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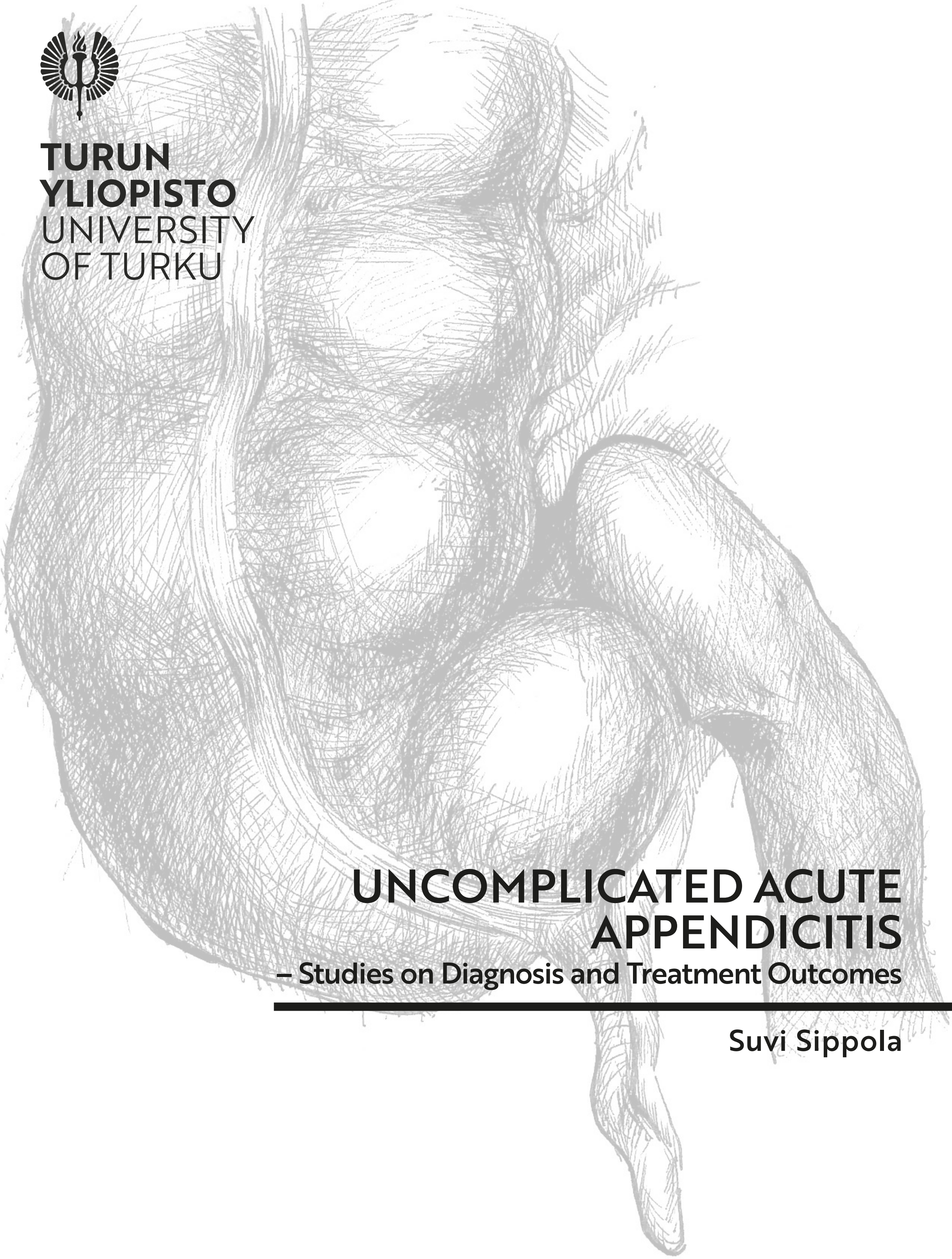

UNCOMPLICATED ACUTE APPENDICITIS

– Studies on Diagnosis and Treatment Outcomes

Suvi Sippola

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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To my boys,
Juho, Leo, and Erik

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ABSTRACT

Appendectomy has been the indisputable treatment of acute appendicitis for over a century. Acute appendicitis has been evaluated to always progress to perforation. Current evidence suggests complicated and uncomplicated acute appendicitis to be different forms of the disease. Complicated appendicitis requires emergency appendectomy with the exception of a restricted periappendicular abscess. Evidence of the feasibility of antibiotic therapy in the treatment of uncomplicated acute appendicitis has been provided by several randomized trials and meta-analyses mainly investigating combinations of intravenous followed by peroral antibiotics. In addition to treatment success, we need to consider treatment costs and patient-centered factors in assessing all different treatment options. With the emerging possibility of non-operative treatment, accurate diagnosis and differential diagnosis of the appendicitis severity is of vital importance. Computed tomography (CT) is the current gold standard in appendicitis diagnostics, but it is accurately criticized for ionizing radiation, especially with appendicitis patient population consisting of mainly young adults. Low-dose CT protocols have been developed to address this issue.

This series of studies aimed at comparing overall treatment costs (Study I) and patient quality of life (QOL), satisfaction, and treatment preference (Study III) between appendectomy and antibiotic therapy. To assess the issue of CT radiation, a low-dose protocol was compared with standard CT in the OPTICAP trial (Study II). The APPAC II trial (Study IV) aimed at optimizing antibiotic therapy for uncomplicated acute appendicitis by comparing p.o. monotherapy with i.v. followed by p.o. antibiotics. The possibility of symptomatic treatment is visited in the APPAC III study protocol (Study V).

The overall cost of antibiotic therapy was significantly lower compared to appendectomy with similar QOL, but the patient satisfaction was higher in the appendectomy group. The low-dose CT protocol had comparable diagnostic accuracy with standard CT with significantly less radiation. Treatment success of the peroral monotherapy was clinically comparable to intravenous followed by peroral in the treatment of uncomplicated acute appendicitis.

KEYWORDS: acute appendicitis, antibiotics, appendectomy, computed tomography imaging, costs, quality of life, uncomplicated acute appendicitis.

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TIIVISTELMÄ

Umpilisäkkeen poisto on ollut umpilisäketulehduksen hoito yli vuosisadan ajan. Umpilisäketulehduksen on aiemmin ajateltu johtavan aina umpilisäkkeen puhkeamiseen, mutta nykyään tunnistetaan erikseen lievä ja vaikea tautimuoto. Vaikea umpilisäketulehdus vaatii kiireellisen leikkaushoidon lukuun ottamatta umpilisäkkeen vieruskudoksen paisetta. Useat satunnaistetut tutkimukset ja meta-analyysit ovat osoittaneet, että lievempää muotoa voidaan turvallisesti ja tehokkaasti hoitaa suonensisäisten (i.v.) ja tablettimuotoisten (p.o.) antibioottien yhdistelmällä. Verrattaessa leikkaus- ja antibioottihoitoa toisiinsa tulee hoidon tehon lisäksi huomioida hoidon kustannukset ja potilaskohtaiset tekijät. Antibioottihoidon mahdollisuus korostaa lievän umpilisäketulehduksen oikean diagnoosin ja tautimuotojen erottamisen välttämättömyyttä. Tietokone-kuvantaminen (TT) on diagnostiikan kultainen standardi, mutta sen ongelmana on säderasitus. Tämä korostuu umpilisäketulehduksen yhteydessä, koska potilaat ovat pääasiassa nuoria aikuisia, minkä vuoksi on kehitetty matala-annoksisia TT-kuvantamistapoja.

Tämän tutkimuksen tavoitteena oli verrata leikkaus- ja antibioottihoidon kokonaiskustannuksia (Työ I) sekä potilaiden elämänlaatua ja tyytyväisyyttä (Työ III). Säderasituksen vähentämiseksi vertasimme matala-annoksista TT-kuvantamista standardiin TT-kuvantamiseen OPTICAP-tutkimuksessa (Työ II). APPAC II-tutkimuksessa vertasimme p.o. antibioottia i.v. ja p.o. antibiootin yhdistelmään antibioottihoidon optimoimiseksi (Työ IV). Oireenmukaisen hoidon mahdollisuutta arvioitiin suunnittelemalla lumekontrolloitu APPAC III -tutkimus (Työ V).

Antibioottihoidon kustannukset olivat leikkaushoitoa merkittävästi alhaisemmat eikä potilaiden elämänlaadussa ollut eroa, mutta leikatut potilaat olivat tyytyväisempiä saamaansa hoitoon. Matala-annoksisen TT:n diagnostinen tarkkuus vastasi standardia TT:tä merkittävästi alhaisemmalla säderasituksella. Lievän umpilisäketulehduksen hoidossa p.o. antibiootti oli kliinisesti yhtä tehokas kuin i.v. ja p.o. hoidon yhdistelmä.

