Health Policy Advisory Committee on Technology

Technology Brief

Antibiotics versus appendectomy for uncomplicated appendicitis

February 2013
**Technology, Company and Licensing**

**Register ID**  
WP 146

**Technology name**  
Antibiotics versus appendectomy for uncomplicated appendicitis

**Patient indication**  
 Patients with acute appendicitis

**Description of the technology**

Acute appendicitis has been managed surgically for over 100 years; it is assumed that without surgery, perforated appendicitis and its potentially very serious sequelae may result. For patients with early uncomplicated appendicitis, non-operative management with antibiotics and supportive treatment is being explored as a treatment option. It has been stated that the role of antibiotic treatment in acute uncomplicated appendicitis may have been overlooked mainly on the basis of tradition rather than evidence, considering that the management of diverticulitis and other intra-abdominal inflammatory processes is generally managed with antibiotics rather than surgery.¹

The main issue with utilising antibiotics to treat appendicitis is that they are generally only a useful treatment option in uncomplicated appendicitis and it is the definition and identification of uncomplicated appendicitis that is difficult, particularly pre-treatment without laparoscopic investigation.

**Company or developer**

Not applicable

**Reason for assessment**

The use of antibiotics may be a non-invasive alternative treatment for acute uncomplicated appendicitis with lower costs and complication rates compared to surgery, the current treatment of choice.

**Stage of development in Australia**

☐ Yet to emerge  ☐ Established

☐ Experimental  ☐ Established but changed indication or modification of technique

☒ Investigational  ☐ Should be taken out of use

☐ Nearly established

**Licensing, reimbursement and other approval**

Not applicable
Antibiotics versus appendectomy for uncomplicated appendicitis: February 2013

Australian Therapeutic Goods Administration approval

☐ Yes
☐ No
☒ Not applicable

Technology type
Procedure

Technology use
Therapeutic

Patient Indication and Setting

Disease description and associated mortality and morbidity

Acute appendicitis is one of the most common causes of acute abdominal pain. Lifetime risk is seven to eight per cent with the highest incidence in the second decade of life.² Recent World Health Organization data reveal that Australia reported 14 deaths from appendicitis (year not provided), placing it 25th in the world (Brazil was highest at 450 and the United States was second at 371).³

Most cases of acute appendicitis are caused by obstruction of the appendiceal lumen by fecaliths, lymphoid hyperplasia, foreign bodies, parasites or very rarely tumours (primary or metastatic). Once obstruction occurs, mucus secretion results in elevated pressure, luminal distension, venous engorgement, arterial compression and tissue ischemia. Local bacteria multiply and cause inflammation: the most common are Escherichia coli (E. coli) and Bacteroides fragilis.² Appendiceal infarction and perforation can result. However, recent opinion is that complicated (e.g. perforated) and uncomplicated appendicitis are different entities, and that many cases of uncomplicated appendicitis may resolve without surgical treatment.²

The classification of acute uncomplicated versus acute complicated appendicitis is generally unclear in a pre-treatment setting. Laparoscopic investigation appears to be the most reliable method to distinguish uncomplicated versus complicated appendicitis and whilst computed tomography can be used, in many cases, this is often reserved for the elderly and those who are not surgical candidates. Published literature suggests that it is standard clinical practice to carry out appendectomy in patients with suspected acute appendicitis without further diagnostic investigation. In many cases where laparoscopic investigation does take place, the appendix is removed regardless of the diagnosis of uncomplicated/complicated appendicitis, as the patient is already under general anaesthesia and the laparoscopic instruments are already in position.⁴

Number of patients

Australian Institute for Health and Welfare hospital statistics for acute appendicitis and uncomplicated appendectomy (2010–2011) are shown below.⁵
Overall statistics for acute appendicitis

- 28,195 cases (84 per cent occurred in public hospitals)
- 20th in the list of top diagnoses for overnight acute separations
- Top reason for emergency admission involving surgery (24,889 cases of which 20,415 [82%] were identified as uncomplicated)
- Most common surgical procedure for emergency admissions involving surgery (88% in public hospitals)

Uncomplicated appendectomy

- 22,880 separations
- 18,605 (81%) in public hospitals
- Mean length of stay (LOS) 2.2 days

Complicated appendicitis

- 1,409 cases identified (described as ‘appendicitis with generalised peritonitis’)
- Targeted as a reason for potentially preventable hospitalisation ‘provided adequate and timely care was received’

Speciality: Surgery

Technology setting: Specialist Hospital / General Hospital

Impact

Alternative and/or complementary technology

Additive and substitution: Management of acute uncomplicated appendicitis with antibiotics may be used as a substitute for surgery in some cases of uncomplicated appendicitis, or in combination with surgery in others.

