Acute appendicitis in the developing world is a morbid disease

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ABSTRACT

INTRODUCTION Acute appendicitis in the developing world has a markedly different disease profile to that in the developed world.

METHODS A retrospective study was undertaken over a four-year period at a university hospital in South Africa to review the disease spectrum and the clinical outcome of acute appendicitis.

RESULTS A total of 1,004 patients (54% male, median age: 18 years) with intraoperatively confirmed appendicitis were reviewed. Over half (56%) were from the urban district within the city of Pietermaritzburg and the remaining 44% were from the rural health district. The median duration of illness from onset to definitive care was 4 days. Sixty per cent of appendices were perforated and associated with intra-abdominal contamination. Forty per cent of patients required reoperation to control intra-abdominal sepsis. Ten per cent required admission to the intensive care unit. The median overall length of hospital stay was 5 days. The mortality rate was 1%.

Rural patients had a longer median duration of illness (3 vs 5 days, $p<0.001$) as well as a more advanced disease profile associated with perforation and severe intra-abdominal sepsis (19% vs 71%, $p<0.001$). Female patients had a longer median duration of illness (3 vs 4 days, $p<0.001$), were more likely to present with severe intra-abdominal sepsis (31% vs 54%, $p<0.001$) and were more likely to require a laparotomy (50% vs 73%, $p<0.001$). The total cost of managing the entire cohort of 1,004 patients over the 4-year period was £2,060,972.

CONCLUSIONS Acute appendicitis in South Africa is a serious disease associated with significant morbidity. Late presentation is common. Female and rural patients have the worst clinical outcomes, with significant cost to the health system.

KEYWORDS

Appendicitis – Complication – Spectrum

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Acute appendicitis is the most common surgical emergency worldwide.¹ The estimated overall lifetime incidence is approximately 10% and there is evidence that this is increasing.^{2,5} There has been renewed interest in this condition in both the developed and the developing world.⁴ In the developed world, the focus of research has been on the role of advanced imaging, non-operative management and the benefits of laparoscopic appendicectomy.⁵ However, the available literature shows that appendicitis in the developing world has a very different profile, which is associated with significant morbidity and even mortality.^{2,6,7} Late clinical presentation and difficulty in accessing healthcare facilities are often major contributing factors to this advanced disease profile.^{8,9}

Appendicitis has also been the focus of research on the different outcomes according to social status and of systems type research, which sees the disease as a marker of the quality of a surgical service in the developing world.¹⁰ This review of acute appendicitis over a four-year period in a major university hospital in South Africa provides an

overview of the spectrum and outcome of this disease in the region, offering insight into the differences between the disease in the developing world and the developed world.

Methods

This was a retrospective study undertaken at Edendale Hospital (EDH) in Pietermaritzburg, South Africa. A prospectively maintained clinical registry was reviewed retrospectively over a period of four-years (January 2010 – December 2013). Ethics approval for this study was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (reference BE 237/12). EDH serves a predominantly black African population. The catchment area encompasses the city of Pietermaritzburg, the periurban Umgungundlovu health district and the rural Sisonke health district, with a total population of over 1.5 million people.

All patients who presented to EDH with intraoperatively confirmed acute appendicitis were eligible for inclusion in

the study. Basic demographic details (age, sex) were collected from admission charts and specific information regarding the mode of presentation was sought. Any patients who presented from the city of Pietermaritzburg and the Umgungundlovu health district were classified as 'urban' patients while those who were referred from any hospital in the Sisonke health district (SHD) were classified as 'rural' patients.

The clinical symptoms, physical examination findings, baseline vital signs and laboratory results were obtained directly from patient charts. Operative details included the type of surgical approach (local incision [Lanz or gridiron], laparoscopic or laparotomy), the macroscopic appearance of the appendix, presence of perforation, degree of intra-abdominal contamination and the need for temporary abdomen closure. The clinical course of each patient was followed up until discharge (or death). This included the need for reoperation, intensive care unit (ICU) admission, any major complications and death.

Costing

In a previous study, we constructed a microcosting model on the management of acute appendicitis at our institution using an index sample of 200 consecutive patients over a 1-year period.¹¹ The costing was based primarily on disease severity. The mean cost for managing each patient was 6,578 ZAR (£566) for uncomplicated appendicitis, 14,791 ZAR (£1,272) for perforation with localised intra-abdominal sepsis, 34,773 ZAR (£2,990) for perforation with generalised intra-abdominal sepsis without ICU admission and 77,816 ZAR (£6,692) when ICU admission was required. We used this cost model to establish the total cost of acute appendicitis to our institution over the current four-year study period.