AVAINSANAT: akuutti umpilisäketulehdus, antibiootti, elämänlaatu, kulut, lievä umpilisäketulehdus, umpilisäkkeen poisto, tietokonekuvantaminen

Table of Contents

Abbreviations

APPAC	APPendicitis ACuta
APR	Appendiceal perforation rate
BMI	Body mass index
COR	Cumulative Odds Ratio
$CTDI_{vol}$	Volume CT dose index
CRP	C-reactive protein
CT	Computed tomography
DNI	Delta neutrophil index
GALT	Gut-associated lymphoid tissue
IBD	Inflammatory bowel disease
IL-6	Interleukin-6
i.v.	Intravenous
LAMN	Low-grade appendiceal mucinous neoplasm
LRG	Leucine-rich-alpha-2-glycoprotein
MRI	Magnetic resonance imaging
NAR	Negative appendectomy rate
NLR	Neutrophil-to-lymphocyte ratio
NPV	Negative predictive value
OPTICAP	OPTImization of Computed tomography for acute APpendicitis
OR	Odds ratio
p.o.	Peroral
PPV	Positive predictive value
QOL	Quality of life
RLQ	Right lower quadrant
SD	Standard deviation
sIgA	Secretory immunoglobulin A
US	Ultrasound
WBC	White blood cell
95% CI	95% confidence interval

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Sippola S, Grönroos J, Tuominen R, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Hurme S, Salminen P. Economic evaluation of antibiotic therapy versus appendicectomy for the treatment of uncomplicated acute appendicitis from the APPAC randomized clinical trial. Br J Surg. 2017;104(10):1355-1361.

II Sippola S, Virtanen J, Tammilehto V, Grönroos J, Hurme S, Niiniviita H, Lietzén E, Salminen P. The Accuracy of Low-dose Computed Tomography Protocol in Patients with Suspected Acute Appendicitis: the OPTICAP Study. Ann Surg. 2020;271(2):332-338.

III Sippola S, Haijanen J, Viinikainen L, Grönroos J, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Hurme S, Mecklin J-P, Sand J, Jartti A, Salminen P. Quality of Life and Patient Satisfaction at 7-year Follow-up of Antibiotic Therapy vs Appendectomy for Uncomplicated Acute Appendicitis: A Secondary Analysis of a Randomized Clinical Trial. JAMA Surg. 2020;155(4):283-289.

IV Sippola S, Haijanen J, Grönroos J, Rautio T, Nordström P, Rantanen T, Pinta T, Ilves I, Mattila A, Rintala J, Löyttyniemi E, Hurme S, Tammilehto V, Marttila H, Meriläinen S, Laukkarinen J, Sävelä E-L, Savolainen H, Sippola T, Aarnio M, Paajanen H, Salminen P. Effect of Oral Moxifloxacin vs Intravenous Ertapenem Plus Oral Levofloxacin for Treatment of Uncomplicated Acute Appendicitis: The APPAC II Randomized Clinical Trial. JAMA 2021;325(4):353-362.

V Sippola S, Grönroos J, Sallinen V, Rautio T, Nordström P, Rantanen T, Hurme S, Leppäniemi A, Meriläinen S, Laukkarinen J, Savolainen H, Virtanen J, Salminen P. A randomised place-controlled double-blind multicentre trial comparing antibiotic therapy with placebo in the treatment of uncomplicated acute appendicitis: APPAC III trial study protocol. BMJ Open. 2018;8(11):e023623.

1 Introduction

Acute appendicitis is one of the leading causes behind emergency room visits, and appendectomy has been the indisputable treatment for acute appendicitis for over a century. More than 300 000 appendectomies are performed in the United States each year.[1] In Finland, an average of 7700 appendectomies are performed per year.[2] Appendectomy is a well-tolerated surgical procedure, however it is still major surgical intervention which can be associated with postoperative morbidity.[3,4] Acute appendicitis has been previously considered a single entity, but epidemiological and clinical studies have indicated that complicated and uncomplicated acute appendicitis follow different epidemiological trends, indicative of different pathology behind them.[5] This challenges the old paradigm that acute appendicitis always leads to perforation.

In 1886, Fitz published his paper that outlined the appendix as the most common source of right lower quadrant (RLQ) inflammatory disease and recommended the surgical removal of the appendix.[6] A few years later, McBurney contributed to the diagnosis of appendicitis by outlining the symptoms and clinical findings and the operative approach for the removal of the appendix.[7,8] In the times of Fitz and McBurney, i.e. in the pre-antibiotic era, early appendectomy reduced the risk of severe abdominal infection and associated mortality. In 1956, Coldrey reported promising results with low mortality of treating patients with acute appendicitis with antibiotics instead of appendectomy.[9] These results were lost in history until recent years and current intense research on treating uncomplicated acute appendicitis with nonoperative therapy.[10-14] Although antibiotic therapy is be inferior to appendectomy in terms of treatment success, it has been concluded a safe, efficient, and viable alternative to appendectomy in uncomplicated acute appendicitis, as there are multiple other factors to be taken into consideration when assessing all treatment options.[15-17]

The diagnosis of acute appendicitis is based on patient history, clinical signs and symptoms, laboratory tests, as well as imaging studies. Although acute appendicitis is one of the most common surgical emergencies, its diagnosis and especially differential diagnosis of appendicitis severity remains challenging. Imaging studies, especially the utilization of computed tomography (CT), has significantly aided in diagnostic accuracy and decreased the rate of negative appendectomies.[18,19] CT protocols are advantageous in relation to ultrasound and magnetic resonance imaging, but CT is associated with ionizing radiation and exposes the patient to radiation-related risks such as potential increase of life-time cancer risk. To address this concern, low-dose CT protocols have been developed to aid in making the accurate diagnosis while decreasing the radiation dose.[20] As antibiotic therapy is established as a safe and feasible alternative to appendectomy in the treatment of uncomplicated acute appendicitis, diagnostic accuracy is of great importance.

The aims of this study were to compare the overall societal and treatment costs of antibiotic therapy and appendectomy in the treatment of uncomplicated acute appendicitis in the randomized clinical APPAC trial (Study I), to compare the diagnostic accuracy of an optimized contrast-enhanced CT protocol to standard CT in patients with suspected acute appendicitis (Study II), to compare the long-term quality of life (QOL), and patient satisfaction after antibiotic therapy and appendectomy in the APPAC trial (Study III), to compare peroral (p.o.) monotherapy with intravenous (i.v.) followed by p.o. antibiotics in terms of treatment efficacy, post-intervention complications, and length of hospital stay (Study IV), and to plan a double-blinded randomized study protocol comparing i.v. followed by p.o. antibiotics with placebo in terms of treatment efficacy, post-intervention complications, length of hospital stay and appendicitis recurrence (Study V).

2 Review of the Literature

2.1 Anatomy and physiology of the appendix

The vermiform appendix is a relatively narrow, funneled-shape, and closed-end extension with a length of approximately 9 cm arising from the posteromedial border of the cecum on average 1.7 to 2.5 cm below the terminal part of the ileum.[21,22] The appendix is supplied by the appendiceal artery, which most commonly derives from the ileocolic artery, which in turn derives from the superior mesenteric artery. The appendix has a small mesentery, called the mesoappendix, which contains the appendiceal artery in its free border.[23] Sympathetic innervation to the appendix is provided through the celiac and superior mesenteric ganglia, while parasympathetic innervation is provided by the vagal nerve.

The position of the appendix varies between individuals with the position of the cecum, the most typical location in the right lower quadrant of the abdomen. This location, termed McBurney's point, is located one-third of the distance from the anterior superior iliac spine to the umbilicus. Additional locations include the upper left quadrant, the left anterior midline, and the lower midline.[23] The location can vary in cases of malrotation or maldescent of the cecum and more commonly with pregnancy due to the growth of the uterus.[21,24] Also, the position of the appendix varies between individuals with the most common position being an ascending appendix in the retrocecal recess (65%). The other alternative positions for the appendix are a descending appendix in the iliac fossa (31%), a tranverse appendix in the retrocecal recess (2%), an ascending paracecal and pre-ileal appendix (1%), and an ascending paracecal and post-ileal appendix (0.4%).[22]

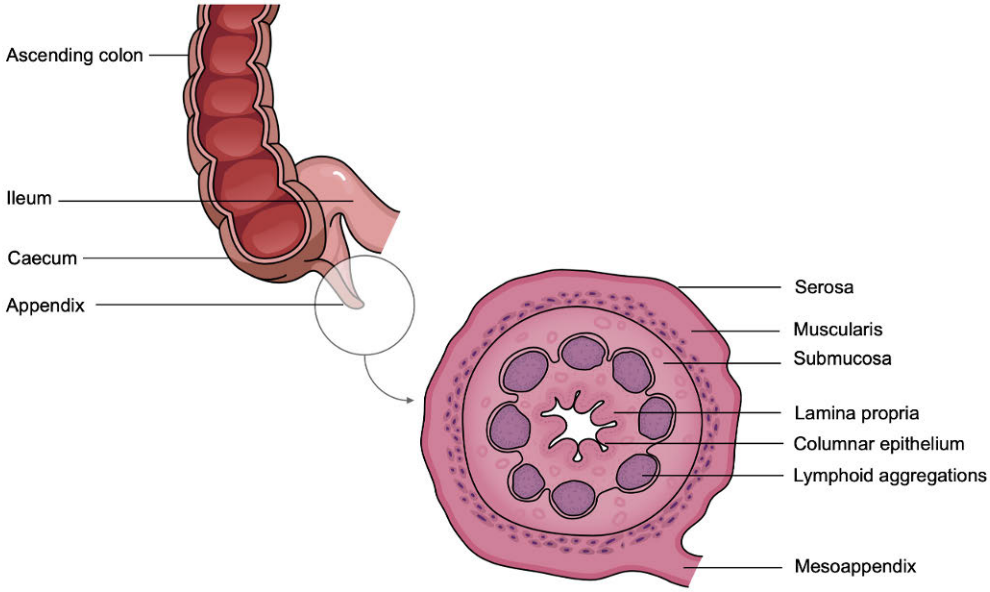

Figure 1. Cross-sectional structure of the appendix. Created by MindtheGraph.

