11] The WHO has emphasised the importance of a systematic approach to healthcare.[11,12]

Systems thinking

A healthcare system involves inputs, processes and outcomes.[11,12] Improving the health of a population must address the inputs of healthcare and the processes of delivery of healthcare. The inputs are the money and resources invested in the system, and the processes the way in which healthcare is delivered. The inputs and the processes interact to produce a health outcome. The term 'health system' covers the entire spectrum of care from the recognition and diagnosis of a pathology, through to transfer of the patient to the appropriate facility, up to operative management and postoperative care. Effective treatment depends on all the steps of the healthcare system working harmoniously. Patients must be able to access healthcare facilities easily and timeously. Primary caregivers must be able to recognise surgical pathology and refer the patient to an appropriate facility. Logistics must be organised to ensure quick and efficient transportation of the patient to the appropriate facility, and the receiving facility must be adequately resourced to deal with the problem. If any links in this chain of care are broken, pathology may complicate, and this translates into poor outcomes.

It is important to understand that poor outcomes reflect systematic failure rather than individual failure. To understand the efficiency of the system, administrators need to develop metrics that measure the quality of the system. Mainz has provided an excellent review of quality metrics for healthcare and has identified the following objective criteria for a good metric:[13] It must be relevant, acceptable, feasible, reliable, sensitive to changes, valid, and able to differentiate. In addition, whatever disease is chosen as an indicator needs to be sufficiently common to provide a large enough denominator, and ideally should be curable.

What is the current state of surgery at district hospital level in South Africa?

In *Surgical Care at the District Hospital*, the WHO states that basic abdominal surgery should be undertaken at district hospitals. The following procedures are described: laparotomy for trauma, laparotomy for the diagnosis and management of intestinal obstruction, peritonitis, complicated peptic ulcer disease, and appendicitis.[11] However, there remains a discrepancy between the package of care that a district hospital is expected to deliver and the care that is actually delivered, and it is apparent that very few of the procedures discussed in the WHO text are routinely performed in South African district hospitals.

Voss and Duvenage audited the surgical output of 7 district hospitals in the rural Western Cape.[14] The volume of general surgical procedures undertaken was low, and almost no abdominal surgery was undertaken. In their year-long review, only 21 appendicectomies were performed at the 7 district hospitals. Of these, 19 were performed in one hospital and 2 in another. The most commonly performed operations in rural South Africa are obstetric procedures, yet the competency to deliver obstetric anaesthesia safely seems to be deficient in the South African district health system.[15]

We recently published our experience with acute appendicitis at Edendale Hospital, Pietermaritzburg, South Africa, which differs markedly from that in the developed world. In our setting, acute appendicitis is a disease that presents late and is associated with diagnostic delay and significant morbidity and even mortality.[16] We reviewed 1 000 consecutive patients with acute appendicitis treated at Edendale Hospital between 2008 and 2012. Two-thirds were male, and the median age was 19.5 years. Medical care was sought on average 4 days after the onset of symptoms. Twenty-three per cent required temporary abdominal closure and 40% required repeat operation. The mortality rate was 2%, and just under 10% required intensive care unit (ICU) admission. There were significant complications, which included pneumonia (12.5%), wound dehiscence (7%) and renal failure (3%), and 11% required admission to the ICU. Our cohort had a perforation rate of 54%, and the high incidence of perforation often mandated formal laparotomy rather than a local incision. This is very different to the published experience with acute appendicitis from the developed world, where perforation rates are generally in the order of 20% or less and temporary abdominal closure and the need for ICU admission are almost unheard of.[17] Table 1 compares the outcomes of acute appendicitis at our institution with those in the developed world.

These poor outcomes reflect a dysfunctional system of surgical care, and it is apparent that the surgical system in the district hospitals of South Africa is deficient and has been allowed to deteriorate alarmingly. Strategies to turn this situation around are urgently required. Part of such a turnaround strategy must be the development of appropriate metrics to allow us to benchmark current performance, to develop targets, and to assess whether we ultimately reach these objectives.

