Practical issues in treatment of appendicitis
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CHAPTER 5

Duration of antibiotic treatment after appendectomy for acute complicated appendicitis

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ABSTRACT

**Background |** Antibiotic treatment after appendectomy for complicated appendicitis aims to reduce postoperative infections. However, available data on the duration of treatment are limited. This study compared the difference in infectious complications between two protocols, involving either 3 or 5 days of postoperative antibiotic treatment.

**Methods |** This was an observational cohort study of all adult patients who had an appendectomy between January 2004 and December 2010 at either one of two hospitals in the same region. At location A, the protocol included 3 days of postoperative antibiotic treatment, whereas at location B it specified 5 days. The primary outcome was the development of postoperative infections as either superficial wound infection or deep intra-abdominal infections.

**Results |** A total of 1143 patients with acute appendicitis underwent appendectomy, of whom 267 (23.4 per cent) had complicated appendicitis. The duration of postoperative antibiotic treatment was 3 days in 135 patients (50.6 per cent) and at least 5 days in 123 (46.1 per cent). No difference was found between antibiotic treatment for 3 or 5 days in terms of developing an intra-abdominal abscess (odds ratio (OR) 1.77, 95 per cent confidence interval 0.68 to 4.58; \( P = 0.242 \)) or a wound infection (OR 2.74, 0.54 to 13.80; \( P = 0.223 \)). In patients with complicated appendicitis, the laparoscopic approach was identified as a risk factor for developing an intra-abdominal abscess in univariable analysis (OR 2.46, 1.00 to 6.04; \( P = 0.049 \)), but was not confirmed as an independent risk factor for this complication in multivariable analysis (OR 2.32, 0.75 to 7.14; \( P = 0.144 \)).

**Conclusion |** After appendectomy for complicated appendicitis, 3 days of antibiotic treatment is equally effective as 5 days in reducing postoperative infections.
Duration of antibiotic treatment after appendectomy for acute complicated appendicitis

INTRODUCTION

Acute appendicitis is still the most common intraabdominal infection requiring surgical intervention. Definitions of severity can be assigned to acute appendicitis, but grossly the disease can be divided into two entities: uncomplicated or non-perforated, or complicated disease with perforation of the appendix or the presence of purulent peritonitis. Several randomized clinical trials\(^1\)\(^2\) have shown the feasibility of antibiotic treatment alone for uncomplicated appendicitis, although it is associated with considerable recurrences requiring appendectomy within 1 year. Therefore, appendectomy is still considered the treatment of choice for acute appendicitis. The most frequent complication after appendectomy is infection, seen as wound infection (3.6 per cent for laparoscopic surgery and 7.3 per cent for open surgery) and intra-abdominal abscess (1.6 and 0.6 per cent respectively)\(^3\). The latter is often associated with readmission and need for reintervention. As expected, these complications are more frequent after complicated appendicitis\(^4\).

Perioperative administration of antibiotics has been proven to reduce the number of infectious complications in acute appendicitis\(^5\). Complicated appendicitis is commonly treated by a prolonged antibiotic regimen, although there is no consensus on the exact duration. American guidelines\(^6\) advise restriction of postoperative antibiotic treatment of complicated intra-abdominal infections to 4–7 days. Continuing antibiotics for more than 5 days does not provide further benefit, although the available evidence is restricted mainly to children\(^7\)\(^9\). Currently, many clinics continue antibiotic treatment for between 3 and 5 days after surgery for complicated appendicitis depending on local protocols. However, there is only limited evidence available on duration of antibiotic treatment after appendectomy for complicated appendicitis in adults. This study compared outcomes between two hospitals practising different durations of antibiotic treatment in adults with complicated appendicitis.

METHODS

All adult patients who underwent surgery at Tergooi Hospital for suspected acute appendicitis between January 2004 and December 2010 were included. Tergooi Hospital is a general community teaching hospital situated in the centre of the Netherlands; it has two locations less than 7 km apart at Hilversum and Blaricum (location A and B respectively). Hospital referral is based on the postal code of the patients. Although the hospitals are not far apart, both had their own region of care in the study interval.

A laparoscopic or open approach was selected by the operating surgeon. In laparoscopic appendectomy, three trocars were used and the appendix was removed by means of a linear stapling device. Patients who underwent conversion from a laparoscopic to an open approach were analysed in the laparoscopic group according to the intention-to-treat principle.