The appendix was identified in humans more than 400 years ago, and until rather recently, it has been seen as mostly a rudimentary part of the intestine. Recent studies, however, have suggested its immunological importance for the development and preservation of the intestinal immune system. The appendix contains substantial amounts of gut-associated lymphoid tissue (GALT), and thus is has been proposed that as the appendix has characteristics of a well-developed lymphoid organ, it also has important immunological functions.[25-27] It has also been shown that such lymphoid tissue supports the growth of beneficial bacteria in the gut.[28] Proteins abundant in GALT, secretory immunoglobulin A (sIgA) and mucin, support the growth of biofilms, or adherent colonies of beneficial bacteria, whereas sIgA stimulates the agglutination of bacteria, and mucin binds the bacteria to the mucus layer.[29] These biofilms have been found in higher concentrations in the human appendix than any other part of the intestine.[27,28] The improved understanding of the immune system, GALT, and gut flora has led to the deduction of the human appendix serving as a "safe-house" for maintaining mutualistic gut bacteria.[23,28,30] It has been proposed that biofilm formation in the appendix, in addition to improving the survival of normal gut bacteria, also impairs the adherence of pathogens within the colon[28]. It is stipulated that an immunologically malfunctioning appendix and this interaction with gut microbiota might play a role in the etiology and onset of for example ulcerative colitis.[29,30]

2.2 History of acute appendicitis

"*The history of appendicitis includes examples of great resistance to changing concepts, brilliant but unaccepted early observations, emotional support for unsupportable views, the importance of timing, and, finally the development of a highly satisfactory solution*".[31]

-G. Rainey Williams, 1983

The first descriptions of the appendix date back to the late 15th and early 16th centuries, and although they clearly illustrate the anatomical structure of the appendix, they do not specifically describe it.[32] The first anatomical drawing is considered to be by Leonardo Da Vinci in 1492, but this work was not published until the 18th century. The physician-anatomist, Berengario Da Carpi, is credited for the first description of the anatomical structure of the appendix in 1521.[32] Later, in his work "De Humani Corporis Fabrica" (1543), Andrea Vesalius illustrated the appendix, although it was not described in the text as the appendix.[31] Later drawings and studies provided little additional information of the anatomy of the appendix.

In the early 18th century, Lorenz Heister performed an autopsy on an executed criminal and performed what is considered to be the first post-mortem dissection of the appendix. He gave an unequivocal description of a perforated appendix and speculated that the appendix might be the origin of RLQ inflammation.[33] Shortly after, Mestivier also described the perforation of the appendix by a pin and an abscess on autopsy, and in the next 100 years, several cases of appendicitis on autopsy were described. The conditions were termed as paracecal inflammation, typhilitis, and perityphilitis. Repeated observations of perforated and inflamed appendices enhanced the notion that the appendix could be the cause of inflammatory processes in the right lower quadrant.[34] The idea of the surgical removal of the appendix was proposed by Melier in 1827, but it is said that it was largely ignored at the time because of the influence of Baron Dupuytren, who did not believe the appendix to be the cause of RLQ inflammation.[34] The first recorded appendectomy was performed by Claudius Amyand in 1735 in a boy with a scrotal hernia containing a perforated appendix. Great advancements in surgery in the mid-1800s, general anesthesia and antiseptic techniques, made way for the consideration of appendectomy for appendicitis.[33] A great contribution to the debate of RLQ inflammation was by Reginald Fitz, in 1886, with his paper entitled "Perforating inflammation of the vermiform appendix; with special reference to its early diagnosis and treatment".[6] This paper greatly impacted the history of appendicitis as it emphasized the appendix as the source of most RLQ inflammatory disease, described the clinical symptoms related to appendiceal disease, and suggested surgical removal of the appendix. His perceptive correlation between clinical and pathological findings emerged as a clear concept, which he called appendicitis. After this, terminology became straightforward with terms such typhilitis and perityphilitis remaining in history. Charles McBurney significantly contributed to the diagnosis and treatment of appendicitis. In 1889, he outlined symptoms and clinical findings related to acute appendicitis, and especially the migration of pain to the eventual location one-third distance between the anterosuperior iliac spine and the umbilicus, "McBurney's Point".[7]

Operative techniques for appendectomy were not standardized, with midline or paramedian incisions being used. McBurney developed and published his right lower quadrant lateral muscle-splitting incision technique in 1894 and it became known as "McBurney's incision".[8] Interestingly, McBurney was not the first to describe the muscle-splitting technique, as Lewis McArthur is said to have described the same technique one month prior.[32] Surgeons rapidly accepted appendectomy for appendicitis. Open appendectomy became the standard treatment of appendicitis, technically similar to modern open surgery. With the recognition of the importance of fluid resuscitation and operating before peritoneal contamination, mortality after appendectomy started to decrease.[32] As surgical endoscopy began to emerge, also the method of appendectomy was affected. Kurt Semm, a German gynecologists and an early laparoscopist, performed the first laparoscopic appendectomy in 1980[35,36], but was harshly criticized and censored for his achievement.[37] The laparoscopic technique slowly gained popularity, and today laparoscopic appendectomy is the treatment of choice for surgery of appendicitis in Western countries.[38]

The more recent history of appendicitis research has focused on the possible role of antibiotics in treating acute appendicitis. The discovery of antibiotics followed the studies of Fitz and McBurney by 40 years when early appendectomy for appendicitis reduced this risk for uncontrollable abdominal infection and thus reduced mortality.[31] The development of antibiotics in the 1940's further reduced morbidity and mortality from appendicitis.[32] In 1956, Coldrey reported having treated patients with acute appendicitis with antibiotics gaining promising results of low mortality (0.2%) and low appendicitis recurrence (14.4%).[9] This pioneer study was deliberately ignored and lost in history until recently. During the last decade, the treatment of uncomplicated acute appendicitis with antibiotic therapy[11-14] or symptomatic therapy[39-41] has been under intense research.

2.3 Epidemiology of acute appendicitis

Appendicitis is a global disease which seems to vary with age, sex, race, geographical location, and time of year. In developed countries, acute appendicitis occurs at a rate of approximately 9–10 patients per 10 000 inhabitants per year.[42] In the United States, between 1970 and 1984, approximately 250 000 cases of acute appendicitis occurred and the incidence was 11 per 10 000 population.[1] The estimated lifetime risk is reported to be 7–8%[43], and more specifically, 8.6% for males and 6.7% for females.[1] Addiss et al[1] observed that the incidence is 1.4 times higher in males of all ages when compared to females of all ages. The highest incidences are found in males aged between 10 and 14 years, and in females aged between 15 and 19 years. The median age at diagnosis was 21 years. They found the overall trend in incidence of appendicitis to be decreasing. Buckius et al[44] studied the changes in the epidemiology of acute appendicitis in the United States between 1993 and 2008. The annual rate of appendicitis increased from 7.62 to 9.38 per 10 000 inhabitants between 1993 and 2008. Acute appendicitis was still more common in males, and the frequency was highest in the age group 10 to 19 years, although its occurrence in this group had decreased.[44] In Finland, the incidence of acute appendicitis was 9.8 per 10 000 inhabitants in 2007; having declined 32% over the previous 30 years.[45] The lifetime risk of acute appendicitis in Finland is 7%, and approximately 7700 appendectomies are performed annually.[46] The incidence of acute appendicitis does not differ significantly between the Scandinavian countries.[47,48]

Incidence of appendicitis is higher in developed countries than in non-developed countries, and it is 1.4 to 1.6 times higher in whites than in non-whites.[1] Between 1993 and 2008 in the United States, the frequency increased in Hispanics, Asians, and Native Americans, while it decreased among Whites and Blacks.[44] The incidence of appendicitis seems to be rather stable in Western countries, but rising in newly industrialized countries, especially in Asia, the Middle East and Southern America.[49,50] The risk of perforating appendicitis was found to be lower in Hispanics and similar in blacks and Asians as compared to whites.[51] Appendicitis has been rare in economically less-developed countries, but increases with the adoption of westerns standards of living and economic development.[52]

Interestingly, also seasonal variation in the incidence of appendicitis has been observed in several studies.[1,53] Appendicitis has a low incidence during winter months with a sharp increase during the summer. This trend is consistent in the Finnish population as well.[45] The reasons for this trend are unclear but have been widely speculated from the effect of dehydration, the effect of infections or allergens on GALT, diet, less bowel movements, to humidity or changes in atmospheric pressure.