Statistical analysis

Statistical analysis was performed using Stata® version 13.0 (StataCorp, College Station, TX, US). Specific analysis was performed to determine whether there is any difference in clinical features and outcome of patients who were from either urban or rural regions. Further analysis was performed to determine whether any sex difference influenced the clinical outcome. Pearson's chi-squared test was used to identify significant differences in frequencies of categorical explanatory variables by group (ie urban vs rural or male vs female). If the expected cell count was less than 5 observations, then the Fisher's exact test was used instead. The Mann-Whitney U test was performed to identify any significant differences in the mean rank of a given continuous explanatory variable by group (urban vs rural or male vs female) as the assumptions of the standard t-test were not met. Statistical significance was set at a *p*-value of <0.05.

Results

During the 4-year study period, a total of 1,004 patients were identified. Of these, 541 (54%) were male and the median age of all patients was 18 years (interquartile range [IQR]: 12–26 years). More than half of the patients

Table 1 Clinical symptoms

Clinical symptoms	Frequency
Nausea +/- vomiting	707 (70%)
Non-migratory pain	680 (68%)
Anorexia	578 (58%)
Migratory pain	324 (32%)
Diarrhoea	46 (5%)
Constipation	41 (4%)
Dysuria	23 (2%)

(*n*=563, 56%) were urban, with 441 (44%) being rural in origin.

Clinical presentation

The median duration from onset of symptoms to first contact with the healthcare system was 4 days (IQR: 2–6 days). A third (32%) of patients described a migratory pattern of abdominal pain and the remaining two-thirds (68%) had non-migratory, non-specific abdominal pain. The relative frequency of the associated symptoms is summarised in Table 1.

Overall, 544 patients (54%) had localised peritonitis on presentation while the remaining 460 (46%) had generalised peritonitis. The median temperature on presentation was 37.5°C (IQR: 37.0–38.0°C), the median heart rate was 101bpm (IQR: 90–113bpm) and the median leucocyte count was $14.5 \times 10^9/l$ (IQR: 12.0 – $17.5 \times 10^9/l$).

Operative findings

A total of 610 patients (61%) required a laparotomy, 361 (36%) underwent an appendicectomy via a local incision and 33 (3%) had a laparoscopic appendicectomy. Intraoperatively, 405 appendices (40%) were found to be inflamed without perforation. The remaining 599 (60%) were perforated and associated with intra-abdominal contamination. Of the 599 patients with perforated appendices, 181 (30%) were associated with localised intra-abdominal contamination and the remaining 418 (70%) were associated with generalised intra-abdominal sepsis.

Clinical outcome

Ten per cent of all patients required admission to the ICU. The median duration of ICU stay was 5 days (IQR: 2–7 days). All other patients were admitted to the general surgical wards. The median overall length of hospital stay for all patients was 5 days (IQR: 2–10 days). Almost a quarter of patients (*n*=234, 23%) required temporary abdominal closure. A total of 406 patients (40%) required one or more reoperation to control intra-abdominal sepsis. Fifteen per cent (*n*=146) developed minor wound sepsis, eight per cent (*n*=83) developed nosocomial pneumonia, six per cent (*n*=57) developed renal failure and two per cent of complications (*n*=20)

Table 2 Urban versus rural patients

Characteristics	Urban (n=563)	Rural (n=441)	p-value
Male	367 (65%)	174 (39%)	<0.001
Female	196 (35%)	267 (61%)	
Median age (years)	18 (IQR: 12–26)	18 (IQR: 12–26)	0.815
<i>Clinical presentation</i>			
Median duration of illness (days)	3 (IQR: 2–4)	5 (IQR: 4–7)	<0.001
Localised peritonitis	439 (78%)	105 (24%)	<0.001
Generalised peritonitis	124 (22%)	336 (76%)	<0.001
Median temperature (°C)	37.2 (IQR: 36.9–37.9)	37.9 (IQR: 37.0–38.2)	<0.001
Median heart rate (bpm)	99 (IQR: 88–110)	105 (IQR: 96–120)	<0.001
Median leucocyte count (x 10 ⁹ /l)	14.0 (IQR: 11.9–16.0)	15.7 (IQR: 12.5–19.6)	<0.001
<i>Surgical approach</i>			
Local incision	330 (59%)	64 (15%)	<0.001
Laparotomy	233 (41%)	377 (85%)	<0.001
<i>Operative findings</i>			
Inflamed, non-perforated	345 (61%)	60 (14%)	<0.001
Perforated	218 (39%)	381 (86%)	<0.001
Perforated, localised intra-abdominal sepsis	111 (20%)	70 (16%)	0.116
Perforated, generalised intra-abdominal sepsis	107 (19%)	311 (71%)	<0.001
<i>Clinical course</i>			
Temporary abdominal closure	57 (10%)	177 (40%)	<0.001
Relaparotomy	108 (19%)	298 (68%)	<0.001
Intensive care unit admission	18 (3%)	77 (17%)	<0.001
Median hospital stay (days)	3 (IQR: 2–6)	9 (IQR: 6–13)	<0.001
<i>Outcome</i>			
Wound sepsis	43 (8%)	103 (23%)	<0.001
Pneumonia	22 (4%)	61 (14%)	<0.001
Renal failure	9 (2%)	48 (11%)	<0.001
Other	5 (1%)	15 (3%)	0.005
Death	4 (1%)	9 (2%)	0.064

