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ON THE TREATMENT OF ACUTE APPENDICITIS IN CHILDREN

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On the treatment of acute appendicitis in children
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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"IF AN OPERATION IS DIFFICULT YOU ARE NOT DOING IT PROPERLY"

On the wall of the operating room of Robert E. Gross, Boston

To A and C

ABSTRACT

Acute appendicitis is a common condition in children and the treatment of this condition is both straightforward and complex at the same time. An appendectomy is the most common acute surgical intervention in children and the vast majority of children make a swift recovery without any complications. The surgical modality is however shifting from open to minimal access surgery and now further onto non-operative treatment. A well-performed clinical examination is still imperative but is currently aided by both evolving scoring systems and imaging. Imaging is developing from ultrasound via computed tomography-scanning to magnetic resonance imaging. The traditional belief that an inflamed appendix always progresses to gangrene and perforation does not hold its ground. Spontaneous resolution of acute appendicitis appears to be common.

The aim of this thesis was to present modern benchmarks of different treatment modalities of acute appendicitis today, to present current evidence of non-operative treatment of acute appendicitis and to test if non-operative treatment of acute appendicitis in children is safe and feasible. All clinical studies have been based on children treated at the Astrid Lindgren Children´s Hospital, Stockholm, Sweden.

In **paper I** we conducted a review of all children who underwent an appendectomy for acute appendicitis between 2006 and 2010. 1744 patients were operated, 1009 had a laparoscopic operation. We found no difference in the rate of complications between the two methods. We found that the operating time was longer for laparoscopic surgery and that the initial assumption that the postoperative length of stay in the laparoscopic group was shorter than in the open group was not due to the surgical modality but to a general trend over time.

In **paper II** we studied recurrence of acute appendicitis in children after successful non-operative treatment of an imaging-confirmed appendiceal abscess. 89 patients were included in this study. Nine patients had an appendectomy during the 5.1 years of follow-up but only 2 had a recurrent acute appendicitis. Hence, the recurrence rate was 2.4% during 5.1 years of follow-up. This finding supports the strategy of not performing interval appendectomies on a routine basis.

In **paper III** we performed a meta-analysis on randomised controlled trials on non-operative treatment of acute appendicitis in adults. We included 4 trials with a total of 896 patients. There were no difference in treatment failure but there were fewer complications in the non-operative treatment group. 73% of patients were found not to have had an appendectomy during 1 year of follow-up. We concluded that a randomised controlled trial in children was warranted.

In **paper IV** we conducted a randomised controlled pilot trial of non-operative treatment versus surgery of acute appendicitis in children. We enrolled 50 patients in the trial, 26 were randomised to surgery. In the surgery group, all patients had a histologically confirmed acute appendicitis; none of these patients had any significant complications. Of the patients treated non-operatively with antibiotics, 92% had initial resolution of symptoms and only one patient (5%) had recurrence of acute appendicitis during the one-year follow-up period. Overall, 62% of patients have not had an appendectomy during the follow-up.

LIST OF SCIENTIFIC PAPERS

I. **Svensson JF**, Patkova B, Almström M, Eaton S, Wester T.
   Outcome after introduction of laparoscopic appendectomy in children with a standardized surgical protocol, a prospective cohort study
   Submitted manuscript

II. **Svensson JF**, Johansson R, Kaiser S, Wester T.
   Recurrence of acute appendicitis after non-operative treatment of appendiceal abscess in children: a single-centre experience
   Pediatr Surg Int 2014;30:413-6

III. **Svensson JF**, Hall NJ, Eaton S, Pierro A, Wester T.
   A review of conservative treatment of acute appendicitis
   Eur J Pediatr Surg 2012;22:185-94

IV. **Svensson JF**, Patkova B, Almström M, Naji H, Hall NJ, Eaton S, Pierro A, Wester T.
   Nonoperative Treatment With Antibiotics Versus Surgery for Acute Nonperforated Appendicitis in Children: A Pilot Randomized Controlled Trial
   Ann Surg 2015;261:67-71

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AIR	Appendicitis Inflammatory Response
AUC	Area under the ROC-curve
CI	Confidence Interval
CPR	Clinical prediction rule
CRP	C-reactive protein
CT	Computed Tomography
IQR	Interquartile range
LA	Laparoscopic appendectomy
LR-	Negative likelihood ratio
MAS	Minimal access surgery
MRI	Magnetic Resonance Imaging
OA	Open appendectomy
PAS	Paediatric Appendicitis Score
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
SBO	Small bowel obstruction
SEK	Swedish kronor
US	Ultrasound
VS	Versus
WBC	White Blood Cells

1 SUMMARY OF THE STUDIES

Study I: Outcome after introduction of laparoscopic appendectomy in children with a standardized surgical protocol, a prospective cohort study

Aim and methods: The aim of the study was to compare the outcome of open and laparoscopic appendectomy during a transition period. This was a cohort study with prospectively collected data. All patients who underwent an operation for suspected appendicitis at the Astrid Lindgren Children´s Hospital in Stockholm between 2006 and 2010 were included in the study.

Results and conclusions: 1744 children were included in this study, of whom 1009 underwent a laparoscopic intervention. There were no significant differences in the rate of postoperative abscesses, wound infections or re-operations between the two groups. The median operating time was longer for laparoscopic appendectomy than for open appendectomy, 51 vs 37 minutes ($p<0.0005$). The postoperative length of stay was similar in the two groups. A simple comparison between the groups suggested that laparoscopic appendectomy had a shorter median postoperative length of stay, 43 vs 57 hours ($p<0.0005$). However, there was a trend in time for a shorter postoperative length of stay, and a trend for more of the procedures to be performed laparoscopically over time so on regression analysis, the apparent decrease in length of stay with laparoscopy could be ascribed to the general trend towards decreased length of stay over time, with no specific additional effect of laparoscopy. Our data show no difference in complications between open and laparoscopic surgery for acute appendicitis in children. The assumed difference in post-operative length of stay was due only to a trend of shorter postoperative length of stay over time, regardless of the surgical intervention.

Study II: Recurrence of acute appendicitis after non-operative treatment of appendiceal abscess in children: a single-centre experience

Aim and methods: The aim of this study was to evaluate the incidence of recurrence of acute appendicitis after initial successful non-operative treatment of appendiceal abscess in children. This was an observational cohort study including all patients who were discharged after successful non-operative treatment with antibiotics for an imaging confirmed appendiceal abscess at Astrid Lindgren Children´s Hospital from January 2006 to December 2010. A search of the discharge diagnosis data-base was done to find the patients.

Results and conclusions: Eighty-nine patients were included in this study. Nine patients had an appendectomy during the follow-up period. Seven interval appendectomies were performed; five patients readmitted with symptoms within the first month after the initial presentation and two asymptomatic patients on consultant/parental decision. There were two late re-admissions due to a recurrent appendicitis and these two patients underwent acute appendectomy. Hence, the recurrence rate of acute appendicitis after successful non-operative treatment of appendiceal abscess treated with antibiotics was 2/82, 2.4% during a median follow-up of 5.1 years.

Study III: A review of conservative treatment of acute appendicitis

Aim and methods: The aim of this study was to determine if there is a role for conservative, non-operative treatment of acute appendicitis in children. A literature search was performed to look for studies on conservative, non-operative, treatment of acute appendicitis in children or/and in adults. Both case series, non-randomised and randomised trials were included and the search included both non-perforated and perforated appendicitis. A meta-analysis of the randomised, controlled trials on non-perforated appendicitis in adults was performed, based on per-protocol data.

Results and conclusions: We found five randomised controlled trials on non-operative treatment of acute appendicitis in adults. One of them was retracted from the journal of publication at the time of this meta-analysis and was excluded from the analysis. A total of 896 patients were included in the meta-analysis, 383 treated with antibiotics and 513 with surgery. There was no difference in regards of treatment failure, defined as failure of non-operative treatment requiring appendectomy (non-operative treatment arm), or negative appendectomy (surgical treatment arm). There were fewer complications in the non-operative treatment arm compared with the surgery arm. The estimated proportion of patients with acute appendicitis that could be treated without appendectomy at all, either during initial illness or during first year of following-up, was 73%.

Study IV: Non-operative treatment with antibiotics versus surgery for acute non-perforated appendicitis in children. A pilot randomized controlled trial

Aim and methods: The aim of this study was to evaluate the feasibility and safety of non-operative treatment of acute non-perforated appendicitis with antibiotics in children. A pilot randomised controlled trial was performed comparing non-operative treatment with antibiotics and surgery for acute appendicitis in children. Follow-up was one year.

Results and conclusions: Fifty patients were enrolled; 26 were randomised to surgery and 24 to non-operative treatment with antibiotics. All children in the surgery group had histopathologically confirmed acute appendicitis and there were no significant complications in this group. 2/24 patients in the non-operative treatment group had appendectomy within the time of primary antibiotic treatment and one patient after nine months for recurrent acute appendicitis. Another six patients have had an appendectomy due to recurrent abdominal pain (n=5) or parental wish (n=1) during the follow-up period; none of these six patients had evidence of appendicitis on histopathological examination. 22/24 (92%) of patients treated with antibiotics had initial resolution of symptoms. Of these 22, only one (5%) patient had recurrence of acute appendicitis during follow-up. Overall, 62% of patients have not had an appendectomy during the follow-up period. This pilot trial suggests that non-operative treatment of children with acute appendicitis is feasible and safe and that further investigation of non-operative treatment is warranted.

2 BACKGROUND

2.1 THE APPENDIX

2.1.1 Embryology

The appendix is the terminal portion of the embryonic caecum that can be seen as a swelling of the embryonic midgut during the fifth week of gestation. The appendix is visible at about the eights week of gestation. The development is thought to stem from a difference in growth rate of the caecum and the appendix. This difference in growth rate continues in postnatal life. Collins reported on 4.680 specimens and found that the diameter of the colon is 4.5 times greater than the appendix at birth and 8.5 times greater in the adult[1].

2.1.2 Anatomy

The appendix arises from the posteromedial side of the caecum, virtually invariably at the junction of the tenia coli. It can be positioned in any possible relation to the caecum, retro-caecal, retro-colic and pelvic or descending being the most common[2]. The length of the adult appendix is normally between 6 and 12 cm, single reports of an appendix over 30 cm has been presented. The arterial blood supply stems from the superior mesenteric artery via the ileocolic artery, an ileal branch or from a caecal artery into a usually single appendicular artery. The appendicular vein joins caecal veins to become the ileocolic vein. The lymphatic drainage follows the arterial pattern and drains into the celiac nodes. Interestingly, the lymph nodules in the wall of the appendix do not drain in this way but rather passes its formed lymphocytes into the lumen of the appendix. The sympathetic nerve supply to the appendix reacts to distention/stretch in the visceral peritoneum leading to the early periumbilical pain in appendicitis. Thoracic somatic sensory nerve fibers respond to inflammation of the parietal peritoneum leading to the classic pain migration to the right iliac fossa[3].

2.1.3 Epidemiology

Appendicitis is the most common surgical abdominal disorder in children aged 2 years or older[4-6]. Of all children presenting to paediatric ER with abdominal pain, 1% to 8% will ultimately be diagnosed with acute appendicitis. The lifetime risk of developing acute appendicitis is 6.7% for females and 8.6% for males[7]. The incidence increases from 1-2 cases per 10.000 children per year between birth and 4 years of age to 25 cases for every 10.000 children per year between 10 and 17 years of age[7, 8].

2.1.4 Why do humans have an appendix?

The general opinion has been that the appendix has no significant function in the human, often considered a vestigial organ, meaning that it has lost most or all its ancestral function in a given species but has been retained through evolution. The caecum has been considered to be a vestigial organ. The ancestral caecum would have been a large, blind diverticulum in which restraint plant material would have been fermented in preparation for absorption in the colon. As the appendix is the continuum of the caecum, it may have had a related function.

This is supported by the fact that the caecum in herbivores is long and well developed. In carnivores like dogs, wolfs, lions and cats the appendix is absent. In omnivores like humans, apes and wombats, the terminal caecum is small in diameter, has a prominent lymphoid component and is susceptible to similar pathological processes and atrophic changes.

Charles Darwin was one of the first to speculate on the function of the appendix, which in his days had been identified only in humans and other great apes[9]. He hypothesised that the distant ancestors of these animals survived on a diet of leaves, and so they require a large caecum. Later, he speculated, these ancestors shifted to a largely fruit-based diet that was easier to digest. A large caecum was no longer necessary and it began to shrink. Darwin thought that the appendix was one of its former folds that shrivelled up as the caecum shrank.

But, maybe the appendix is not vestigial, and if it is, it has maybe been "vestigial" only for the last 50 years.

De Coppi and co-workers presented a paper in 2006[10], showing that the vermiform appendix was capable of producing mesenchymal stem cells. They showed that Appendix-Derived Mesenchymal Stem cells were present in the vermiform appendix both in infancy and at an older age. These cells can develop into osteoblasts, lipoblasts and myoblasts, depending on the stimulation. They speculate that the vermiform appendix is a reservoir for stem cells capable of bowel repair throughout life. A group from North Carolina has presented a number of papers on this subject as well[11-13]. The authors suggest that the appendix is a well-suited reservoir for bacteria that normally constitutes the gut flora, and is needed to re-colonise the bowel after bacterial infections, e.g. diarrhoeal disease. They showed that a biofilm, adherent colonies of microbes growing within an extracellular matrix, is most prominent in the appendix and decreases progressively to the distal end of the bowel. They hypothesise that this function was important only under conditions in which modern medical care and sanitation practices are absent. This is supported by the hygiene hypothesis, the suggestion that modern medicine and sanitation may led to an under-stimulated and subsequently overactive immune system that could lead to an increase in allergies and auto-immune disease. Such activation could, hypothetically, cause appendicitis due to obstruction by the lymphoid tissue in the appendix. Barker and co-workers presented an association with bathroom availability and risk of acute appendicitis to support this hypothesis[14].

2.2 HISTORY

The first known image of an appendix was made by Leonardo da Vinci in 1492 and was called an "oreccio", or "little ear". DaCapri described the appendix formally in 1521 and Vesalius presented in 1543 a drawing of the appendix with a round stone in the lumen (figure 1), a condition today known as an appendicolith, or fecalith, and a well-recognised cause of luminal obstruction and subsequent appendicitis[15] (figure 2).
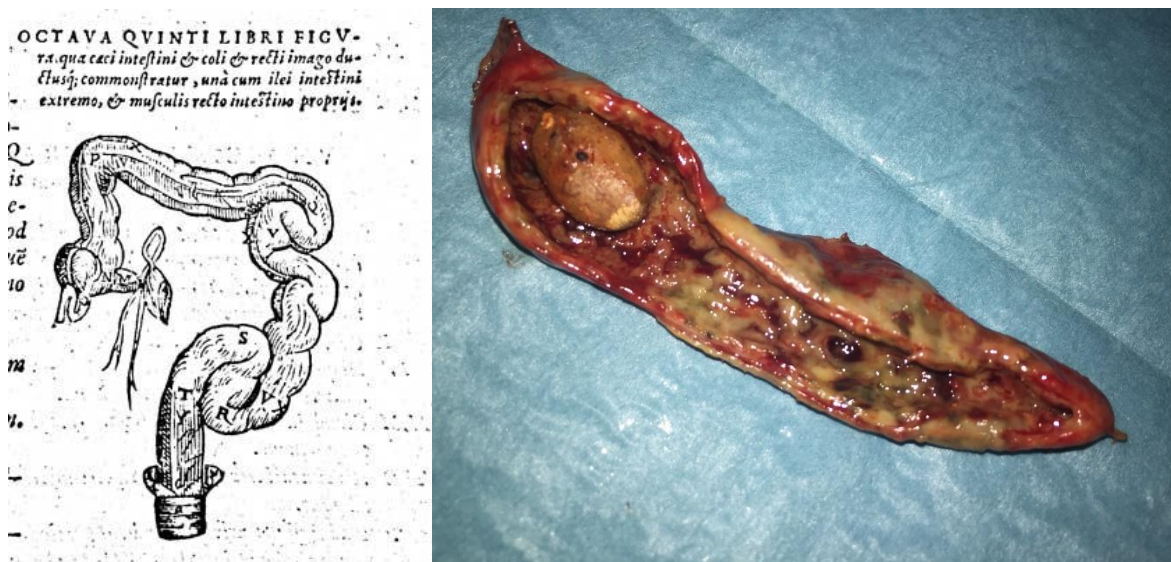
Figure 1 and 2. Vesalius drawing of an appendix with an obstructing stone (left) and a specimen of a gangrenous appendix with a fecalith (right).

The first description of an appendectomy was made by the British military surgeon Claudius Amyand whom in 1735 worked at St. Georges Hospital in London[16]. In his care was an 11-years old boy by the name of Hanvil Andersson. He had a right sided inguinal hernia since birth without any major problems. He subsequently developed a fistula from the scrotum down to the thigh and when Amyand opened this tract it was obvious that it originated from the hernia. That was the indication for a second procedure on the eighth of December when the hernia was opened only to reveal a mass of omentum covering an inflamed appendix that had perforated on the basis of a pin. During the operation the appendix was removed and the patient recovered. Unfortunately the hernia recurred later but without inflammation.