Epidemiologic studies have illustrated that perforating appendicitis and non-perforating appendicitis behave differently suggesting that they are two different forms of the condition.[3,5,47] The rate of nonperforated appendicitis decreased between 1970 and 1995, but subsequently began to increase, whereas the rate of perforated appendicitis steadily increased during the same period. The increase of nonperforated cases parallels increased utilization of computed tomography (CT) imaging and the use of laparoscopic appendectomy.[5] While the general rate of acute appendicitis is on the rise, Buckius et al[44] found that the ratio of simple to complex acute appendicitis has remained around 3:1, however this varies at the extreme ends of age groups. In patients younger than 10 years old, about 40% of cased are complex appendicitis. The number of complex cases increased with age; in the over 50 years of age group, complex cases account for about 50% of cases of appendicitis. The differing epidemiological trends propose that non-perforating and perforating appendicitis have different pathophysiological mechanisms and are different forms of appendicitis.[5]

Epidemiological observations over geographical zones and different time points indicate that acute appendicitis is influenced by multifactorial environmental factors. Acute appendicitis seems to be dependent on the industrialization of society.[49] Acute appendicitis is less commonly seen in communities of poor hygiene and its incidence has increased as hygiene and cleanliness have improved in the Western world.[54] A higher incidence of acute appendicitis is also seen with diets low in fiber content and with higher socioeconomic status.[55] Golz et al found a lower incidence of uncomplicated acute appendicitis to strongly associate with higher socioeconomic status.[56] They also demonstrated that the incidence of acute appendicitis was not distributed randomly in terms of geography when age and sex were standardized, and this trend was more clear with uncomplicated acute appendicitis. Air pollution has been linked to the increase in incidence of acute appendicitis, and especially perforating appendicitis, suggesting that it may play a role in the pathogenesis of this form.[57] Smoking has also been shown to increase the risk of appendectomy, especially in females, as compared to nonsmokers.[58] The epidemiology of acute appendicitis is clearly complex and multifactorial, and further research is needed to understand the epidemiological trends.

2.4 Etiology, pathogenesis, and pathophysiology of acute appendicitis

The etiology and pathophysiology of acute appendicitis are not entirely known. The concepts of pathogenesis originate from 1886 from the histopathological analyses by Fitz[6] and the observation that the appendix developed mucosal ulcerations that seemed to cause inflammation, gangrene and subsequent perforation. In describing the relationship between acute appendicitis and right lower quadrant sepsis, Fitz assumed that acute appendicitis would always progress to perforation. Conversely, Fitz also noted that in one-third of patients undergoing autopsy, the appendix showed signs of previous inflammation, hinting at the possibility of spontaneous resolution of acute appendicitis.[6]

The most commonly accepted theory behind the pathogenesis of acute appendicitis is that the obstruction of the appendiceal lumen eventually results in infection.[59] The obstruction may be caused by for example an appendicolith or fecalith, lymphoid hyperplasia, tumor, parasites and foreign bodies. The luminal diameter of the appendix is small in relation to its length, and it is thought that this configuration predisposes to closed-loop obstruction. The appendix secretes mucus, which accumulates in the obstructed lumen, causing the intraluminal pressure within the appendix to rise. Virulent bacteria convert the accumulated mucus into pus. This in turn results in the obstruction of the lymphatic drainage, which causes edema of the appendix. Continued luminal secretion of mucus and increasing edema further increase the intraluminal pressure and the subsequent tissue pressure, resulting in venous obstruction and ischemia of the appendix. This allows for invasion of the appendiceal wall by bacteria; suppurative appendicitis follows. As the process continues in the appendiceal wall, arterial and venous thromboses occur, leading to gangrenous appendicitis. Small infarcts in the appendiceal wall allow for leakage of bacteria and contamination into the peritoneal cavity. In the final stage of the disease, accumulated pus and feces spill through a gangrenous infarct in the appendiceal wall leading to perforated acute appendicitis.[60] If the spillage is contained, a periappendical abscess forms, and if not, it leads to diffuse peritonitis.

The theory of obstruction of the appendiceal lumen by appendicolith or lymphoid hyperplasia was supported by earlier studies[59], but more modern studies contradict this theory. In 1981, Butler observed that the clinical course of appendicitis may vary with the notion that appendicitis appears to result from mucosal injury but not all appendixes show clear indication of lumen obstruction.[61] He continued with the idea that perforation is the consequence of transmural necrosis which is related to prolonged disease process rather than the end result of lumen obstruction.

It has been thought that lymphoid hyperplasia is the more common reason for obstruction in younger patients, while appendicoliths are more usual in the older patients. However, a study found appendicoliths to be more frequent in children with a rate of 56% of perforated and 23% of nonperforated cases of appendicitis, as compared to 28% of perforated and 12% of nonperforated cases in adults.[62] Appendicoliths have also been observed as incidental findings[63] but surprisingly uncommonly in resected appendixes.[64] Singh et al found appendicoliths in 3– 18% of surgically removed appendixes.[62] A large American study including 1522 patients found appendicoliths in 27% of the patients on imaging.[65] Appendicoliths seem to be more prevalent in developed countries, suggesting that low fiber diets lead to appendicolith formation, which then might predispose to acute appendicitis. Appendicoliths were found on incidental palpation in 32% and with appendicitis in 52% of study patients in a Canadian population, while the corresponding numbers were 4% and 23% in a South African population.[66] Lymphoid hyperplasia has also been observed to be surprisingly uncommon, with only 0.8% having residual histological evidence of it.[67]

The role of infectious agents in the pathogenesis of acute appendicitis remains unclear. Bacterial infections, such as yersinia species, bacteroides species, and campylobacter species, may cause appendicitis or mimic the symptoms, with or without simultaneous involvement of the surrounding bowel. However, the infectious agent is often determined only after the removal of the appendix. Bacteria may be important pathogens of acute appendicitis and play a role in its complications, but their specific role is not known.[68] In 1938, William Altemeier described the polymicrobial nature of appendicitis, and this together with the concept of bacterial synergy advanced the understanding of mixed intra-abdominal infections, especially appendicitis.[33,69] Aerobic infections are common in early appendicitis, while mixed infections of aerobes and anaerobes are predominant in later cases of the disease.[70] E. coli and Bacteroides fragilis are the most common findings in removed inflamed appendixes.[42] No correlation has been found between appendicitis and the incidence of blood cultures positive for bacteria.[71]

The correlation of viral infections and acute appendicitis have also been studied through epidemiology, and although the examined viral infections did not have similar seasonal peak incidences, they did have similar year-to-year incidences suggesting the possibility of a viral etiology for appendicitis.[72] Fungal infections are rare. Parasites have been found in the lumen of the appendix in both inflamed and normal appendixes, but their possible role remains uncertain.[68]

Appendicitis caused by obstruction or perforation by a foreign object was quite common around the turn of the 20th century. Nowadays, it is very rare with an estimated incidence of 5 per 10 000 appendectomies.[73] The risk of appendiceal tumor with acute appendicitis is also fairly rare, varying from 0.6% to 3%.[74-76]

Epidemiological studies suggest the nonperforated and perforated acute appendicitis have different pathophysiology and epidemiology, and today it is generally accepted that acute appendicitis does not consistently progress to perforation.[5,47] As Livingston et al concluded, uncomplicated and complicated acute appendicitis seem to be different diseases with different natural histories.[3,5]

2.5 Classification of acute appendicitis

2.5.1 Uncomplicated acute appendicitis

Several names are used for the more common, less severe form of acute appendicitis: non-perforated acute appendicitis, suppurative acute appendicitis, simple acute appendicitis, and uncomplicated acute appendicitis. The latter will be used throughout this thesis. Depending on the definition, uncomplicated acute appendicitis is estimated to comprise 75–80% of acute appendicitis cases.[5] Uncomplicated acute appendicitis can be defined as acute inflammation present in either a segment of or in the entire appendix. It involves the infiltration of neutrophils transmurally into muscularis propria and is commonly circumferential. Additionally, inflammation and usually ulcerations are seen in the mucosa on histopathological examination. Other common microscopic findings related to uncomplicated acute appendicitis are edema, microabscesses of the appendiceal wall, vascular thromboses, and fibrinopurulent serositis. It is hypothesized that the inflammation may be related to mucin extravasation into the wall.[77] Macroscopic findings of uncomplicated acute appendicitis include congestion, increased diameter, color change, pus and exudate.[42] According to one theory, this uncomplicated form, which can present as phlegmonous or advanced inflammation (without gangrene or perforation), does not proceed to perforation.[42]

The classification of gangrenous appendicitis into either uncomplicated or complicated acute appendicitis is not uniform. Gangrenous appendicitis is characterized by necrosis of the appendiceal wall, which is thought to develop as a result of vascular thromboses seen in the uncomplicated form. In histopathological analyses, transmural inflammation with areas of necrosis and extensive mucosal ulceration are seen.[78] As the appendiceal wall becomes necrotic, perforation eventually follows leading to either diffuse peritonitis, pelvic phlegmon, or a restricted periappendicular abscess.[42]