IQR = interquartile range

were classified as 'other'. The overall mortality rate was 1% (n=13).

Urban versus rural patients

There were 563 patients from the urban regions and 441 from the rural regions. Rural patients had a longer median duration of illness prior to contact with the healthcare service (3 vs 5 days, $p<0.001$), and a more advanced disease profile associated with perforation and severe intra-abdominal sepsis (19% vs 71%, $p<0.001$). Significantly more rural patients required ICU admission (3% vs 17%, $p<0.001$) and a longer median hospital stay (3 vs 9 days,

$p<0.001$). Table 2 summarises the comparison of 563 patients from the urban regions against the 441 patients from the rural regions.

Male versus female patients

Of the 1,004 patients, 541 were male and 463 were female. Female patients had a longer median duration of illness (3 vs 4 days, $p<0.001$), were more likely to present with severe intra-abdominal sepsis (31% vs 54%, $p<0.001$) and were more likely to require a laparotomy (50% vs 73%, $p<0.001$) as well as a relaparotomy (31% vs 52%, $p<0.001$) to control intra-abdominal sepsis. The median length of

Table 3 Male versus female patients

Characteristics	Male (n=541)	Female (n=463)	p-value
Urban	367 (68%)	196 (42%)	<0.001
Rural	174 (32%)	267 (58%)	
Median age (years)	17 (IQR: 11–25)	19 (IQR: 14–28)	<0.001
<i>Clinical presentation</i>			
Median duration of illness (days)	3 (IQR: 2–5)	4 (IQR: 2–6)	<0.001
Localised peritonitis	357 (66%)	187 (40%)	<0.001
Generalised peritonitis	184 (34%)	276 (60%)	<0.001
Median temperature (°C)	37.3 (IQR: 37.0–38.0)	37.8 (IQR: 37.0–38.0)	<0.001
Median heart rate (bpm)	100 (IQR: 89–110)	104 (IQR: 95–120)	<0.001
Median leucocyte count (x 10 ⁹ /l)	13.8 (IQR: 11.2–16.0)	15.2	<0.001
<i>Surgical approach</i>			
Local incision	268 (50%)	126 (27%)	<0.001
Laparotomy	273 (50%)	337 (73%)	<0.001
<i>Operative findings</i>			
Inflamed, non-perforated	262 (48%)	143 (31%)	<0.001
Perforated	279 (52%)	320 (69%)	<0.001
Perforated, localised intra-abdominal sepsis	109 (20%)	72 (16%)	0.059
Perforated, generalised intra-abdominal sepsis	170 (31%)	248 (54%)	<0.001
<i>Clinical course</i>			
Temporary abdominal closure	106 (20%)	128 (28%)	0.003
Relaparotomy	166 (31%)	240 (52%)	<0.001
Intensive care unit admission	47 (9%)	48 (10%)	0.365
Median hospital stay (days)	4 (IQR: 2–9)	7 (IQR: 3–12)	<0.001
<i>Outcome</i>			
Wound sepsis	56 (10%)	90 (19%)	<0.001
Pneumonia	36 (7%)	47 (10%)	0.045
Renal failure	19 (4%)	38 (8%)	0.001
Other	6 (1%)	14 (3%)	0.031
Death	4 (1%)	9 (2%)	0.093

hospital stay was significantly longer (4 vs 7 days, $p<0.001$). Table 3 summarises the comparison of the 541 male against the 463 female patients.

Cost of management

Based on our previously published microcosting model, the total cost of managing the entire cohort of 1,004 patients over the 4-year period was £2,060,972. The cost components according to the disease severity are shown in Table 4.

Discussion

Acute appendicitis is the most common surgical emergency worldwide, with an overall incidence of approximately

52 cases per 100,000 population.^{1,12,15} Papers from South Africa published over a decade ago estimated that the incidence among black Africans was 10 per 100,000,^{12,15} with more recent studies suggesting a progressive increase approaching that of the developed world.¹ It has been postulated that rapid westernisation and changes in dietary habits are responsible for this increase.^{12,15} Compared with the developed world, appendicitis in South Africa is a far more sinister disease that is frequently associated with significant morbidity and even mortality.^{1,6,8,9}

Acute appendicitis is a time dependent pathology and once the pathological process is initiated, it pursues a relentless course.^{14,15} If perforation has occurred, further delay in treatment leads to dissemination of the intra-

Table 4 Cost of management for all 1,004 patients by disease severity				
	Non-perforated appendix	Perforated, localised sepsis	Perforated, generalised sepsis, no ICU	Perforated, generalised sepsis, ICU
Number of patients	405	181	323	95
Mean cost per patient	£566	£1,272	£2,990	£6,692
Total cost	£229,230	£230,232	£965,770	£635,740
ICU = intensive care unit				

abdominal sepsis.^{14,15,16} It has been suggested that the risk of perforation is low initially following the onset of symptoms but this increases dramatically after 12–36 hours (5–8%).^{14,15}

The commonly quoted perforation rate from literature in the developed world ranges from 15% to 30%.¹⁷ Our current study, however, shows a rate of over 60%. Although this far exceeds the rates seen elsewhere in the developed world, it is similar to that from other studies from sub-Saharan Africa (40–50%).^{1,6,7} Timely surgical intervention has been shown consistently to be the most appropriate means to abate the pathological process and is still the most widely accepted management approach.¹ Despite this, there is some evidence to suggest that intravenous antibiotics alone may be considered in highly selected cases.⁵ Nevertheless, given the severity of disease seen in the developed world, the case for conservative treatment in sub-Saharan Africa may be difficult to justify at present.

Delay in clinical presentation due to poor access to appropriate surgical facilities has been considered as one of the most important determinants of clinical outcome.^{8,9} We have shown that the majority of patients from the rural regions have a protracted delay in presentation and fare worse than their urban counterparts, with over 70% presenting with severe intra-abdominal sepsis.

Our previous study suggested that the reasons for this delay are multifactorial.^{8,9} Delay due to health seeking behaviour is difficult to quantify and is influenced by numerous sociological factors. When patients attempt to access the health system, geographical distance from the rural hospital facilities may be problematic and this is often referred to as ‘prehospital delay’. On the other hand, there is evidence to suggest that significant delays are also encountered frequently when patients are assessed at rural hospitals. This is termed ‘in-hospital delay’. As the experience of staff at these facilities is extremely heterogeneous, inappropriate management is common and includes inappropriate periods of observation or inappropriate discharge. Once the decision to refer has been made, there are numerous logistical difficulties associated with transporting patients to facilities for definitive surgery. These factors all contribute to this significant difference in clinical outcome.

Appendicitis remains a clinical diagnosis that is notoriously difficult to make.¹⁸ The classic textbook presentation is relatively uncommon. Although sophisticated imaging technology has allowed early diagnosis in many centres in

the developed world, this is often not available in the developing world. The diagnosis is particularly difficult in female patients as it can be easily confused with a large number of gynaecological pathologies. A study by Rothrock *et al* showed that up to 33% of women of childbearing age with appendicitis were initially misdiagnosed, leading to significant adverse outcome.¹⁹ We have shown that for female patients, the perforation rate and subsequent clinical course (including the need for relaparotomy) were comparatively higher than for male patients. We believe that delay in diagnosis may have contributed to this difference in outcome.

Appendicitis is known to have a worse outcome among immigrants, racial minorities, rural patients, women and socially disadvantaged people in many regions of the world.^{8,9,20} We have highlighted these differences in clinical outcomes in a racially cohesive cohort of patients, and have shown that female sex and rural origin were important individual risk factors for poor outcome.

The previous neglect of surgical services by public health planners and advocates is being challenged by burgeoning research in global surgery and global health.¹⁰ Appropriate surgical services are understood increasingly to be cost effective health interventions even in the developing world.^{10,11} The financial implications of inadequate and poor quality surgical services are stark. Delay in diagnosis and in definitive treatment certainly contributed significantly to an estimate of over £2 million spent managing this single disease entity over the four-year study period. More efficient surgical services are a key investment if we wish to reduce the morbidity associated with this disease and to contain cost.

Conclusions

Acute appendicitis in South Africa is a serious disease associated with significant morbidity. Complications associated with appendiceal perforation far exceed those reported in the developed world. Late presentation is common, with female rural patients suffering the worst clinical outcomes. The cost to the healthcare system is substantial.

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