In 1812, James Parkinson, after whom Parkinson´s disease is named, aided his son John Parkinson in communicating the first case of a patient who died due to a perforated appendicitis[17]. This patient was a 5 year old boy who died 48 hours after the onset of severe abdominal pain. The autopsy revealed a perforation at the middle part of the appendix, distal to a piece of hard faecal material. The proximal appendix and the caecum were unaffected. The first appendectomy performed for the diagnosis of acute typhlitis was performed in Edinburgh by Robert Lawson Tait in 1880[18]. He operated on a 17-year old girl and successfully removed a gangrenous appendix. The girl recovered despite Tait´s strong opposition against Listerism. This was more than thirty years after the first presentation of ether anaesthesia in 1846 in Boston by Dr. William Morton. The hospital in Edinburgh was the first hospital in Europe to use ether anaesthesia and general anaesthesia obviously changed the surgeon's possibilities tremendously. As an anecdote, it may be of interest to the reader to know that Charles Darwin, author of the book "Origin of the species" and the father of evolution, studied medicine in Edinburgh in the 1830´s but dropped out as he could not stand witnessing the horrors of surgery. Mr Darwin moved on to Cambridge to studies in theology. This operation of Lawson Tait preceded both the Canadian Abraham Groves who in 1883, unaware of Tait's operation, undertook an appendectomy on a 12-year old boy who

recovered[19], the first presentation by Reginald Heber Fitz in 1886[20] and the more famous Charles McBurney who in 1889 presented his first series of patients with acute appendicitis[21]. Five years later, McBurney published his paper on the muscle-splitting procedure that bears his name[22], even though this grid-iron incision was apparently first performed by Louis L. McArthur[23]. The open appendectomy (OA) through a McBurney incision was the principal method of treating acute appendicitis until Kurt Semm performed the first laparoscopic appendectomy (LA) in an adult on the 13th of September 1980[24]. Ure and co-workers presented the first series of laparoscopic appendectomies in children in 1992[25]. See 2.8.2 for details.

2.3 FAMOUS PEOPLE WITH APPENDICITIS

Harvey Cushing was a young surgical resident at Johns Hopkins Hospital in Baltimore in 1897 when he diagnosed himself with acute appendicitis just one week after one of his patients died following an operation for the same condition. He had to convince his senior colleague Halsted to perform the operation. It all went well and Dr Cushing went on to become one of the pre-eminent neurosurgeons of his times, giving his name to a condition where the pituitary gland overproduces cortisol. Halsted has given his name to one of the more common haemostatic forceps used during surgery for acute appendicitis to this day. Harvey Cushing was the author of the book "The Life of Sir William Osler". The book was once given to the bright student Robert Gross who after reading it decided to start to study medicine[26].

King Edward VII had planned his coronation for the 26th of June 1902. As the oldest son to Queen Victoria, who had been queen for 64 years, he was the longest serving hear apparent at age 59. Thirteen days before the planned coronation he developed abdominal pain and fever and was unwell for five days when he developed a mass in the lower right side of his abdomen. He was then fulfilling some of his pre-coronation duties until a full relapse on the 23rd that lead to an operation under ether anaesthesia on the 24th of June. Formally this was not an appendectomy but rather drainage of a large appendiceal abscess. He recovered and the postponed coronation took place on the 9th of August. This was a turning point in the medical worlds view on the condition of appendicitis and also the view on ether anaesthesia. Both his surgeon, Sir Frederick Treves from Guy´s Hospital and his anaesthetist Sir Frederick Hewitt were knighted by the king just BEFORE the procedure. It is sad irony that Treves own daughter later died of acute appendicitis at the age of 18 years.[27]

Winston Churchill saw his physician in 1922 due to indigestion and ended up with an appendectomy. This was during a down-turn in his career and he was later quoted to having said to be "without an office, without a seat, without a party, and even without an appendix." His successful recovery has without a doubt made a huge difference to the world[28].

Harry Houdini died of perforated appendicitis on the 31st of October 1926 at the age of 52. It has been stated that he died after a punch to the abdomen but actually he died six days after the punch and even after an operation for perforated appendicitis. It is unclear whether Houdini had appendicitis before the punch, but blunt abdominal trauma is regarded as one of a number of aetiologies causing acute appendicitis[29, 30].

Marilyn Monroe had her appendectomy on the 28th of April 1952. She was concerned both of her inner organs and outer appearance and left a note on her abdomen for her surgeon, with the text:

Dear Dr. Rabwin,
cut as little as possible I know it seems vain but that doesn't really enter in to it. The fact I'm a woman is important and means much to me.
Save please (I can't ask enough) what you can – I'm in your hands. You have children and you must know what it means – please Dr Rabwin – I know somehow you will!
thank you – thank you – thank you – For God's sakes Dear Doctor no ovaries removed – please again do whatever you can to prevent large scars.

Thanking you with all my heart.
Marilyn Monroe

Dr Rabwin did very well and the appendix scar is hardly visible on later photos. This opposed to the later pictures taken just after her gallbladder surgery in 1962 by Bert Stern. Miss Monroe would most likely been a strong proponent for minimal access surgery (MAS) today.

Felix Mendelssohn (distantly related to the even more famous Felix Mendelssohn-Bartholdy) had his appendix successfully removed and dedicated a musical score, the "Appendix two-step", to his physician, an honour rarely given today[31].

2.4 SELF-SURGERY

On the 15th of February 1921, Dr. Evan O´Neill Kane, at the age of 60, laid on a table in his own hospital, waiting to have his appendix removed when he decided to see whether it was possible to remove his own appendix under local anaesthetic. After injecting the operating site with cocaine and adrenalin he swiftly performed an auto-appendectomy. The procedure took 30 minutes; the only perioperative problem was the bowels popping out of the wound as he was leaning too far forward. He made a swift recovery and was back in practice after 14 days[32]. This success made him undertake another auto-operation ten years later, an inguinal hernia repair. Unfortunately, he never regained his strength and died three month later of pneumonia. Apart from this self-surgery, Dr. Kane is also remembered for the habit of marking his patients with a Morse-code K, **-.-** , at the scar at the end of the operation.

Dr Leonid Rogozov, being a 27 year old Russian General Practitioner left with the sixth Soviet Antarctic Expedition in 1960. He started to feel unwell on the 29th of April 1961 and the next day it became obvious that he needed an appendectomy. Being the only doctor within 1000 miles, in a blizzard, he performed an auto-appendectomy under local anaesthesia with the help of a driver and a meteorologist. From the days of Kane, the development of local anaesthetic agents had evolved and Dr. Rogozov used 0.5% Novocain for infiltration. The procedure took one hour and forty-five minutes, including a short pause when he all but fainted (figure 3). He also had the benefit of antibiotics that was introduced into the peritoneal cavity. He resumed his duties two weeks after the procedure but the event led to Soviet medical staff posted in remote areas having to have prophylactic appendectomies. The Americans, however, made another conclusion and started treating appendicitis in remote places with primary antibiotic treatment[33].

Figure 3. Dr. Leonid Rogozov auto-appendectomy (courtesy of Dr. V. Rogozov).

2.5 HISTORY OF CONSERVATIVE TREATMENT OF ACUTE APPENDICITS

If operative treatment goes back a little more than 100 years, non-operative treatment is as old as man. In 1910, Smith and Wood Jones described a case of non-operatively treated perforated appendicitis in a young Nubian woman where the appendix was found attached with a thick adhesive band to the left pelvic wall suggesting that she had survived appendiceal rupture with abscess formation.[34] At the time of diagnosis, she was an uneviscerated mummy from the Byzantine era. This is not absolute proof that this woman survived an episode of acute appendicitis as it is well known that the serosa of the appendix could be inflamed due to other inflammatory processes in the pelvis. According to Aufderheide in his book "The scientific studies of mummies"[35] there are no other examples of suspected appendicitis in the paleo pathological literature. He writes that this may be due to the fact that ancient people had a highly fibrous, bulky diet that prevented faecal desiccation in the caecum. He remarks that the fact that acute appendicitis is rare in tribal societies as described by Burkitt[36] supports this theory. Bailey presented his non-operative treatment algorithm in 1930[37]. Coldrey described a large series in 1959 of 471 patients treated non-operatively with intravenous antibiotics[38]. In this series, there was one death and nine patients who required drainage of an abscess. The recurrence rate was 48/470 (10.2%) during the follow-up period. A Chinese group described 500 patients with the clinical diagnosis of appendicitis[39]. Four hundred and twenty-five of these had conservative treatment with Chinese traditional medicine and antibiotics were given to some. Only 7/100 patients had a recurrence during follow-up. Conservative treatment has also been reported from both the United States Navy[33] and the Soviet fishing fleet[40]. In this Russian paper, the best effect was seen when early intervention with antibiotics was combined with antihistamines and

spasmolytics. In total, 208/247 (84%) of the adult patients with suspected acute appendicitis recovered without surgery.

All these trials are hampered by a non-confirmed diagnosis and poor follow-up, but suggest that conservative treatment of acute appendicitis is an alternative to surgery.

2.6 WHY QUESTION SURGICAL TREATMENT?

Despite advances in surgical care, there is still a significant morbidity and mortality associated with appendectomy. An article by Blomqvist and co-workers discussed a cohort of 117,424 patients who underwent appendectomy in Sweden between 1987 and 1996 and analysed the 30-day postoperative mortality ratio[41]. They reported a 3.5-fold excess mortality after an operation for non-perforated appendicitis and a 6.5-fold excess mortality after perforated appendicitis. The standardised mortality rate after negative appendectomy with a discharge diagnosis of non-specific abdominal pain was increased by 9.1-fold. This excess mortality may only partly be explained by an underlying condition that was concealed by the appendectomy. This result is in accordance with the report by Flum and Koepsell who found a threefold increase in mortality after negative appendectomy compared with appendectomy for appendicitis[42]. Another study from Sweden showed that 1.3% of patients subjected to an appendectomy had a small bowel obstruction (SBO) during a 30-year follow-up compared with 0.2% of controls[43]. Others have reported rates of SBO between 0.16 and 10.7%[44, 45]. A recent review from Leung et al reports the incidence of SBO after appendectomy at 2.8%, and the incidence of reoperation for SBO after appendectomy to be 1.1% during the 5-year follow-up[46]. A recent paper from Wu and co-worker presented support for the hypothesis that patients subjected to an appendectomy had an increased risk of colonic cancer in the post-appendectomy period[47]. In addition to these "medical" reasons for avoiding appendectomy, we believe there are also social reasons, which should be considered. Although we are not aware of any supporting literature, we believe that successful resolution of appendicitis with antibiotics is preferable to successful resolution with an operation. The latter by definition involves a general anaesthetic (with its small but present risks) and the trauma of surgery. From talking to our patients and their parents, it is our impression that if both a non-operative approach with antibiotics and an operative approach had a similar chance of successful resolution, the majority would prefer the non-operative treatment.

2.7 DIAGNOSIS

The diagnosis of appendicitis has always been challenging. In the earliest of days the diagnosis was often made at autopsy. Later the signs could often be seen but there was no proper cure for the disease. As surgery become common, many surgeons got to know the signs and got better, by experience, to distinguish acute appendicitis from other conditions with similar presentation. In the past, as today, it was important not to miss any cases of acute appendicitis and the concept of early intervention in suspicious cases was adopted, accepting a high rate of negative appendectomies. In Stockholm, Sweden, the rate of negative appendectomy in children was 23%, 8.7%, 8.0% and 4.0% in 1991, 1994, 1997 and 2000, respectively[48]. Howie presented a negative rate of 29.5% for patients above 12 years of age operated in 1963[49]. Andersson and co-workers presented a negative appendectomy rate of 31% in Jönköping County, Sweden in 1984-1989[50].

The urge for early intervention was based partly on the assumption that all cases of acute appendicitis would progress to gangrene and perforation, if left untreated. An early suggestion that this may not be true was presented by Howie in 1964[49]. In this paper he compared five surgeons at Western Infirmary, Glasgow. Three surgeons adopted an expectant approach to equivocal cases of appendicitis with repeated examinations to await spontaneous regression or regress of another self-limiting disease. Two surgeons adopted a more radical attitude and operated most patients with a suspicion of appendicitis. The rate of negative appendectomies was 32% for the radical surgeons and 27% for the conservative surgeons. Furthermore, the proportion of complete inflammation was higher among the conservative group, 67% vs 60% for the radical surgeons. These results could be taken as support for a radical approach as the rate of advanced disease was somewhat higher in the conservative group. There was, however, another finding in this material supporting the opposite. The per-surgeon number of negative appendectomies was 50% lower among the conservative surgeons and the per-surgeon cases of complicated appendicitis were reduced with 34%, compared with the radical surgeons. Thus, this paper strongly suggests acute appendicitis as a self-limiting disease to some extent.

Andersson and co-workers presented further evidence to support the theory of spontaneous resolution of appendicitis in 1994[50]. They pooled data from 4717 patients who underwent an operation for suspected appendicitis in Jönköping, Sweden 1970-1989 with data from 48426 patients from six other reported studies and they found that the rate of appendectomy had no influence on the incidence rate of perforated appendicitis, but a strong correlation of the incidence of non-perforated appendicitis. In settings where the clinicians have a more restrictive attitude towards exploration, with a low incidence rate of negative appendectomies, fewer patients with non-perforated appendicitis were diagnosed compared with others who apply a more active attitude towards exploration. This opposed to the incidence rate of perforated appendicitis where this difference in attitude made no difference. Once again, as in Howie's presentation, it is the denominator that makes the difference in the ratio of perforated appendicitis.

Decadt and co-worker randomised 120 patients with abdominal pain of uncertain aetiology to either early (within 18 hours) laparoscopy (n=59) or watchful waiting (n=61)[51]. 23 patients in the early laparoscopy group had a histopathologically confirmed diagnosis of acute appendicitis as opposed to 8 patients in the watchful waiting group. The authors conclude a benefit of early laparoscopic exploration as this leads to a higher proportion of definitive diagnosis but this was likely do to the fact that a proportion of the patients in the watchful waiting group had a self-limiting appendiceal inflammation.

More support came from Andersson in 2007[52]. In this landmark paper he explores the support for spontaneous resolution of acute appendicitis. He presents support for the above, that the difference in the denominator is the reason for differences in the rate of perforations. The denominator can be influenced by the attitude to exploration, age of the population and/or by the duration of symptoms. A restrictive attitude towards exploration leads to a higher rate of perforations due to the detection of fewer patients with non-perforated appendicitis. The reason for a high proportion of perforations in the elderly, and maybe also in the very young, is likely due to the relatively low incidence of non-perforated appendicitis in these age groups. The reason why the proportion of perforated appendicitis increases by the duration of

symptoms can also be explained by spontaneous resolution of non-perforated appendicitis over time. Andersson presents an alternative model for understanding of the progression of appendicitis and non-specific abdominal pain over time as presented in figure 4.
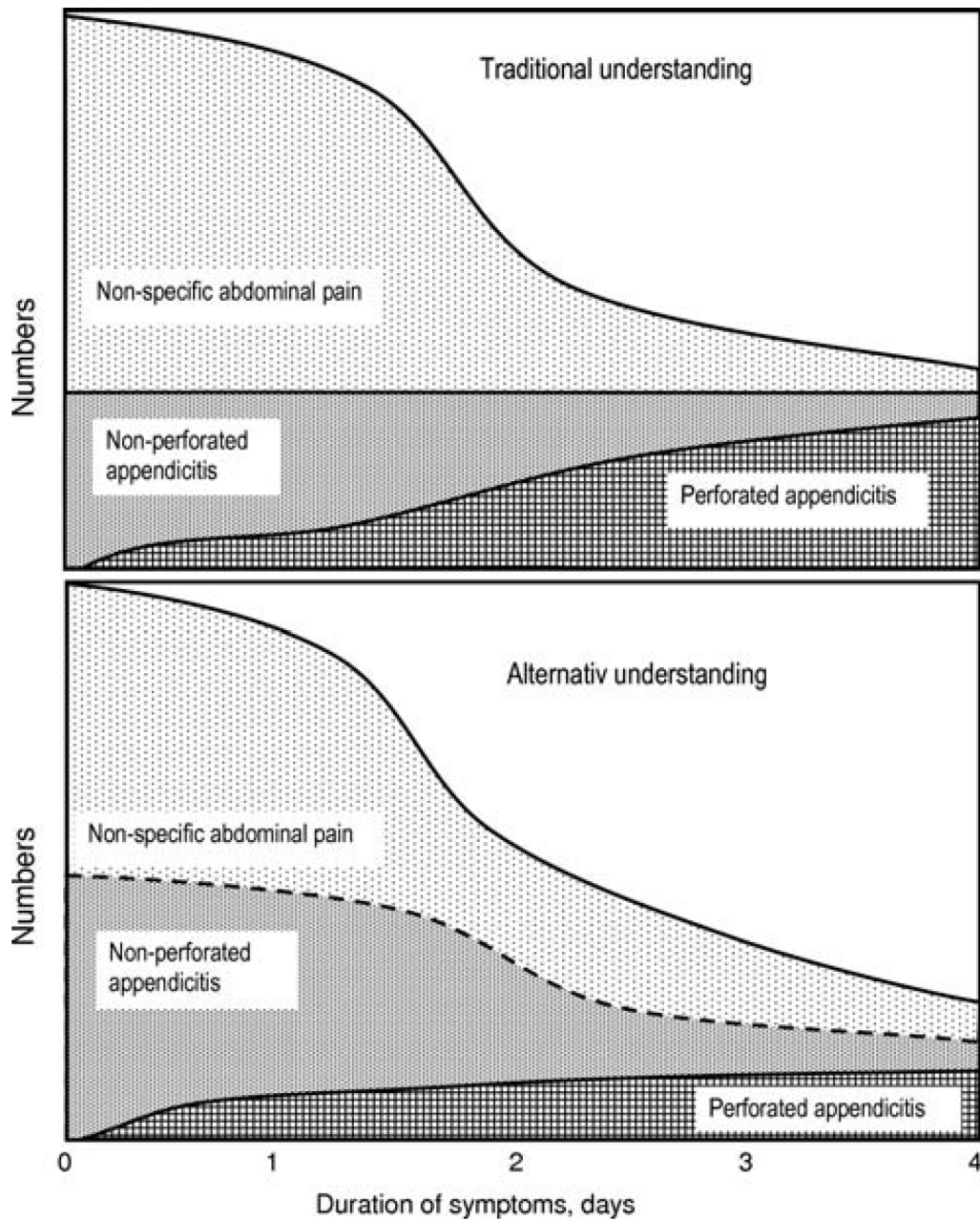
Figure 4. The traditional and the alternative description of the progression of appendicitis and non-specific abdominal pain over time. Both models have the same proportion of perforations at each moment in time and the proportion of perforations increases over time in both models. In the traditional model this is due to an increase in the number of perforations and in the alternative model this is due to resolution of non-perforated appendicitis. (from Andersson RE[52], with permission)