The management of uncomplicated acute appendicitis has been under intense research in the past years. The idea of a spontaneously resolving acute appendicitis was born by Fitz with his observation of appendixes showing signs of previous inflammation at autopsy in a third of his patients.[6] In histological analysis, inflammatory infiltrate of cell clusters consisting of mainly lymphocytes and eosinophils, scattered throughout the muscularis propria as well as granulation tissue, are signs of resolution of appendicitis.[79] The true incidence of spontaneously resolving appendicitis is unknown. In their retrospective study, Kirshenbaum et al included patients with clinical acute appendicitis confirmed by CT whose symptoms resolved within 1 to 2 days after onset. Of the 69 patients with CT confirmed acute appendicitis, 12 (17%) did not appendicitis did not undergo surgery and showed signs of resolution either clinically or on CT imaging.[80] Spontaneously resolving appendicitis is estimated to occur in 7% of cases of acute appendicitis with an overall recurrence rate ranging from 4% to 25%.[81] It has been suggested that the increase in CT imaging for suspected acute appendicitis has led to an increase in detection of acute appendicitis and unnecessary appendectomy in patients with spontaneously resolving appendicitis, who may not need anything but symptomatic therapy. The number of appendectomies for complicated acute appendicitis remained the same, but the number of appendectomies for uncomplicated acute appendicitis increased with the introduction of CT.[82,83] Park et al conducted a randomized trial of antibiotic therapy and symptomatic treatment for uncomplicated acute appendicitis, questioning the role of antibiotics in the management of uncomplicated appendicitis, and suggesting spontaneous resolution. They found no difference in treatment failure between the two groups, however, their study was unblinded and the study groups were very selective, facilitating possible selection bias.[41]

2.5.2 Complicated acute appendicitis

Acute appendicitis is complicated in approximately 20% to 30% of cases.[5] The definition of complicated acute appendicitis also varies, but perforation is a constant component. In addition, the definition of complicated acute appendicitis may include the following components: gangrenous unperforated appendicitis, the presence of a appendicolith, the presence of pus, purulent peritonitis, and abscess.[84] In this text, complicated acute appendicitis is defined as acute appendicitis with perforation, abscess, appendicolith and tumor.[14]

Perforation is a clear feature complicating acute appendicitis. Perforation increases the risk of wound infection, abscess, and sepsis, and morbidity.[85] Factors affecting perforation have been studied. The effect of age of the patient is not clear. Kraemer et al illustrated higher perforation rates in elderly patients as compared to younger patients (35% compared with 13%)[86], but another study found the same rate of perforation in elderly and young patients[87]. The incidence rate of perforated appendicitis is rather stable regardless of age or indication for surgery. The proportion of perforations might result mostly from variation in the incidence rate of the subtype of non-perforating appendicitis.[88] The influence of delay on perforation is debated. Perforation is thought to be a pre-hospital event with delay taking place already before admission to the hospital, and without association to post-admission delay.[88-91]

Periappendiceal abscesses, or inflammatory masses containing pus, form following perforation when the leakage is contained by the patients' own defense mechanisms, such as omental coverage. They often present as a palpable mass several days after symptom onset.[92] They are found in 3–10% of adult patients with acute appendicitis.[93,94] Periappendiceal masses are commonly managed with antibiotics combined with drainage, if necessary. However, a Finnish study found laparoscopic surgery to be a safe and feasible alternative to conservative treatment for appendiceal abscesses when performed by an experienced surgeon.[95] The risk of recurrence after conservatively managed periappendiceal abscess varies from 5% to 26%.[75,96] In patients with interval appendectomy following treatment for previous periappendiceal abscess appendiceal tumor rates are reported to be clearly higher than the risk of appendiceal tumor underlying acute appendicitis.[76,97,98] A Finnish randomized study found an overall neoplasm rate of 20% after interval appendectomy for periappendiceal abscess, and the study was prematurely terminated.[99] In patients with periappendiceal abscess, appendicoliths were found in 24% of cases.[100]

Fecalith, appendicolith, coprolith, stercolith, and appendiceal calculi all refer to the same concept of fecal concrement found in the lumen of the appendix.[101] These are thought to commonly cause mechanical obstruction of the appendiceal lumen, but they have also been found incidentally.[63] In children, appendicoliths have been associated with higher rates of perforation and earlier perforations[102] and in adults, they have been linked to complicated appendicitis[103]. The classification of presence of appendicolith as complicated appendicitis is not completely clear but has gained attention through studies on nonoperative management for acute appendicitis. Vons et al noted that the presence of an appendicolith on computed tomography (CT) imaging was associated with complicated acute appendicitis and the only risk factor for failure of antibiotic therapy in acute appendicitis. Once they excluded patients with appendicoliths on imaging, there was no significant difference between the appendectomy and antibiotic groups in treatment success.[13] A recent large American trial also found appendicoliths to be related to a higher risk for appendectomy (41%) than those without an appendicolith (25%) after nonoperative management of acute appendicitis.[65] Studies in pediatric populations have corroborated this finding with one study finding failure rates of antibiotic therapy in 24% of patients without appendicoliths and 50% of patients with appendicoliths.[104] Another study was terminated because of an unacceptably high failure rate of 60% in children having an acute appendicitis with an appendicolith.[105] On the other hand, Talishinskiy et al found appendicoliths to have no significance in predicting antibiotic treatment failure in children.[106] Specific characteristics of appendicoliths associated with acute appendicitis are multiple appendicoliths and appendicoliths with a diameter greater than 5 mm.[107] One study found significantly different histopathological characteristics between verified cases of uncomplicated acute appendicitis and acute appendicitis complicated by appendicolith.[108]

Histopathological traits of the normal appendix and the two forms of acute appendicitis are outlined in Table 1.

Table 1. Histopathological characteristics indicative of uncomplicated and complicated acute appendicitis.

Normal appendix	**Uncomplicated acute appendicitis**	**Complicated acute appendicitis**
No abnormalities	Transmural inflammation, ulceration or thrombosis	Transmural inflammation and necrosis (gangrenous)
Only luminal neutrophils	Possible extramural pus	Transmural inflammation and possible visible perforation (perforated)
Mucosal or submucosal neutrophils		Transmural inflammation with pus and possibly visible perforation (abscess)
Possible ulceration		

Adapted from Carr 2000, Bhangu et al 2015.

2.5.2.1 Appendiceal neoplasms

Overall, appendiceal tumors with acute appendicitis are rather rare. The risk of underlying appendiceal neoplasm in acute appendicitis varies from 0.6% to 3%.[74-76] The tumors are usually found on histopathological examination of the removed appendix.[109] The percentage of malignant tumors ranges from 28% to 50% of all neoplasias in appendix[110,111]. Appendiceal neoplasms can roughly be divided into epithelial, for example adenomas or adenocarcinomas, or nonepithelial neoplasms, for example neuroendocrine tumors, lymphoma and gastrointestinal stromal tumors. The epithelial group is further divided into mucinous and non-mucinous tumors. Most noninvasive epithelial lesions are categorized as low-grade appendiceal mucinous neoplasms (LAMN). Adenocarcinomas can be mucinous or non-mucinous. Goblet cell carcinomas are a kind of adenocarcinoma with some features similar to neuroendocrine tumors. Appendiceal neoplasms can perforate and spread in the peritoneal cavity. Pseudomyxoma peritonei is a strictly clinical expression to describe the spread and ample mucin production of a mucinous neoplasm on the peritoneum.[112]

Appendiceal tumors are more often related to complicated acute appendicitis and especially periappendicular abscesses. One population-based study found the risk of having an appendiceal tumor to be significantly higher in patients with complicated acute appendicitis (3.2%) than in patients with uncomplicated acute appendicitis (0.9%).[113] They found a risk of having an appendiceal tumor to be even higher in a subgroup of patients with periappendiceal abscess (5.0%), and concluded that the risk of a missed appendiceal tumor due to antibiotic treatment for uncomplicated acute appendicitis was low. However, the risk of missed malignancy must be considered when considering conservative treatment for uncomplicated acute appendicitis.

2.6 Diagnosis of acute appendicitis

2.6.1 Clinical symptoms, physical examination, and laboratory tests

Despite acute appendicitis being so common, its diagnosis remains a challenge. The overall accuracy for diagnosing acute appendicitis clinically is about 80%.[114] Traditionally, acute appendicitis has been diagnosed based on clinical symptoms and findings on physical examination. The use of laboratory markers aided in diagnosis and are now a key part of patient workup. The use of imaging studies has increased, and they are now widely used to aid in the diagnosis of acute appendicitis.

2.6.1.1 Clinical symptoms and physical examination

Patient history is important in the diagnosis of acute appendicitis.[115] Acute appendicitis presents with typical clinical symptoms including abdominal pain, pain migration, nausea, vomiting and pain aggravation by movement. Patient details of age and sex as well disease history in terms of symptom duration and fever history are noted. In classic presentation, the pain is periumbilical or diffuse at first, followed by migration to McBurney's point in the RLQ of the abdomen.[7,116] However, this classic presentation occurs in only 50-60% of patients.[114] Localizing symptoms might be absent depending on the location of the appendix. If present, nausea and/or vomiting follow the onset of pain. Fever and loss of appetite develop as acute appendicitis progresses from a localized to a systemic inflammatory process.[117]

Physical examination is an essential part of the clinical assessment of the patient. Findings on physical examination include abdominal tenderness, rebound tenderness, muscular guarding, indirect tenderness, localization of tenderness, and sign of peritoneal irritation.[118] Tenderness at McBurney's point on abdominal palpation is still a key finding.[115] Other signs suggestive of acute appendicitis are pain with the flexion of the right hip against resistance (Psoas sign), pain in the RLQ with palpation of the left lower quadrant (Rovsing sign), and pain with the flexion of the right knee and internal rotation of the hip (Obturator sign).[114] Signs of peritoneal irritation (guarding, abdominal rigidity, and rebound tenderness) should also be noted[119].