All patients received a single intravenous dose of cefamandole (1000 mg) and metronidazole (500 mg) as antibiotic prophylaxis before induction of anaesthesia. For complicated appendicitis, defined as a perforation of the appendix before
or during operation, or appendicitis in the presence of purulent peritonitis, antibiotic treatment was continued for 3 or 5 days after surgery, depending on hospital. The therapeutic antibiotic regimen was cefuroxime (750mg 3 times daily) and metronidazole (500mg 3 times daily), administered intravenously. During the study interval, the standard duration of antibiotic treatment was 3 days at location A and 5 days at location B.

**Data collection** | The patients’ charts, operative reports and discharge letters were reviewed for the presence of complicated appendicitis or prolonged post-operative antibiotic treatment. The primary endpoint was development of a clinically relevant infectious complication, namely an intra-abdominal abscess or wound infection for which readmission, reintervention or antibiotic treatment was necessary. Only in-hospital data were registered; outpatient clinic data were not retrieved. The STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement checklist\(^\text{10}\) was used in this observational cohort study and for preparing the manuscript.

**Statistical analysis** | After assessing the data distribution, normally distributed variables were analysed using Student’s t test. Comparison of the length of hospital admission was done by Mann–Whitney U test. The distribution of dichotomous outcomes was compared using the \(\chi^2\) test. To identify risk factors for infectious complications, univariable odd ratios (ORs) were calculated using logistic regression analysis for each variable. A multivariable logistic regression model was carried out for duration of antibiotic regimen and surgical approach, including all variables with \(P < 0.200\) in univariable analysis. Finally, sensitivity analyses were performed that excluded all patients who did not receive the antibiotic regimen specified in the protocol. \(P < 0.050\) was considered statistically significant. Statistical analyses were done using SPSS\textsuperscript* version 20 (IBM, Armonk, New York, USA).

**RESULTS**

Between January 2004 and December 2010, 1232 adult patients underwent surgery for suspected appendicitis. In 89 patients the appendix was not infected or another diagnosis was found as the primary cause; 1143 patients with an intraoperative diagnosis of acute appendicitis underwent appendectomy. Of these, 597 procedures were performed at location A and 546 at location B. Half of the patients were men, mean age was 42 years and mean duration of hospital admission was 3.7 days.

An open appendectomy was done more frequently than a laparoscopic procedure (655 versus 488; 7.4 per cent converted). The laparoscopic technique was introduced from the end of 2006, and this technique prevailed during the final years. Mean operating time was 51 min, 43 min for open surgery and 61 min for laparoscopic surgery.

Infectious complications developed following appendectomy in 4.6 per cent of patients; 3.1 per cent developed an intra-abdominal abscess and 2.0 per cent a wound infection. A laparoscopic approach was identified as a risk factor for development of an intra-abdominal abscess (OR 2.06, 95 per cent confidence interval 1.04 to 4.10; \(P = 0.039\)). An open approach proved to be a risk factor for wound infections (OR 3.62, 1.22 to 10.69; \(P = 0.020\)).
Complicated appendicitis | Complicated disease in 267 patients (23.4 per cent) was treated after surgery with either 3 or 5 days of antibiotics, according to the local protocol. Baseline characteristics of patients with complicated appendicitis are shown in Table 1. Complicated appendicitis was a risk factor for infectious complications compared with uncomplicated disease (OR 3.59, 2.04 to 6.29; \( P < 0.001 \)). In the event of complicated appendicitis, the antibiotic regimen was prolonged for 3 days in 135 patients (50.6 per cent) and 5 days or more in 123 patients (46.1 per cent). Antibiotic treatment lasted longer than 5 days in seven patients at location B. In nine patients (3.4 per cent) the exact duration of antibiotics could not be retrieved. The median duration of hospital admission was 4 and 6 days in patients who received antibiotics for 3 and 5 days respectively (\( P < 0.001 \)).