2.7.1 Scoring systems

A recent paper by Andersson[53] gave a thorough background on the scoring system for suspected acute appendicitis. He describes the evolution from the traditional view that the most important diagnostic tool was the hand of the surgeon, that inflammatory markers were "useless" and that we had to accept a rate of negative appendectomies of 30%. Also, this means that you build up your personal experience over the years and only very experienced doctors would be able to make the best decisions. This is not today´s scenario, no one would accept this level of negative appendectomies and in many places fairly junior doctors will have to make decisions on management of a large number of patients with different degrees of abdominal pain and disease. Andersson writes "The clinical diagnosis is a complicated process where information from many sources is processed in our brains. The problem is that every surgeon uses his own subjective and badly calibrated model. Pain and tenderness are often given too much attention and the inflammatory response too little. The diagnostic accuracy is dependent on the surgeon´s knowledge and previous experience of similar cases. The inexperienced surgeon is lost as he has no reference".

A large number of scoring models for aiding the diagnosis, or exclusion, of acute appendicitis have been developed [54-69].

The first score that caught any significant attention was presented by Alvarado in 1986[58]. He conducted a retrospective study of 305 patients hospitalised with abdominal pain suggestive of acute appendicitis. Of these 305, 254 had an appendectomy and 51 were discharged home with other diagnoses. Today we know that some of these may very well have had a self-limiting appendicitis. 277 patients had a complete set of data and were included in the analysis. A large number of diagnostic indicants were recorded, and each indicant was put in a 2 x 2 table to calculate probability, sensitivity, specificity and predictive values. Eight indicants were found to have an impact on the diagnosis: migration of pain from the epigastrium to the right lower quadrant; anorexia and/or acetoneuria; nausea/vomiting; tenderness in the right lower quadrant; rebound pain; elevation of temperature; leukocytosis; differential shift to the left. These symptoms, signs and laboratory findings were given a value of two (tenderness and leukocytosis) or one. A score of 5-6 is compatible with the diagnosis of acute appendicitis, a score of 7-8 indicates a probable appendicitis, and a score of 9-10 indicates a very probable appendicitis.

The modified Alvarado score was presented in 1994 by Kalan and co-workers[63] by omitting the shift to the left in neutrophils maturation, a blood test that was not readily available at the time in the UK. Hence, their score ranged from 0-9 points. Their initial study included 49 patients of whom 11 were children. Their cut-of value was 7 and all 11 children had a score of 7 or above, all had surgery and all had histologically confirmed appendicitis.

The Appendicitis Inflammatory Response(AIR)-score was developed in Sweden and presented in 2008[62]. Following a somewhat different pathway of development, the authors used data prospectively collected from 545 patients admitted for suspected appendicitis in four hospitals in 1992-1993 and 1997. The first part of this dataset has been presented previously[70]. 60% of the patients were used for construction of the score and the remaining 40% of the patients were used for validation. By weighted ordered logistic regression, eight variables were found to have discriminating capacity and were included in the final model.

As opposed to the dichotomised values in the Alvarado score, some clinical values were graded. The score may be between 0 and 12, 0-4 suggests a low probability (may be discharged), 9-12 a high probability (renders a surgical intervention), and 5-8 puts the patient in the intermediate group that would undergo further diagnostics. In this initial presentation of the AIR-score it was found to outperform the Alvarado score in adults. Using Receiver Operating Characteristic (ROC) and Area under the ROC-curve (AUC) as a measure of performance the AIR-score AUC was 0.97 for advanced appendicitis and 0.93 for all appendicitis compared to the Alvarado score AUC 0.92 and 0.88, respectively. The AIR-score has not yet been evaluated in children.

Recently, Sammalkorpi and co-workers presented yet another score, the adult appendicitis score[71]. They designed their score on 829 patients with prospectively collected data aided by logistic regression. They then tested the adult appendicitis score against the AIR-score and the Alvarado score with AUC for all appendicitis. AUC for the adult appendicitis score was 0.882 (95%Confidence Interval (CI) 0.858-0.906), for the AIR-score 0.810 (95%CI 0.779-0.840) and for the Alvarado-score 0.790 (CI95% 0.758-0.823). The AUC for the AIR-score was a lot lower than in the original presentation by Andersson and co-worker[62] 0.927 and for the Alvarado-score 0.879.

Two scoring systems have been designed to be used on a paediatric population, the Paediatric Appendicitis Score (PAS)[64] and the Lintula score[60]. PAS was the first paediatric score, developed by Samuel in 2002. It is based on data collected prospectively from 1170 patients over five years. Using logistic regression, 8 variables were found to be independently statistically significant; migration of pain, anorexia, nausea/emesis, tenderness in the right lower quadrant, cough/percussion tenderness, hopping tenderness, pyrexia, leukocytosis and polymorphonuclear neutrophilia. All variables were given a score of one, apart from the cough/percussion tenderness and tenderness over the right iliac fossa who were given the score of two to produce a maximum score of 10. A score $\geq$6 is said to be compatible with appendicitis and scores of 7-10 indicates a high probability of appendicitis. PAS in the 1,170 children analysed had a sensitivity of 1, specificity of 0.92, positive predictive value of 0.96, and negative predictive value of 0.99.

The Lintula score was developed in a similar fashion as most adult scoring systems. In a first stage, 35 items of clinical data was collected in 131 consecutive patients After excluding 15 parameters that were shown to have no prognostic significance in differentiating between acute appendicitis and non-appendicitis, and also excluding the variable of menstrual period, 19 parameters were included in a backward stepwise binary logistic regression analysis. This analysis resulted in a model that included nine variables: gender, intensity of pain, relocation of pain, vomiting, fever, pain in the lower right quadrant, guarding, bowel sounds and rebound tenderness. This resulted in an equation that gave a score of minimum zero and maximum 32. With two different cut-of levels, three groups were developed; no appendicitis equals discharge, observation group equals necessitating further observation and acute appendicitis equals justifying emergency laparotomy. This scoring system was then evaluated in a prospective phase of the study, including 109 patients that presented to the emergency department with abdominal pain suggestive of appendicitis.

An evaluation of the benefits of the scoring system in children were presented by Kulik and co-workers in 2013[72]. The aim of their study was to identify "clinical prediction rules" (CPRs) for children with acute appendicitis and compare their methodological quality and performance. They found 12 studies assessing a total of 6 different scoring systems[58, 60, 64, 66, 69, 73]. They extracted data to be able to calculate sensitivity, specificity and negative likelihood ratio (LR-). They used sensitivity >0.95; lower limit of the sensitivity 95%CI >0.95; LR- <0.1 and upper limit of LR- 95%CI <0.1 as the four performance benchmarks for identifying high-performing CPRs. PAS and Alvarado were the most validated but neither met the pre-determined performance benchmarks.

Finally, a recent publication from Salö and co-workers[74] presented an evaluation of PAS in younger and older children. Despite the fact that children ≥4 years of age had more severe appendicitis they had a lower mean PAS. Also they found that with a threshold of ≥6, PAS had a sensitivity of 70.5% and a specificity of 14.2%. It is likely that the signs of symptoms of appendicitis in younger children are less specific than in older children.

The nature of the development of any scoring system, with regression statistics of one's own population, makes it natural that the score performs better than any other score tested on the same population and also that it is unlikely that any given score would perform as well in another population[71, 75].

2.7.2 Imaging

Deutsch and Leopold presented the first case report of an ultrasound (US) diagnosis of an inflamed appendix (figure 5) in a three years old boy with a two day history of abdominal pain[76]. The US technique with graded compression for diagnosis of acute appendicitis was first described by Puylaert in 1986[77]. He performed US in 60 consecutive patients with suspicion of acute appendicitis and found that 25 out of 28 patients with confirmed appendicitis had a US diagnosis.
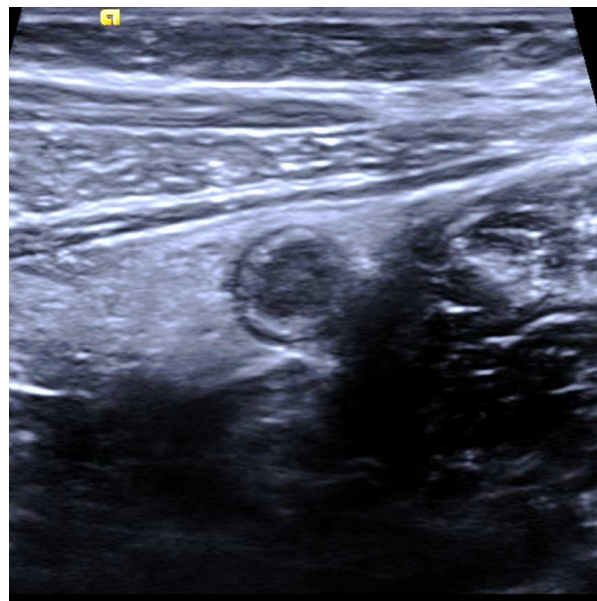
Figure 5. US-image of phlegmonous appendix with intact layers of the thickened wall (courtesy of Dr S. Kaiser).

Gale and co-worker presented Computed Tomography(CT)-images (figure 6) of acute appendicitis in 1985[78]. The first presentation of Magnetic Resonance Imaging (MRI) in the diagnostic workup of acute appendicitis was presented by Incesu and co-worker in 1997[79] as a comparison between US and MRI. In our institution Kaiser and co-workers[80] performed a randomised controlled trial (RCT) where 600 children were randomised to undergo either US alone or US and CT. 244 patients had acute appendicitis. US alone had a sensitivity of 86%, a specificity of 95% and an accuracy of 92%. US and CT combined had a sensitivity of 99%, a specificity of 89% and an accuracy of 93%. The negative appendectomy rate was 3.7% and the perforation rate 21%, in 1999-2000. The same group followed up this paper in 2004[48] looking on the impact of imaging on the negative appendectomy rate and compared data from 1991, 1994, 1997 and 2000. The negative appendectomy rate was 23%, 8.7%, 8.0% and 4.0%; the perforation rate was 32%, 34%, 34% and 29%; the rate of patients that underwent US and CT was 1.0% and 0.0%, 41% and 0.0%, 91% and 21% and 98% and 59.9%, respectively. So, this paper shows that it was possible to decrease the number of negative appendectomies without increasing the rate of perforations. Nor did this transition increase the incidence of appendectomy in our region, calculated as 1.31, 1.17, 1.32 and 1.29 ‰, in the same years as above.

The rate of CT-scan in 2000 was exceptionally high, 59.9%. From the non-published quality report from 2013, the negative appendectomy rate was 4.7%, the perforation rate was 22.4%, the rate of patients that underwent US and CT was 99% and 11%, respectively.

Figure 6. CT-image of inflamed appendix with multiple appendicoliths (courtesy of Dr S. Kaiser).

A recent paper by Kulaylat and co-workers presented contemporary diagnostic characteristics of MRI on paediatric appendicitis[81]. A review or their 30-month institutional experience with MRI as the primary diagnostic evaluation for suspected appendicitis on 510 children rendered a sensitivity of 96.8% (95%CI: 92.1%C-99.1%), a specificity of 97.4% (95%CI: 95.3%-98.7%), a positive predictive value of 92.4% (95%CI: 86.5%-96.3%) and a negative predictive value of 98.9% (95%CI: 97.3%-99.7%). In this dedicated centre with 24/7 availability of MRI the median time from request to scan was 71 minutes (interquartile range (IQR): 51-102) and the median time for the examination was 11 minutes (IQR: 8-17).

One important aspect regarding imaging is to keep the dose of ionising radiation as low as possible. As children are more sensitive to radiation than adults this becomes even more important in this population. Apart from a strong indication for the investigation, the examination needs to be optimised to the individual patient. It is not acceptable to use the CT-settings for adults on a child.

2.8 SURGICAL TREATMENT

2.8.1 Open surgery

Open surgery for acute appendicitis has been performed since it was first described in 1880[18]. The grid-iron incision in the right iliac fossa, the McBurney incision, has been the standard for well over 100 years[22]. This method is safe, straight-forward and carries a low morbidity. The difficulty increases in cases where the appendix is in an unusual position, like at the gallbladder or in the pelvis.

2.8.2 Minimally access surgery

MAS was developed at the turn of the last century and the first series of laparoscopy on humans was presented by the Swedish internist Hans Christian Jacobeus in 1910[82]. Another pioneer was the Swedish-born French gynaecologist Raoul Palmer who presented a ground-breaking paper in 1947 that lead to wide spread acceptance of laparoscopy in gynaecology and Obstetrics[83]. In an early paper by Leape and co-workers from 1980 laparoscopy was used as a diagnostic tool in 32 children in whom the clinical findings were equivocal and not sufficient to establish the diagnosis[84]. In these 32 patients, 12 were "spared an operation" thanks to the laparoscopic examination.

Kurt Semm was a specialist of obstetrics and gynaecology who dedicated his career, or life, to laparoscopy. From the early 1960s onwards he developed and designed multiple laparoscopic inventions like the CO2-insufflator, a uterine manipulator and later thermocoagulation. His techniques were often criticised by fellow gynaecologists and general surgeons. In 1970, after Semm became the chairman of Obstetrics and Gynaecology at the University of Kiel, his co-workers demanded that he should undergo a brain scan because "only a person with brain damage would perform laparoscopic surgery"[85]. Nevertheless, he performed the first LA in 1980 and presented this case in a lecture in 1981, after which the President of the German Surgical Society wrote to the board of Directors of the German Gynecological Society suggesting suspension of Semm from medical practice. Nevertheless he presented his technique in the first paper on this subject in 1983[24]. Semm died in 2003 at the age of 76 from Parkinson's disease, the same Parkinson that published the first case of

appendicitis in 1812. Ure and co-workers presented the first paper on LA in children from Cologne in 1992. They presented 43 patients less than 18 years of age, where 20 were children 8-15 years of age. Diagnostic laparoscopy was successful in 84% of patients and a LA was performed in 77%. They found no statistical difference for pain intensity and consumption of analgesics after LA versus open ditto. The first paper to present a benefit of LA versus OA was presented by Gilchrist and co-workers in 1992[86]. They compared 14 laparoscopic procedures with 50 open procedures. The trial was non-randomised, based on consultant preference only. They stated that there was no difference in disease severity between the two groups. With regards to outcome, the laparoscopic procedure was more expensive and took longer, but patients who had a laparoscopic operation had a shorter post-operative stay and a shorter time to return to unrestricted activity. Stronger support for the laparoscopic method was presented in a Cochrane review by Sauerland and co-workers in 2004[87], concluding that "in those clinical settings where surgical expertise and equipment are available and affordable, we would generally recommend to use laparoscopy and LA in all patients with suspected appendicitis unless laparoscopy itself is contraindicated or not feasible". In 2006, Aziz and co-workers presented a meta-analysis[88] that included 23 studies with a total of 6477 patients. They showed that there were fewer post-operative complications after LA compared with OA. Further support for LA came in a paper by Esposito and co-workers in 2012[89]. They performed a meta-analysis on 26 published studies between 1997 and 2010 including a total of 123.628 patients between 0 and 18 years who had either a LA (34.1%) or an OA (65.9%). They found that the operative time was shorter for OA than for LA in complicated appendicitis but found no difference in the case of simple appendicitis and that the length of stay was shorter after LA than after OA, both in simple and complicated appendicitis. It is not clear how the significance of these differences was calculated, as there is no meta-analysis performed on the data.