2.6.1.2 Laboratory tests

Patients suspected of having an acute abdomen usually undergo laboratory workup including assessment of hemoglobin, white blood cell count (WBC counte), C-reactive protein (CRP) electrolytes, creatinine, and a pregnancy test for fertile females.

Inflammatory laboratory markers add important diagnostic information and should be included in the workup of patients with suspected acute appendicitis.[120] No inflammatory marker alone has sufficient diagnostic utility but are useful when used in combination. WBC count is the most used marker in the diagnosis of acute appendicitis, but it is also commonly elevated in other inflammatory conditions and thus is not a particular marker for acute appendicitis. Acute appendicitis is likely at a WBC count of > 15 x 10^{-9} cells/L and unlikely at a WBC count of < 8 x 10^{-9} cells /L.[120] WBC count alone is not suitable to predict acute appendicitis.[121,122] WBC count is considered a better marker for diagnosing uncomplicated acute appendicitis than CRP.[123] CRP is acute phase protein, which usually rises 8-12 h after the beginning of an inflammatory process and peaks around 24-48 h. Different CRP cutoff values on the first three days after symptom onset could serve as useful predictors in the diagnosis of acute appendicitis.[124] Elevated CRP is not considered a very good indicator for uncomplicated or early acute appendicitis but is a strong marker for complicated or advanced disease; and it can aid in diagnosing acute appendicitis.[124,125] One study found a sensitivity of 82% and specificity of 72% for using WBC count and CRP together in diagnosing acute appendicitis.[126] When WBC count and CRP are both normal, acute appendicitis is highly unlikely.[123] However, Atema et al concluded that no WBC count or CRP level can be used to confirm or exclude acute appendicitis when symptom duration is five days or less.[127] These are the most commonly used markers in Finland.

Neutrophil count reflects active and continuing inflammation[128] and higher neutrophil counts have been observed in patients with uncomplicated and complicated acute appendicitis as compared to negative appendectomy patients.[122] Further, the neutrophil-to-lymphocyte ratio (NLR), has been shown to be significantly elevated in patients with appendicitis compared to those without appendicitis as well as higher in patients with complicated acute appendicitis than in patients with the uncomplicated form.[128] The delta neutrophil index (DNI), which measures the fraction of immature granulocytes in blood, has been proposed as a new inflammatory marker in the diagnosis of acute appendicitis. One study found it helpful in the more accurate diagnosis of acute appendicitis as well as an aid in differentiating between uncomplicated and complicated acute appendicitis.[129]

Other markers for acute appendicitis have been widely studied. The events in the pathogenesis of acute appendicitis result in bacteria being released into the circulatory system and traveling to the hepatic parenchyma through the portal venous system. This in turn leads to elevated levels of bilirubin and other inflammatory markers.[130] Infection and inflammation can also cause coagulopathy.[131] Hyperbilirubinemia has been shown to indicate gangrene or perforation.[130,132] Akai et al found that hyperbilirubinemia in conjunction with increased CRP and fever were useful predictors of acute appendicitis severity, especially in patients younger than 65 years. One study found that hyperbilirubinemia had higher specificity than WBC count and CRP in patients with appendicitis.[133] On the other hand, Muller et al found elevated bilirubin levels to have limited diagnostic accuracy and add only little to information from WBC count and CRP in diagnosing non-perforated or perforated acute appendicitis.[134] Hyperbilirubinemia could be useful combined together with other laboratory markers, but alone it is not sensitive enough.[135] Plasma calprotectin has also been observed to be elevated in adult and pediatric acute appendicitis patients, but further studies are needed to optimize its use both alone and combined with other markers.[136,137] Procalcitonin was found to have little value in the diagnosis of acute appendicitis, but a higher diagnostic value in predicting complicated acute appendicitis.[138] Li et al proposed that fibrinogen could be a marker for excluding complicated acute appendicitis after finding that in patients with acute appendicitis endotoxemia activates the extrinsic coagulation pathway.[139]

Increased accuracy in diagnosis of acute appendicitis has been searched for in novel inflammatory markers such as cytokines and leukocyte adhesion molecules. Interleukin-6 (IL-6) has been shown to have higher sensitivity, specificity and diagnostic value than WBC count and CRP, but any single marker alone has not significantly improved the diagnosis of acute appendicitis.[140] Andersson et al also concluded that after investigating six new inflammatory markers, diagnostic performance in acute appendicitis was not further improved.[141]

Inflammation is a significant cause of abnormal findings on urinalysis; its use in diagnosing acute appendicitis has been studied in the diagnosis of acute appendicitis, especially in children. Leucine-rich-alpha-2-glycoprotein (LRG) is a promising urine marker for identifying acute appendicitis, as it is significantly elevated in patients with acute appendicitis as compared to those without.[142,143] Elevated levels of LRG also seem to correlate with the histological severity of acute appendicitis. One study found that positive ketone bodies and nitrate in urine were significant in predicting perforated acute appendicitis in children.[144]

Individual clinical findings and laboratory markers have limited diagnostic value, but when used in combinations their value is significantly increased. The combination of history of pain migration, clinical signs of peritoneal irritation and inflammatory laboratory markers give important diagnostic information and should be included in the diagnostic workup.[118]

2.6.1.3 Scoring systems

Different scorings systems have been created to aid in the diagnosis of acute appendicitis by combining different symptoms, clinical findings and laboratory values to evaluate the probability of acute appendicitis. Clinical scoring systems aim to categorize patients into low, intermediate and high-risk patients and direct further investigations.

The earliest score, the Alvarado score, aimed at differentiating between appendicitis and other causes of abdominal pain by assessing nausea/vomiting, anorexia, pain in RLQ, migration of pain, rebound tenderness/muscular guarding, body temperature >37.5°C, leukocytosis shift and WBC count.[145] It was created based on a review of patients who had been operated on based on suspected appendicitis. The Alvarado score has been validated in several populations. The diagnostic performance in terms of sensitivity and specificity have been reported to vary between around 81% and 76%, respectively.[146,147]

The Acute Inflammatory Response (AIR) score included variables to take into consideration the inflammatory response and aimed to decrease the need for imaging and laparoscopy. It includes vomiting, pain in RLQ, rebound tenderness/muscular tenderness, body temperature >38.5°C, polymorphonuclear leucocytes, WBC count, and CRP. It was created based on a retrospective analysis of patients with sudden-onset non-traumatic abdominal pain. The AIR score has been shown to outperform the Alvarado score in comparative studies.[147]

The New Adult Appendicitis Score aimed at reducing the need for imaging studies. It includes pain in RLQ, pain relocation, RLQ tenderness, guarding, blood leucocyte count, proportion of neutrophils, CRP if less than 24 hours from symptom onset, and CRP if over 24 hours from symptom onset.[148] It was created based on a prospective population of patients with sudden-onset non-traumatic abdominal pain. Patients with under 10 points have a low probability of appendicitis and can be discharged, patients with 11-15 points have an intermediate probability of appendicitis and are recommended to undergo diagnostic imaging, and patients with over 16 points have a high probability of appendicitis and laparoscopy is recommended. The diagnostic performance of this score in terms of sensitivity and specificity in patients with more than 11 points has been reported to be 95% and 60%, respectively.[148]

2.6.2 Diagnostic imaging

2.6.2.1 Ultrasound

The graded compression technique with ultrasonography (US) in the diagnosis of acute appendicitis was introduced by Puylaert in 1986.[149] The graded compression displaces normal or gas-containing bowel loops out of the way or compresses them allowing for the visualization of the non-compressible inflamed appendix. Characteristics of an acutely inflamed appendix on ultrasound include non-compressibility, thickened appendix >6 mm, periappendiceal fluid, local sonopalpation tenderness over the appendix, hyperechoic, inflamed, periappendiceal fat, mural hyperemia, and possible appendicolith.[114,150,151] In gangrenous appendicitis, loss of definition of the appendiceal wall may be seen. Abscess formation is seen as an actual fluid component. Signs suggesting perforated appendicitis are no visualization of the distended appendix with US and gas bubbles within a collection.[114] An appendix greater than 6 mm under compression on US is the most accurate single characteristic of acute appenedicitis.[152] Two or more characteristics accurately identify a true positive diagnosis of acute appendicitis.[150,153] Especially in pediatric patients, lymphoid hyperplasia can be mistaken as acute appendicitis as it similarly presents a slightly thickened (6-8 mm) and non-compressible appendix.[150]

Imaging modalities have been widely compared in terms of their advantages and disadvantages. The negative appendectomy rate (NAR) represents the share of removed appendixes in which no histopathological signs of inflammation could be detected, and it is used to evaluate diagnostic performance and quality of treatment. Negative appendectomies are costly and include unnecessary risks for the patient.[154] The NAR varies with gender and age but the aimed NAR threshold is under 10%.[155,156] NAR based on clinical examination only was reported to be 20%.[18] NARs after US imaging vary from 6–9% [154,157] CT imaging has led to a greater reduction in NAR[19] and is considered better performing in terms of diagnostic accuracy.[158] US has been reported to have 68–88% sensitivity and 78–100% specificity in diagnosing acute appendicitis.[159-163] A meta-analysis found US to have a pooled sensitivity of 83% and specificity of 93%, and these to be lower than for CT imaging, but concluded that the use of US should be considered from a safety perspective especially in children.[164]