Among the patients with continued antibiotic treatment because of complicated disease, 21 (7.9 per cent) developed an intra-abdominal abscess and nine (3.4 per cent) a wound infection. The intraoperative diagnosis in those who developed an abscess was perforation at the start of surgery in 20 patients and purulent peritonitis in one. No difference was found between antibiotic treatment for 3 or 5 days in terms of developing an infectious complication. This was the case for both intra-abdominal abscesses (OR 1.77, 0.68 to 4.58; \( P = 0.242 \)) (Table 2) and wound

| TABLE 1 Baseline characteristics of complicated appendicitis |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Total \((n = 267)\) | Location A \((n = 126)\) | Location B \((n = 141)\) | \( p^* \) |
| Mean age (years)               | 49              | 51              | 46              | 0.062†   |
| Sex ratio (M : F)              | 142 : 125       | 70 : 56         | 72 : 69         | 0.539    |
| Appendectomy                   |                 |                 |                 |          |
| Open                           | 180 (67.4)      | 54 (42.9)       | 126 (89.4)      | < 0.001  |
| Laparoscopic                   | 87 (32.6)       | 72 (57.1)       | 15 (10.6)       | < 0.001  |
| Converted laparoscopy          | 19 (22)         | 19 (26)         | 0 (0)           | 0.003    |
| Mean operating time (min)      |                 |                 |                 |          |
| Open                           | 52              | 74              | 42              | < 0.001† |
| Laparoscopic                   | 77              | 82              | 53              | < 0.001† |
| Type of complicated disease    |                 |                 |                 |          |
| Preoperative perforation       | 212 (79.4)      | 101 (80.2)      | 111 (78.7)      | 0.522    |
| Intraoperative perforation     | 22 (8.2)        | 8 (6.3)         | 14 (9.9)        |          |
| Purulent peritonitis           | 33 (12.4)       | 17 (13.5)       | 16 (11.3)       |          |

Values in parentheses are percentages. *\( \chi^2 \) test and †Student’s \( t \) test.
infections (OR 2.74, 0.54 to 13.80; \( P = 0.223 \)). In univariable analysis, laparoscopy was identified as a statistically significant factor for abdominal abscess formation (\( P = 0.049 \)). However, laparoscopy was not an independent risk factor for any infectious complication in multivariable analysis.

In 16 of 126 patients treated at location A the specified 3-day antibiotic treatment period was prolonged for 2 days (total 5 days) because clinical findings were suggestive of infectious complications. Two of these patients developed an intra-abdominal abscess. Because the prolonged antibiotic treatment in these patients was not in accordance with the local protocol, these patients were excluded from a sensitivity analysis. In this analysis, comparable results were found for the effect of duration of antibiotic treatment (3 versus 5 days) on development of any infectious complication (OR 1.92, 0.76 to 4.85; \( P = 0.168 \)), a wound infection (OR 2.44, 0.48 to 12.35; \( P = 0.280 \)) or an intra-abdominal abscess (OR 2.17, 0.75 to 6.30; \( P = 0.153 \)).

In addition, some patients at location B received postoperative antibiotics for a shorter or longer time (3 days or more than 5 days) than the 5 days specified in the protocol. These patients were excluded from the final analysis together with those who received prolonged antibiotic treatment at location A. No significant differences were found for the impact of duration of antibiotic treatment (3

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Univariable logistic regression analysis of risk factors for all infectious complications and intra-abdominal abscesses after appendectomy for complicated appendicitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence in the first group (%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic treatment (3 versus 5 days)*</td>
<td>50.6</td>
</tr>
<tr>
<td>Sex (M versus F)</td>
<td>53.2</td>
</tr>
<tr>
<td>Age (&gt; 50 versus &lt; 50 years)</td>
<td>39.7</td>
</tr>
<tr>
<td>Operator (resident versus surgeon)</td>
<td>52.4</td>
</tr>
<tr>
<td>Location (A versus B)</td>
<td>47.2</td>
</tr>
<tr>
<td>Approach (laparoscopic versus open)†</td>
<td>32.6</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 per cent confidence intervals. *In multivariable logistic regression analysis, antibiotic treatment (3 versus 5 days) corrected for location and approach yielded an odds ratio of 1.56 (95 per cent c.i. 0.53 to 4.6; \( P = 0.215 \)) for all infectious complications and 1.13 (0.33 to 3.85; \( P = 0.844 \)) for intra-abdominal abscess formation. †In multivariable analysis, approach (laparoscopic versus open) was no longer a significant risk factor for intra-abdominal abscess formation, with an odds ratio of 2.32 (0.75 to 7.14; \( P = 0.144 \)).
versus 5 days) on development of any infectious complication (OR 1.92, 0.68 to 5.40; *P*= 0.219), a wound infection (OR 1.50, 0.25 to 9.18; *P*=0.661) or an intra-abdominal abscess (OR 2.63, 0.80 to 8.71; *P*=0.112).