Current technology

Surgical appendectomy; either open or laparoscopic surgery.

Diffusion of technology in Australia

The diffusion of antibiotic treatment for uncomplicated acute appendicitis in place of appendectomy in Australia was unable to be determined; however, it is worth noting that the Victorian Government’s ‘Better Health Channel’ has a fact sheet on appendicitis which notes that antibiotic therapy is an alternative to surgery but is usually reserved for patients too frail to undergo surgery.
**International utilisation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>✓</td>
<td></td>
<td>Probaby, based on the fact that some of the published research includes retrospective reviews</td>
</tr>
<tr>
<td>France</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

Medicare Benefits Schedule (MBS)\(^7\) costs associated with an appendectomy are listed in Table 1. Pharmaceutical Benefits Scheme (PBS)\(^8\) costs of the antibiotics used to treat uncomplicated appendicitis are listed in Table 2. The antibiotics listed in Table 2 and their quantities are those used in two studies\(^9,10\) in a meta-analysis by Varadhan et al\(^1\) on safety and efficacy of antibiotics compared to appendectomy for the treatment of uncomplicated acute appendicitis. The antibiotic therapy included 2 g of cefotaxime 12 hourly and 800 mg of tinidazole daily for two days. This was followed by oral treatment on discharge of 200 mg of ofloxacin twice daily and 400 mg of tinidazole twice daily for eight days. One of the antibiotics used (ofloxacin) is only listed by the PBS for ophthalmologic use and so is not listed in Table 2. Based on Table 1 and Table 2, if hospital LOS was not affected, the antibiotic route would be less costly and this would extrapolate to significant savings as appendectomy is such a common procedure.
The use of antibiotics instead of surgery for uncomplicated acute appendicitis is also appealing as the risks to patients that are inherent in surgery can be avoided; however, this must be balanced by ‘failures’ in therapy that ultimately lead to appendectomy, and worse, to sicker patients with perforations and other complications. The need for readmission for unplanned (delayed) surgery is also a consideration.

**Ethical, cultural or religious considerations**

No specific considerations were identified.

**Evidence and Policy**

**Safety and effectiveness**

Evidence for this brief comes from a meta-analysis of four randomised controlled trials (RCTs) (level I interventional evidence).¹ A 2011 Cochrane Collaboration review is also available (level I interventional evidence)² and is mentioned here, though there is significant overlap between these two reviews with respect to included studies.

---

Table 1 MBS fees and benefits associated with having an appendectomy

<table>
<thead>
<tr>
<th>Item number</th>
<th>Description</th>
<th>Fee</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>20840</td>
<td>Initiation of management of anaesthesia for all procedures within the peritoneal cavity in lower abdomen including appendicectomy, not being a service to which another time in this subgroup applies</td>
<td>$118.80</td>
<td>75% = $89.10 85% = $101.00</td>
</tr>
<tr>
<td>30394</td>
<td>Laparotomy for drainage of subphrenic abscess, pelvic abscess, apendiceal abscess, ruptured appendix or for peritonitis from any cause, with or without appendicectomy (anaes. assist.)</td>
<td>$492.85</td>
<td>75% = $369.65</td>
</tr>
<tr>
<td>30571</td>
<td>Appendicectomy, not being a service to which item 30574 applies (anaes. assist.)</td>
<td>$445.40</td>
<td>75% = $334.05</td>
</tr>
<tr>
<td>30572</td>
<td>Laparoscopic appendicectomy (anaes. assist.)</td>
<td>$445.40</td>
<td>75% = $334.05</td>
</tr>
<tr>
<td>30574</td>
<td>Appendicectomy, when performed in conjunction with any other intra-abdominal procedure through the same incision</td>
<td>$123.25</td>
<td>75% = $92.45</td>
</tr>
</tbody>
</table>

MBS: Medicare Benefits Schedule, anaes. assist., anaesthesia assisted.