3   AIMS OF THE THESIS

The overall aim of this thesis was to evaluate the outcomes of current treatment modalities in acute appendicitis in children today.

The specific aims were

- to present our outcome data during a period of transition from OA to LA,

- to evaluate the incidence of recurrence of acute appendicitis in patients with appendiceal abscess confirmed with imaging successfully treated with antibiotics at the initial presentation,

- to present the support for non-operative treatment of acute appendicitis in children and in adults,

- (i) to evaluate the feasibility of recruiting children with acute appendicitis to a randomised controlled comparing non-operative treatment with appendectomy; (ii) to evaluate the safety of non-operative treatment with antibiotics of acute non-perforated appendicitis in children; and (iii) to generate pilot data to inform our future planned efficacy study.

4 PATIENTS AND METHODS

All patients in study I, II and IV were treated at the Department of Paediatric Surgery at Astrid Lindgren Children´s Hospital, Karolinska University Hospital in Stockholm (ALB/KS), Sweden. This is a large tertiary care facility treating all children within the greater Stockholm area for surgical conditions. We diagnose over 400 patients each year with different kinds of acute appendicitis. In 2007 we decided to change our routine procedure from OA to LA for acute appendicitis. With regards to appendiceal abscess and appendix mass, we adhere to a conservative policy of non-operative treatment and do not routinely perform interval appendectomy. In 2006 we started with yearly quality reports on all patients with acute appendicitis and this was the reason for the start of inclusion of patients in study I and II. Later, we have expanded this data-base to include any patient treated for any kind of appendicitis, acute appendicitis, non-operative treatment for non-perforated appendicitis and appendiceal abscess. The patients in study IV were recorded in this data-base but were also in a separate system for the RCT. Study III is a meta-analysis and a literature review based on available studies searchable on PubMed in the autumn of 2011. Hence, no patients have been included in this study.

Study I is a cohort trial comparing the outcome after open and laparoscopic surgery for acute appendicitis in children at ALB/KS between January 2006 and December 2010. The patients were found through the department's quality data-base and a second search in the computerised discharge data base and the computerised theatre log-book was performed for accuracy.

In 2007 we designed a protocol for LA with the ambition to minimise the learning curve and to minimise the postoperative complications. The choice of procedure was based on surgeon preference only; many of the surgeons were novices in the field of laparoscopic surgery when the study started.

This protocol states that the umbilical port should be introduced with an open technique according to Hasson[90]. We use a 12 mm Bluntport[TM] trocar (Covidien, USA) to accommodate a staple device and a specimen bag. Two 5mm STEP[TM] trocars (Covidien, USA) are inserted in the lower left quadrant and suprapubically under direct vision. The base of the appendix is stapled with an Endo-GIA[TM] (Covidien, USA), 2.0 or 2.5mm depending on the size of the appendix. If the abdominal cavity does not accommodate the Endo-GIA[TM] (Covidien, USA), Endo-loops are used. The mesoappendix is divided with either Endo-GIA[TM] (Covidien, USA) or monopolar hook-diathermy. We advocate a liberal use of an Endo-Catch[TM] bag (Covidien, USA) in all cases, to avoid contamination from the area of division. Suction and irrigation is used according to surgeon's choice.

All patients who underwent an operation for suspected appendicitis in our department from January 2006 to December 2010 were included in this study. Baseline data as age and gender, as well as temperature, C-reactive protein (CRP) and white blood cell (WBC) count on admission was collected. Surgical modality, conversion, surgeon, operating time, time of surgery, time of discharge, surgeon's assessment of disease, histopathological assessment of disease, wound infection, presence of postoperative abscess and reoperation within three months were also collected. Most of the data presented in this paper has been retrieved on a

yearly basis with at least three months follow-up. A repeated search for the whole period was performed for this paper, for accuracy.

The final diagnosis was made in accordance with Carr[91], and thus on the histopathology finding. For the missing data in the open group (n=23/734) the clinical assessment has been used. As we did not have a pre-defined clinical criteria for perforation these data may not be accurate.

To be able to stratify patients for statistical purposes, the outcome parameters needed to be defined. We have defined a post-operative abscess as a localised fluid collection seen with imaging at least three days after the initial operation. Both an inserted drain and a drainage procedure without leaving a drain were considered as drain treatment.

A wound infection was considered when a patient had been seen by a physician either as an in-patient, as an out-patient at the out-patient clinic or at the emergency room, or seen by the local general practitioners. Either pus or foul fluid had to been seen together with signs of inflammation. Antibiotic treatment was not necessary for the inclusion. The search was made through the regional computerised notes database that includes all non-private general practitioners and all public hospitals in the region.

All data were put into our computerised notes database (Take Care[TM], GCM, Germany) and our computerised theatre log-book (Orbit 4[TM], Evry, Norway). As the initial database was incomplete, some data were retrospectively collected from these databases.

The study period was determined to get an equal number of patients with each procedure.

Study II: A retrospective search of the discharge diagnosis database was done to find all patients that were discharged with non-operatively treated appendiceal abscess confirmed by imaging from January 2006 to December 2010. During this study, these categories of patients were included in the quality report data base. Any patients that had a failure of treatment during their initial admission or had primary surgical treatment despite an imaging-confirmed abscess were not found with this search strategy and were thus not included in this study.

According to our protocol, we drain abscesses with a diameter exceeding 5 cm or if the infection is symptomatic longer than 5-7 days. We use both trans-abdominal and/or trans-rectal drainage guided by US. In this study a drain insertion was considered as an adjunct to non-operative treatment. These patients were included in the study if discharged without an appendectomy.

The primary outcome variable in this study was recurrent acute appendicitis requiring an operation. Secondary outcome variables included re-admissions and interval appendectomy.

For the patients included in the study, we conducted a manual search through their medical notes and extracted the following information: age, gender, temperature on admission, CRP on admission, WBC on admission, use of drain, the presence of an appendicolith on imaging, re-admission and late surgery.

Study III: This was a literature review including studies on conservative, non-operative treatment of non-perforated appendicitis in adults and in children as well as a description of studies on non-operative treatment of perforated appendicitis in children. PubMed was used as search engine and references of relevant papers were double-checked for completeness. All previously published RCTs were found and also all previously published meta-analyses on non-operative treatment of non-perforated acute appendicitis in adults. All previously presented meta-analyses were performed based on intention-to-treat. Because of a high number of patients crossing over in one of the RCTs, we believed that including these data on an intention-to-treat basis was problematic. The significant number of patients crossing over from being assigned to initial non-operative treatment to actually receiving an appendectomy suggests that it was unlikely that the clinician treated the patient intended to treat the patient non-operatively.

Study IV: This study was a pilot RCT. As this treatment modality had never been evaluated in a paediatric population we had no good data to base a power-calculation on. Also, for the same reason, we wanted to perform a limited trial to assess the feasibility of the treatment, the feasibility of the randomisation and, not the least importantly, the safety of this treatment modality. On the basis of our yearly case-load of approximately 400 cases of acute appendicitis per year, and estimated recruitment of one third of eligible cases, we aimed to enrol 50 patients within a six-month period. All children between 5-15 years of age with a clinical diagnosis of acute appendicitis that before the trial would have been subjected to an appendectomy, including those with an appendicolith, were eligible. Imaging diagnosis was not mandatory for inclusion but this is standard at our department and all patients in this trial had imaging confirmation of acute appendicitis prior to their intervention. Exclusion criteria were suspicion of perforated appendicitis on the basis of generalised peritonitis; an appendiceal mass diagnosed by clinical examination or imaging or previous non-operative treatment of acute appendicitis. The included patients were randomised to either appendectomy or non-operative treatment with antibiotics.

The randomisation was computer-based randomisation program (Simin v 6.0; Institute of Child Health, London, U.K.). The allocation to groups (1:1 ratio) was made via weighted minimisation at the time of enrolment in the study using the following criteria; age (5-10 years or 11-15 years), gender (male or female) and duration of symptoms (<48h or >48h). All factors were weighted equally. Minimisation [92, 93] is a dynamic process to ensure that per-specified prognostic factors are evenly distributed between treatment groups. As patients are included in the trial they are allocated to the group that will minimise the differences in the distribution of the pre-specified factors between the groups. Minimisation alone is not sufficient as the allocation is not random and could be predicted. This problem is addressed by randomising each patient but weighting the randomisation towards the treatment group that suits best with the minimisation. Minimisation does not prevent imbalance of factors not included in the minimisation process. In this present study, there were no differences in the pre-specified factors age, sex or duration of symptoms or in CRP on admission, WBC on admission, neutrophils on admission or temperature on admission between the two treatment groups.

4.1 STATISTICS

4.1.1 Paper I

Data are presented as frequencies or median values (range). Data were compared using Mann-Whitney U-test and Fisher exact test where appropriate using IBM SPSS Statistics version 21.

Multiple linear regression was used to analyse association between surgical method and postoperative length of stay. Due to the condition with a large number of cases making a swift recovery and a smaller number of cases with complications that hampers discharge for many days, the data on postoperative length of stay was not normally distributed; which is a pre-requisite for a multiple linear regression. By recalculating the data to log10 postoperative length of stay we produced a more normally distributed dataset.

4.1.2 Paper II

Data are presented as median values (range). Only summary statistics were used. Data were analysed using the statistical analytic programme SAS version 9.2.

4.1.3 Paper III

A meta-analysis of extracted data was performed and the data was presented as forest plots. Failure of treatment and incidence of complications were analysed using RevMan v5.1 (The Cochrane Collaboration, Copenhagen, Denmark) with a random effects model as there were significant heterogeneity between the trials. The proportion of patients successfully treated non-operatively was analysed using MetaAnalyst 3.13 (Tufts University, Massachusetts, USA) with a random effects model.

4.1.4 Paper IV

Data are presented as proportion of participants or median (range). Data were compared using Mann-Whitney U test or Fisher's exact test as appropriate using IBM SPSS Statistics version 22. As no prior trials had been conducted of non-operative treatment of acute appendicitis we decided to design this trial as a pilot trial without a power calculation assessing safety and feasibility.

4.1.5 Overall

$P < 0.05$ was considered as cut-off for statistical significance in all trials.

5 ETHICS

Approval for the studies reported in paper I, II and IV was obtained from the Regional Ethical Review board at the Karolinska Institutet, Stockholm, Sweden, Dnr 2011/1234-31/4. In paper III we reported a meta-analysis and a literature review that do not require an ethical approval. The studies have been performed in accordance with the Declaration of Helsinki[94]. Study I has been reported in accordance with the STROBE-guidelines for reporting of cohort trials[95] and study IV in accordance with the CONSORT-guidelines for reporting or parallel randomised trials[96, 97]. In paper IV we designed the study with safety and feasibility as priority, using our primary broad-spectrum antibiotic treatment for abdominal sepsis to minimise the risk of complications.

6   RESULTS

6.1   OPEN VERSUS LAPAROSCOPIC SURGERY FOR ACUTE APPENDICITIS IN CHILDREN (STUDY I)

For this trial we identified 1913 patients with the diagnosis of appendicitis. Patients with successful non-operative treatment of suspected acute appendicitis (n=62), patients discharged after successful non-operative treatment of an appendix abscess/mass (n=95), and patients who underwent an interval appendectomy (n=12) were excluded from further analysis and thus 1744 patients had an operation for suspected acute appendicitis during the study period. This group constituted the study population.

	OA n=735	LA n=1009	
Age (years)	11.30 (1.93-15.00)	11.24 (2.06-14.99)	p=0.411
Male gender (n)	446	604	p=0.729
Temp (^{o}C) (n=1730)	37.6 (35.6-40.3)	37,5 (35.5-40.1)	p=0.218
CRP(mmol/l) (n=1575)	23 (1-409)	22 (1-464)	p=0.390
WBC (10^9/l) (n=1186)	15.1 (4.1-43.0)	14.1 (3.3-36.7)	p=0.005

Table 1. Basic characteristics for patients in study I for open appendectomy (OA) and laparoscopic appendectomy (LA).

The basic characteristics for the included patients are presented in table 1. The only significant difference between the two groups was a higher median white blood cell count in the patients treated with an OA. However, missing data were more common in the OA group.

6.1.1   Complications

There were no significant differences in the rate of postoperative abscesses, wound infections or re-operations between the two groups, as shown in table 2. There were more re-admissions in the open group. There were no differences in the final histopathological diagnoses in the two groups as shown in table 3. In the open group, the "other" cases included three cases of carcinoid tumours, one case of granulomatous appendicitis, and one of chronic inflammation. In the laparoscopic group the "other" cases were also three carcinoid tumours and two cases of chronic inflammation.

	OA n=735	LA n=1009	
Wound infection	9 (1.2%)	25 (2.5%)	p=0.078
Abscess formation	35 (4.8%)	36 (3.6%)	p=0.221
Reoperation	20 (2.7%)	26 (2.6%)	p=0.880
Readmission	42 (5.7%)	37 (3.7%)	p=0.047

Table 2. Complication after open appendectomy (OA) and laparoscopic appendectomy (LA)

	OA n=712	LA n=1009	
No inflammation	19 (2.7%)	39 (3.9%)	p=0.165
Phlegmonous	307 (43.2%)	464 (45.9%)	p=0.273
Gangrenous	214 (30.1%)	298 (29.5%)	p=0.909
Perforated	167 (23.5%)	203 (20.1%)	p=0.095
Other	5 (0.7%)	5 (0.5%)	p=0.587

Table 3. Histopathological diagnosis of removed appendices after open appendectomy (OA) and laparoscopic appendectomy (LA). Note that 23 specimens after OA were not sent to histopathology, as it was not part of the protocol early in the series.

6.1.2 Postoperative time in hospital

The postoperative time in hospital was longer for the patients who had an OA compared with the patients who had an LA, 57 (10-580) vs 43 (10-583) hours (p<0.0005). However, there was a trend towards increasing use of laparoscopy over the period of the study, so we were concerned that the apparent benefit of laparoscopy in terms of hospital stay in fact represented a general trend towards decreased length of hospital stay during the study. We therefore performed a multiple linear regression. The dependent variable was $\log_{10}$ (hospital stay in hours) as hospital stay was not normally distributed and a log transformation yielded data that were approximately normally distributed. The independent variables examined were; gender, age, and interaction terms for open or laparoscopic operation * years since start of study. The results of the multiple linear regression analysis are shown in table 4.

	Unstandardised Coefficients		p value	95% Confidence Interval for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	2.034	.031	<.0005	1.972	2.095
Age	-.020	.002	<.0005	-.024	-.015
Gender	.049	.015	=.001	.019	.078
lap * time	-.043	.005	<.0005	-.053	-.033
open * time	-.043	.010	<.0005	-.062	-.024

Table 4. Multiple linear regression analysis of the effects of age, gender, open appendectomy and laparoscopic appendectomy over time on length of hospital stay. The dependent variable was $\log_{10}$(hospital stay in hours).

Hence there was a significant age effect, with older patients staying in hospital -0.020 $\log_{10}$ hours (p<0.0005), and a significant gender effect, with females having a significantly longer hospital stay (+0.049 $\log_{10}$ (hospital stay in hours); (p=0.001)). For both laparoscopic and open operations, there was a significant decrease in length of hospital stay during the period of study, with the magnitude of decrease exactly the same for each type of operation (i.e. a 0.043 decrease in $\log_{10}$ (hospital stay in hours)) for each year since the start of study (p<0.0005 for each.) As it is difficult to consider the magnitude of these changes in $\log_{10}$ (hospital stay in hours), we have shown an example of these trends over time for a 10 year-old boy in Figure 7. The trends over time are almost identical for open and laparoscopic operation, with wider 95%CIs for open surgery, due to the lower number of open operations.
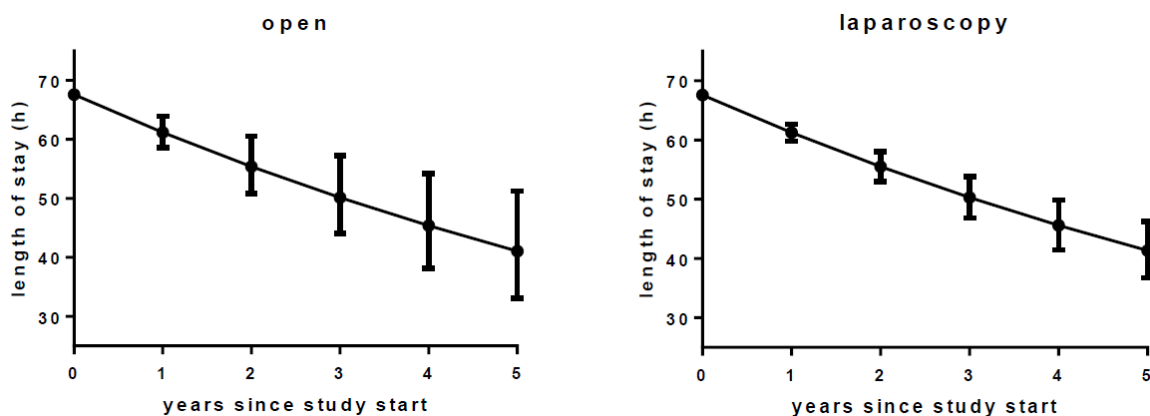
Figure 7. Effects of time and laparoscopic/open operation on length of hospital stay. Data are calculated from the multiple linear regression analysis in Table 4, for a 10 year-old boy. Data are given with 95% confidence intervals.

