ANTIBIOTIC THERAPY AS SINGLE TREATMENT OF ACUTE APPENDICITIS

Jeanette Hansson

UNIVERSITY OF GOTHENBURG

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Department of Surgery
Institute of Clinical Sciences at Sahlgrenska Academy
University of Gothenburg

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To Johan, Josefine & Jakob

Of all the ills within the abdomen
which cause affliction to the sons of men
there's none more often puts them in a fix
than trouble in the worm-like appendix

"The diagnosis of the acute abdomen in rhyme"
by signature Zeta (1947)

ABSTRACT

BACKGROUND

Appendectomy has been the established treatment of acute appendicitis during the last century, regarded as a simple and safe procedure, although hampered with postoperative complications and increased standard mortality. Modern research has indicated that selected patients with acute appendicitis can be treated by antibiotic therapy alone. The aim of this thesis was therefore to explore antibiotic therapy as single treatment of acute appendicitis in unselected adult patients. A secondary aim was to suggest a model for prediction of antibiotic response.

MATERIALS AND METHODS

Two prospective interventional studies were performed on consecutive patients with acute appendicitis. First, a randomized controlled trial (paper I) with 369 patients compared antibiotic therapy with appendectomy. Primary outcome was treatment efficacy and major complications. Second, a population based study (paper II) with antibiotics as first line therapy included 558 patients. The patients were followed for one year in both studies. In paper III, retrospective analyses of preoperative parameters for 384 patients were linked to the histopathological reports of resected appendices regarding the stage of appendicitis in order to create a model for prediction of antibiotic response. The model was then validated on the patients in the population based study (paper II). In paper IV we used the same patients as in paper II, where sequential measures of procalcitonin were analysed in order to evaluate the efficacy of initiated antibiotic therapy.

RESULTS

A majority of patients with acute appendicitis could be treated with antibiotics in both prospective studies; 5-10% were clinically judged to need primary surgery. The recovery rate on antibiotics was 91% in the RCT and 77% in the population based study. The recurrence rate after one year was 14% and 11% respectively. Antibiotic treatment displayed less overall complications compared to primary surgery in both studies. Complications after antibiotic therapy consisted mainly of side effects to the antibiotics or postoperative complications after rescue surgery, but intra-abdominal abscesses were also seen. Prediction models for patient selection, based on standard laboratory parameters, could identity patients with positive antibiotic response at increased probability but at low sensitivity. Procalcitonin had limited value for early evaluation of the efficiency of provided antibiotic therapy in acute appendicitis.

CONCLUSIONS

Acute appendicitis in unselected adult patients can be treated with antibiotics as single therapy with high recovery rate and low recurrence rate within one year. Antibiotics can be offered to a majority of patients without the risk of increased complications. Long-term follow up are warranted.

Keywords: Appendicitis, Antibiotic therapy, Appendectomy, Procalcitonin

LIST OF PUBLICATIONS

This thesis is based on the following publications and manuscripts, referred to in the text by their Roman numerals (I-IV).

I. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients.

   Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K

   Br J Surg 2009;96(5): 473-481.

II. Antibiotics as first line therapy for acute appendicitis: evidence for a change in clinical practice.

   Hansson J, Körner U, Ludwigs K, Johnsson E, Jönsson C, Lundholm K

   World J Surg 2012 May 9 (Epub ahead of print)

III. A proposed model to select patients who may benefit from antibiotic therapy as the first line treatment of acute appendicitis at defined probability.

   Hansson J, Khorram-Manesh A, Alwindawe A, Lundholm K

   Submitted for publication

IV. Evaluation of procalcitonin as marker to predict efficacy in treatment of acute appendicitis following institution of antibiotic therapy for cure.

   Hansson J, Körner U, Lundholm K

   Submitted for publication

ABBREVIATIONS

CRP	C-reactive protein
CT	computer tomography
ESBL	extended spectrum beta-lactamase
NSAP	non-specific abdominal pain
PCT	procalcitonin
PPV	positive predictive value
RCT	randomized controlled trial
US	ultrasound
WCC	white cell count

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INTRODUCTION

Medical history – from typhlitis to appendicitis

During a major part of the 19th century, an inflammatory condition in the right iliac fossa was regarded to originate from typhlitis, a term that described inflammation of the caecal mucosa. This condition could be complicated by peri- or paratyphlitis when the process progressed. The mortality was high and the only surgical option available was incision of abscesses. However, already in 1824 Louyer-Villermay described the vermiform appendix as the origin of inflammation [1] but without impact on the medical society. It would take until the end of the 19th century before appendicitis was generally recognized as a disease entity.

The pathologist Reginald Fitz stated in 1886 that perforated appendicitis was the cause of most cases of paratyphlitis [2] and that appendectomy could result in cure of the disease. It is still unclear which surgeon who actually performed the first successful appendectomy. Charles McBurney reported his experience of appendectomy in 1889 [3] with description of the point of maximum tenderness, McBurney's point. A few years later he also described the classical muscle-splitting grid iron incision for performing the procedure [4]. Karl Gustav Lennander did the first appendectomy in Sweden in 1889.

Medical history – from early appendectomy to active observation

In the beginning of the 20th century, the number of appendectomies was rapidly increasing as mortality after appendectomy was declining. In Sweden, 600 appendectomies were performed in 1901 compared to 14000 in 1920 [5] with only 1% mortality in 1920 [6]. Early appendectomy to avoid perforation became the generally accepted treatment of acute appendicitis for many decades to come.

At the end of the 20th century, the trend in managing appendicitis changed towards a more conservative approach with repeated clinical and laboratory examinations, referred to as active observation, resulting in reduced number of negative explorations without an increased perforation incidence [7-10].

Epidemiology

Suspected appendicitis is the most common cause of acute abdominal surgery in the Western World, where 7% of all individuals may develop acute appendicitis sometimes during their lifetime [11]. The incidence in Sweden during 2009 was 106 cases per 100 000 [12] and approximately 10 000 appendectomies were performed in Sweden the same year.

The incidence of perforated appendicitis has been found to be independent of age, stable over time and uninfluenced by the rate of explorations [7, 13]. By contrast, the incidence of non-perforated appendicitis has shown to increase with a liberal attitude towards exploration [14]. These findings have been interpreted to indicate that spontaneously resolved non-perforated appendicitis is common and that the proportion of perforated appendicitis only reflects the attitude towards exploration and that the proportion of negative explorations may be a more adequate measure of surgical quality.

The rates of negative explorations (findings of a non-inflamed appendix) and appendix perforations vary in different materials. In a report from Sweden the mean negative appendectomy rate was 30% from 1969-1990 and the mean perforation rate was 15% [15]. A Cochrane review comparing laparoscopic and open appendectomy updated 2010 showed a negative appendectomy rate of 10% in studies from 1992-2003 [16].

Diagnostics

Ultrasound (US) and especially computer tomography (CT) as diagnostic tools for acute appendicitis have become more frequently used as the 24-hour availability of radiological imaging is increasingly common. However, the roles of both US and CT are controversial. Several studies have shown good sensitivity and specificity for US and CT in diagnosis of appendicitis [17-18] with subsequently declining negative appendectomy rates and fewer cases of missed perforation [19]. Still, the benefit compared to rigorous clinical assessment with repeated examinations has not been proved [20].

Inflammatory variables such as body temperature, CRP, WCC have important diagnostic value in acute appendicitis, especially in advanced appendicitis, and should be included in the diagnostic work-up [21-22]. The diagnostic value also increases when re-evaluated after observation in combination with clinical re-examination [23]. Moreover, acute appendicitis in adults is very unlikely when both CRP and leukocytes are normal [24].