Developing quality metrics for surgical care

There is a need to develop tools to measure the quality of our surgical care system in South Africa. Maternal and child health

Table 1. A comparison between outcomes of acute appendicitis at Edendale Hospital, South Africa, and those in the developed world

	US Department of Defense[17]	Edendale Hospital[16]
Year	1997	2008 - 2012
Patients, *N*	4 950	1 000
Centres, *N*	197	1
Patients for each centre per year, *N*	25	250
Mortality, %	0.08	2
ICU admission, %	NA	10 (mean 5 days)
Re-operation, %	0.5	41
Temporary abdominal closure, %	NA	23

ICU = intensive care unit; NA = not applicable.

is very developed in terms of applying routinely collected statistics to assess the quality of a system. Infant mortality rates and maternal mortality rates are crude markers that reflect the overall quality of the service. Developing a marker for the efficiency of a modern surgical service remains a challenge. A number of operations and surgical conditions fit this definition. These include amputation, which generally occurs in the more elderly group and is associated with both morbidity and mortality, elective hernia repair, which is not generally associated with significant mortality, and traumatic brain injury.[18]

Acute appendicitis is a disease that may allow for the development of a qualitative measure of output of a surgical system. It is a common disease, which is completely cured by a relatively straightforward surgical intervention. Systems failure in the form of delayed diagnosis and recognition results in significant morbidity. A number of clinical outcomes in the management of acute appendicitis many be useful as markers of quality of care. These potential metrics include delay to definitive treatment, perforation rates, laparotomy rates, re-operation rates, ICU admission rates, open abdomen rates and mortality rates. These criteria meet the listed requirements for an effective indicator of quality of care and should be routinely collected by hospital and surgical administrators. Ongoing efforts must be directed at developing and validating quality metrics for surgical care and using them to drive a turnaround strategy for district level surgery in South Africa.

Conclusion

The surgical capacity of district hospitals in South Africa has been allowed to deteriorate at an alarming rate, and a turnaround strategy is urgently needed. Part of this strategy must be the collection of a data set that functions as a quality metric for surgical services. This is analogous to the routine data collected to assess the quality of maternal and child health services. A number of potential pathologies and procedures meet the criteria to be considered markers of the quality of the system. Acute appendicitis in our environment is associated with prolonged delays to definitive treatment as well as significant morbidity, and is a good example of a potential quality metric. We suggest that the routine collection of basic data on acute appendicitis may well provide hospital managers with a tool to measure the output of a surgical system. These data would be relatively easy for managers to collect and collate and would expedite a repeatable and reproducible system of monitoring the effectiveness of a surgical service. Further research is needed to identify and validate a number of other potential quality markers, which include diabetic foot sepsis, traumatic brain injury and inguinal hernia repair.

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Appendix 2: Research Protocol

RESEARCH PROTOCOL

Doctor of Philosophy in Surgery (PhD)
University of Kwa-Zulu Natal

Principle Investigator: Dr. Victor KONG
Supervisor: Dr. Colleen ALDOUS
Co-supervisor: Dr. Damian CLARKE

Title

The spectrum, outcome and cost of acute appendicitis at Edendale Hospital and its related catchment areas

Aims

1. To assess the clinical spectrum and outcome of acute appendicitis at Edendale Hospital.

2. To quantify the financial cost of management of acute appendicitis at our institution.

3. To investigate the difference in clinical outcomes for patients from rural and urban areas who present with acute appendicitis.

4. To identify possible reasons for late presentation and the contributing factors to poor outcome.

5. To assess the applicability of the Alvarado scoring system in the diagnosis of acute appendicitis for our local Black South African population.

6. To develop a clinical tool to assist with clinical decision making for the surgical management of patients with complicated acute appendicitis.

Objectives

1. To collect data (both prospectively and retrospectively) for all patients who present with acute appendicitis, and to perform an in depth analysis of the clinical spectrum and outcomes of the disease.

2. To construct a cost model, using the bottom up (micro analysis) approach, in order to estimate the total costs associated with management of acute appendicitis in this cohort of patients.

3. To perform a detail statistical analysis to identify any differences in clinical outcomes comparing patients from urban versus rural areas.

4. To identify possible factors associated with delay in presentation by using a structured questionnaire to trace the narrative of patients' journeys from onset of illness to definitive surgery.

5. To apply the Alvarado scoring system retrospectively, and to assess its accuracy and applicability for this cohort of patients.

6. To construct a mathematical prediction model using clinical parameters based on the sub-set of patients who require re-laparotomy for complicated appendicitis, in order to aid decision making to predict the need for such intervention.

Background

Acute appendicitis is common in both the developed and developing world [1]. The incidence of this disease appears to have increased over the last decade [2]. It continues to be an important disease associated with significant morbidity and mortality, especially in the developing world [3].