As treatment of acute appendicitis is highly protocol driven in terms of antibiotic administration etc., we therefore repeated this analysis considering only those patients in whom a difference in hospital stay might be possible due to the type of surgery performed; i.e. those patients with operative findings of either a non-inflamed or phlegmonous appendix. The results were almost identical, i.e. there was a significant decrease in length of hospital stay for both open and laparoscopic operated patients of the same magnitude (0.044 decrease in $\log_{10}$ (length of hospital stay in hours) for each year since study start). Taken together, these data strongly suggest that the apparent decrease in length of hospital stay in laparoscopic versus open operated patients is entirely due to a general trend in decreased hospital stay rather than anything specific to the operative method.

6.1.3 Operating time

The operative time was longer for LA than for OA, 51 (11-307) vs 37 (11-185) minutes in the whole group (p<0.0005). There was a significant decrease in operative time from study start for both the laparoscopic (0.014 $\log_{10}$minutes operative time per year since study start(p=0.019)) and open (0.016 $\log_{10}$minutes operative time per year since study start(p=0.022)) groups.

For LA, the median operating times for individual surgeons who performed more than a few procedures were between 31 minutes (99 operations) and 73 minutes (59 operations). A total of 42 different surgeons/trainees were registered as primary surgeon in the laparoscopic group, trainees assisted by senior surgeons until a level of proficiency were acquired. The corresponding figure for the open group was 70. The majority of surgeons performed both the procedures during the study period.

6.2 NON-OPERATIVE TREATMENT OF APPENDICEAL ABSCESS IN CHILDREN (STUDY II)

During the trial period, a total of 1782 patients were treated for acute appendicitis at our institution. Eighty-nine children with a median age of 10.1 (1.3-16.3) years were included in this study. Thirty of these patients were diagnosed with US, one with CT (figure 8) and 58 with both US and CT.

Figure 8. CT-image of an appendiceal abscess in the right iliac fossa (courtesy of Dr S. Kaiser).

The treatment consisted of intravenous antibiotics followed by oral antibiotics for an average total time of 15 (4-51) days. The time on intravenous antibiotic treatment was 5 days (0-31) and the time on oral antibiotic treatment was 10 days (0-28). Seventy-one (80%) of the children were treated with intravenous cefotaxime and metronidazole, 14 (16%) were given ceftriaxone and metronidazole, 3 (3%) were treated with meropenem and metronidazole and one (1%) received imipenem/cilastatin.

Thirteen patients had their initial abscess drained percutaneously or transrectally in addition to their antibiotic treatment. All these procedures were performed under general anaesthesia. Forty-one patients had an appendicolith shown by radiologic imaging. One of the two patients with recurrent acute appendicitis had an appendicolith, one had not. Only one of the five patients re-admitted with an abscess had an appendicolith on imaging.

The time to follow-up was 5.1 (2.8-7.7) years. The characteristics of the patients at the time of admission are presented in Table 5.

Age (years)	10.1 (1.3-16.3)
Gender (M/F)	39/50
Temperature (°C)	38.4 (35.7-40.0)
CRP (mg/l) n=85	140 (25-375)
WBC (x10^9/l) n=68	18.1 (7.42.9)

Table 5. Patient characteristics at the time of admission.

There were fourteen re-admissions due to recurrent or on-goings symptoms (16%), five of the children presented with an abscess and two with acute appendicitis without abscess. Another seven patients were re-admitted after 5 (2-25) days due to on-going abdominal pain and/or fever but no abscess was found on imaging. Five of these patients received additional antibiotic treatment. Another 29 patients (33%) were seen at the emergency department with a total of 36 episodes of non-specific abdominal pain. 21 of these had imaging; 17 US, one CT and three both US and CT. None of these episodes required any surgical intervention.
The time from discharge to re-admission was 26 (2-32) days for the re-admitted patients that later had an interval appendectomy. The median age of these patients was 9.8 (2.6-12.9) years. Two patients presented with a new episode of acute appendicitis without abscess after 122 and 123 days respectively, they were 7.5 and 11.3 years old.

Nine patients (10%) underwent surgery during the follow-up period. Seven patients had interval appendectomy and 2 had acute appendectomy. The indication for interval appendectomy was re-admission with an abscess in 2 patients, re-admission without an abscess in three patients and consultant decision/parental wish in 2 patients. Recurrent acute appendicitis was the indication for acute appendectomy in both cases (figure 9).
Hence, 2/82 patients (2.4%) had surgery due to a recurrent acute appendicitis during the follow-up period.
All removed appendices were analysed by histopathology. Both patients with acute appendectomy had histologically confirmed acute appendicitis. No patient had a carcinoid or any other malignancy.
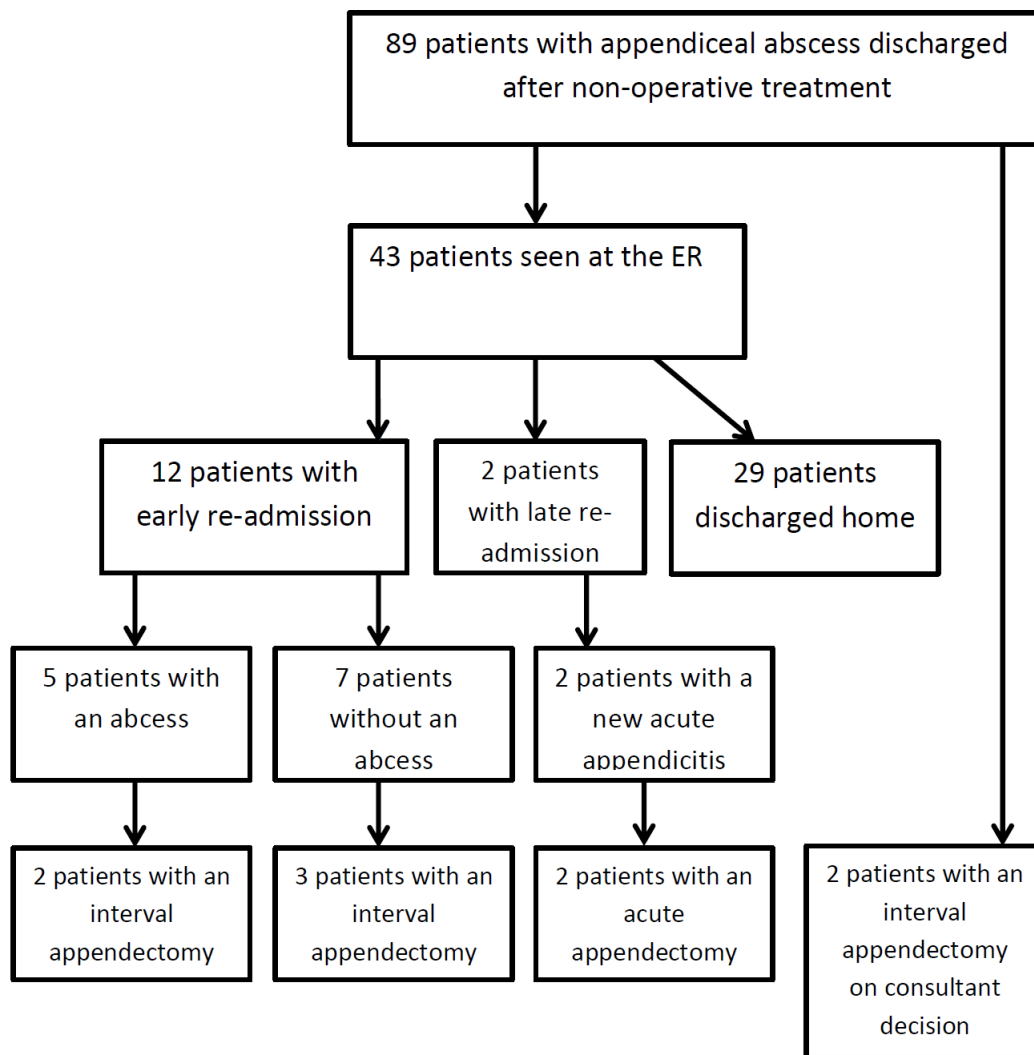
Figure 9. Study flowchart

6.3 META-ANALYSIS OF NON-OPERATIVE TREATMENT VERSUS SURGERY FOR ACUTE APPENDICITIS AN ADULTS (STUDY III)

Five trials were found in our literature search[98-102]. One of these trials[100] had been withdrawn from the journal at the time of this analysis[103]. This was based on suspicion of plagiarism as significant portions of this paper had been previously published in papers by Eriksson[98] and Horton[104]. This paper was included in an early version of this study that was presented at the European Paediatric Surgeons' Association, (EUPSA) congress in Rome 2011 but was not included in this meta-analysis. In our per-protocol meta-analysis, we found no significant difference between non-operative treatment and operative management for the proportion of patients failing treatment as defined above (Figure 10). However, there were fewer complications in the group of patients treated non-operatively (Figure 11). This result should be regarded with caution as the complications are stated differently in different trials and it is not possible to differentiate between more or less severe complications.

Study or Subgroup	Antibiotics Events	Antibiotics Total	Surgery Events	Surgery Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Eriksson	1	20	3	20	13.9%	0.30 [0.03, 3.15]	1995
Styrud	15	128	4	124	27.0%	3.98 [1.28, 12.36]	2006
Hansson	11	119	30	250	32.3%	0.75 [0.36, 1.55]	2009
Vons	13	116	4	119	26.7%	3.63 [1.15, 11.48]	2011
Total (95% CI)		383		513	100.0%	1.58 [0.52, 4.77]	
Total events	40		41				
Heterogeneity: Tau² = 0.85; Chi² = 10.43, df = 3 (P = 0.02); I² = 71%							
Test for overall effect: Z = 0.80 (P = 0.42)							

Figure 10. Forest plot of 'treatment failure' defined as failure of non-operative treatment requiring appendectomy (non-operative treatment arm), or negative appendectomy (surgical treatment arm).

Study or Subgroup	Medical Events	Medical Total	Surgical Events	Surgical Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Eriksson	0	20	1	20	6.0%	0.32 [0.01, 8.26]	1995
Styrud	4	128	17	124	51.0%	0.20 [0.07, 0.62]	2006
Hansson	3	119	25	250	43.0%	0.23 [0.07, 0.79]	2009
Total (95% CI)		267		394	100.0%	0.22 [0.10, 0.49]	
Total events	7		43				
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%							
Test for overall effect: Z = 3.70 (P = 0.0002)							

Figure 11. Forest plot of risk of complications following either non-operative treatment with antibiotics or appendectomy.

37

6.4 NON-OPERATIVE TREATMENT OF ACUTE APPENDICITIS IN CHILDREN (STUDY III)

At the time of this study the scientific support for non-operative treatment of acute non-perforated appendicitis in children were scarce. There were no RCTs but a few cohort studies published.

In 2007 Abes and co-workers presented a cohort of 136 children with suspected acute appendicitis diagnosed with a combination of clinical findings and US between 2003 and 2006[105]. Of these 41 had perforated appendicitis and 95 had acute appendicitis. Sixteen of the patients with acute appendicitis had a history of less than 24 hours, localised abdominal pain and were also haemodynamically stable and were selected for non-operative treatment. The non-operative treatment consisted of parenteral antibiotics (Ampicillin with Sulbactam and Ornidazol) until abdominal tenderness had resolved. Fifteen of 16 patients recovered without surgery. As this was a retrospective review, it was neither clearly stated that these inclusion criteria were used in a prospective fashion nor if there were any drop-out from this strategy. Also, it is not stated how the pre-operative diagnosis of perforated appendicitis was made.

Wiegering and co-workers presented in 2008 five cases of non-operatively treated children with acute appendicitis in a cohort of 113 cases of appendicitis in children with haematological malignancies[106]. Five of these children received non-operative treatment and were given parenteral antibiotics of diff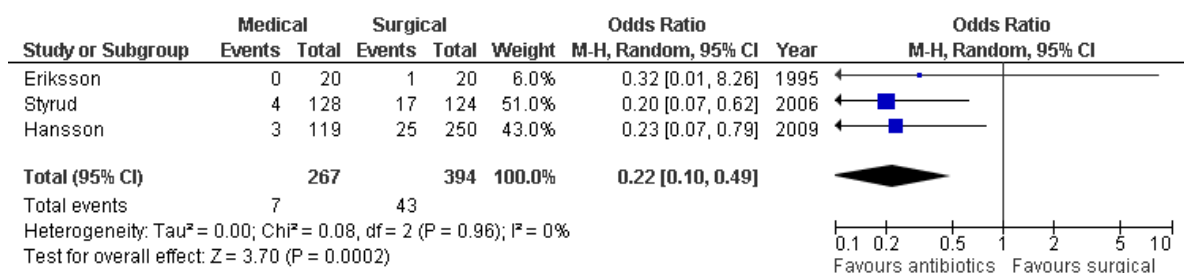erent regimens, all including Meropenem. In all cases, the appendicitis developed during severe neutropenia. The appendicitis resolved in all these five cases, included one case of suspected perforated appendicitis with an abscess. One had a preventive interval appendectomy before allogenic bone marrow transplantation. This study is also hampered by its retrospective design with unclear inclusion criteria for non-operative treatment. Also, one of these patients had a radiologically confirmed retrocaecal abscess and thus should be assessed as an appendiceal abscess.

6.5 NON-OPERATIVE TREATMENT OF PERFORATED APPENDICITIS IN CHILDREN (STUDY III)

Non-operative treatment of children with perforated appendicitis who have developed an appendiceal mass or abscess is routine today. Non-operative treatment of perforated appendicitis without abscess, phlegmon or mass is less so. In this study we presented the published series on this subject as seen in table 6[107-115].

Series	Year	N treated non-operatively	N (%) successfully treated non-operatively	Selection criteria
Weiner	1995	17	17 (100%)	-
Bufo	1998	41	34 (83%)	-
Kogut	2001	101	79 (78%)	-
Weber	2003	25	16 (64%)	Only included "less ill", illness >4days, non-septic
Nadler	2004	73	54 (74%)	Only included history >72hours, no generalised peritonitis
Vane	2006	27	27 (100%)	Only included history >72hours, non-toxic, no generalised peritonitis
Henry	2007	48	43 (90%)	-
Aprahamian	2007	75	66 (88%)	-
Whyte	2008	58	36 (62%)	Excluded septic shock, electrolyte disturbance, medical comorbidities

Table 6. Published series of non-operative management of perforated appendicitis in children without an abscess, phlegmon or mass (Please note that the paper by Emil and co-workers[116] is not included in this table).

Selection criteria for non-operative treatment are shown where reported. All data were retrospectively collected and the diagnosis was based on clinical suspicion, abdominal US or CT-scan. Non-operative treatment was successful in 62% to 100% of cases. The pooled estimate of success of non-operative treatment based on these studies is seen in figure 12.

Proportion: 95% Confidence Interval

Study Name	N		Confidence Interval
Weiner (1995)	17		1.000 (0.678, 1.000)
Bufo (1998)	41		0.829 (0.683, 0.916)
Kogut (2001)	101		0.782 (0.691, 0.852)
Weber (2003)	25		0.640 (0.440, 0.801)
Nadler (2004)	73		0.740 (0.628, 0.827)
Vane (2006)	27		1.000 (0.770, 1.000)
Henry (2007)	48		0.896 (0.773, 0.956)
Aprahamian (2007)	75		0.880 (0.785, 0.936)
Emil (2007)	32		0.875 (0.711, 0.952)
Whyte (2008)	58		0.621 (0.491, 0.736)
Overall			0.808 (0.729, 0.868)

Figure 12. Estimate of proportion of children with uncomplicated perforated appendicitis who can be successfully treated non-operatively based on existing cohort studies.

Blakely and co-workers performed a prospective RCT comparing non-operative treatment to early appendectomy in 131 unselected children with perforated appendicitis, but without evidence of an abscess or mass[117]. Their protocol stipulated an interval appendectomy following successful non-operative treatment after a time interval of 6 to 8 weeks. Overall, 89% of the children suspected of having perforated appendicitis who underwent early appendectomy had this as a final diagnosis. The advantage of a prospective randomised study in which demographic and clinical parameters are similar between groups is that the proportion of children with the correct diagnosis of perforated appendicitis can be assumed to be equal in both treatment groups. The primary outcome measure of time away from normal activities was significantly shorter in the group who underwent early appendectomy compared with those initially treated non-operatively and who returned for interval appendectomy (13.8 vs 19.4 days; $p < 0.001$). Predefined adverse events were significantly more common in the non-operative treatment group (55% vs 30%; $p = 0.003$) and were most commonly: recurrent appendicitis, abscess development, SBO, and unplanned readmission.

On the basis of these findings, from the only RCT of unselected children with perforated appendicitis, the authors propose a clear preference for early appendectomy.