Table 2 PBS costs for antibiotics used to treat acute, uncomplicated appendicitis

<table>
<thead>
<tr>
<th>Code</th>
<th>Product name</th>
<th>Form</th>
<th>Unit price to government</th>
</tr>
</thead>
<tbody>
<tr>
<td>1086E</td>
<td>Cefotaxime</td>
<td>2 g vial</td>
<td>$43.12/vial</td>
</tr>
<tr>
<td>1465D</td>
<td>Tinidazole</td>
<td>500 mg tablet</td>
<td>$10.89/four tablets</td>
</tr>
</tbody>
</table>

PBS: Pharmaceutical Benefits Scheme.
**Varadhan et al meta-analysis**

Researchers from the United Kingdom (UK) compared the safety and efficacy of antibiotics to appendectomy (laparoscopic or open) for the primary treatment of uncomplicated acute appendicitis in adults. The literature search ended in December 2011 and four RCTs met inclusion criteria (n=900 patients; 470 for antibiotics and 430 for appendectomy). The treatment protocol in the antibiotic arms of all four trials was antibiotics, with surgery if required, versus immediate surgery, i.e., both trial arms achieve 100 per cent resolution of appendicitis at one year. For the purpose of this meta-analysis, patients in the antibiotic group were defined as those having treatment with antibiotics at initial presentation when the diagnosis of acute appendicitis was made.

The primary outcome measure was complications. Complications were defined:

- in the antibiotic group as perforated/gangrenous appendicitis or wound infection (if antibiotic treatment failed and the patient subsequently underwent appendectomy)
- in the appendectomy group as perforated appendicitis or peritonitis.

Secondary outcome measures were efficacy of treatment, LOS, incidence of complicated appendicitis and hospital readmissions. Additional secondary outcomes were incidence of perforation, pain and body temperature, where these were reported. Median follow-up across studies was one year.

The four included RCTs were assessed for quality based on method of randomisation, concealment of allocation, blinding, description of dropouts and withdrawals, intention-to-treat analysis and duration of follow-up. Quality was generally deemed to be low to moderate. A separate sensitivity analysis for complications was conducted to assess whether differences in the antibiotic regimen influenced treatment outcome. Of the four included studies, it appears that only one confirmed the diagnosis of uncomplicated appendicitis by computed tomography and excluded those patients shown to be suffering complicated appendicitis. It is unclear what classification was used to determine if appendicitis was uncomplicated in the remaining included studies.

**Safety (primary outcome measure)**

Meta-analysis of complications showed a relative risk reduction of 31 per cent for antibiotic treatment compared with appendectomy (risk ratio [RR] 0.69, 95% CI [0.54, 0.89], p=0.004). A secondary analysis, excluding a study that allowed crossover of patients between the two interventions after randomisation, showed a relative risk reduction of 39 per cent for antibiotic therapy (RR 0.61, 95% CI [0.40, 0.92], p=0.02). Of the 68/345 (20%) patients who had appendectomy after readmission, nine had perforated appendicitis and four had gangrenous appendicitis. Risk of complicated appendicitis did not differ between antibiotic treatment and appendectomy arms (RR 0.58, 95% CI [0.18, 1.90], p=0.37).
Effectiveness

Antibiotic treatment was associated with a 63 per cent (277/438 patients) success rate at one year, that is, surgery was not required. The data for conversion to surgery for patients in the antibiotic group is shown in Table 3.

Table 3  Antibiotic groups in the four included studies: progression to appendectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients in antibiotic arm</th>
<th>Number of patients progressing to appendectomy</th>
<th>Notes about progress to appendectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>120</td>
<td>44 (37%)</td>
<td>• 14 within 30 days (9 complicated, 4 uncomplicated, 1 normal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 30 between 30 days and 1 year (3 complicated, 23 uncomplicated, 4 normal)</td>
</tr>
<tr>
<td>#2</td>
<td>202 (crossover allowed)</td>
<td>21 of 119 (18%)*</td>
<td>Of the 202 patients initially assigned to this arm, 119 had antibiotics and 83 crossed over to surgery.</td>
</tr>
<tr>
<td>#3</td>
<td>128</td>
<td>31 (24%)</td>
<td>15 primary, 16 readmissions; 12 perforated</td>
</tr>
<tr>
<td>#4</td>
<td>20</td>
<td>8 (40%)</td>
<td>1 primary, 7 readmissions; 1 perforated</td>
</tr>
</tbody>
</table>

* Per protocol

No significant differences were seen for LOS or risk of developing complicated appendicitis.

The authors concluded:

An early trial of antibiotics merits consideration as the initial treatment option for uncomplicated appendicitis. The possibility that perforated and non-perforated appendicitis could have different patterns and pathological processes needs further evaluation. Perhaps uncomplicated acute appendicitis should be treated akin to other conditions such as acute colonic diverticulitis in which antibiotic treatment plays an important role.^

A similar Cochrane review² by authors in The Netherlands included five RCTs comparing antibiotic treatment to appendectomy (laparoscopic or open) in patients with suspected acute appendicitis (n=901); the literature search ended in June 2011. Three of the five studies were included in the meta-analysis by Varadhan et al (2012).¹ However, unlike the meta-analysis, the Cochrane review was not specifically on ‘uncomplicated’ acute appendicitis. That is, this review focused on all acute appendicitis and did not differentiate between uncomplicated/complicated appendicitis prior to treatment in the included studies consequently the effect of pre-treatment diagnosis was not included as a factor in determining treatment success.

Studies were again assessed as being of low to moderate quality. Results showed that 73 per cent (95% CI [62.7, 81.9]) of patients who were treated with antibiotics and 97 per cent (95% CI [94.4, 98.8]) of patients who directly received an appendectomy were cured within two weeks without major complications (including recurrence) within one year. Also, 83 per
cent (95% CI [72.0, 90.5]) of the antibiotic group and 97 per cent (95% CI [92.6, 98.9]) of the appendectomy group did not experience major complications.

The authors were less convinced than Varadhan et al\(^1\) that antibiotics are an appealing first treatment step, that is:

*the outcome is inconclusive...therefore we conclude that appendectomy remains the standard treatment for acute appendicitis. Antibiotic treatment might be used as an alternative treatment in a good quality RCT or in specific patients or conditions where surgery is contraindicated.*

**Economic evaluation**

Information comparing costs of care using antibiotics versus appendectomy for cases of uncomplicated appendicitis is not yet available. However, of possible interest is a US study\(^11\) that retrospectively examined costs of managing paediatric appendicitis for nearly 50,000 children treated at 38 hospitals from 2006 to 2010. Cases were classified by the authors as uncomplicated (LOS ≤ 2 days, all were treated with appendectomy) and complicated. The median total hospital cost per case of acute appendicitis attributable to the index admission was US$7,625 (approx. A$7,909). This varied significantly across treatment groups: uncomplicated (all received appendectomy), US$6,355 (approx. A$6,591); complicated appendectomy, US$12,300 (approx. A$12,757); drainage without appendectomy, US$14,319 (approx. 14,850); and antibiotics alone (only applied to complicated cases), US$10,909 (approx. A$10,464). The median-adjusted total hospital cost per case attributable to readmission was US$3,401 (approx. A$3,527), reflecting a 44 per cent relative increase in cost over the median index admission cost for readmitted patients.

**Ongoing research**

ClinicalTrials.gov lists a number of trials of appendectomy versus antibiotics; some are complete, some are recruiting and some are not yet recruiting. A selection of these studies is included in Table 4.

- **NCT01421901** (Italy):\(^12\) An RCT will compare results for 218 patients with acute appendicitis without peritonitis randomised to appendicectomy or antibiotic treatment with ertapenem (an injectable antibiotic indicated for moderate-to-severe infections including intra-abdominal infections) once a day for three days. Recruitment was to start mid-2011 with study completion in mid-2013. (Note: the record has not been updated for 15 months.) The primary outcome is freedom from symptoms two weeks post-treatment. Secondary outcomes are major complications by one year of follow-up, wound infection, negative appendicectomy, LOS and absence from work.

- **NCT01022567** (Finland):\(^13\) A similar RCT at seven centres will compare appendicectomy with antibiotic treatment (parenteral ertapenem daily x 3 followed by oral levofloxacin and metronidazole) in 600 patients with appendicitis confirmed by computed
tomography (CT). The primary outcome is resolution of appendicitis with secondary outcomes covering complications, recurrence and cost. The study was to start enrolment in 2009 and complete data collection in April 2012. (Note: the record has not been updated since May 2011.)

- NCT01572558 (Sweden): This pilot study will test the willingness of 50 paediatric patients/families to be enrolled in an RCT randomising children with appendicitis to antibiotic treatment or surgery. Data collection is apparently complete, although results have not been identified.

- NCT01718275 (US): A prospective, case-control study at an Ohio hospital will enrol 70 children aged seven to 17 with early appendicitis confirmed by CT or ultrasound. There will be two cohorts: (a) those who agree to antibiotic management (drugs not specified); and (b) surgical cases who permit tracking of outcomes. Primary outcomes are conversion to surgery, and 30-day, six-month and one-year recurrence rates. Secondary measures are complications, LOS, days off school, cost of care and quality of life. Final data collection is estimated for October 2013. The authors hypothesise that non-operative management of early appendicitis in children with antibiotics alone will be successful in 80 per cent of children at one-year follow-up.

Table 4 Examples of additional studies underway of antibiotics versus appendectomy

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>N</th>
<th>Study design</th>
<th>Antibiotic</th>
<th>Estimated study completion</th>
<th>Primary outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01421901 (Italy)</td>
<td>218 adults</td>
<td>RCT</td>
<td>Ertapenem (parenteral)</td>
<td>Mid-2013</td>
<td>Freedom from symptoms two weeks post-treatment</td>
</tr>
<tr>
<td>NCT01022567 (Finland)</td>
<td>600 adults</td>
<td>RCT</td>
<td>Ertapenem followed by oral levofloxacin and metronidazole</td>
<td>April 2012</td>
<td>Resolution of appendicitis</td>
</tr>
<tr>
<td>NCT01572558 (Sweden)</td>
<td>50 children</td>
<td>RCT</td>
<td>Not specified</td>
<td>October 2012</td>
<td>Resolution of symptoms at 30 days without significant complications</td>
</tr>
<tr>
<td>NCT01718275 (US)</td>
<td>70 children</td>
<td>Case-control</td>
<td>Not specified</td>
<td>October 2013</td>
<td>Conversion to surgery; recurrence rates</td>
</tr>
</tbody>
</table>

N: number of patients; RCT: randomised controlled trial; US, United States.

Other issues

One author commented that the advent of laparoscopic surgery and a low threshold for operative intervention have led to a risk of high negative appendectomy rates with unnecessary surgery-related morbidity. This suggests that the paradigm for surgical management is shifting, with perhaps less reluctance to go ahead with appendectomy. However it should be noted, that in Australia, almost all patients undergoing diagnostic laparoscopy for suspected appendicitis also have an appendicectomy. A counterbalance
may be the increasing use of CT or ultrasound imaging to radiologically assess the likelihood that acute abdominal pain is appendiceal in origin.

**Summary of findings**

The evidence for this review, a recent UK meta-analysis of four RCTs (n=900) of the management of patients with uncomplicated appendicitis, showed a significant relative reduction in risk of complications for the antibiotic treatment arm compared with the appendectomy arm (31%, \( p=0.004 \)). Surgery was ultimately avoided in 63 per cent of patients in the antibiotic arm at one-year follow-up (range among studies, 60–82%). A contemporary Cochrane review from The Netherlands that included three of the four UK meta-analysis studies, plus two more, reported that 73 per cent (antibiotics) versus 97 per cent (surgery) of patients were cured within two weeks without major complications (including recurrence) within one year, although major complications were more common in the antibiotic group (17 versus 3 per cent). Both sets of authors deemed the quality of studies to be low to moderate. The UK authors concluded optimistically, noting that an early trial of antibiotics merits consideration as the initial treatment option for uncomplicated appendicitis; however, the Dutch Cochrane authors were more cautious, stating that their results were inconclusive.

**HealthPACT assessment**

The evidence in this brief indicates there is little difference in the average length of hospital stay of patients with acute appendicitis treated with antibiotics versus appendectomy, and that the administration of antibiotics is an ideal strategy to avoid a surgical approach to treatment in patients with uncomplicated appendicitis. However, given the difficulties in distinguishing uncomplicated versus complicated appendicitis without laparoscopic investigation and the need for appropriate patient selection considering the risks associated with sequelae if complicated appendicitis is not appropriately managed, there is unlikely to be a change in clinical practice. As a result, this technology will be archived.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of Level I interventional studies</td>
<td>2</td>
</tr>
</tbody>
</table>

**References**

from: http://www.bmj.com/content/344/bmj.e2156?view=long&pmid=22491789 [Accessed 6 Jan 2013].


Search criteria to be used (MeSH terms)

MeSH: Appendicitis, Anti-Bacterial Agents, Amoxicillin, Amoxicillin-Potassium Clavulanate Combination, Cefotaxime, Metronidazole, Tinidazole

PubMed: (appendicitis) AND ((anti-bacterial agents) OR antibiotics)