Several diagnostic scoring systems, combining clinical parameters with laboratory variables, have been proposed, among which the Alvarado score is the most well recognized [25-27]. However, no scoring system has become of widespread use so far.

Morbidity and mortality

Population-based studies have shown long-term serious risks following surgical exploration for appendicitis such as small bowel obstruction, requiring operation in 1.3% of patients within a 30-year period and 30-day mortality of 0.24% with increased standard mortality ratio [28-30]. Negative appendectomy appears at least as dangerous as perforated appendicitis concerning both small bowel obstruction and mortality [31]. Overall complication rate after appendectomy is hard to specify because definitions and reporting of complications are inconsistent, but a complication rate of 10-20% in large randomized trials has been shown [32-34]. A Cochrane review found that wound infections were less likely after laparoscopic appendectomy than after open surgery, but in contrary, intraabdominal abscesses were more common after laparoscopy [16].

Aetiology/pathogenesis

The aetiology and pathogenesis of appendicitis are not fully understood but are probably multifactorial [35]. Obstruction of the appendix lumen - for example by fecalith, foreign bodies, lymphoid hyperplasia (in some cases secondary to viral infection) and adhesions - has been the most popular theory. Obstruction is thought to result in increased intraluminal pressure leading to vascular compromise with mucosal or transmural necrosis and subsequent secondary bacterial infection [36]. However, obstruction is evident only in a minority of resected appendices [37].

Other theories claim that bacteria play an essential role from the initial phase of the pathogenesis. Microbiological cultures from patients with acute appendicitis revealed a wide variety of anaerobic and aerobic bacteria [38-40]; the most common strains are E. Coli, Bacteroides fragilis, Klebsiella and Proteus. It appears that aerobic bacteria dominate in early appendicitis with a shift towards a mixture of aerobes and anaerobes in later stages of the disease [38]. Significant differences in microbiological spectrum between phlegmonous, gangrenous and perforated appendicitis have not been demonstrated. However, clusters in the population have been identified, which could support an infectious aetiology, although the infectious agents were not recognised [41]. Dietary factors, ischemia, trauma and genetics have also been presented as possible contributing causes [35].

Histopathology

No ideal criteria for diagnosis of acute appendicitis exist. Clinical diagnosis, radiological imaging, per-operative findings and histopathological picture do not always correspond.

Nevertheless, the histopathological diagnosis is regarded as golden standard despite the fact that there are no universally accepted histopathological criteria for acute appendicitis and the different stages of inflammation.

The classic definition of acute suppurative or phlegmonous appendicitis is transmural leukocyte infiltration [35, 42]. In gangrenous appendicitis there should also be areas of necrosis and in perforated appendicitis the appendiceal wall is ruptured to the serosal surface. However, perforation may be difficult to demonstrate in microscope although obvious per-operatively [35].

Mucosal inflammation with or without underlying mucosal leukocyte infiltration is sometimes accepted as an early sign of appendicitis [37, 43], and occasionally referred to as catarrhal appendicitis, but such changes may be found in up to one third of incidentally removed appendices from asymptomatic patients [44]. Many authors therefore recommend leukocyte infiltration in the muscularis propria as criteria for appendicitis [35].

The history of antibiotics

In 1928, sir Alexander Fleming made the historical observation, that colonies of Staphylococcus aureus were destroyed by a mould he later named Penicillum notatum [45]. It would last until the end of the 2nd world war before the active substance could be isolated and produced for treatment of allied soldiers. Sulfa was discovered in 1935 by a German chemist named Gerhard Domagk. The following decades several new antibiotics were developed and began to be used in common medical practice. Access to antibiotics has changed the medical panorama in a radical way, not least in the surgical principles where antibiotic prophylaxis before surgery and the possibility to treat postoperative infections have been of major importance. Along with the widespread use of antibiotics, including animal care, the phenomenon with antibiotic resistance has however become a growing problem worldwide.

Antibiotic prophylaxis in surgical treatment of acute appendicitis

Antibiotic prophylaxis has shown to be effective in prevention of postoperative wound infections and abscess formation in appendectomised patients, whether the drug is administered pre-, peri- or postoperatively [46]. Single dose pre-operative prophylaxis, and continued postoperative treatment only when the appendix appears gangrenous or perforated, is routine in most hospitals in Sweden as well as in our hospitals.

Treatment of appendiceal abscess or phlegmone

Abscess or phlegmone are found in less than 5% of patients with acute appendicitis [47]. Appendectomy is then often technically difficult and the surgery is sometimes associated with unnecessary ileocaecal resection or right-sided hemicolectomy due to distorted anatomy and suspicion of malignancy. Recent meta-analyses [47-48] support the practice of conservative treatment with antibiotics and percutaneous drainage if needed without interval appendectomy in each complicated case. This approach is associated with less morbidity compared to immediate surgery and the procedure also has a low risk of recurrence (7.4%, CI 3.7-11.1) [47]. Additional prospective studies concerning early drainage and length and choice of antibiotic treatment are warranted [48-49].

Antibiotic treatment of acute appendicitis

Antibiotic therapy as single treatment for acute appendicitis is not a novel idea. In 1959 Eric Coldrey published a series of 471 patients with suspected appendicitis treated conservatively with antibiotics, bed rest and bowel rest [50]. He concluded this approach to be safe and satisfactory with only one death among the patients. The concept was controversial at the time and did not bring any change to clinical practice. Smaller case series of conservative treatment at sea without surgical options have also been described [51-52].

The first prospective randomized controlled study comparing antibiotic treatment with appendectomy was published in 1995 [53]. This was a pilot study with 40 adult patients and promising results. Only one of twenty patients (5%) who received antibiotic therapy did not recover on this treatment (iv cefotaxime 2gx2 and tinidazole 800mgx1 for 2 days followed by oral ofloxacin 200mgx2 and tinidazole 500mgx2 for 8 days) and required surgery. Seven patients (37%) experienced recurrent appendicitis within one year. The authors concluded that antibiotic therapy was as effective as surgery, but with high recurrence rate.

A prospective multicenter randomized controlled trial was presented a decade later by Styrud et al – 252 male patients between 18 – 50 years old with clinically assumed appendicitis, CRP >10mg/l and without suspicion of perforation were included [54]. The antibiotic recovery rate was 88% and the recurrence rate within one year was 14%. This was compared with a complication rate of 14% in the surgery group. The antibiotic regimen was the same as in the pilot study from 1995. Unpublished data, presented at a surgical symposium 2007 [55], showed a recurrence rate of 24% after 5-year follow-up.

The RCT by Styrud et al inspired us to extend the RCT on unselected patients with acute appendicitis as presented in this thesis (paper I). During the completion of this thesis, antibiotic treatment of acute appendicitis has become in focus [56-59] and several other studies, meta-analyses and systematic reviews on the subject have been published. The RCTs [53-54, 60-61] have had similar antibiotic recovery rates around 90% and similar 1-year recurrence rates around 10-15% (with some exceptions) (Table 8). The conclusions of the meta-analyses and systematic reviews have been inconsistent and have varied from stating that antibiotics may be used only for selected patients with uncomplicated appendicitis with appendectomy remaining the gold standard [62-64] to a much more positive attitude towards antibiotic therapy incurring fewer complications compared to surgery [65-68]. A Cochrane report claimed that further trials are necessary to determine whether antibiotics are an inferior, equal or superior option to surgery [69].