Our experience at Edendale Hospital suggests a high incidence of complicated cases. Those who come from the rural areas of the province seem to experience significant delay in accessing care, and consequently there is a higher incidence of adverse outcomes.

The majority of complicated cases require complex management strategies (e.g. substantial resuscitations), significant operative time (multiple laparotomies are often required to control severe sepsis), antibiotics usage (often empiric), prolonged hospital stays and intensive care admissions. These patients are also at high risk of developing further nosocomial complications (e.g. pneumonia and renal failure etc.). These can all negatively impact on the already resource constrained public health system [4].

The exact causes of delayed presentation among patients from rural areas, and the subsequent high complication rates experienced remains unclear. However, contributing factors may include difficulties experienced by the patient in accessing the health care system, and logistical factors such as transportation problems to the hospital etc. Delay is also known to be associated with higher perforation rate [5] which substantially increases morbidity and mortality [6].

While several prediction models have been designed to assist in the diagnosis of appendicitis, e.g. the Alvarado score, there is currently no reliable predictor for the need for re-laparotomy, specifically for complicated appendicitis [7]. Clinical decision making in this respect is often subjective and those for whom re-laparotomy is not required are often difficult to exclude. Therefore, there is an urgent need to clearly identify factors which are accurate for predicting those patients who require a mandatory re-laparotomy. This prediction will have significant impact on clinical outcomes and associated costs for the management of these complicated cases.

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Study Design

This will be a single centre study conducted at the Department of Surgery, Edendale Hospital, Pietermaritzburg, KwaZulu Natal, South Africa.

Study Population

The sample will comprise all patients (who consent to take part) presenting to Edendale Hospital with acute appendicitis. The sample will include patients from the following drainage areas (A2) within the province of KwaZulu Natal; self-presentation; referrals from GPs; local clinics; and four referring district hospitals: Rietvlei Hospital, Christ the King Hospital, St. Apollinaris Hospital and East Griqualand Usher Memorial Hospital.

Sampling Strategies

All patients, regardless of their mode of referral, are sent initially to the Department of Surgery for specialist input of management. After having been assessed in the Surgical Emergency Unit with a diagnosis of acute appendicitis (on clinical grounds), they are referred directly to the on-call surgical registrar for further management. At this point each patient will be considered as a potential participant in this study.

Statistical Planning and Sampling

There are several uncommon causes that may mimic acute appendicitis and that have the potential to confound the selection of candidates for participation in this study. A total sample of 1000 patients is considered sufficient for accurate statistical analysis, in order to satisfy the objectives of this study. 500 patients will be collected prospectively, and a further 500 will be collected retrospectively from hospital records.

Inclusion Criteria

All patients, regardless of their age, who present at Edendale Hospital, who have a clinical diagnosis of acute appendicitis, and who have intra-operative findings that are consistent with the diagnosis, will be invited to participate in the study. Those patients who have an alternative initial diagnosis to appendicitis, but who are subsequently confirmed intra-operatively as having appendicitis will also be invited to be included in the study.

Exclusion Criteria

All patients who present with non-specific abdominal pain with no definitive diagnosis and those who have previously undergone an appendectomy, found intra-operatively, will be excluded from the study.

Data Collection

Once patients are admitted to the Surgical Ward, explicit written consent to take part in the study will be obtained from each patient. Also, consent will be sought to access patients' medical records and any laboratory results held at the hospital. All consent gained will be in the form of written consent, to be signed by the patient. Data will be collected by means of direct patient interview, as well as using case files, admission sheets and hospital records. A consent pro-forma has been prepared specifically for this purpose.

The data collected will include details of basic demographics for each patient, and a brief description of their mode of presentation, i.e. if they were admitted by means of direct self-referral to the hospital emergency department, by referral from a general practitioner, by referral from the local community health clinic, or by referral from one of the four rural district hospitals that feed into Edendale Hospital (Rietvlei Hospital, Christ the King Hospital, St. Apollinaris Hospital and East Griqualand Usher Memorial Hospital).

Patients will be specifically asked about their health seeking behaviour, including being questioned about the onset and duration of symptoms prior to seeking contact with the health system. Details such as clinical symptoms, physical examination findings, baseline vital signs, and laboratory results will be recorded and used for analysis. Clinical and operative detail records will include: the type of incision, the macroscopic appearance of the appendix, the presence of perforation, the degree of abdominal contamination, the need for temporary abdomen closure, and the need for a repeat operation. The clinical path each patient takes will be followed up until discharge, and this will detail items such as the type and nature of any major complications, the need for a repeat operation, or admission to the intensive care unit (ICU). Also, the total length of any ICU stay and hospital stay will be recorded.