US imaging is considered advantageous because it is a rapid and noninvasive technique, results in lower costs, does not require contrast agent, and does not utilize ionizing radiation.[114,165] It can also be performed bedside. On the other hand, US has been criticized for being user dependent, depending on patient characteristics, and resulting in a high number of inconclusive cases. Patient characteristics that may limit US performance include body mass index, anatomical position of the appendix and overlaying bowel gas.[121] US may be useful especially in patients with a BMI under 22.[166] Keyzer et al found that although there was no significant difference in diagnostic performance in terms of sensitivity, specificity, PPV or NPV between US and CT, clearly more inconclusive results were obtained from US studies.[167] One study reported US to result in inconclusive or negative findings in 47% of patients.[168] Inconclusive or negative US results do not rule out appendicitis and further imaging with CT is needed to reach a diagnosis.[169] A further limitation of US is its usability in diagnosing perforated cases of acute appendicitis because a non-compressible appendix may be visualized in as 38%–55% of patients.[114]

The meta-analysis by Giljaca et al concluded that US should not be included in the general diagnostic pathway of acute appendicitis as its sensitivity and specificity are not greater than that of clinical examination or validated clinical scores.[170] Still, US is a safe and generally effective imaging modality, and it should be considered as the first-line imaging modality especially in patient, such as children and pregnant women, in which the radiation dose should be minimized.[162,164,171]

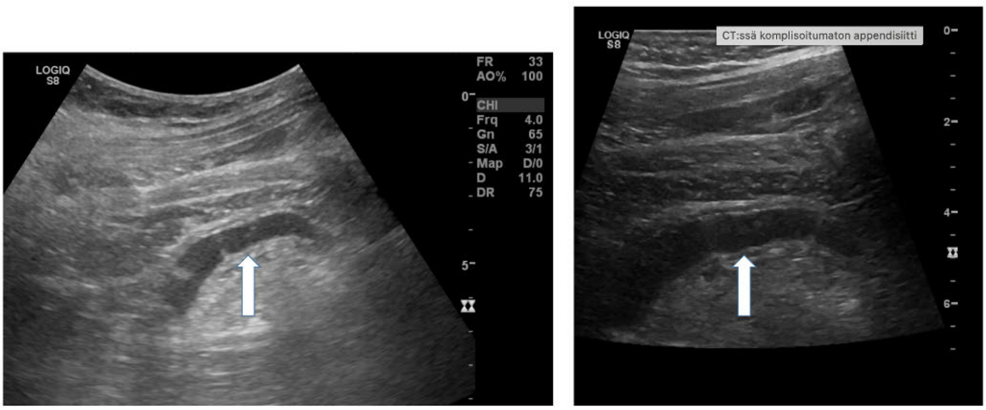

Figure 2. Ultrasound images of uncomplicated acute appendicitis. A noncompressible distended appendix is seen.

2.6.2.2 Computed tomography

Early studies describing CT in the diagnosis of acute appendicitis were published in the 1980s focusing on patients with atypical presentations for diagnosis confirmation.[172-174] With the intent of lowering the NAR, preoperative CT imaging has been developed and its utilization has widely increased.[18,175] Nowadays, CT is the can be considered the gold standard for acute appendicitis imaging. Key CT findings for acute appendicitis can be grouped into three main groups: 1) appendiceal change, 2) cecal changes, and 3) inflammatory changes in the RLQ. Appendiceal changes include appendiceal thickening over 6 mm (Figure 3), appendiceal wall thickening over 3 mm, appendiceal wall hyperenhancement, and intramural gas. Appendicoliths may be seen, although they are not a diagnostic criterion on their own. Cecal findings include cecal apical thickening, the cecal bar sign, and the arrowhead sign (the latter two only apply to patients receiving enteric contrast). Inflammatory changes in the RLQ suggestive of acute appendicitis on CT comprise of periappendiceal fat stranding, thickening of the mesoappendix, extraluminal fluid, phlegmon, abscess, minor ileocecal lymphadenopathy, and inflammatory thickening of adjacent bowel.[176] A statistical analysis of CT findings found appendiceal thickening, appendiceal wall thickening, periappendiceal fat stranding, and appendiceal wall enhancement to be more indicative of acute appendicitis than other findings.[177] However, several alternative conditions can mimic these findings making the differential diagnosis challenging. Such conditions are mesenteric adenitis, mesenteric panniculitis, epiploic appendagitis, infectious terminal ileitis, and Crohn's disease among others.[176] The single most specific finding on CT with the highest sensitivity is appendiceal thickening over 6 mm, together with periappendiceal fat stranding, was present in 93% of appendicitis cases.[178] Findings suggestive of complicated acute appendicitis are extraluminal or intraluminal air, extraluminal appendicolith, abscess, phlegmon, ascites, ileus, periappendiceal fluid collection, and a defect in the enhanced appendiceal wall.[179-181] CT has demonstrated the highest ability to discriminate between uncomplicated and complicated acute appendicitis when compared to other imaging modalities.[181] Findings suggestive of uncomplicated and complicated acute appendicitis are summarized in Table 2.

Table 2. CT findings indicative of uncomplicated and complicated acute appendicitis.

Uncomplicated acute appendicitis	**Complicated acute appendicitis**
Appendiceal diameter over 6 mm	Defect in the enhanced appendiceal wall
Appendiceal wall thickening over 3 mm	Periappendiceal abscess
Abnormal contrast enhancement of the appendiceal wall	Extraluminal air
Inflammatory edema	Appendicolith (intra- or extraluminal)
	Periappendiceal fat stranding
	Periappendiceal fluid
	Acute inflammation of the appendix with tumor

Adapted from Kim et al 2019, Kim et al 2018, Pinto Leite et al 2003.

Figure 3. CT image of uncomplicated acute appendicitis. An appendix with a diameter of 8.5 mm is shown.

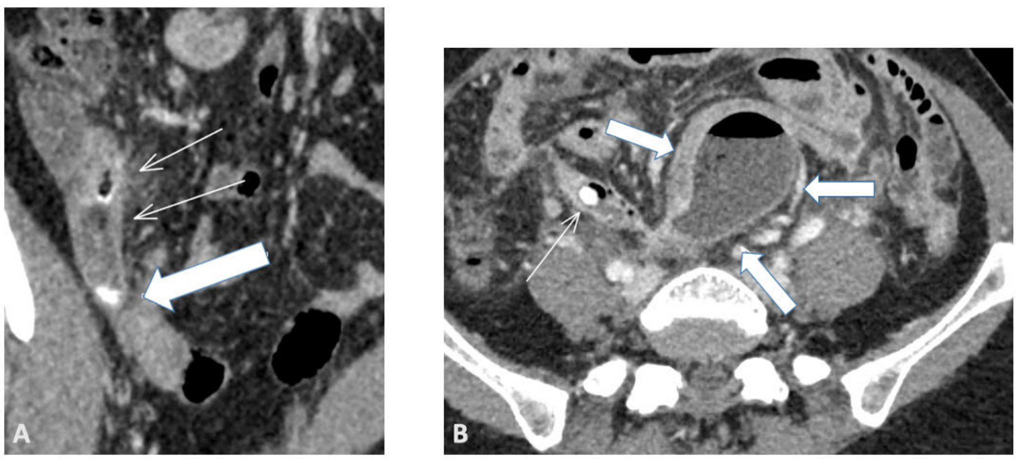

Figure 4. CT image of complicated acute appendicitis. A) Complicated by appendicolith (thin arrows: appendix, thick arrow: appendicolith). B) Complicated by large abscesses and appendicolith (thin arrow: appendicolith, thick arrows: abscess).

CT techniques are variable in their technical details. It is generally accepted that the identification of the appendix is improved when thin slices (5 mm) are used to scan the RLQ. There is controversy regarding the use of i.v. contrast agents, the use and route of enteric contrast agents, and the need to scan the entire abdomen/pelvis compared to focused imaging of the RLQ.[176] I.v. contrast agents help to better characterize findings of complicated acute appendicitis such as perforation and abscess. It is also beneficial in patients with elusive findings and marginal intra-abdominal fat by enhancing the appendiceal wall.[182] Another strength of using i.v. contrast is that it aids in the differential diagnosis of other causes of abdominal pain such as inflammatory bowel disease and pyelonephritis.[176] In Finland, typical CT imaging is performed by scanning from the xiphoid process to the symphysis, and i.v. contrast material is used in patients with normal kidney function and no known allergy to iodine contrast.

CT has high diagnostic accuracy with sensitivities ranging between 95% and 99% and specificities 96% and 98% to identify appendicitis.[156,175,183] The use of preoperative CT has significantly increased in the 2010s, and the performance of CT has been measured through the NAR and appendiceal perforation rate (APR). CT has been shown to decrease the NAR to even as low as 1.7% in patients undergoing preoperative CT imaging as compared to 10% to 20% in patients without preoperative imaging.[184,185] As mandatory preoperative imaging was implemented in the Netherlands, preoperative imaging with either US or CT increased accordingly from 43% to 99%, and simultaneously NAR decreased from 19% to 5%, also showing a reduction in costs due to decrease in negative appendectomies.[19] These findings were corroborated by Lahaye et al who additionally observed a significant reduction in the overall complication rate after surgery.[18] In Korea, the imaging rate was reported to be 99.7% with nearly all patients undergoing preoperative imaging; CT utilization was 93.1% for primary imaging and the NAR was 3.3% in patients undergoing CT .[157] Other advantages of CT, in addition to diagnostic performance, are that it is rarely affected by bowel gas, severe abdominal pain, or large body habitus.[186] The availability of CT is good and it simple to perform.