Acute appendicitis in children

Children were not included in our own studies, both because of theoretical and practical reasons. Theoretically, acute appendicitis in small children may be a somewhat different disease. The course may be faster, the perforation rate is higher and children can change from relatively unaffected to severely ill in short time due to good physiologic compensation ability up to a certain limit. Thus, conservative treatment may carry a higher risk of sudden deterioration in children. However, there are studies in children as well indicating that acute appendicitis in some cases can be treated with antibiotics [70-73]. Practically, child surgery (in Sweden) is a separate speciality at university hospitals, including our own hospital. Children with abdominal pain are therefore taken care of at the child clinic by child surgeons. Hence, we lacked practical experience of children with appendicitis at our own surgical clinic for adult patients.

Appendectomy – findings of malignancy

Malignant disease may be found in 1% of appendectomies [74-75]. However, surgical exploration in patients with assumed appendicitis should not be based on the risk to have an underlying malignant disease. Such diagnostic considerations must rely on the integrated clinical condition and do not differ between patients with assumed appendicitis compared to other diagnoses like non-specific abdominal pain.

Procalcitonin (PCT)

PCT is a calcitonin precursor and may be a marker for inflammation and infection. The role of PCT, in comparison to traditional laboratory tests like CRP and WCC, is not yet fully elucidated. PCT correlates closely to bacterial infection and may show fast dynamics during infections [76]. For patients with severe sepsis or respiratory tract infections PCT has been reported to show prognostic value and could be used in algorithms to help deciding whether antibiotics should be initiated or terminated [77-80]. For patients with acute appendicitis elevated levels may indicate gangrene or perforation although with poor sensitivity [81-82]. Accordingly, we hypothesized that PCT may function as a fast laboratory responder to indicate whether provided antibiotic therapy is effective or represents a suboptimal treatment (paper IV).

AIM

The aim of this thesis was to explore antibiotic therapy as single treatment of acute appendicitis in unselected adult patients.

In specific:

- Establish the efficacy of antibiotic treatment in comparison to surgical appendectomy in terms of primary recovery and 1-year recurrence rate.

- Study the spectrum of complications associated with an antibiotic treatment strategy in comparison with surgery. Could there be adverse consequences related to antibiotic failure (i.e. rescue surgery) or recurrence? Common side effects of the antibiotics itself were to be expected.

- Study if secondary outcomes like duration of hospital stay, sick leave and hospital costs differed between antibiotic treated patients compared to surgically treated patients.

- Develop a model for prediction of treatment response in order to select patients most suitable for antibiotic therapy.

- Explore procalcitonin (PCT) as a tool for early evaluation of the efficiency of provided antibiotic therapy in acute appendicitis.

PATIENTS AND METHODS

This thesis on antibiotic treatment of acute appendicitis is based on three different studies reported in four papers.

- Paper I:
  A prospective randomized controlled clinical trial comparing antibiotics with appendectomy as treatment of acute appendicitis *[the RCT]*
- Paper II:
  A prospective interventional population based clinical trial introducing antibiotics as the first line therapy offered to all unselected patients with acute appendicitis *[the follow up population based study]*
- Paper III:
  A retrospective observational study of preoperative parameters in appendectomised patients to improve the selection of patients with antibiotic response *[the prediction model]*
- Paper IV:
  A prospective observational study on evaluation of procalcitonin (PCT) for prediction of early therapeutical efficiency of provided antibiotic therapy; based on the same patients as in paper II *[the PCT model]*

PATIENTS AND HOSPITALS

Gothenburg is the second largest city in Sweden with an area of population of around 700,000 individuals. Sahlgrenska University Hospital consists of two separate hospitals, Sahlgrenska and Östra Hospital, which together provide 24-hours emergency surgical care for inhabitants around Gothenburg and Mölndal. Kungälv is a smaller city, not far from Gothenburg, and Kungälv Hospital serves a population of around 100 000 individuals.

All patients in our studies were consecutive adult patients (Table 1). In the RCT (paper I) the patients were treated at Sahlgrenska and Kungälv Hospital. Patients treated at Östra Hospital were included as a reference cohort for comparison (no intervention) during the same period. In the second follow-up study (paper II, IV) all patients were treated at Sahlgrenska and Östra Hospital and in our report on the prediction model (paper III) patients were recruited from all three hospitals. Patients in the prospective studies (paper I, II, IV) were given both oral and written information. The prospective studies were approved by the regional Committee of Ethics in Gothenburg.

Table 1. Patients studied in this thesis.

	No.	Hospital	Study design		Year
Paper I					
- RCT	369	SS, KS	Prospective	Interventional	2006-2007
- Reference cohort	159	ÖS	Prospective	Observational	2006-2007
Paper II (population based study)	558	SS, ÖS	Prospective	Interventional	2009-2010
Paper III (prediction model)	384	SS, ÖS, KS	Retrospective	Observational	2005-2007
Paper IV (PCT model)	316[a]	SS, ÖS	Prospective	Observational	2009-2010

[a] patients from paper II
SS, Sahlgrenska Hospital, *ÖS,* Östra Hospital, *KS,* Kungälv Hospital

METHODS

Prospective studies (paper I, II and IV)

Inclusion criteria

All adult patients diagnosed with presumed appendicitis according to best available clinical practice were included in the studies. The diagnosis was based on anamnesis, clinical condition, abdominal status, body temperature and laboratory tests. Radiological imaging (CT, US) was used in doubtful cases when the diagnosis appeared uncertain. Examination by a gynaecologist, often with vaginal US, was made liberally, especially in young women.

Exclusion criterion in the PCT model (paper IV) was absence of PCT analyses.

Randomization procedure (paper I)

The patients were randomized according to their birthdate; patients with uneven birthdate were scheduled to antibiotic treatment and patients with even birthdate to appendectomy. Thus, the surgeon knew in advance into which group of treatment the patient belonged. The primary data analyses were based on these intention to treat groups. Nevertheless, randomization could be abandoned due to defined criteria in the protocol in accordance with our ethical permission. Patients randomized to antibiotic treatment could be operated upon when deemed clinically necessary by the surgeon in charge or when the patient preferred operation. Patients primarily randomized to surgery could choose antibiotic treatment as their first choice. These per protocol groups were also analysed according to the protocol design.

Interventions (paper I, II)

The antibiotic treatment principles were similar among the RCT (paper I) and the second follow up population based study which offered antibiotics to all patients as their first line option (paper II).

The antibiotics were given as intravenous therapy for at least one day. Initially, patients received intravenous fluids and were not allowed oral intake. Patients were then discharged to continue with oral antibiotics for at total antibiotic treatment period of ten days if their clinical status had improved after 12-24 hours. This decision was made according to a clinical assessment based on clinical condition, body temperature, abdominal status and standard laboratory parameters (CRP, WCC). Intravenous antibiotic therapy could be prolonged if the clinical condition did not improve clear-cut. Appendectomy was performed if patients deteriorated clinically or continued to show no sign of improvement according to the responsibility of the surgeon in charge.

Before the start of our investigations, the choice of antibiotic regimen was made in consult with specialists of infectious diseases and in accordance with the regional antibiotic resistance pattern by the time. Therefore, we used different intravenous antibiotics in the RCT (cefotaxim 1gx2 and metronidazol 1,5gx1) compared to the follow up population based study (piperacillin/tazobactam 4gx3). Oral antibiotics were the same for both studies (ciprofloxacin 500mgx2 and metronidazol 400mgx3).

The follow up population study was designed based on the experience from the RCT. The main principle was to offer all patients antibiotic treatment as their first line option with a few exceptions: 1) surgery deemed necessary (for instance general peritonitis, high fever, sepsis) according to a clinical decision made by the surgeon in charge, 2) pregnancy (not previously studied), 3) recurrent appendicitis (not previously studied). Patients also had the possibility to decline antibiotic therapy when they preferred surgery as alternative.

Appendectomy was performed according to established procedures regardless if the operation was primary or performed as rescue surgery due to failing antibiotic therapy. All patients received single dose antibiotic prophylaxis. Decision to use open or laparoscopic techniques was made by the operating surgeon and postoperative antibiotic treatment was initiated when the appendix was gangrenous or perforated. The recommendation was to send all extirpated appendices for histopathological examination.

Data collection and follow up

Pre-treatment data such as body temperature, abdominal status, laboratory parameters (CRP, WCC) were registered for each patient according to protocol at the occasion of diagnosis. Body temperature and laboratory tests were subsequently analysed at least every 12-24 hours until discharge of antibiotic treated patients. In the follow up population based study, additional analyses of PCT were made both pre-treatment and subsequently without influence on the clinical decision process. These observational data on PCT were used in the PCT model (paper IV).

Per-operative findings, duration of antibiotic treatment, complications, re-operations and duration of hospital stay were registered at discharge. In addition, the total costs for the primary hospital stay (materials, medical drugs, laboratory tests, radiology, surgical and anaesthesiologic resources, postoperative surveillance, pathology and hospital care) were registered and analysed for each patient in the RCT in co-operation with our hospital controller.

Questionnaires were sent to all patients after defined intervals within one year regarding symptoms after discharge, sick-leave, new episodes with abdominal pain, contact with medical services, admission to any hospital and surgical procedures. Telephone calls were made to all patients in the RCT who did not return the questionnaire. Patient data journals and other files were searched after one year and further admissions, complications, recurrences and re-operations were retrieved.

Outcome measures

Primary endpoints were treatment efficacy and major complications. Efficient antibiotic treatment was defined as clinical recovery without the need of surgery during the primary hospital stay and without recurrence after one year. Efficient surgical treatment was positive findings at exploration (appendicitis or any other surgical diagnosis). Major complications were re-operation, abscess formation, small bowel obstruction, wound rupture, wound hernia, serious anaesthesia related problems or serious cardiac/respiratory problems. Secondary endpoints were minor complications, length of antibiotic therapy, duration of hospital stay, abdominal pain after discharge and total costs for the primary hospital stay.

Retrospective study (paper III)

Inclusion criteria in the prediction model were adult patients with presumed acute appendicitis who underwent appendectomy with histological examination of their appendix. For these patients, preoperative clinical and laboratory variables (age, gender, body temperature, abdominal status, CRP and WCC) were retrieved from medical data files. The written histopathological reports were manually examined for each patient. The relation between the pre-operative parameters and the final histopathological diagnoses were analysed by logistic regression and mathematical models were evaluated to predict phlegmonous appendicitis. Our hypothesis was that phlegmonous appendicitis should have the highest probability to heal on antibiotics compared to gangrenous and perforated appendicitis. The final model was tested on the prospective patient material from the follow up population based study (paper II).

Definitions

Abdominal status

Abdominal status was classified as local tenderness, local peritonitis or general peritonitis. Classification of abdominal status was obligatory to indicate in the protocol in the prospective studies. In the retrospective study, this information was retrieved from the medical data files and interpreted to match one of the three categories.

Histopathological classification of appendicitis

The degree or extent of appendicitis was characterized as either phlegmonous, gangrenous or perforated according to the histopathological reports. The different stages of appendicitis were defined as:

- phlegmonous: transmural leukocyte infiltration
- gangrenous: as phlegmonous plus areas of necrosis
- perforated: as gangrenous plus rupture of the serosal surface

(See introduction, paragraph histopathology)

Statistics

SPSS® version 15.0-18.0 software (SPSS, Chicago, Illinois, USA) was used for the statistical calculations. Student's t-test or analyses of variance (ANOVA) were used for comparisons between groups on continuous variables and χ^2 test to check for differences between proportions. Non-parametric methods were used when appropriate. $p<0.05$ was considered significant in two-tailed tests. Logistic regression with odds ratios and ROC-curves were used to describe the diagnostic performance of variables.

In the RCT, pre-study estimates suggested that 200 randomized patients should be necessary to confirm a 10-15% difference in treatment efficacy and complications at a significance level of 5% and a power of 80%. The analyses were primarily made by intention to treat (randomized groups according to birth date) and secondarily per protocol treatment.

METHODOLOGICAL CONSIDERATIONS

Paper I (RCT)

A high quality randomized controlled trial provides the strongest evidence for evaluation of treatment effects due to therapy. Strict inclusion criteria give high internal validity, but this characteristic may correlate with low external validity (low generalizability).

What characterises an ideal RCT?

1. *Correctly powered to allow definite conclusions.*

   Power analysis was made on primary outcomes (treatment efficacy and major complications) and the number of included patients (369) exceeded the minimum number required (200) according to our estimates.

2. *Clear-cut and specific inclusion and exclusion criteria.*

   No generally excepted criteria for definite diagnosis of acute appendicitis are available. Radiological imaging has not convincingly proved better results than clinical diagnosis [20, 83]. Clinical diagnosis is subjective, but different scoring systems have not overcome this limitation and have not been widely used.

   Our inclusion criterion was clinical diagnosis of presumed appendicitis with radiology used only when regarded necessary. An advantage with this approach is that it mimics the widespread clinical situation and creates a high generalizability. A disadvantage is that patients who may not have appendicitis could be included.

However, our hospital prerequisite for performing this study was not to raise costs due to mandatory radiological examinations. Therefore, we did not consider to have CT-verified appendicitis as inclusion criterion. It was also our belief that introduction of CT for all patients with presumed appendicitis would be ethically doubtful considering that many of the patients are young and the radiation hazards are not negligible.

3. *Consecutive patients with all eligible patients to be included.*

   Great effort was made to include *all* eligible patients diagnosed to have presumed appendicitis. The data journal systems (the patient medical files and the operation register) were searched in several ways.

   - patient reason to appear at the surgical emergency ward: abdominal pain
   - surgical procedures: appendectomy (open and laparoscopic), diagnostic laparoscopy
   - diagnosis at discharge: appendicitis, non-specific abdominal pain

4. *Correctly performed randomization procedure to balance confounding factors.*

   We chose an unconventional randomization procedure with birth dates that meant no allocation concealment. The surgeons knew in advance into which group the patient would be randomized. We had several reasons for the choice of this procedure. In the earlier RCT by Styrud et al [54] a classic randomization with concealed envelopes was used. Their inclusion criterion was a clinical diagnosis of suspected appendicitis and, moreover, suspicion of perforation was an exclusion criterion. Still, they only included around 25% of all eligible patients.

   We intended to perform our study in a large university hospital, where more than a hundred physicians would be involved in taking care of these patients most often during non-office hours and with surgeons, urologists, vascular surgeons and physicians at the emergency ward, sometimes at service from other hospitals in our region. We would then anticipated a similar inclusion rate as in the RCT by Styrud et al [54]; the intellectual stand in the department at the time was characterized by scepticism towards the possibility to use antibiotics as treatment of acute appendicitis. Therefore, we chose randomization according to birthdates as a simple procedure, which should not require any extra material or work efforts from the doctors on call to include patients.

According to the ethical permission we also allowed a change of treatment group without patient exclusion from the study. The surgeons were allowed to change treatment when deemed clinically necessary as well as when the patients themselves asked for the alternative treatment according to the protocol.

We made subgroup analyses of pre-treatment data comparing patients who did not adhere to their intention to treat with those who correctly follow intention to treat in order to account for bias that our randomization method may have introduced. We also chose to register patients at the Östra Hospital during the same period as a reference group of patients without performing any protocol intervention. Pre-treatment patient characteristics were compared with the study patients [Table 2]. We did not use treatment blinding, since this is almost impossible when comparing surgery to conservative treatments. One can obviously not anaesthesize patients just for blinding purposes.

5. *No dropouts after randomization.*

   We did not have any dropouts after randomization because our inclusion criterion was diagnosis of presumed appendicitis (not patient´s acceptance to participate in the study). However, non-compliance or discontinuation of treatment was common as expected, especially in the antibiotic group.

6. *Sufficiently long follow up with minimal losses.*

   One year was judged to be a reasonable follow-up period in this study even if long-term follow-up after five and ten years are warranted. Efforts were made to minimize dropouts; patients who did not answer the written questionnaire after one reminder were contacted by telephone. The response frequency obtained after one month was 90% and after one year 80%. In addition, all our medical data files for each patient were searched after one year as described previously.

7. *Analyses according to intention to treat and per protocol.*

   Analyses according to intention to treat were decided the prime goal. Non-compliance or discontinuation of treatment was not negligible. The reasons for such alterations were described and per protocol analyses were provided.

Paper II (population based study)

The comments in paragraph 2, 3 and 6 are valid also for this population based study on unselected patients with acute appendicitis.

Paper III (prediction model)

We chose to base the prediction model on the histopathological diagnosis of appendicitis although many appendices were not examined in microscope and thereby excluded from the study, which may or may not have created a selection bias of patients for the final database. It was not mandatory in participating hospitals to send all appendices for histopathological examination but rather an individual decision by each surgeon.

The histopathological diagnosis is regarded as golden standard despite the lack of universally accepted histopathological criteria for acute appendicitis including the different stages of inflammation (see Introduction, paragraph histopathology). We chose not to accept mucosal inflammation as sole evidence for acute appendicitis because this kind of changes may also be found in asymptomatic patients [44].

Paper IV (procalcitonin)

Analyses of procalcitonin (PCT) were made as an additional test to standard laboratory parameters of the patients in the population based follow up study. The test was actually performed only in 71% of the patients that received antibiotic treatment, which may have created a risk of selection bias and more vague results.

RESULTS

Patients (paper I-IV)

Baseline characteristics (at diagnosis before treatment) for all patients are shown in Table 2. The patients who actually received antibiotics in the RCT (paper I) had slightly lower body temperature and WCC, but this trend was also seen in the intention to treat group on antibiotics selected by chance alone. Nevertheless, in the follow up population based study (paper II) the pattern was similar; the antibiotic group had lower WCC and fewer patients with local or general peritonitis. In the retrospective prediction model (paper III) the connection between higher levels of inflammatory parameters (temperature, peritonitis, CRP, WCC) and more advanced stages of appendicitis was highly significant.

Comment:

The apprehension in the RCT was that primarily operated patients may have more severe disease than patients treated with antibiotics and thereby create biased results. The analyses of pre-treatment patient characteristics did not support this. The per protocol groups were highly comparable with only minor differences that existed also in the strictly randomized groups (intention to treat). However, patients clinically judged to be in the need of surgery (9% in the RCT, 6% in the population based study) could theoretically have contributed in some extent to the small differences as observed. Nevertheless, these patients did not have proportionally more complications than average.

Antibiotic response (paper I, II)

The antibiotic response rate (recovery without surgery) was 91% (108/119) in the RCT (paper I) and 77% (342/442) in the follow up population based study (paper II) as shown in Table 3.

Comment:

The antibiotic response rate in the RCT was in line with other studies [54, 60-61]. The reasons for the lower response rate in the follow up population based study are unknown and we can only speculate about possible explanations: The intravenous antibiotic regimen was changed between the studies, although in accordance with recommendations from specialists of infectious diseases and the regional antibiotic resistance pattern. Also, many colleagues were reluctant to a new treatment regimen and did perhaps not always pursue the conservative

Table 2. Patient characteristics at diagnosis before treatment.

	RCT (*paper I*)					Population based study (*paper II*)		Prediction model (*paper III*)		PCT model[d] (*paper IV*)	
	Intention to treat		Per protocol								
	Antibiotic (n=202)	Surgery (n=167)	Antibiotic (n=119)	Surgery (n=250)	Reference (n=159)	Antibiotics[a] (n=447)	Surgery (n=111)	Non-surgical[b] (n=261)	Surgical[c] (n=123)	Antibiotic success (n=249)	Antibiotic failure (n=67)
Patient variables											
Sex ratio (M:F)	51:49	55:45	52:48	55:45	58:42	229:218	58:53	138:123	78:45	124:125	38:29
Age (y)	38±1	38±1	40±2	37±1	34±1	34±1	35± 2	36±1***	45±2	32±1	35±2
Temp (°C)	37.3±0.1	37.5±0.1	37.2±0.1*	37.5±0.1	37.5±0.1	37.2±0.03	37.3±0.07	37.5±0.1***	37.8±0.1	37.1±0.04**	37.3±0.08
Local perit (%)	17*	26	17	24	17	22**	34	20**	29	23	30
Gen perit (%)	4.5	2.4	2.5	4.0	3.8	0***	3	1**	6	0	0
Laboratory variables											
CRP (mg/l)	55±4	54±4	51±5	56±3	54±5	54±3	68±8	54±4***	100±7	50±4	60±8
WCC ($x10^9$/l)	12.7±0.3*	13.6±0.3	12.2±0.4*	13.5±0.3	14.2±0.3	12.6±0.2*	13.6±0.4	12.7±0.3***	14.8±0.4	12.2±0.3***	14.7±0.5
Neutrophils						9.6±0.2	10.2±1.0				
PCT (ug/L)						0.85±0.29	0.66±0.28			0.76±0.27	1.21±0.91
Diagnostic variables											
CT/US (%)	28	25	31	24	16	37***	54				
Gyn exam (%)	69	61	65	66	47	53	49				

Mean±SEM. * p<0.05, ** p<0.01, *** p<0.001
[a] including five patients with no treatment
[b] including phlegmonous appendicitis
[c] including gangrenous and perforated appendicitis
[d] patients from paper II

therapy when medically possible. Perhaps a population based offer was also regarded of less importance to follow compared to a RCT protocol?

Table 3. Treatment efficacy.

	RCT *(paper I)*			Population based study *(paper II)*	
	Antibiotics	Surgery	Reference	Antibiotics	Surgery
Primary recovery	108/119 (91)	223/250 (89)	142/159 (89)	342/442 (77)**	98/111 (88)
1-year follow up	93/119 (78)*	223/250 (89)	142/159 (89)	304/442 (69)***	98/111 (88)

Values within parenthesis are percentage.
* $p<0.05$ vs surgery, ** $p<0.01$, *** $p<0.001$

Treatment efficacy - antibiotics versus surgery (paper I, II)

Treatment efficacy during the primary hospital stay and after 1-year follow up, respectively, is shown in Table 3. In the RCT, the proportion of patients who failed to respond to antibiotics was similar to the proportion of patients who were exposed to an unnecessary operation. After 1-year follow up the surgery group had significantly higher treatment efficacy due to recurrences in the antibiotic group as expected.

Comment:

Thus, if the goal is to never suffer from acute appendicitis again the preferred treatment should be appendectomy. However, the risk for recurrence after antibiotic therapy must be weighed against the risk for serious complications after surgery.

Recurrences (paper I, II)

Fifteen patients (14%) in the RCT and 39 patients (11%) in the subsequent population based study experienced recurrent appendicitis within 1-year follow up. Patient characteristics and diagnoses at operation are shown in Table 4. Most of the recurrences were phlegmonous and the patients did not suffer proportionally more complications than patients who had primary surgery.

Comment:

The recurrence rate after one year was in line with other studies [54, 60, 84]. Our data did not indicate that recurrences were more advanced than first time appendicitis or that surgery for recurrent appendicitis was more complex and afflicted with complications. An earlier study supported these findings [85].

Table 4. Recurrences within 1-year follow up.

	No.	Age range (years)	Mean time to recurrence (months)	Treatment		Diagnosis at operation		
				Antibiotics	Surgery	Phlegmonous app	Gangrenous app	Perforated app
RCT *(paper I)*	15 (14)	35-83	4	3	12	8	1	3
Population based study *(paper II)*	39 (11)	17-89	5	5	34	27	4	3

Values within parenthesis are percentage.

Complications (paper I, II)

Primary antibiotic treatment displayed less overall complications compared to primary surgery in both the RCT and the follow up population based study (Table 5). Major complications were threefold higher in surgically treated patients in the RCT (p<0.05). This was not explained by a disproportionately high frequency of major complications among patients deemed clinically necessary to operate (9%). In the follow up population based study the proportion of major complications were similar between groups. Patients who had rescue surgery due to antibiotic failure did not have more complications than primarily operated patients.

Table 5. Complications within 1-year follow up.

	RCT *(paper I)*		Population based study *(paper II)*	
	Antibiotics (n=119)	Surgery (n=250)	Antibiotics (n=442)	Surgery (n=111)
Major				
No.	3 (3)*	25 (10)	28 (6)	9 (8)
Patients			21 (5)	8 (7)
Minor				
No.	33 (28)	55 (22)	42 (10)***	26 (23)
Patients			40 (9)***	22 (20)

Values within parentheses are percentage.
* p<0.05, *** p<0.001

Minor complications were similar between the groups in the RCT, but twice as common among surgery patients in the follow up population based study (Table 5). The most common minor complication among antibiotic treated patients was some form of antibiotic side effect (mainly diarrhoea) and among operated patients it was wound infection.

Comment:

We chose to include unnecessary surgery (suspicion of recurrence that could not be verified at operation) as a major complication for antibiotic treated patients. This is of course a disadvantage for the antibiotic group and whether it should be regarded as a complication or not can be considered. Removal of these cases would result in significantly lower rate of major complications for antibiotic treated patients compared to surgically treated patients in the follow up population based study as well. However, we did not want to create any stand to favour antibiotic treatment.

Health economy (paper I, II)

The hospital stay was significantly shorter for antibiotic treated patients in both the RCT and the follow up population based study (Table 6). The total costs for the primary hospital stay were twice as high for patients in the RCT who had primary surgery.

Table 6. Primary hospital stay: duration and total costs.

	RCT *(paper I)*		Population based study *(paper II)*	
	Antibiotics (n=119)	Surgery (n=250)	Antibiotics (n=442)	Surgery (n=111)
Duration (days)	2.3±0.1*	2.9±0.2	2.3±0.1*	2.9±0.3
Total costs (SEK)	18 000±1100***	36 900±2300	-	-

Mean±SEM. * $p<0.05$, *** $p<0.001$
SEK, Swedish krona

Comment:

Data analyses of the costs for the entire follow up period (one year), including re-admissions etc, were not performed.

Prediction of antibiotic response (paper III, IV)

Analyses of pre-treatment patient characteristics, in relation to histopathological diagnosis, showed that age, CRP and WCC were significant predictors of phlegmonous appendicitis (or other non-surgical condition) in multiple logistic regression analysis. A model with age <60 years, CRP <60 mg/L and WCC <$12x10^9$ resulted in 89% probability to have a condition that did not require surgical exploration when all three criteria were fulfilled (Table 7). Subsequent validation of the model on patients receiving antibiotics as their first line therapy (patients from paper II) confirmed the results; 89% recovered on antibiotics when the model criteria were applied compared to 77% of all patients receiving antibiotics as an offer. Procalcitonin had limited additional value compared to traditional laboratory tests, like CRP and WCC, in prediction of early therapeutic efficiency of provided antibiotic therapy (Table 7).

Comment:

A problem with both our mathematical models and laboratory parameters as single predictors is that the diagnostic sensitivity appeared relatively low. This means that the tests will identify only a limited proportion of antibiotic responders despite the fact that positive predictive values are high.

Procalcitonin is appealing in theory as a fast inflammatory responder supporting decision-making regarding initiation and termination of antibiotic therapy. However, for patients with acute appendicitis we were not able to confirm the advantage of PCT compared to traditional inflammatory markers like CRP, WCC and body temperature.

Table 7. Prediction of phlegmonous appendicitis and antibiotic response.

	Cut-off value	Prediction of phlegmonous appendicitis[a] PPV (%)	Prediction of antibiotic response PPV (%)	Evaluation of antibiotic efficacy after 4-24 hours of therapy PPV (%)
Prediction model *(paper III)*:				
- age (years)	<60			
- CRP (mg/L)	<60	89	89	
- WCC ($x10^9$/L)	<12			
PCT model *(paper IV)*:				
- procalcitonin (ug/L)	≤0.1		80	
- procalcitonin (ug/L)	unchanged or decreased			91
- CRP (mg/L)	unchanged or decreased			94

[a] and other non-surgical conditions
PPV, positive predictive value

DISCUSSION

Antibiotic treatment

This thesis explores the possibility of antibiotic treatment of acute appendicitis as a first line option. Alternative and conservative treatment of acute appendicitis compared to surgical appendectomy is still controversial as it was over a century ago, since appendectomy is regarded the gold standard. Therefore, a change in treatment principles would be of great clinical importance and represent a paradigm shift since this topic engage and affects most surgeons independently of sub-specialities. The general opinion regarding treatment of acute appendicitis has changed during the last few years according to our experience. When we initiated our RCT in order to compare antibiotic treatment with appendectomy in unselected patients there was great misbelief and scepticism among colleagues about the possibility to treat appendicitis conservatively with only antibiotics. This was during 2006 and the first large RCT on the subject had just been published [54]; a trial that included only men. Today, some studies later, a beginning acceptance of a conservative approach with antibiotics as a possible means has appeared and become interesting to the surgical society. However, the question whether primary antibiotic treatment of acute appendicitis is inferior, equal or superior to appendectomy is highly debated, although we believe they should be regarded complementary.

Our own study from 2009 (paper I) was the first large RCT to include both men and women without any upper age limit, i.e. to include unselected adult patients. The diagnosis of acute appendicitis was based on pure clinical procedures with support of radiology when deemed necessary only. All patients who appeared with acute appendicitis were included and randomized, but non-compliance to treatment was common for reasons as discussed in the method section. The primary recovery rate (91%) and the 1-year recurrence rate (14%) in our study were in accordance with the RCT by Sturyd et al [54] and we could also observe that antibiotic treatment was associated with fewer major complications compared to primary surgery. The same year (2009) two additional studies were published; one small RCT [60] and one non-randomized prospective study [84]. The diagnostic procedures in these studies were based on the clinical conditions of the patients in combination with ultrasound investigations, but study inclusion and exclusion criteria of their patients were not explicitly expressed or defined in the publications. Recovery and recurrences during antibiotic treatment were reported to be similar to earlier findings, but complications were unfortunately not described.

Table 8. Comparison between RCTs.

	Patients treated with antibiotics	Recovery rate (%)	1-year recurrence rate (%)	5-years recurrence rate (%)
Eriksson et al Br J Surg 1995	20	95	37	
Styrud et al World J Surg 2006	128	88	14	24
Hansson et al Br J Surg 2009	119	91	14	
Malik et al J Gastrointest Surg 2009	40	95	11	
Turhan et al Turk J Trauma & Emerg Surg 2009[a]	107	82	10	
Vons et al Lancet 2011	120	88	25	
Hansson et al World J Surg 2012	442	77	11	

[a] non-randomized

A recent large RCT by Vons et al [61], on patients with clinical assumption of acute appendicitis and with CT-confirmed diagnosis of uncomplicated appendicitis as inclusion criteria, concluded that antibiotic treatment was inferior to appendectomy. The antibiotic recovery rate was in line with earlier studies but the 1-year recurrence rate was higher. Complications in the antibiotic and the surgery group did not differ. However, several comments and concerns about the study design and the conclusions can be raised [86-88]: the radiological criteria for acute appendicitis, the choice of antibiotic regimen with known and considerable resistance problems, lack of description of the proportion of eligible and included patients as well as different follow up protocols for the antibiotic and the surgery group were all less than optimal. Nevertheless, our largest doubt concerns the primary outcome defined as "30-day postintervention peritonitis", a concept not related to clinical outcome and difficult to clearly define. Accordingly, this study does not clarify the scientific merit of primary antibiotic treatment of acute appendicitis, although published in a highly prestigious journal.

Eight meta-analyses and reviews, including a Cochrane report, of the RCTs comparing antibiotics with surgery (Table 8) have been published during recent years [62-69], but the conclusions in these summaries have not been unanimous. Some authors stated that antibiotics might be safely used in selected patients with uncomplicated appendicitis leading to overall reduced complication rate, but the reports emphasized that appendectomy should remain the gold standard treatment [62-64]. Others pointed out that antibiotic treatment incur fewer and less severe complications than surgery and could be regarded an alternative treatment in a majority of patients when such patients are willing to accept a risk of either initial treatment failure or later recurrence [65-68]. However, a majority of the reviewing authors underlined methodological imperfections of published RCT studies mainly regarding selection bias of treated patients. The Cochrane report also judged the RCTs to be of low to moderate scientific quality because of poorly reported randomization procedures without the use of mandatory radiology for diagnosis and without description of the number of withdrawals before the inclusions as well as a lack of properly performed follow-ups and lack of subsequent subgroup analyses. The Cochrane conclusion was that further high quality RCTs with longer follow-up than one year are necessary in order to judge whether antibiotic therapy is an equal option to surgery or not [69].

Thus, main concerns regarding study qualities have been to what extent selection biases have influenced upon reported results, i.e. if patients treated with antibiotics had overall less severe disease compared to surgically treated patients. In our own RCT conducted 2006-2007 (paper I) ethical prerequisites and general opinions among colleagues and patients at that time made it necessary to allow both the surgeons and the patients to have the possibility to decide for surgery against formal treatment allocations. Did this introduce a potential selection bias creating distorted results in our study? Analysis of pre-treatment parameters plus comparisons with a reference population at the nearby Östra Hospital during the same period of time did not support such a limitation of our study. Also, the patients who were deemed necessary by the surgeons in charge to be operated upon (9%) did not show proportionally more complications than observed among patients operated due to randomization.

An approach to circumvent the clear problem with potential selection bias of patients is to perform a population based study. Based on the antibiotic treatment principles that we applied in our RCT study (paper I) we therefore conducted the first population based study with antibiotics as the first line treatment offered to all appearing patients with acute appendicitis in our region (paper II). However, our surgeons could still advocate appendectomy based on strict medical reasons such as general peritonitis and the patients could still choose surgery as their primary treatment after provision of standardized information about the therapy alternatives. This study design resulted in approximately 80% (442/558) antibiotic treated patients, with a primary recovery rate of 77% and a 1-year recurrence rate of 11%. The overall complication rates were lower after antibiotic treatment compared to primary surgery in both our trials.

Safety aspects

Historically, there has been a fear that delayed management of acute appendicitis could be fatal. However, a strategy of 'active observation' instead of 'early appendectomy to avoid perforation' has proven safe and represents a reasonable stand [7, 9]. Also, raised standard mortality ratios among appendectomized patients, including patients with non-perforated appendicitis and with non-specific abdominal pain, suggest that some deaths might rather be caused by the surgical procedures [29, 31].

In both our studies (the RCT and the follow up population based study), antibiotics have proven to be a safe first line possibility for treatment of acute appendicitis. The overall complication rates were lower than for patients treated by primary surgery. Most importantly, patients operated on due to failing antibiotic therapy did not show increased complication rates. Also, surgery in patients with recurrent appendicitis following antibiotic treatments have not been more complex than primary surgery nor afflicted with more complications in our evaluations. On the contrary, recurrences have usually been phlegmonous more often as compared to surgical patients with first time appendicitis, also previously described [85]. These results support conclusions in available meta-analyses claiming that antibiotic therapy has fewer and less severe complications than surgical appendectomy [62, 64-68]. No death has been reported in any of the conducted trials with antibiotics.

General prerequisites for antibiotics to be a safe therapy of acute appendicitis are that individual and up to date clinical assessments of the patients are provided. The surgeon in charge should of course decide for operation when deemed clinically important, although this criteria has not been defined scientifically. This approach may appear necessary in a predicted group of 5-10% of all patients with acute appendicitis and in the group of patients who will subsequently appear to need rescue surgery when there is clinical progression despite provided antibiotic therapy. It should also be considered and emphasized that pregnant women with acute appendicitis and patients with recurrent appendicitis have not been studied systematically in any reported controlled study.

Diagnostic accuracy of acute appendicitis

It is of great importance that the diagnostic accuracy does not decline when introducing changes in medical treatment praxis. This may be especially important concerning antibiotic treatment of acute appendicitis since the diagnosis is not finally and definitely confirmed until eventual surgery has been performed. Diagnosis according to best practice should always be strived for, but final models including clinical diagnosis, mandatory CT/US or clinical scoring systems are still under scientific evaluations and remains to be described in terms of validated applications [89].

CT and US have been claimed to provide high sensitivity and specificity for diagnosis of acute appendicitis in clinical trails, but the only RCT that used routine US for the diagnosis did not confirm any benefit compared to conventional clinical diagnostic procedures and a selective use of US only [83]. Some data in that report and others also implied that routinely used US and CT in patients with presumed appendicitis detects inflamed appendices that would otherwise have remained undiscovered; i.e. that would have resolved spontaneously [20, 83, 90-91]. Moreover, a routine use of CT in a relatively young population with eventual appendicitis also brings significant doses of radiation, which is unwarranted and sometimes too neglected by clinicians [92].

Non-specific abdominal pain (NSAP) represents a mixed group of patients with possible conditions that may include all self-limiting causes of pain where surgical, gynaecological or other medical diagnoses are not clear. The NSAP diagnosis is reported to be common (up to 50%) among emergency department patients with acute abdominal pain [93]. Interestingly, women with NSAP have been randomized to either early laparoscopy or conservative observation in a RCT from 2006 [94]. This study showed that 30% of patients in the laparoscopic group had appendicitis indicating that early appendicitis is highly frequent among patients with unclear abdominal pain referred to as NSAP. This study also implies that acute appendicitis may heal spontaneously, although it remains to be decided how antibiotic treatment should be used in such patients.

In our study materials (paper I+II) at least 10% of patients treated with primary surgery did not have appendicitis. Therefore, a reasonable assumption would be that a similar proportion should also be expected in the group of patients subjected to primary antibiotic treatment based on presumed appendicitis. However, unnecessary antibiotic treatment to such patients may be less problematic compared to unnecessary abdominal surgery in patients without appendicitis.

Prediction models of antibiotic response – patient selection

Optimized antibiotic treatment in terms of patient selection may be warranted compared to a systematic offer to treat all patients initially with antibiotics, since a predictive approach should be more effective compared to just a standardized offer of antibiotic treatment. Development of such a model to predict antibiotic response was therefore our aim in a retrospective study (paper III) where we defined that a combination of age, CRP and WCC improved treatment efficacy significantly. This model had high specificity (93%) and PPV (89%) but low sensitivity (29%); i.e. a positive test was reliable but would not identify the majority of antibiotic responders. In this context, a comparison with the diagnosis of acute pancreatitis with elevated serum amylase can be made. An amylase cut-off level three times higher than the normal upper range limit was reported to have a sensitivity of 72% and a specificity of 99%; normal levels of amylase have been observed in 19-32% of cases of acute pancreatitis [95]. When a lower amylase cut-off limit is used the sensitivity increases at the expense of specificity. However, elevated amylase can also be seen in patients with non-pancreatic abdominal disease and if the test is performed in a population with low suspicion of acute pancreatitis the specificity falls.

In our model for prediction of antibiotic response among patients with acute appendicitis (not a model for diagnosis of acute appendicitis!) we could have chosen different levels of age, CRP and WCC, resulting in higher sensitivity but also lower specificity, meaning that the model should include more patients with antibiotic failure. In such case, the model would be meaningless, since the antibiotic response rate would have fallen and approached the rate for unselected patients. Therefore, our current model may be used as a clinical support instrument to select high probability antibiotic responders among patients with acute appendicitis in a clinical situation where antibiotics are used with caution. Interestingly, a complementary approach for patient selection may be the presence of an appendicolith. The predictive ability of such findings on CT was not studied by us, but data by others indicate that patients with an appendicolith may have a higher risk of failure with non-operative management [61, 67, 71, 96] and also a higher risk for recurrence [97-98].

Our PCT analyses (paper IV) aimed to find a suitable model for monitoring to what extent initiated antibiotic therapy will be effective or not in an early stage of treatment with the aim not to delay rescue surgery when unavoidable and not to use unnecessary antibiotics. In intensive care medicine there are suggestions to use PCT for evaluating the effect of antibiotic treatment and to possibly terminate empirical antibiotic therapy when doubt in precaution [99]. RCTs have shown the efficacy to use PCT algorithms to guide antibiotic decisions for patients with postoperative infections, respiratory tract infections and intensive care patients with sepsis [76]. Further trials are expected in this area. However, regarding acute appendicitis we could not demonstrate any additional value of PCT compared to standard laboratory tests and clinical assessment in prediction of the efficiency of provided antibiotic therapy.

Antibiotic resistance

Antibiotic resistance is a problem of increasing dignity worldwide, perhaps threatening to diminish the possibilities to treat infectious diseases as well as performing surgical procedures in the future. One example is extended spectrum beta-lactamse (ESBL), which is increasing among common bowel bacteria like E.coli and Klebsiella, and brings resistance against penicillins and cephalosporins. In Sweden during 2010, less than 1% of all E. coli strains displayed ESBL, but the figure appeared 5-10% in middle Europe and up to 10-25% in Spain and Italy [100]. The use of antibiotics, particularly broad spectra antibiotics, and the spread of bacterial strains are the main factors that promote antibiotic resistance in hospitals and societies. Thus, standard sanitary routines are crucial in hospital care of patients and in other health care institutions to minimize the spread of resistant strains.

In Sweden approximately 400 recipes of antibiotics per 1000 inhabitants in non-institutional care were prescribed during 2010 [100]. This may be compared with an incidence of acute appendicitis around 1 per 1000 individuals. Thus, antibiotic prescriptions as treatment of acute appendicitis do not seem to have a major impact on the total environmental antibiotic pressure even if we assume that each patient with appendicitis should be treated with antibiotics. This may be an important perspective since strong arguments are frequently provided that may create future restrictions for patients to have the least interventional treatment of acute appendicitis when possible from a medical perspective. Furthermore, there is a substantial use of antibiotics in animal care across a large number of countries in the world including Sweden. The antibiotic animal to human ratio in Sweden during 2009 was 1:4 but the proportions may vary considerably among countries. Nevertheless, it is of great importance and a unanimous responsibility not to use antibiotic therapy on inappropriate indications. The diagnosis of appendicitis should therefore always be made with care and patients should not be treated with antibiotics due to unclear abdominal pain and a low probability of acute appendicitis. Our suggestion to recommend antibiotics as a first line therapy for presumed acute appendicitis is based on the potential evidence of benefits for the patient in relationship to available evidence regarding the risk of antibiotic resistance, allocation of medical and hospital resources as well as complication risks related to present treatment alternatives.

Proposed model

With the premises of our own studies and that of published material by others we conclude that antibiotic therapy is a safe alternative to surgery. The benefits for the patients on antibiotic treatment are avoidance of surgery and thereby a decreased risk of complications that may sometimes be severe and life-long persistent. The risk of recurrence after antibiotic treatment is the main disadvantage for the patient. All patients should be entitled to receive adequate information about different treatment alternatives according to present evidence, which includes offered antibiotic treatment if they are willing to accept a risk of initial antibiotic failure or later on recurrence (in all around 35%). This approach is in accordance with recent Swedish health care regulations stating that each patient has the right to receive correct and best available information for own treatment decisions.

FUTURE PERSPECTIVES

Several important questions remains to be determined in future research on optimal treatment of acute appendicitis. All published data so far provide limited follow up periods and long-term follow ups on recurrences and complications at 5, 10 and 20 years are warranted. Another question concerns the possibility of antibiotic treatment in patients with recurrences as well as in pregnant women. These patient groups have not been studied systematically so far, although observational data in limited number of patients from our own studies indicate that recurrent appendicitis can be treated successfully with antibiotics at least a second round. Another issue regards the choice of antibiotic regimens. Could oral therapy alone - perhaps without hospital care - be adequate for selected patients? Could highly selected patients recover without any therapy at all?? A medical parallel may be the treatment of uncomplicated diverticulitis (Hinchey I), where oral antibiotics and out of hospital care have turned out to be sufficient and safe for many patients [101-102], and case-control studies have even indicated that conservative treatment without antibiotics may be equally effective [103-104]. Such challenging questions are appropriate and now opened for future RCT studies on acute appendicitis.

CONCLUSIONS

- Acute appendicitis in adults can be treated with antibiotics as single therapy with high recovery rate (>75%) and low recurrence rate within one year (10-15%). Long-term recurrence and complications after 5-10-20 years remain to be determined.

- Antibiotics as the first line therapy can be offered to a majority of adult patients with acute appendicitis as a safe treatment strategy that is not impaired by more complications than surgery, although 5-10% of all such patients may need primary surgery. Whether pregnant women or patients with recurrent appendicitis can be treated successfully with antibiotics remains to be studied.

- Rescue surgery after failing antibiotics and surgery for recurrent appendicitis were not associated with more complications than primary surgery and did not have higher proportions of gangrenous or perforated appendicitis in our trials. On the contrary, recurrences were more often phlegmonous.

- The spectrum of complications after antibiotic therapy consists mainly of side effects to antibiotics. Intra-abdominal abscesses were seen but occurred more frequently among surgically treated patients.

- A predictive model with age <60 years, CRP <60 mg/L and WCC $<12x10^9$ can be used to select patients with acute appendicitis to respond to antibiotic treatment with high probability (>85%), but the sensitivity of the model is low.

- Serum procalcitonin (PCT) is of limited value, in comparison to CRP, WCC and body temperature, for early evaluation of antibiotic efficiency in patients with acute appendicitis.

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