All data will be anonymised and entered onto a password protected Microsoft Excel® spread-sheet which will only be accessible by the investigator (i.e. myself, the researcher).

Data Analysis Techniques

Once all the data has been entered into the Microsoft Excel spread-sheet, it will be coded using the statistical software SPSS®. A professional statistician from the Department of Community Medicine at the University of KwaZulu Natal, Mr. Stephen Van der Linde, will be available to provide general advice regarding in-depth analysis of the statistics and data collected. It is intended that the data analysis will be conducted using the defined functions of the SPSS® programme.

For Objective 1

A basic analysis of the data will include an overview of the spectrum of disease. Parameters derived from the data will include basic demographics such as: the total number of cases, the gender of the patients and the mean age of presentation. Also, a summary of clinical features, operative findings, complications, and length of hospital stay will be prepared.

For Objective 2

A cost model will be constructed using the available data. Each element that contributes to the overall cost of the management of treatment for each sample patient will be considered. Then, a cost formula will be constructed based on the estimated cost of operative intervention (operating theatre time), peri-operative intervention (analgesia and antibiotics), and the length of hospital stay. Patients will be divided into two separate groups for the purposes of a costing analysis: uncomplicated acute appendicitis cases and complicated acute appendicitis cases. Uncomplicated appendicitis cases will be defined as those without a perforation, whilst complicated appendicitis cases will be defined as those with appendix perforation. Complicated cases will be further sub-divided to differentiate between patients who experience perforation associated with localised intra-abdominal contamination, and those who experience generalised four-quadrant soiling. Also, patients who require intensive care admission among those who experience generalised four quadrant soiling will be analysed separately.

For Objective 3

Patients will be separated into two groups according to whether they present from a rural or urban area. For the purposes of this study 'rural' areas relate to the Sisonke district, whilst 'urban' areas relates to the Umgungundlovu district. Statistically significant tests will be conducted to identify any differences in clinical outcomes between these two groups.

For Objective 4

A detailed analysis will be conducted to identify the reasons and causes of delayed presentation. A delay will be defined from time of initial contact with a healthcare provider to definitive surgery. The exact reason for delayed presentation for each patient, and the length of time from initial referral to arrival at Edendale Hospital will be recorded.

For Objective 5

An Alvarado score will be retrospectively assigned to all patients based on information available from hospital admission records. Patients will then be assigned a clinical probability of acute appendicitis based on the Alvarado score. A detailed analysis will be performed to assess its accuracy in this cohort of patients.

For Objective 6

Patients will be separated into two groups according to whether a re-laparotomy is undertaken, or not. Statistically significant tests will be conducted in order to identify differences in clinical outcomes between the two groups. Then a mathematical model will be constructed based on preoperative and intra-operative parameters, and its level of accuracy determined.

Study Location

The study will be conducted at Edendale Hospital, Pietermaritzburg, Kwa-Zulu Natal, South Africa. Access to patients' medical records is necessary, and this will be arranged with the medical records department in conjunction with consent from patients. Any additional medical records not immediately available from the above means will be sought.

Study Period

This study will cover the period from January 2008 to December 2012 or until:

1. All 500 prospective cases have been collected.
2. All 500 retrospective cases have been collected.

Limitations

This study will be based on cases admitted to a single surgical unit in South Africa. In respect of comparisons, statistics taken from different centres within South Africa may differ slightly. There is no intervention involved in this study. The 500 cases will provide sufficient information regarding patients' narrative regarding delayed presentation.

Ethical Considerations

All patients who are referred to Edendale Hospital for management of acute appendicitis are potentially eligible to take part in this study. All patients will receive standard surgical assessment and management as a part of routine clinical care. However, explicit written consent will be gained from each patient who agrees to become a participant in this study, and it will be reiterated that patient participation in this study is entirely voluntary. Patients will be reminded that participation in the study will not influence or impact on their level of care, according to current management protocol within the Department of Surgery and according to currently accepted internationally recognised medical practice. All patient records will be anonymised immediately for the purposes of this study, and patients will not be identified by name or appearance in the study. There will only be one researcher involved in the collection and analysis of confidential data for this study, who, as noted above is the researcher, with the exception of Mr. Stephen Van der Linde, who will be involved in providing general advice about in-depth statistical analysis using SPSS.