**APPENDIX 1 Duration of antibiotic treatment in complicated appendicitis**

<table>
<thead>
<tr>
<th></th>
<th>3 days</th>
<th>5 days</th>
<th>6 days</th>
<th>7 days</th>
<th>8 days</th>
<th>10 days</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location A</td>
<td>101</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>117</td>
</tr>
<tr>
<td>Location B</td>
<td>34</td>
<td>100</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>141</td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>116</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>258</td>
</tr>
</tbody>
</table>

*In nine patients the exact duration of antibiotic treatment could not be retrieved.*

**DISCUSSION**

This study found no difference in the rate of infectious complications between antibiotic treatment of perforated appendicitis for 3 or 5 days. Available data on duration of treatment are limited, with only one randomized clinical trial in adults comparing the duration of antibiotic administration. That study reported no additional benefit from standard treatment with antibiotics for at least 5 days compared with antibiotic treatment based on the clinical course; the mean antibiotic duration was 5.9 versus 4.3 days, with infectious complication rates of 13 versus 12.5 per cent respectively. Other investigations of the optimal duration of antibiotic treatment in perforated appendicitis are scarce and limited mainly to children. In most paediatric studies, a duration of more than 5 days has been compared with antibiotic treatment for 5 days.

Almost all patients who developed an intra-abdominal abscess after prolonged antibiotic treatment in this study (20 of 21) had perforation as an intraoperative diagnosis at the start of surgery, rather than purulent peritonitis or gangrenous appendicitis with perforation on manipulation during surgery. This is in line with previous findings that patients with a perforated appendix are at a much higher risk of postoperative abscess formation than patients with a non-perforated, purulent or gangrenous appendix.

In the present cohort, patients who had a laparoscopic appendectomy more frequently developed intraabdominal abscesses than those who underwent open appendectomy. This confirmed previous findings, although the cause is still not fully understood. However, for the subgroup of patients with complicated appendicitis, laparoscopy was not a risk factor in multivariable analysis. This implies that a laparoscopic approach can still be used in patients with preoperative suspicion of complicated appendicitis without the risk of infectious complications.

The type of stump closure in laparoscopic appendectomy has been shown to influence postoperative infectious complications, with the evidence favouring endostapling. In the present cohort, all appendiceal stumps were closed with
a stapling device in laparoscopic procedures. The conversion rate among complicated cases attempted laparoscopically was relatively high, probably because the study was carried out at the time when the laparoscopic approach was introduced.

This study included only clinically relevant in-hospital infectious complications (intra-abdominal abscess and wound infection) that altered the treatment, such as readmission, reintervention or antibiotic treatment. Therefore, the number of such complications is probably under-reported; this applies especially to wound infections, which can often be treated in the outpatient clinic. However, any underestimation of the complication rate would be expected to apply equally to both groups. Moreover, reinterventions such as percutaneous drainage without the need for readmission were registered, because these were recorded in the electronic patient database.

The length of hospital stay was significantly shorter in patients who received antibiotics for 3 days compared with treatment for 5 days. Although no cost analysis was performed, lower costs can be expected with a 3-day antibiotic regimen. Some clinics switch their antibiotic regimen from intravenous to oral administration if possible, to reduce hospital stay. This was not done in the authors’ clinic owing to the choice of antibiotics, resulting in a longer hospital stay for the 5-day group.

This is a retrospective study, which has its limitations and risk of bias. For example, the open and laparoscopic approaches were not divided equally between the two locations. On the other hand, a laparoscopic approach was a risk factor for intra-abdominal abscess development and this approach was chosen more often at location A, where a 3-day antibiotic regimen was used. Despite the shorter regimen in this hypothetically ‘high-risk’ group, infectious complications were not increased compared with the rate in the 5-day group.

At both locations the duration of antibiotic treatment in some patients differed from that specified in the local protocol. The sensitivity analyses carried out to account for both protocol violations (either lengthening or shortening of antibiotic duration) yielded results comparable to those of the main analyses. Finally, owing to the proximity of the two hospitals, the study groups were well matched. During the time frame of this study, the surgical departments of the two hospitals already worked together on many levels, although each department still had its own protocols. These hospitals and their surgical departments have now merged, resulting in a standard antibiotic treatment of 3 days for complicated appendicitis.
REFERENCES