6.6 RANDOMISED CONTROLLED TRIAL OF NON-OPERATIVE TREATMENT OF NON-PERFORATED ACUTE APPENDICITIS IN CHILDREN (STUDY IV)

Fifty-one patients were enrolled in this trial between the 7th February and 17th October 2012. The study flowchart is presented in Figure 13. In addition to the defined exclusion criteria and parental non-agreement to participate, two children were excluded on the basis of CT-findings, one with a suspicion of a carcinoid tumour of the appendix and one in whom it was impossible to differentiate between appendicitis and a Meckel´s diverticulitis. Overall, 52 of the 129 children (40%) whose parents were asked whether they would consent to their child being in the trial agreed. Following agreement to participate there was failure of the computer randomisation program affecting one case (this child was not included in the study) and in one case parents withdrew consent to participate in the study after allocation of treatment. This child was withdrawn from the study. To account for these two cases, additional participants were recruited to reach the target sample size of 50.

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                                                                    ┌──────────────────────────────────────────┐
                                                                    │ Excluded (n = 174)                       │
                                                                    │                                          │
                                                                    │  ◆ Age < 5 years (n = 13)                │
                        ┌──────────────────────────────┐            │                                          │
                        │ Assessed for eligibility      │            │  ◆ Declined to participate (n = 77)      │
                        │ (n = 225)                     │            │                                          │
                        │                               │            │  ◆ Clinical and/or imaging suspicion of  │
                        └──────────────────────────────┘            │     perforation (n = 39)                 │
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Figure 13. Study flowchart

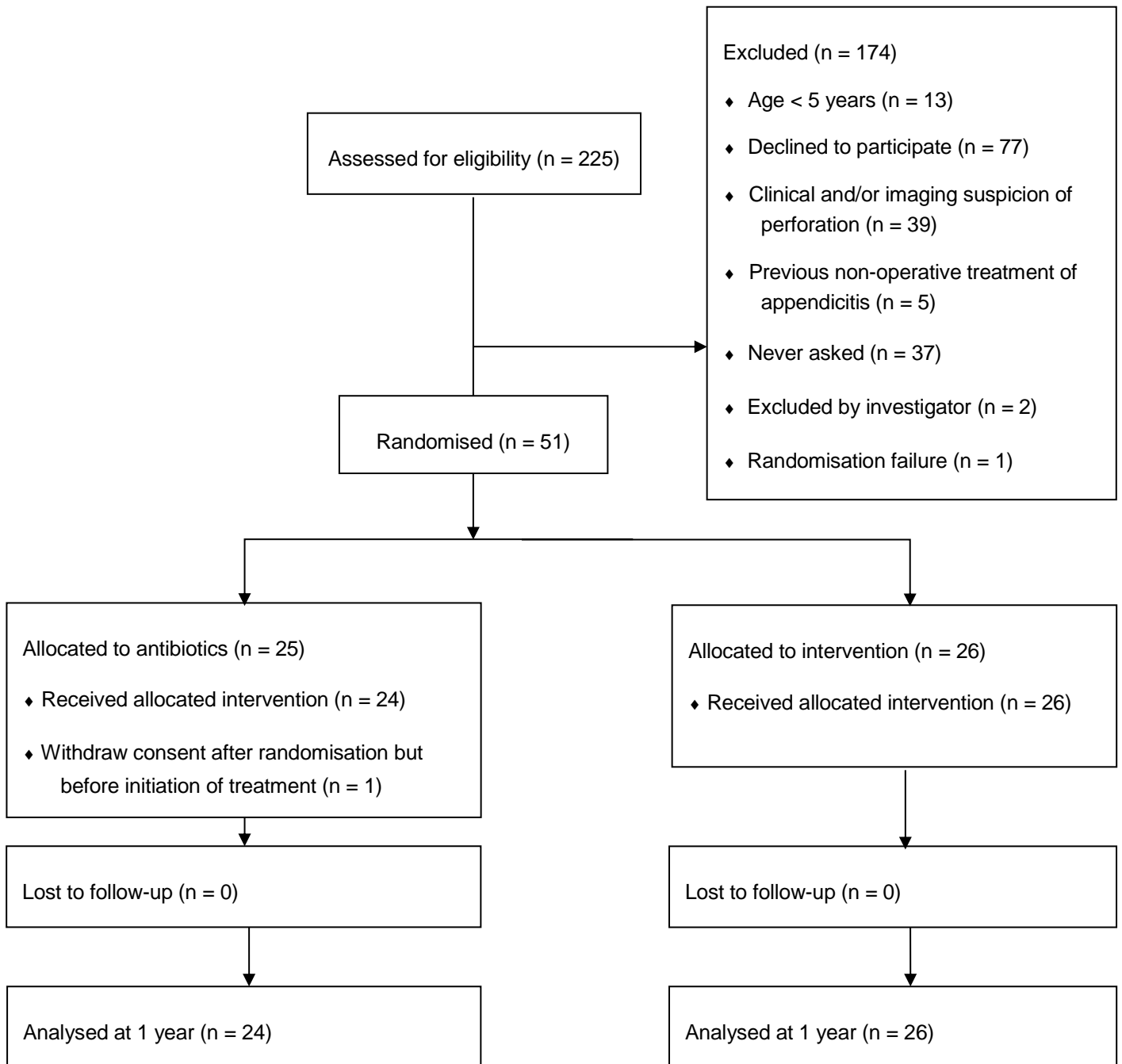
Figure 13. Study flowchart

Participants had similar demographic and admission characteristics compared both to those children whose parents declined participation and to those children who were not invited to participate (Table 7), except that the proportion of children with symptom duration <48h was significantly lower in the group who were not offered to participate in the trial. The reason for this is unclear, although it is possible that surgeons felt that there was a clearer need to perform an appendectomy in children with longer symptom duration.

	Randomised children (n=50)	Declined to participate (n=77)	P*	Not invited to participate(n=37)	P**
Age (years)	11.2 (5.9-15.0)	11.0 (5.8-14.9)	0.369	10.8 (5.3-14.9)	0.268
Male gender, n (%)	26 (52)	42 (55)	0.779	23 (62)	0.345
Duration of symptoms <48 hrs, n (%)	43 (86)	61 (79)	0.332	25 (68)	0.04
CRP (mg/l) on admission	28 (1-185)	19 (1-152)	0.414	17.5 (1.0-150.0)	0.909
WBC $(x10^9/l)$ on admission	14.3 (4.5-26.9)	15.0 (5.2-27.2)	0.086	15.0 (6.1-33.5)	0.297
Neutrophils $(x10^9/l)$ on admission	11.5 (2.5-23.5)	12.5 (1.5-24.0)	0.155	13.6 (12.5-30.1)	0.295
Temperature on admission (˚C)	37.4 (36.3-39.0)	37.3 (35.9-37.3)	0.177	37.1 (35.7-39.3)	0.392

Table 7. Comparison of participants, those eligible but not enrolled and those not invited to participate (A typing-error is corrected in this table, compared to the published paper)
*Comparison between randomised children and those who declined to participate.
**Comparison between randomised children and those who were not invited to participate.

The surgery and non-operative treatment groups also had similar demographic and admission characteristics (Table 8). All patients had at least one US examination, one had a second US, and four had a CT following the initial US. The reason for repeated examination was, in all cases, that the appendix was not seen during the initial examination.

	Randomised children		
	Surgery (n=26)	Non-operative treatment (n=24)	p-value
Age (years)	11.1 (6.2-14.8)	12.2 (5.9-15.0)	0.130
Male gender n (%)	12 (46)	14 (58)	0.389
Duration of symptoms <48 hrs, n (%)	23 (88)	20 (83)	0.602
CRP (mg/l) on admission	27.0 (1.0-175.0)	30.5 (1.0-185.0)	0.892
WBC ($x10^9$/l) on admission	14.5 (4.5-26.9)	14.0 (4.8-19.0)	0.918
Neutrophils ($x10^9$/l) on admission	11.6 (2.9-23.5)	11.5 (2.5-16.8)	1.0
Temperature (°C) on admission	37.5 (36.5-38.5)	37.3 (36.6-39.0)	0.199

Table 8. Comparison of treatment groups

6.6.1 Primary outcome

All children randomised to surgery had a LA with a three-port technique. Histological examination confirmed the diagnosis of acute appendicitis in all cases (i.e. no negative appendectomy, 21 phlegmonous appendicitis, three gangrenous appendicitis and two perforated appendicitis) and there were no significant complications in this group.

All children randomised to non-operative treatment with antibiotics received antibiotics per protocol. Two of these children had a significant complication. One child underwent an early appendectomy on day two as symptoms had failed to improve; a macroscopically normal appendix was removed and the child was diagnosed with mesenteric lymphadenitis.

Histological examination of the appendix was normal. This patient had had an inconclusive US and a CT-scan suggestive of appendicitis with a tubular structure measuring 9-10 mm.

The final report on this CT-scan (produced after the surgery) was changed to a negative finding. A second child returned to the emergency room on day nine after randomisation with moderate abdominal pain following initial successful antibiotic treatment according to the study protocol. US revealed signs of on-going inflammation and a walled-off perforated appendicitis was found at LA.

The primary outcome was similar in each group (appendectomy group 26/26 (100%) vs non-operative treatment group 22/24 (92%); p=0.23).

6.6.2 Secondary outcomes

During the one-year follow-up period there were no significant or minor complications in the surgery group. In the non-operative treatment group there were no minor complications. However, one child had appendectomy for histopathologically confirmed recurrent acute appendicitis nine months after randomisation, and one asymptomatic child underwent (histopathologically normal) appendectomy following parental request. A further five children returned with mild abdominal pain and had laparoscopic appendectomies at surgeon and parental discretion. All had a varying degree of fibrosis in the appendix but no inflammation. In all cases symptoms resolved after surgery.

Therefore, after one year of follow-up 15/24 children (62%) randomised to primary antibiotic treatment had not undergone an appendectomy.

Twelve children were diagnosed with an appendicolith on imaging, 7/26 in the surgery group and 5/24 in the non-operative treatment group (p=0.74). Of the 5 with an appendicolith in the non-operative treatment group, three had appendectomy (none as primary failure, one due to recurrent acute appendicitis, one due to recurrent symptoms without appendicitis and one for parental request). Thus in the non-operative treatment group 2 children with an appendicolith did not have appendectomy within one year of follow-up and of the nine total that have had an appendectomy only three had an appendicolith on imaging at initial presentation.

Time from randomisation to actual discharge home was calculated for each participant. The median time to discharge was significantly shorter in the surgical group than in the non-operative treatment group 34.5 (16.2-95.0) hours vs 51.5 (29.9-86.1) (p=0.0004). Despite this, the cost for the initial inpatient stay was significantly lower for non-operative treatment 30 732 (18 980-63 863) Swedish kronor (SEK) vs surgery 45 805 (33 042-94 638) SEK; (p<0.0001).

The total cost of treatment, including the cost of those patients having an appendectomy during the follow-up period, was similar in both treatment groups, non-operative treatment 34 587 (19 120-14 6552) SEK vs surgery 45 805 (33 042-94 638) SEK; (p=0.11).

7 GENERAL DISCUSSION

In the study presented in **paper I**, the only preoperative difference between the two groups was a higher level of WBC-count in the patients operated with open surgery. The reason for this is probably that this test was not mandatory in the early part of the series when OA was more common. At this time, WBC was taken in more severe cases and this is shown by the fact that perforated appendicitis was more common in patients with WBC (127/434) than in patients without WBC (60/303) p=0.003. There was no difference in any assessed complications, apart from an increased rate of re-admissions after OA. The reason for this is not clear, but as there was no difference in the rate of re-operations it may be due to pain or mobilisation after swift discharges. The operating time was longer for LA than for OA but there was a large inter-surgeon difference in operating time supporting the need for training and continuous assessment of individual surgeons to decrease operating times.

We show that the patients who had a LA had a shorter postoperative stay than patients who had an OA, but that this is related to a change of management over time and not due to the surgical modality. Interestingly, there has been no change in the treatment protocol for patients after an appendectomy during the trial period. Thus, we suggest that introduction of LA showed that the patients could be discharged early but that this was also true for the patients treated with an OA.

One significant aspect of this study is that the two parts of the cohort are different in time. This is best shown by the fact that the postoperative time in hospital is shorter assessed by basic statistics but was shown to be dependent on time rather than on surgical modality. This finding has implications for other studies, which compare laparoscopic with open techniques. Even though the patients operated on laparoscopically and open were operated in the same time period, a simple statistical comparison may lead to erroneous conclusions unless other factors are carefully considered.

Historically, an appendectomy performed on a patient with a well-formed abscess or appendiceal mass has been associated with significant morbidity[118]. Therefore, a non-operative strategy was presented with the recommendation to perform an interval appendectomy 4-6 weeks[119] or as late as 20 weeks[120] later. In many centres, amongst them all Swedish paediatric surgical units, this has evolved further to non-operative treatment without interval appendectomy. In other places, for instance in the United Kingdom, the interval appendectomy remains the current standard. A recent study by Hall and co-workers[121] concluded that there is a lack of prospective data to support any of these treatment modalities and that up to 80% of children may not need an interval appendectomy. After this systematic review, Zhang and co-workers[122] presented a large series of 105 patients with non-operative treatment of an appendiceal abscess. Summarising their subgroups, the total failure rate was 14/103 (13.6%) during a median follow-up of 2.4 years.

In **paper II** we presented our results with conservative management (no interval appendectomy) after an appendiceal abscess. As all re-admissions leading to an interval

appendectomy occurred within one month (32 days) after the initial presentation we introduced the concept that these should be regarded as a continuation of the initial disease. Hence the recurrence rate of acute appendicitis was 2/82, 2.4% excluding the interval appendectomies after early re-admissions and 9/89, 10%, if all appendectomies in the follow-up period were included. In conclusion, we present a lower incidence of failure of non-operative treatment compared to previously published data, even after including the interval appendectomies that were performed outside the protocol as failures.

The finding of an appendicolith has been regarded as a risk factor for recurrence after non-operative treatment of an appendix abscess[122] or a factor that delays resolution of appendicitis following non-operative treatment[123]. In this study, despite the fact that 41/89 patients had an appendicolith on imaging, we were not able to correlate this with an increased risk of a recurrence or the risk of delayed resolution.

In **Paper III** we had the ambition to assess the evidence for non-operative treatment of acute appendicitis in children but found no relevant RCTs. With regards to similar trials in adults we found that the presentation of outcome was different between the trials, which made the comparison difficult. We also found more meta-analyses than there were original RCTs. All these prior meta-analyses were performed based on intention to treat. We found this methodology of low value as there were a large proportion of cross-over in one of the trials. Additionally, we found it of a greater interest to assess the true biologic effect of the treatment rather than to assess the result of implementation of a non-operative strategy. Apart from the meta-analysis we also assessed published series on non-operative treatment of perforated appendicitis without an abscess. These trials were also hampered by selection bias, most commonly due to the clinical status at presentation determining the treatment regimen that the child received.

In the pilot RCT presented in **paper IV**, we have shown that non-operative treatment is feasible and safe. Overall 40% of families asked to participate accepted and were enrolled, suggesting that non-operative treatment is of interest to this patient population and their families. We consider it possible that in future randomised trials in children, this recruitment rate might be improved, as during this study we were unable to provide the parents with any evidence of safety or efficacy of antibiotics alone, whereas future studies would have such evidence from this pilot trial. On the basis of the recruitment rate achieved we believe a future RCT would be feasible.

Although this pilot trial was not adequately powered to detect differences in treatment efficacy, outcome data are useful in informing future studies. As defined, effective treatment was achieved in 100% and 92% in the surgery and non-operative treatment groups respectively. In the non-operative treatment group only 2/24 patients failed to meet criteria for the primary endpoint. One of them had mesenteric lymphadenitis, which may explain the failure to respond to antibiotics, as the symptoms of this disease is not affected by antibiotic treatment. The other returned following initial improvement of symptoms with antibiotics and was found to have perforated appendicitis.

An important consideration for surgeons and parents following successful non-operative treatment of acute appendicitis is the fate of the appendix. In this study we did not offer

routine interval appendectomy. A potential benefit of non-operative treatment is the avoidance of an appendectomy (and associated general anaesthesia) at all. For this benefit to be realised the recurrent appendicitis rate must be low and acceptable to both surgeons and parents. In this study there was one case of histologically proven recurrent appendicitis during the follow-up period (5%). However, a further six children had appendectomy within the one-year follow-up period for reasons other than recurrent acute appendicitis including one at parental request. As this was a pilot trial of a novel treatment strategy (antibiotics for acute appendicitis in children) we were liberal in regards of indications for surgery during the follow-up period in children in the non-operative treatment group. It is possible that patients in this group would not have had surgery if they had presented with their symptoms outside the trial setting. This may have contributed to the high rate of surgery during follow-up and raises the important question of what is an appropriate threshold for appendectomy in children who have been successfully discharged home following non-operative treatment.

For non-operative treatment to be considered equivalent to appendectomy some may believe that the length of hospitalisation should be similar. In this pilot trial the post-randomisation length of stay was longer for children in the non-operative treatment group compared to children undergoing appendectomy. A possible explanation for this is that we stipulated a minimum of 48 hours of intravenous antibiotics in our protocol. In the future it may be possible to reduce this duration without affecting efficacy. During analysis of these time-related data it became apparent that significant delays between randomisation and surgery would impact on the time from randomisation to discharge and therefore potentially influence the interpretation of this outcome measure. Delays between randomisation and surgery may occur due to hospital workload and/or time of presentation, as typically appendectomy is no longer performed during the night. Median time between randomisation and surgery in this study was 5.8 hours but with a range of 0.8 – 26.2 hours. These factors must be considered carefully in any future RCT.

Whilst overall cost was similar between the two treatment groups, the cost of the initial inpatient treatment was significantly higher in the surgery group. Thus, the additional admissions for recurrent symptoms in the non-operative treatment groups were a significant determinant of cost in this group. A cost effectiveness analysis should be performed as part of any future study.

Although the number of patients treated non-operatively was small, there were no safety issues during either the acute admission or during the follow-up period and so this trial provides no evidence that non-operative treatment of acute appendicitis is unsafe.

7.1   STRENGTHS
The foremost strength of the clinical **papers, I, II and IV** is the fact that all children with acute appendicitis are seen at our department and that any surgical complication would return to us for assessment. Furthermore, as we have computerised notes and a computerised theatre log book in place since 2006, all patients are readily found in our systems. Finally, as all data is taken from notes written at the time of the event, all data is considered prospective without recall bias or other forms of information bias.

7.2 LIMITATIONS

In **paper I** the major limitations are the selection bias. As we switched from open to laparoscopic surgery we did not propose strong guidelines in regards of the individual surgeon. Initially the transition was made by surgeons with prior training in MAS in adults and over time this method was taught to the other members of staff. It could have been the case that "easier cases" may have been chosen for laparoscopic surgery. The fact that the two groups of patients are similar with respect to basic characteristics makes it unlikely to have had an effect on the analysis. The only parameter that was statistically different was the level of WBC on admission. This is most likely due to the fact that we only have WBC counts in 1186 of 1744 patients. WBC was not a standard blood-test in the early part of this series and only taken in more advanced cases which would mean a higher median in the open, early group. This brings up the other aspect of the second trial, the fact that the two groups differ in time. This resulted in the initial finding that the postoperative length of stay was shorter after laparoscopic surgery. This is further described in 6.1.2.

Paper II presents the second-largest published cohort of patients with successful non-operative treatment of an appendiceal abscess in children but the events, or failure rate, is still too small to assess the impact of an appendicolith on outcome. Despite being comparably long, the follow-up of 5.1 years is still short in children. There would be a benefit to re-assess this cohort later.

In the meta-analysis in **paper III** we present the complications after non-operative treatment and surgery. A weakness of this analysis follows the weaknesses of the included trials. Especially the assessment of complications was difficult, as this was not uniformly presented in the trials. In the Eriksson trial[98], they mention in the text one patient in the surgery group developing a wound infection. In the Styrud trial[99] they conclude that "during the one year follow-up period there were 17 complications in the surgery group, most of them wound infections. Four patients had complications after surgery in the antibiotic treated group". In the Hansson trial[101] they presented a detailed list of complications, described as major and minor. Finally, in the Vons trial[102] they mention postoperative wound infections and intestinal adhesive obstruction in the text.

The major limitation of the study presented in **paper IV** is that is a pilot trial without any power calculation.

8 CONCLUSIONS

In this thesis we conclude that

- OA and LA have a similar risk of complications and that the apparent difference in postoperative length of stay is not due to the surgical method but to a general trend of shorter postoperative length of stay over time,

- the risk of a new episode of acute appendicitis after successful non-operative treatment of an appendiceal abscess is small and that routine interval appendectomy cannot be recommended,

- non-operative treatment of acute appendicitis in adults is safe and feasible,

- non-operative treatment of non-perforated appendicitis in children is safe and feasible and that it would be possible to perform a large power-calculated RCT in children.

9 FUTURE CHALLENGES AND DIRECTIONS

Acute appendicitis is a very common disease in children and despite the fact that most surgeons have a vast experience of diagnosing and treating this condition there is a lack of consensus on virtually every aspect of this disease. Furthermore, wide-spread literature appears to support all the differing opinions.

Should we diagnose acute appendicitis solely by hand and experience, based on scoring aids or on imaging? Should we perform surgery without delay or wait and see who recovers spontaneously? Should we treat everyone with surgery or can we give antibiotics instead? And, if we perform surgery should this be open, laparoscopic three port, single port, transumbillically or maybe by natural orifice transluminal endoscopic surgery, NOTES?

The ultimate aim has to be to diagnose the disease as accurately as possible and to treat any individual patient separately. In all probability, some patients with true acute appendicitis resolve spontaneously, some are cured by adding antibiotic treatment to the non-operative approach and some require surgery to prevent disease progression to perforation. Most patients with confined perforations would most likely not need an operation but some may need surgery.

Thus, the aim for the future would be how to allocate patients to these different treatment modalities as accurately as possible. To me, there is no better way to determine the presence of an acute appendicitis than with imaging. But, imaging includes CT-scanning and hence ionising radiation. There is, therefore, a need to improve imaging diagnostics, both the US with higher resolution, 3D capabilities and contrast enhancement. The CT-scanning needs further optimisation to reduce the radiation. Much has already been done, especially in children's hospitals. MRI has been used with promising results. At present, it is too expensive and unavailable as an emergent diagnostic modality, but this will surely change in the future as can be seen with the development of both US and CT-scanning.

Scoring will likely evolve into common practice as an aid to less experienced doctors in the emergency room as a selection tool for further investigations.

Other clinical markers, maybe developed through the use of proteomics, may in the future aid in the differentiation of patients into different treatment modalities.

With regards to surgery, I am convinced that the open "McBurney" approach to acute appendicitis will be obsolete in the future. MAS, or minimal scarring, will be the standard approach in the cases that need surgery. The operation is simple, if performed correctly, and with a new generation of surgeons skilled in MAS the operating time and conversion rate will be low.

In an era of evolving antibiotics resistance it is not likely that non-operative treatment with antibiotics will be a first-line treatment for non-selected cases of acute appendicitis, especially not outside devoted centres with high diagnostic accuracy. I believe non-operative treatment with antibiotics will be offered in selected cases, based on future markers for suitability.

The next important step for our group will be the APPY trial, a multinational RCT based on the outcome of study IV, randomising children with a clinical diagnosis of acute appendicitis to either non-operative treatment or surgery. This will be performed based on non-inferiority. The study group consists of about 20 paediatric surgical centres in Canada, US, France, Germany, Sweden and Finland and will, based on the power calculation, recruit approximately 880 patients.

10 SVENSK SAMMANFATTNING

Den här avhandlingen handlar om olika aspekter på behandling av blindtarmsinflammation, främst hos barn men delvis också hos vuxna. Blindtarmsinflammation är den vanligaste orsaken till akut operation hos barn. Under livet opereras ca 7% av alla människor för blindtarmsinflammation. Barnkirurgiska kliniken vid Astrid Lindgrens Barnsjukhus/Karolinska Sjukhuset i Stockholm opererar flest barn av alla svenska kliniker och är även en relativt stor klinik internationellt sätt. Därför är detta en lämplig klinik att bedriva denna typ av forskning vid. Dessutom ger datoriserade journalsystem det lätt att följa patienter över tid.

I **delarbete I** ville vi utvärdera behandlingsresultaten vid akut blindtarmsoperation under den tid vi skiftade från öppen operation till laparoskopisk operation, titthålskirurgi. På kliniken beslutade vi hösten 2007 att börja operera barn med akut blindtarmsinflammation laparoskopiskt istället för med öppen teknik som varit förhärskande i över 100 år. Det fanns då ett vetenskapligt stöd för att den laparoskopiska operationen gav en snabbare hemgång och minskade sårinfektioner jämför med öppen operation. För denna studie använde vi klinikens årliga kvalitetsuppföljning där samtliga patienter som opererats från januari 2006 och framåt finns beskrivna. Sammanlagt var det 1744 patienter som opererats från januari 2006 till december 2010. Av dessa var 1009 opererade laparoskopiskt. Vi kunde inte påvisa någon skillnad i andelen komplikationer såsom sårinfektioner, intraabdominella infektioner eller re-operationer mellan grupperna. Vi kunde konstatera att det tog längre tid att operera laparoskopiskt, 51 jämfört med 37 minuter. Vi tyckte oss se att patienterna som opererats med laparoskopisk operation gick hem tidigare än de som opererats med öppen operation men vid en närmare analys visade det sig att denna skillnad berodde på att alla patienter skickades hem tidigare i den senare delen av studien och att de flesta laparoskopiska operationer utfördes i den senare delen av studien. Den kortare tiden mellan operation och hemgång berodde i vårt fall inte på den kirurgiska metoden.

I **delarbete II** studerade vi de patienter som vårdats på Astrid Lindgrens barnsjukhus för en blindtarmsabscess och skrivits ut efter lyckad behandling mellan 2006 och 2010. Syftet med studien var att se hur många barn som kommit tillbaka med en ny akut blindtarmsinflammation efter sin första behandling. Bakgrunden till denna studie är att det finns internationella skillnader mellan behandlingen. I Sverige har vi länge varit mycket restriktiva till att operera bort blindtarmen efter tillfrisknandet medan det till exempel i Storbritannien varit rutin att alla patienter som behandlats framgångsrikt med antibiotika kommit tillbaka efter 6-12 veckor för en blindtarmsoperation. Vi ville visa på den förväntat låga risken med vårt förfarande. I denna studie hittade vi 89 patienter som uppfyllde kriterierna enligt ovan. Nio av dessa hade blivit opererade efter under uppföljningstiden av fem år. Men, bara två var opererade på grund av en ny episod av akut blindtarmsinflammation. Fem patienter kom tillbaka redan första månaden efter behandling med kvarstående besvär och blev opererade. Vi uppfattade de som inte helt ha blivit av med sin sjukdom första gången. Två patienter opererades utan att ha fått nya besvär, på grund av att dess doktor och/eller föräldrar ansåg att det var att föredra. Således beskrev vi risken för att få en ny blindtarmsinflammation efter en framgångsrik första behandling till 2,4%, en låg siffra som vi inte anser kan motivera att alla patienter skall opereras i efterförloppet.

Syftet med **delarbete III** var att utvärdera det vetenskapliga stödet för icke-operativ behandling av akut blindtarmsinflammation hos barn och vuxna. Vi gjorde en litteraturgenomgång för att identifiera all relevant vetenskaplig litteratur. Vi fann inga randomiserade kontrollerade studier som jämfört kirurgi med icke-operativ behandling av akut blindtarmsinflammation hos barn, det fanns bara ett par fallserier på selekterade patienter. En studie beskrev fem barn med blodcancer som fick blindtarmsinflammation under behandlingstiden och fick antibiotikabehandling istället för operation. Alla tillfrisknade utan kirurgi. En annan studie presenterade 136 barn med akut blindtarmsinflammation där 16 var så pass lindrigt sjuka att man behandlade med antibiotika istället för operation. 15 av 16 tillfrisknade av den behandlingen. Båda dessa studier var av relativt låg vetenskaplig kvalitet. Vi fann fem studier som randomiserat vuxna patienter till antingen kirurgi eller antibiotikabehandling av akut blindtarmsinflammation. En av dessa studier har efter publiceringen dragits tillbaka på grund av misstänkt plagiering så det fanns vid studietillfället fyra studier att analysera. Vi analyserade dessa studier med en meta-analys som innebär att de slås ihop till ett större material. Vi jämförde hur många patienter som behandlats med antibiotika men som tvingats till kirurgi under det närmaste året efter behandling med andelen patienter som opererats med en negativ blindtarmsoperation, dvs. operationen var "i onödan". Med de definitionerna var det ingen skillnad i utfall mellan de två behandlingarna. Vi jämförde också komplikationer av de två behandlingarna. Det visade sig att det var mer vanligt med komplikationer efter kirurgisk behandling än efter antibiotikabehandling. Vi sammanfattade denna del av studien med att 73% av alla patienter med akut blindtarmsinflammation som behandlats med antibiotika hade undvikit kirurgi under det första året efter sin behandling. Slutligen tittade vi i denna studie på studier på barn som behandlats med antibiotika för en perforerad blindtarmsinflammation. Här kunde vi efter en sammanslagning visa att 81% av barn med okomplicerad perforerad blindtarmsinflammation kunde behandlas framgångsrikt utan kirurgi.

Delarbete IV var en randomiserad kontrollerad studie där vi lottade patienter med akut blindtarmsinflammation till antingen kirurgi eller antibiotikabehandling utan operation. Som vi konstaterade i vårt tredje delarbete finns det ingen sådan studie gjord förut. Vi valde därför att göra en pilotstudie, en lite mindre studie för att se om det var möjligt att lotta barn till denna behandling och om behandlingen skulle vara lika säker på barn som på vuxna. Vi valde att inkludera 50 patienter i studien. Studien pågick mellan februari och oktober 2012. Sammanlagt behandlade 225 patienter för akut blindtarmsinflammation under den perioden. Då vi valt att inte inkludera barn under 5 år, barn med misstänkt perforerad blindtarm eller barn som tidigare behandlats för akut blindtarmsinflammation försvann dessa ur urvalet. Dessutom var de en andel patienter (77) som tackade nej till att deltaga och ytterligare 37 som aldrig blev tillfrågade. Slutligen var det en patient som ändrade sig efter lottningen men innan behandlingen påbörjats. Patienterna lottades med hjälp av ett dataprogram som gjorde att de två grupperna såg lika ut med avseende på ålder, kön och sjukdomsduration. Detta lottningsförfarande innebär inte att grupperna måste bli lika stora så 24 patienter blev lottade till antibiotikabehandling och 26 till operation. Av de som lottats till operation visade sig alla ha en akut blindtarmsoperation ingen av dessa patienter fick heller några allvarliga komplikationer efter sina operationer. Av de patienter som lottats till antibiotikabehandling behövde en patient opereras efter två dagar på grund av smärtor (denna patient visade sig senare vid mikroskopisk undersökning av blindtarmen inte ha någon akut

blindtarmsoperation), och en patient kom tillbaka en vecka efter operationen med kvarstående besvär, blev då opererad och visade sig ha en akut blindtarmsinflammation. Under den ett år långa uppföljningen kom en patient tillbaka med en ny akut blindtarmsoperation, en patient blev opererad enbart på grund av oro för ny sjukdom och fem patienter blev opererade på grund av vaga återkommande buksmärtor. Ingen av de sista sex hade tecken till akut blindtarmsinflammation på mikroskopisk undersökning. Vi kunde sammanfatta denna studie med att 40% av tillfrågade barn och föräldrar accepterade att vara med i studien, att det inte medförde några negativa effekter och att 62% av patienterna som behandlats med icke-operativ behandling inte var opererade ett år efter behandlingen.

Sammanfattningsvis kan vi presentera stödet för primär icke-operativ behandling av såväl akut blindtarmsinflammation som för blindtarmsabscesser. Vi har också kunnat visa att det gått bra att byta över till laparoskopisk kirurgi och att vi kunnat anamma den metoden utan negativa effekter för våra patienter. Vår forskningsgrupp kommer framöver att presentera resultaten av de senare årens operationsresultat och förhoppningsvis kan vi påvisa att vårt byte av metod över tid medfört förbättringar för våra patienter. Vi kommer också snart att delta i en stor internationell studie av icke-operativ behandling av akut blindtarms-inflammation, baserad på resultaten av vårt delarbete IV.

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12 APPENDICES (!)

12.1 APPENDIX 1: THE CONSAPP PILOT TRIAL PARENTAL INFORMATION

Föräldrainformation

Konservativ behandling av akut appendicit hos barn

(Conservative treatment of acute appendicitis in children)

1. Inbjudan

Ni och Ert barn erbjuds att medverka i en forskningsstudie. Innan Ni beslutar Er för att medverka är det viktigt att förstå varför forskningen görs och vad det kommer att innebära. Ta tid på Er och läs igenom denna information. Fråga oss gärna om något är oklart eller om Ni önskar mer information.

Tack för att Ni läser detta.

2. Vad är syftet med denna studie?

Ert barn har diagnostiserats med blindtarmsinflammation. Det är en inflammation av blindtarmen, ett maskformigt bihang som sitter på tjocktarmen. Ingen vet varför denna inflammation uppstår. Ibland leder inflammationen till att blindtarmen spricker.

Standardbehandlingen av akut appendicit är en operation där man tar bort den inflammerade blindtarmen. Detta kräver att Ert barn sövs och opereras med öppen kirurgi eller titthålsoperation.

Denna behandling har ifrågasatts på senare år. Det finns vetenskapligt stöd för att akut blindtarmsinflammation ibland läker spontant utan operation. Vetenskapliga studier på vuxna har visat att blindtarmsinflammation kan behandlas med antibiotika. Det finns ännu ingen vetenskaplig studie som har värderat för- respektive nackdelar med antibiotikabehandling istället för operation av blindtarmsinflammation hos barn.