Appendix 3: Data Collection Proforma

Demographics			**Outcome**			
Age			Open Abdomen			
Sex			Relaparotomy	Number	Indication	Findings
Referral	Self Presentation					
	Local Clinic		Penumonia			
	GP		Renal Failure			
	Distrcit Hospital		Wound Sepsis			
			Others			
Delay						
			Post Operative Stay			
Previous Contact with HCP						
Location			Ward	Days		
Admission			ICU	Days		
Representation						
Transfer Time			ICU Stay	Days		
Others			Hospital Stay	Days		
Clinical Presentation						
			Antibiotics Type			
Anorexia			Antibiotics Duration	Days		
Nausea Vomiting						
Migratory Pain						
Non Migratory Pain			**Notes**			
Dysuria						
Diarrhoea						
Constipation						
Tender RIF Only						
Local Peritonitis						
General Peritonitis						
Temp						
Heart Rate						
White Cell Count						
WCC Shift						
Operative Data						
Incision						
Lanz						
Gridiron						
Laparoscopy						
Laparotomy						
Findings						
Inflammed Appendix						
Perforated, Localised Sepsis						
Perforated, Generalised Sepsis						
Others						

Appendix 4: Patient Questionnaire

Template used for Part Three of the study relating to factors associated with delay presentation.

Patient Questionnaire

Demographics:

Please circle the appropriate answer:

Which healthcare facility did you visit prior to being admitted at Edendale Hospital?

1. You came directly to the Emergency Department at Edendale Hospital.
2. Your local clinic.
3. Your GP's clinic.
4. Another hospital:
    a) Rietvlei Hospital
    b) Christ The King Hospital
    c) St. Apollinaris Hospital
    d) East Griqualand Usher Memorial Hospital
    e) Another hospital

Delay:

Please answer in the space provided, or circle the relevant answer:

1. How long did it take you to get to Edendale Hospital from the above named facility? (If you came directly to the Emergency Department, how long did it take you to get here?/ please state N/A.)

    ………………………………………………………………………………………………

2. Were you admitted to or discharged from any of the above facilities prior to being referred to Edendale Hospital?

    Yes/No

3. On what date were you admitted to the facility you have named above?

    ………………………………………………………………………………………………

4. In hours and/or minutes, approximately how long did you spend in the above named facility?

    ………………………………………………………………………………………………

5. Did you present to the above named facility because your condition/symptoms changed?

    ………………………………………………………………………………………………

6. How long did you have to wait for an ambulance to arrive?

……………………………………………………………………………………………..

7. In hours and/or minutes, approximately how long was your ambulance journey to Edendale Hospital?

……………………………………………………………………………………………..

8. Have you at any stage during this illness sought help from traditional healers?

   Yes/No

   If so, when

   ……………………………………………………………………………………………..

Clinical Presentation:

Please circle the appropriate answer:

Have you at any stage during this episode of illness experienced any of the following symptoms?

1. Poor appetite.
2. Nausea or vomiting.
3. Abdominal pain (occurring in different locations).
4. Abdominal pain (occurring in the same location).
5. Pain on passing urine.
6. Diarrhoea.
7. Constipation.
8. Other (Please specify)

   ………………………………………………………………………………………………

Appendix 5: UHERB Ethics Approval

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

U. H. E. R. B
UMGUNGUNDLOVU HEALTH ETHICS REVIEW
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19 March 2011

Dr. Victor KONG, Dr. Bojana BULAJIC
Department of General Surgery
Pietermaritzburg Metropolitan Hospital Complex
KwaZulu Natal, SOUTH AFRICA

Dear Dr. Kong, Dr. Bulajic

Re: - An audit of outcomes of complicated appendicitis

UHERB has reviewed your proposal and is happy with it.

You have been granted full ethical approval to proceed with your study.

D L Clarke

DR DL CLARKE
CHAIRPERSON – U H E R B.
PIETERMARITZBURG

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

Appendix 6: BREC Ethics Approval

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
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14 March 2013

Dr V Kong
Department of General Surgery
School of Clinical Medicine
University of KwaZulu-Natal

Dear Dr Kong

PROTOCOL: The spectrum, outcome and cost of acute appendicitis at Edendale Hospital and its related catchment areas. REF: BE237/12

EXPEDITED APPLICATION - RATIFICATION

This letter serves to notify you that at a full sitting of the Biomedical Research Ethics Committee meeting held on **12 March 2013**, the Committee **RATIFIED** the sub-committee's decision to approve the above study.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics