The role of treatment delays in surgical site infection after appendicectomy in a South African rural regional hospital

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Background. Delays to surgery for acute appendicitis in low- and middle-income countries lead to significant morbidity.
Objectives. To investigate the role of time to surgery in the development of complicated appendicitis and surgical site infection (SSI) in a rural referral hospital in South Africa (SA).
Methods. A prospective cohort study was conducted of all patients presenting to a regional hospital in SA with acute appendicitis during 2017. Inpatient interview and data collection were followed by 30-day post-surgical follow-up to assess time periods to surgery and operative outcomes.
Results. A total of 188 patients underwent surgery for acute appendicitis. The median (interquartile range (IQR)) age was 19 (3 - 73) years, and 62% were male. The median (IQR) time from symptoms to surgery was 60 (42 - 86) hours and from hospital admission to surgery 8 (4 - 16) hours. Forty-one percent were managed laparoscopically, 62% had complicated appendicitis, and 25% developed SSI. Time from symptoms to surgery >72 hours was associated with an increased risk of complicated appendicitis (odds ratio (OR) 4.32; 95% confidence interval (CI) 1.36 - 13.75; p=0.013). Patients with SSI had an increased median delay of 15 hours (p=0.05) compared with those without SSI. Multivariable analysis showed that the risk of SSI increased with complicated appendicitis (OR 8.96; 95% CI 2.73 - 29.41; p<0,001) and decreased with laparoscopic surgery (OR 0.21; 95% CI 0.07 - 0.59; p=0.003). Time to surgery had no effect on the risk of SSI in adjusted analyses.
Conclusions. Delays to surgery beyond 72 hours significantly increased complicated appendicitis, an important risk factor for SSI. Access to facilities with surgical capability and the use of laparoscopic surgery are modifiable risk factors for SSI.

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Surgical site infection (SSI), also known as surgical wound infection, is a major contributor to postoperative morbidity and mortality and is now the most common hospital-associated infection in the USA.[1,2] SSI is a major contributor to healthcare costs through increased length of hospital stay (LoS), antibiotic use, use of diagnostic modalities, surgical procedures and wound care consumables.[3,4]

The presence of complicated appendicitis (gangrenous, perforated with local collection or perforated with general peritonism) is a major predictor for the development of SSI.[5-7] In high-income countries (HICs), the incidence of complicated appendicitis varies between 12.8% and 45%.[8,9] The reported risk of developing SSI is 0.6 - 3.2% for uncomplicated and 3.9 - 19% for complicated appendicitis.[6,9,10] In low- and middle-income countries (LMICs), barriers to quality surgical care profoundly affect outcomes of patients in need of emergency surgery.[11] Patients in these countries with acute appendicitis often present with significant delay and subsequently more advanced disease, such as general peritonitis or four-quadrant pus.[12] Rates of complicated appendicitis of >60% have been reported, leading to an increase in SSI, reoperation, critical care unit admission and mortality.[13]

Determining the effect of time to treatment on the development of SSI in appendicitis is necessary, because time is a variable in the pathogenesis of appendicitis that can be addressed by healthcare providers and systems. Improved access to surgical care and better in-hospital logistics and patient flow may reduce the rate of SSI.

Objectives

The primary objective of this study was to assess the role that time to definitive surgery plays in the development of SSI in patients undergoing surgery for acute appendicitis. Secondary analyses assessed the effect of time to surgery on the development of complicated appendicitis, and the influence of surgical modality on the development of SSI.