Denna studie genomförs för att ta reda på vilken av behandlingarna, operation eller antibiotika, som effektivast behandlar blindtarmsinflammationen och ger minst komplikationer.

3. Varför har vi blivit utvalda?

Ert barn har blivit utvalt för att han/hon har blivit diagnostiserat med akut blindtarmsinflammation och kommer att behöva behandlas för detta. De kirurger som deltar i denna studie har stor erfarenhet av att behandla blindtarmsinflammation hos barn och utför blindtarmsoperationer regelbundet. De har också erfarenhet att undersöka Ert barn och bedöma om inflammationen blir bättre eller sämre.

4. Måste vi medverka?

Nej, det är helt frivilligt att medverka i denna studie. Om Ni beslutar Er för att vara med kommer Ni att få skriva under ett godkännande. Även om Ni beslutar Er för att delta har Ni när som helst möjlighet att utgå ur studien utan att behöva förklara varför. Ett beslut att inte delta eller att senare utgå från studien kommer inte på något sätt att påverka behandlingen negativt.

5. Vad händer om mitt barn deltar i studien?

Det första som händer är att Ert barn kommer att lottas slumpmässigt till en av två grupper. En grupp kommer att behandlas med antibiotika och den andra kommer att opereras.

Båda grupperna kommer att övervakas noga.

Grupp 1 – kirurgisk behandling

Om Ert barn opereras kommer han/hon att behandlas på det sätt som är standard på sjukhuset. Det innebär fasta innan och ibland efter operationen och antibiotika före och ibland efter operationen.

Om Ert barn får komplikationer i samband med kirurgin kommer han/hon att behandlas på det sätt som är standard på sjukhuset. Det kan innebära förlängd fasta, behandling med antibiotika under en längre tid och i enstaka fall ett dränage för att tömma en varböld i buken.

Grupp 2 – Antibiotikabehandling

Om Ert barn behandlas med antibiotika kommer han/hon att få intravenös antibiotika i 24-48 timmar och sedan per oral (via munnen) antibiotika i en vecka. Han/hon kommer att fasta i 24 timmar.

Om ert barn inte blir bra av antibiotikabehandlingen kommer han/hon att få ytterligare behandling. Det kommer vanligen att innebära en operation men kan också innebära förlängd antibiotikabehandling eller ett dränage för att tömma en varböld i buken.

Vid utskrivningen kommer vi att planera ett återbesök 4-6 veckor efter hemgång. Sedan kommer vi att höras på telefon tre månader efter hemgång för att slutligen ses på mottagningen ett år efter behandlingen. Vi avser att kontakta Er på telefon tre år efter behandlingen för att se att allt gått bra. Varje besök tar ca 10 minuter och Ni kommer att kunna ställa vilka frågor Ni vill till kirurgen.

6. Vad behöver jag göra?

Ni behöver inte göra någonting annorlunda för att Ert barn deltar i studien.

7. Vad är det för behandling som testas?

Den behandling som testas i studien är antibiotikabehandling för blindtarmsinflammation, vilken jämförs med kirurgi.

8. Vad finns det för olika behandlingsalternativ?

Kirurgi har aldrig jämförts med antibiotikabehandling hos barn. Studier på vuxna har visat att antibiotikabehandling fungerar bra men att en del av patienterna får tillbaka sin sjukdom och har behandlats en gång till efter sin första lyckade behandling. Antibiotikabehandling används i stället för kirurgi på barn med komplicerad blindtarmsinflammation där blindtarmen spruckit och en böld har bildats. Det finns också tecken på att lindrig blindtarmsinflammation kan gå tillbaka av sig själv utan någon behandling alls.

9. Vad är biverkningarna av behandlingen?

Biverkningarna kan vara olika beroende på vilken behandling Ert barn får. Om Ert barn behandlas med kirurgi kommer han/hon att få ärr, antingen ett i buken nedre högra del om operationen görs öppet eller tre små ärr om operationen görs med titthålsteknik. Ert barn kommer också att sövas för operationen. Komplikationer till kirurgi kan vara sårinfektion, en varansamling inne i buken, tarmparalys (att tarmen står stilla) och i sällsynta fall ett hinder i tarmen som kräver en ytterligare operation. Det finns också en risk att operationen visar att blindtarmen är frisk och att operationen inte hade behövt göras.

Om Ert barn behandlas med antibiotika kan det visa sig att behandlingen inte fungerar utan att Ert barn blir sjukare och måste opereras. Det kan innebära att blindtarmen hunnit bli sjukare än den annars skulle varit. Det finns en risk för en varansamling inne i buken och för tarmparalys. Vid antibiotikabehandling finns en risk för övergående tarmproblem, främst i form av diarré.

10. Vad är de möjliga nackdelarna med att vara med i studien?

Som nämnts ovan finns det risker med båda behandlingarna. Detta är den första studien som jämför antibiotika med kirurgi för behandling av akut blindtarmsinflammation hos barn. Det betyder att vi inte känner till hur stor risken är för återfall i sjukdomen som kan innebära ytterligare en behandling på sjukhus.

11. Vad är de möjliga fördelarna med att vara med i studien?

Målet med studien är att vi skall lära oss om det finns fördelar med antibiotikabehandling istället för kirurgisk behandling. Möjliga fördelar är att undvika en operation och en narkos, undvika ärr, mindre smärta, kortare tid på sjukhus och mindre risk för stopp i tarmen senare i livet.

12. Vad händer om ny information blir tillgänglig?

Ibland blir ny information tillgänglig under det att ett forskningsprojekt pågår. En "Datamonitoreringsgrupp" kommer att mötas och diskutera eventuella åtgärder i sådana fall. Om så sker kommer Er forskningsansvariga läkare att informera Er och diskutera om Ni fortfarande skall vara med i studien. Om Ni beslutar er för att utgå ur studien kommer Er läkare att se till att Ni fortsatt får en bra behandling. Om ni beslutar Er för att fortsätta i studien kommer Ni att få skriva under ett nytt modifierat godkännande.

13. Vad händer efter det att studien avslutats?

Vi kommer att följa Ert barn i tre år efter hans/hennes behandling. Vid behov kommer uppföljningen att fortsätta längre.

14. Vad händer om något går fel?

Patienterna som ingår i studien vårdas inom det vanliga sjukvårdssystemet och skyddas av den sedvanliga patientförsäkringen.

15. Kommer mitt barns deltagande i studien att förbli anonymt?

Ja, all information som samlas in i studien kommer att hållas strikt konfidentiell. Ingen information som lämnar sjukhuset kommer att vara utan namn och adress så att den inte kan identifieras. Om Ni vill kommer vi att informera Er husläkare om studien.

16. Vad kommer att hända med studiens resultat?

Resultatet av studien kommer sannolika att publiceras i medicinska tidskrifter. Ni kan få en kopia på de studier som publiceras. Ert barn kommer inte att kunna identifieras i någon publicerad studie.

17. Vem organiserar och betalar forskningen?

Barnkirurger vid Astrid Lindgrens barnsjukhus och Karolinska institutet i Stockholm tillsammans med doktorer vid Great Ormond Street Hospital and the Institute och Child Health i London leder och organiserar denna studie. Studien stöttas ekonomiskt av Karolinska Sjukhuset, Stiftelsen Barnhuset och HKH Kronprinsessan Lovisas förening för barnsjukvård. Patienter kommer inte att få ersättning för deltagande i studien.

18. Kontakt för ytterligare information

Biträdande överläkare
Jan F. Svensson
Astrid Lindgrens Barnsjukhus Q3:03
17176 Stockholm
Jan.f.svensson@karolinska.se
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12.2 APPENDIX 2: CONSENT FORM

1 (1)

Astrid Lindgrens
Barnsjukhus
vid Karolinska
Universitetssjukhuset

MEDGIVANDEFORMULÄR

The CONServatie treatment of acute APPendicitis in children

En prospektiv Randomiserad utvärdering av icke-operativ jämfört med operativ behandling av akut blindtarmsinflammation hos barn

Barnets namn och personnummer:_____

1. Jag intygar att jag läst och förstått föräldrainformationen för denna studie och har haft tillfälle att ställa frågor.

2. Jag förstår att mitt barns medverkan är frivilligt och jag när som helst kan gå ur studien utan att behöva förklara varför och utan att mitt barns behandling påverkas.

3. Jag är medveten om att delar av mitt barns journal kommer att läsas av forskningspersonal om det behövs för studien. Jag accepterar att det sker.

4. Jag godkänner att mitt barn deltar i studien.

eller

5. Jag godkänner INTE att mitt barn deltar i studien men jag godkänner att uppgifter om mitt barn samlas in i forskningssyfte.

Namn på förälder	Datum	Underskrift

Frivillig underskrift för barn mellan 12-15 år som fått läsa informationen:

Barnets namn	Datum	Underskrift

Ansvarig läkare som ber om medgivande:

Namn	Datum	Underskrift

Patientdata:

The CONSAPP Pilot trial
(CONServative treatment of acute APPendicitis in children)

Flödesschema för inklusion:

	Ja	Nej
Har patienten misstänkt akut appendicit som innan studien skulle ha opererats?	☐	☐
Är patienten mellan 5 och 15 år?	☐	☐
Har patienten en misstänkt perforation?	☐	☐
Har patienten en appendix mass?	☐	☐
Har föräldrar och patient fått muntlig och skriftlig information?	☐	☐
Har målsman skrivit under informerat samtycke?	☐	☐
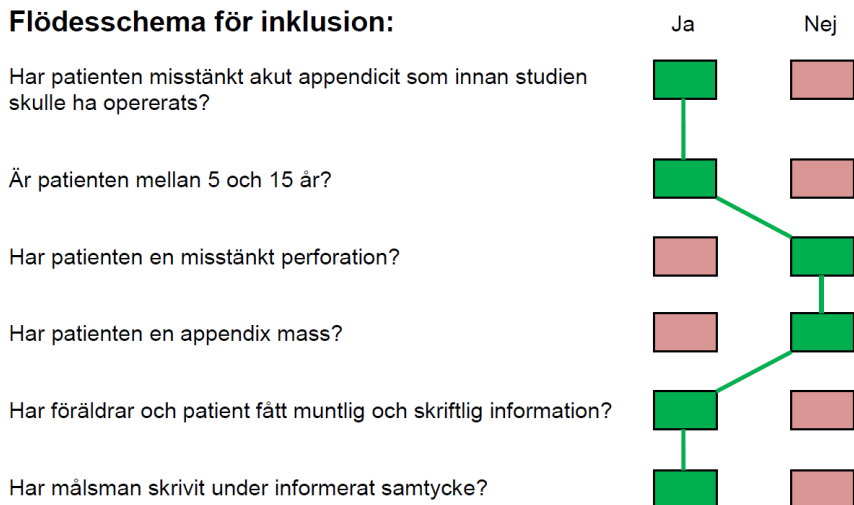
Om alla svar är gröna, fyll i nedanstående information:

	[5-10 yrs]	[11-15 yrs]
Ålder:	☐	☐

	[Male]	[Female]
Kön	☐	☐

	[<48hrs]	[>48 hrs]
Symptomduration	☐	☐

Kontakta nu studieansvarig för randomisering!

Allokering: Operation   Icke-operativ behandling
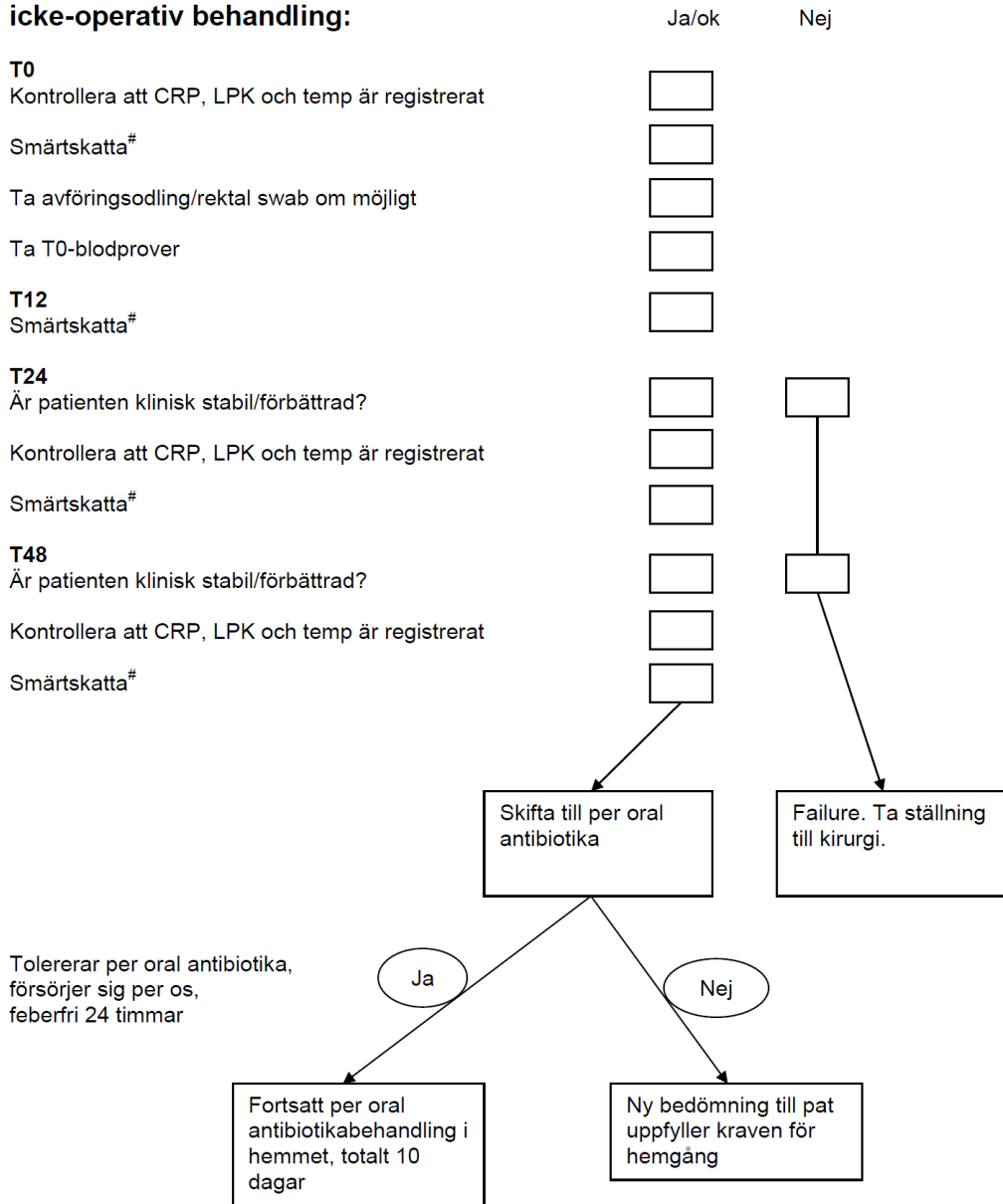
12.4 APPENDIX 4: FLOWCHART AFTER INCLUSION, NON-OPERATION GROUP

Patientdata:

The CONSAPP Pilot trial
(CONServative treatment of acute APPendicitis in children)

**Flödesschema efter inklusion
icke-operativ behandling:**

Ja/ok   Nej

T0
Kontrollera att CRP, LPK och temp är registrerat   ☐

Smärtskatta[#]   ☐

Ta avföringsodling/rektal swab om möjligt   ☐

Ta T0-blodprover   ☐

T12
Smärtskatta[#]   ☐

T24
Är patienten klinisk stabil/förbättrad?   ☐   ☐

Kontrollera att CRP, LPK och temp är registrerat   ☐

Smärtskatta[#]   ☐

T48
Är patienten klinisk stabil/förbättrad?   ☐   ☐

Kontrollera att CRP, LPK och temp är registrerat   ☐

Smärtskatta[#]   ☐

Skifta till per oral antibiotika

Failure. Ta ställning till kirurgi.

Tolererar per oral antibiotika, försörjer sig per os, feberfri 24 timmar

Ja   Nej

Fortsatt per oral antibiotikabehandling i hemmet, totalt 10 dagar

Ny bedömning till pat uppfyller kraven för hemgång

65

12.5 APPENDIX 5: FLOWCHART AFTER INCLUSION, SURGERY GROUP

Patientdata:

The CONSAPP Pilot trial
(CONServative treatment of acute APPendicitis in children)

Flödesschema efter inklusion
Operation:

	Ja/ok	Nej

T0
Kontrollera att CRP, LPK och temp är registrerat ☐

Smärtskatta[#] ☐

Ta avföringsodling/rektal swab om möjligt ☐

Ta T0-blodprover ☐

T12
Smärtskatta[#] ☐

T24
Kontrollera allmäntillstånd ☐

Smärtskatta[#] ☐

Kontrollera att CRP, LPK och temp är registrerat ☐

T48
Kontrollera allmäntillstånd ☐

Smärtskatta[#] ☐

Kontrollera att CRP, LPK och temp är registrerat ☐

Patienten är hemgångsklar när den försörjer sig per os, har varit feberfri i 24 timmar och inte behöver intravenös antibiotika.

Smärtskatta med Ansiktsskala enligt Bieri 1-10, notera i journalen.

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