Methods

A prospective cohort of consecutive patients undergoing surgery for acute appendicitis was recruited over a period of 1 calendar year (2017) at Worcester Regional Hospital, a rural referral centre in Western Cape Province, South Africa. The hospital functions as the primary referral centre for eight district (primary-level) hospitals and a local community health centre. The Department of General Surgery services a public healthcare population projected at ~850 000.[14]

Data were prospectively captured for time to definitive operative management, in hours, from symptom onset and hospital admission. Data on age, sex, inflammatory markers, presence of complicated appendicitis and operative modality were collected on admission, together with in-hospital mortality, total length of stay (LoS), and duration of any readmission. The severity of the appendicitis found at operation was classified according to the American Association for the Surgery of Trauma (AAST) grading system for acute appendicitis.[5]

Presumed appendicitis was diagnosed on clinical and biochemical grounds only, and confirmed at surgery; only then was the patient enrolled into the study. Computed tomography scans were not used for the diagnosis of appendicitis, and no patient with appendicitis was managed conservatively. Laparoscopic surgery was the planned standard of care for patients with localised peritonism, and open surgery was the primary approach for those with diffuse peritonism and haemodynamic instability. Amoxicillin-clavulanic acid was given per protocol to >90% of patients within 2 hours of the provisional diagnosis of appendicitis. It was stopped in uncomplicated appendicitis and continued for 5 days after surgery in the complicated appendicitis group.

The presence and severity of SSIs was assessed during the 30-day time period after surgery using the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) SSI classification.[15-17]

Telephonic follow-up at 30 days from surgery was attempted in all patients not readmitted for SSIs, and those with mobile phones were supplied with a 30-day airtime/data voucher to facilitate this process. In addition, the provincial electronic data-keeping system was used to evaluate the nature of any healthcare contact during the 30-day period following surgery for those patients who could not be directly contacted.

Stata version 13.1 (StataCorp, USA) was used for statistical analysis. Measures of central tendency and distribution were calculated as the mean with standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. Comparative analysis was performed on numerical data using unpaired t-tests for continuous data and χ^2 tests for categorical data. Missing data were handled using complete case analysis.

Logistic regression modelling was used to explore the effect of time and other risk factors on the odds of both complicated appendicitis and SSI. Exploratory data analysis showed that data for treatment delays were highly right-skewed. Although normally distributed data are not required for logistic regression, regression using log-transformed time data showed a smaller log likelihood, indicating a better fit to the logistic model and greater power. SSI was regressed on time from first symptom to surgery, using both log-transformed time and untransformed 24-hour intervals, and adjusted for age, sex, complicated appendicitis and operative modality. Statistical significance was set at $p<0.05$.

Research ethics approval was obtained from the Stellenbosch University Human Research Ethics Committee (ref. no. S16/09/166) and permission to conduct the study from the Department of Health, Western Cape Government (ref. no. WC_2017RP42_521). Informed consent was obtained from all study participants.

Results

One hundred and eighty-eight consecutive patients underwent operation for acute appendicitis. The median (IQR) age was 19 (3 - 73) years, and 62% of patients were male. Seventy-seven of 188 patients (41%) had a laparoscopic appendicectomy. Forty-one patients (22%) received open surgery when a laparoscopic approach was indicated, owing to lack of availability of shared laparoscopic resources at the time of the operation. Ten laparoscopic procedures were converted to open surgery and the operative outcome was captured as such. Conversion was not related to surgeon experience. Two patients presented with advanced appendicitis and died of sepsis-related multiorgan failure without developing SSI. Their times between symptom onset and definitive treatment were 206 and 111 hours. Overall, the median (IQR) LoS was 3 (2 - 5) days, and 24 patients required readmission for SSI.

Thirty-day follow-up was possible for only 117 patients. Together with the 2 patients who died, 119/188 (63%) of patients were recorded as having complete follow-up. Five patients were unable to supply a contact number, and 64 could not be contacted on the telephone numbers they had provided. The provincial electronic health system showed no evidence of healthcare contact in the public sector other than suture removal during the follow-up period for these patients, but those without telephonic or personal follow-up were recorded as having missing outcome data. Patients with missing and complete follow-up data are compared in Table 1. There were minimal differences between the two groups, apart from younger age in those with incomplete follow-up.

Treatment delays

The median (IQR) time from symptom onset until definitive surgery was 60 (41 - 85) hours, from first healthcare contact to surgery 25 (13 - 42) hours, from regional hospital admission to surgery 8 (4 - 16) hours, and from decision to operate to surgery 5 (2 - 8.25) hours. The detailed breakdown of the delays from symptom onset and from regional hospital admission to definitive treatment are shown in Table 2. One hundred and twenty-seven of 188 patients (67%) were referred from a district hospital that had a functioning operating theatre but lack of surgical expertise. These patients experienced an additional median (IQR) delay of 12 (7 - 33) hours compared with patients presenting directly to the regional hospital.

Complicated appendicitis

Sixty-two percent of patients (117/188) had complicated appendicitis (AAST II - V) (Table 3). Logistic regression analysis of the relationship between complicated appendicitis and time to surgery, adjusted for age and sex, is shown in Table 4. Using time to surgery of up to 24 hours as a reference, patients undergoing operation beyond 72 hours showed significantly increased odds of having complicated appendicitis. When log-transformed time was used in the adjusted regression, the odds ratio (OR) was 2.27 (95% CI 1.37 - 3.77), equivalent to an OR of ~1.7 for each doubling of time (p=0.002).

Table 1. Comparison between patients with complete and incomplete 30-day post-discharge follow-up (*N*=188)

Variable	Complete follow-up (*N*=119)	Incomplete follow-up (*N*=69)	*p*-value
Age (years), median (IQR)	21 (13 - 34)	16 (12 - 27)	0.04
Gender male, %	63.9	58.0	0.4
Time from symptom onset to surgery (hours), median (IQR)	59 (43 - 91)	60 (38 - 79)	0.3
Complicated appendicitis, *n* (%)	78 (65.5)	39 (56.5)	0.3
Laparoscopic appendicectomy, %	37.8	44.9	0.3

IQR = interquartile range.

Surgical site infection

Forty-six patients were known to have developed SSI. This figure represents 25% (46/188) of the total cohort, or 39% (46/119) of those who could be contacted postoperatively.

SSIs were superficial surgical site (grade 1) in 18 patients (39%), deep surgical site (grade 2) in 11 (24%), and intra-abdominal collections (grade 3) in 17 (37%). Nine patients required surgical wound debridement and 17 required a relook laparotomy.

For the 119 patients with known outcomes, patients with and without SSI are compared in Table 5. Patients with SSI had a 15-hour increase in median time from symptoms to surgery, less laparoscopic surgery, higher rates of complicated appendicitis and longer LoS.

Regression analysis of risk factors for SSI using complete case analysis did not show a statistically significant increase in odds for time when 24-hour intervals were used as the time variable. Adjusted and unadjusted regressions using log-transformed time are shown in Table 6. Univariable logistic regression analysis showed a significant effect of log-time from symptom onset to surgery on the odds of developing an SSI. An increased odds of 1.89 for each natural log increase is equivalent to an ~66% increased odds for each doubling of time. However, this association lost statistical significance when mode of surgery and the presence of complicated appendicitis were added to the model. The odds of SSI were significantly increased for patients with complicated appendicitis and significantly reduced for males and laparoscopic surgery when adjusting for other factors in the model.

Table 2. Median time to treatment in patients undergoing appendicectomy for acute appendicitis (*N*=188)

Time from symptom onset to surgery (hours)	
Median (IQR)	60 (41.8 - 85.5)
0 - 24, *n* (%)	16 (8.5)
25 - 48, *n* (%)	40 (21.3)
49 - 72, *n* (%)	63 (33.5)
>72, *n* (%)	69 (36.7)
Time from regional hospital admission to surgery (hours)	
Median (IQR)	8 (4 - 16)
0 - 6, *n* (%)	71 (37.8)
7 - 12, *n* (%)	57 (30.3)
13 - 24, *n* (%)	46 (24.5)
>24, *n* (%)	14 (7.4)

Table 3. Operative findings in patients undergoing surgery for acute appendicitis (*N*=188)

Findings	*n* (%)
AAST I (inflamed)	71 (37.8)
AAST II (gangrenous)	7 (3.7)
AAST III + IV (locally perforated)	69 (36.7)
AAST V (perforated with general peritonism/pus)	41 (21.8)
Total	188 (100)

AAST = American Association for the Surgery of Trauma.

Discussion

The patients in this study had a high incidence of complicated appendicitis and SSI. The development of SSI had a profound effect on patient morbidity and healthcare resources; a substantial increase in median LoS was demonstrated with SSI, and more than half of the patients with SSI needed reoperation to control sepsis.

Many patients experienced long delays to surgery, with 37% of patients waiting >72 hours. Longer delays between symptom onset and surgery significantly predicted both complicated appendicitis and SSI in unadjusted analyses, but the effect on SSI was not apparent after adjusting for severity of appendicitis in a multivariable analysis, suggesting that complicated appendicitis is part of a causal pathway between treatment delay and the development of SSI.

Literature from HICs indicates lack of consensus about the relationship between treatment delays and morbidity,[18,19] but this is probably because the delays examined in studies from HICs are much shorter, generally <36 hours.[7,20-22] The finding in this study that extended delays from symptoms to surgery are associated with higher rates of complicated appendicitis and postoperative morbidity is supported by data from other LMICs[13] and a recent systematic review.[23] The discrepancy with literature from HICs is probably a result of the greater magnitude of treatment delays seen in LMICs.

The delays in our context demonstrate the problems in access to surgery for this largely rural population. A median (IQR) in-hospital delay of 8 (4 - 16) hours indicated that the referral hospital logistics were acceptable and that the major source of delay was access to a surgical facility. More than two-thirds of patients in this study presented primarily to a district hospital with a functioning operating theatre but could not receive their definitive operative procedure there, usually because of lack of general surgical or anaesthetic skills at district hospital level.[24,25] These patients experienced an additional median treatment delay of 12 hours.

Female sex and open surgery were shown independently to increase the risk of SSI when treatment delays and severity of appendicitis were controlled for in multivariate logistic regression analysis. Our findings add to the growing evidence that laparoscopic appendicectomy reduces the risk of SSI,[26-28] but the reason for the increased risk of SSI in females is unclear and no similar observation has been made in other studies.

Table 4. Logistic regression analysis showing odds of complicated appendicitis in relation to days from symptom onset to surgery in patients with acute appendicitis (*N*=188)

Time from symptom onset to surgery (hours)	Uncomplicated appendicitis (AAST I) (*N*=71), *n* (%)	Complicated appendicitis (AAST II-IV) (*N*=117), *n* (%)	Univariable regression OR (95% CI)	Univariable regression *p*-value	Multivariable regression adjusted for age and sex OR (95% CI)	Multivariable regression adjusted for age and sex *p*-value
0 - 24	9 (12.7)	7 (6.0)	Ref.	-	Ref.	-
25 - 48	8 (25.4)	22 (18.8)	1.57 (0.45 - 5.05)	0.45	1.61 (0.49 - 5.27)	0.43
49 - 72	26 (36.6)	37 (31.6)	1.83 (0.60 - 5.54)	0.28	1.82 (0.59 - 5.58)	0.29
>72	18 (25.3)	51 (43.6)	3.64 (1.18 - 11.21)	0.02	4.32 (1.36 - 13.75)	0.01

AAST = American Association for the Surgery of Trauma; OR = odds ratio; CI = confidence interval.

Table 5. Comparative characteristics between patients with no SSI and those with SSI (*N*=119)

Variable	No SSI (*N*=73)	SSI (*N*=46)	*p*-value
Age (years), median (IQR)	23 (15 - 32)	18 (11 - 37)	0.37
Gender male, %	71.2	54.3	0.06
Time from symptoms to surgery (hours), median (IQR)	56 (39 - 84)	71 (50 - 116)	0.05
Time from regional hospital admission to surgery (hours), median (IQR)	10 (4 - 17)	8 (4 - 16)	0.53
Complicated appendicitis/AAST II - V, *n* (%)	36 (49.3)	41 (89.1)	0.0001
Surgical modality laparoscopic, *n*/*N* (%)	38/73 (52.1)	8/46 (17.4)	0.0001
Length of stay (days), median (IQR)	2.0 (2 - 4)	9.5 (6.25 - 19.5)	0.0001

SSI = surgical site infection; IQR = interquartile range; AAST = American Association for the Surgery of Trauma.

Table 6. Uni- and multivariable logistic regression analysis showing odds of SSI for patients with known outcomes (*N*=119)

	Univariable logistic regression		Multivariable regression, partially adjusted model		Multivariable regression, full model	
Variable	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Log time from first symptom to surgery	1.89 (1.05 - 3.38)	0.03	2.15 (1.34 - 4.09)	0.02	1.37 (0.69 - 2.70)	0.37
Age	0.99 (0.96 - 1.02)	0.42	0.98 (0.95 - 1.01)	0.15	0.98 (0.95 - 1.02)	0.31
Gender male	0.48 (0.22 - 1.04)	0.06	0.48 (0.22 - 1.06)	0.07	0.33 (0.12 - 0.88)	0.03
Complicated appendicitis	10.79 (3.50 - 33.2)	<0.001	-	-	8.96 (2.73 - 29.41)	<0.001
Laparoscopic surgery	0.20 (0.08 - 0.47)	<0.001	-	-	0.21 (0.07 - 0.59)	0.003

SSI = surgical site infection; OR = odds ratio; CI = confidence interval.

Study limitations

A major weakness of this study was incomplete follow-up for SSI, with almost 37% of the total cohort lost to follow-up during the 30 days following surgery. This probably resulted in an underpowered regression when SSI was regressed on time using 24-hour intervals. Loss to follow-up is a recognised difficulty in SSI surveillance after hospital discharge in LMICs and is a result of limited access to healthcare, financial constraints and transport limitations.[16] In this study, attempts were made to support SSI follow-up by supplementing participants' mobile data costs, but fear of being billed for hospital care may have led to a large number supplying incorrect contact details.

Dealing with missing data is always challenging.[29] Using complete case analysis (CCA) to examine risk factors for SSI resulted in a loss of statistical power and could have led to biased results if the patients with and without follow-up were systematically different. However, CCA has the advantage of transparency, particularly if data are provided that allow comparison of complete and incomplete records. In this study, the group of patients lost to follow-up was younger than patients with complete follow-up but not otherwise significantly different. However, the absence of documented healthcare contact on the provincial central electronic record system in the 30 days following surgery suggests that the CCA may be biased towards patients with higher rates of SSI.

Conclusions

Two modifiable risk factors for SSI were identified. These are the time to reach a hospital with general surgical capability, and use of a laparoscopic approach. Unfortunately, these imply conflicting strategies to reduce SSI. The Lancet Commission on Global Surgery envisaged that the first-level hospital should be the 'core delivery site' for essential emergency surgical services,[11] and in our context, this would mean open appendicectomy by a non-specialist surgeon at the district hospital. While this strategy would reduce time to surgery, it would also reduce access to laparoscopic surgery. The advantages of earlier open surgery at a district hospital closer to the community v. delayed laparoscopic surgery at a more distant regional centre need to be investigated further, but it is likely that the advantage of definitive surgery at the first-level hospital decreases as time required for transfer and delays at the referral hospital decrease. It is difficult to make blanket recommendations about where surgery should take place in LMICs, and strategies to reduce treatment delays can probably be developed more effectively by examining the care pathways of patients who waited >72 hours and using these for local quality improvement initiatives.

Moving forward, we will have to investigate and address the complex socioeconomic factors causing delays in healthcare seeking, support and educate clinicians at district hospitals to rapidly identify and possibly even to surgically manage appendicitis, and apply innovative evolving technology to streamline the referral and movement of this patient population to regional centres if needed.

This study stands in between the appendicitis literature of LMICs and HICs. Prehospital delays, complicated appendicitis and SSIs were similar to other resource-limited settings with barriers in access to healthcare. In-hospital logistics and patient flow in the centre responsible for the operative management, on the other hand, matched studies from HICs. The magnitude of surgical time delays experienced in this study, and others from LMICs, demonstrates the potential effect of delays to definitive management on the morbidity of acute appendicitis.

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