Preoperative CT imaging has been criticized for causing a delay to appendectomy, with a cost of increasing the risk of perforation. Krawjeski et al found the use of CT might delay surgery, but that this delay was not associated with increased APR with 20% and 20% in the pre- and post-CT times.[187] Interestingly, Jones et al observed a decrease in the APR from 25% to 9% with increased utilization of CT.[188] Other potential disadvantages of CT using contrast agents are dye-induced nephropathy and hypersensitivity/allergic reactions, but the main criticism against CT imaging for acute appendicitis is its use of ionizing radiation and exposing patients to an increased future cancer risk.[189] Ionizing radiation from CT imaging is related to an increased lifetime risk of cancer, but this risk is relatively small.[190-192] Based on their study, Brenner et al estimated that with current CT use 1.5–2% of all cancers in the United States may be attributable to radiation due to CT imaging.[191] Clinical benefits at the time of imaging should outweigh the small but potential risks of radiation, and radiation doses should be kept as low as possible.

To address to the concern of exposure to radiation, CT protocols utilizing lower radiation doses have been developed. In 2004, Keyzer et al reported low-dose unenhanced CT to have similar performance to standard-dose unenhanced CT. Regardless of dose, the most predictive signs of acute appendicitis were periappendiceal fat stranding, appendicolith and appendiceal diameter resulting in 90% of correct diagnoses.[193] In their single-blinded randomized trial, Kim et al showed that i.v. contrast enhanced low-dose CT was noninferior to enhanced standard-dose CT with NARs of 3.5% and 3.2% and APRs 26.5% and 23.3.%, respectively. The radiation dose incurred by the patient from low-dose CT was significantly lower than from standard-dose CT.[20] Another study showed that enhanced low-dose CT did not differ from enhanced standard-dose CT in terms of appendiceal visualization, sensitivity or the diagnostic confidence of the radiologist.[194] The radiation dose can be lowered to 2 mSv in adolescents and young adults from the standard approximately 8 mSv without affecting clinical outcomes.[195] In a recent meta-analysis, low-dose CT was found to be highly effective in diagnosing acute appendicitis compared to standard-dose CT with pooled sensitivities of 96.3% and 96.4% and specificities of 93.2% and 92.2%, respectively, and should be considered a valid option for first-line imaging when suspecting acute appendicitis.[196] One study showed that in patients imaged with unenhanced low-dose CT, the patient's BMI had no effect on the accuracy of the radiological diagnosis of acute appendicitis.[197] A preclinical trial conducted at Turku University Hospital created several low-dose protocols, and tested them with a phantom model. The best-performing protocol was selected to be evaluated and compared to the standard CT protocol in the clinical phase of the trial in patients with a BMI of under 30 kg/m^2.[198]

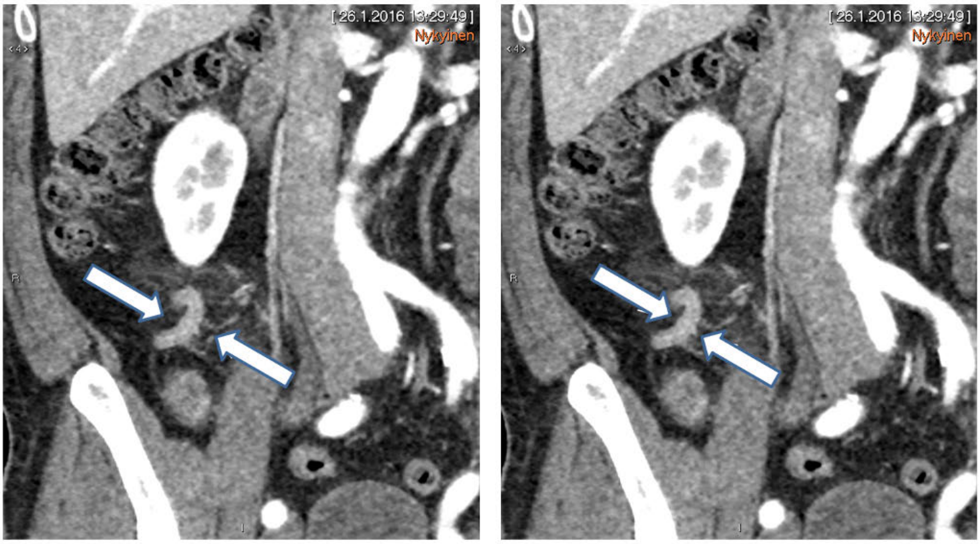

Figure 5. CT image of uncomplicated acute appendicitis in the same patient. A) Contrast-enhanced low-dose protocol (thick arrows: appendix). B) contrast-enhanced standard protocol (thick arrows: appendix).

2.6.2.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) for the diagnosis of acute appendicitis has been evaluated to increase diagnostic performance as compared to US and to remove the potential harms related to ionizing radiation used in CT imaging. Criteria suggestive of acute appendicitis on MRI include: appendiceal diameter >6 mm, wall thickness >2 mm, fluid-filled lumen or absence of gas, appendiceal wall destruction, peri-appendiceal fat infiltration, surrounding edema, fluid or abscess, restricted diffusion of the appendiceal wall or lumen and appendicolith.[199,200] Leeuwenburgh et al found appendiceal diameter, peri-appendiceal fat infiltration and restricted diffusion of the appendiceal wall to be the most significant factors associated with acute appendicitis. The likelihood of appendicitis was 96% if they were present and 2% if they were not.[200]

MRI has been shown to have sensitivity and specificity comparable to CT. A meta-analysis assessing MRI in the diagnosis of acute appendicitis included seven studies and found a sensitivity of 95% and specificity of 92%.[201] The diagnostic accuracy for MRI has been reported to vary, and depend on the expertise of the radiologist reading the MRI image.[202] MRI is also limited in its capability to differentiate between the two forms of acute appendicitis. One study found that MRI correctly diagnosed only 56% of perforated cases of acute appendicitis, and none of the MRI features for perforation had a higher positive predictive value than 53%.[203]

MRI has several advantages when compared to CT, the most significant being that it does not utilize ionizing radiation and expose patients to radiation related risks. MRI is not affected by body habitus like US and no intravenous contrast is needed to identify inflammation when using T2 sequences. Altogether, MRI is considered a safe and low-risk imaging modality.[204] However, MRI also has several disadvantages. MRI is limited by availability and cost, as well as time for image acquisition in the emergence care setting. Ginde et al studied the availability of MRI equipment in a random sample of emergency departments in the United States and found 66% to have access to on-site MRI and 20% to mobile MRI. Only 39% of centers had around-the-clock access.[205] Higher costs are also related to MRI, with its cost five times that of US and twice that of CT[206] and it is more time consuming[121]. MRI is also not necessarily suitable for patients with pacemakers, metallic implants, or claustrophobia. MRI is mostly recommended as a second-line imaging tool after inconclusive US in pediatric and pregnant patients.

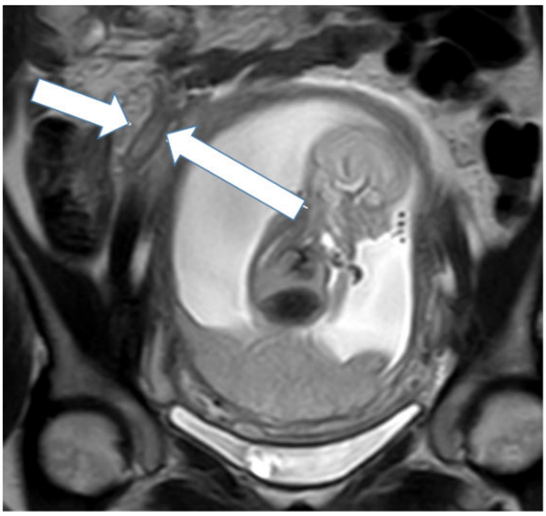

Figure 6. MRI image of uncomplicated acute appendicitis in a pregnant patient (thick arrows: appendix).

2.6.2.4 Scoring systems incorporating imaging

Atema et al developed a novel scoring system incorporating clinical and imaging features to distinguish between uncomplicated and complicated acute appendicitis. Clinical features included were age, body temperature, duration of symptoms, WBW count, and CRP. Imaging features included were extraluminal air (CT only), periappendiceal fluid (CT and US), and appendicolith (CT and US). With this score, 95% of patients with uncomplicated appendicitis were correctly identified.[207]

Currently, imaging with CT or US is widely utilized by emergency departments diagnosing acute appendicitis.

2.7 Management of acute appendicitis

2.7.1 Surgical management

Appendectomy is the most common emergency surgical disease in the world with more than 300 000 appendectomies performed annually in the United States.[1,3] In Finland, the laparoscopic approach has become the more commonly used approach.

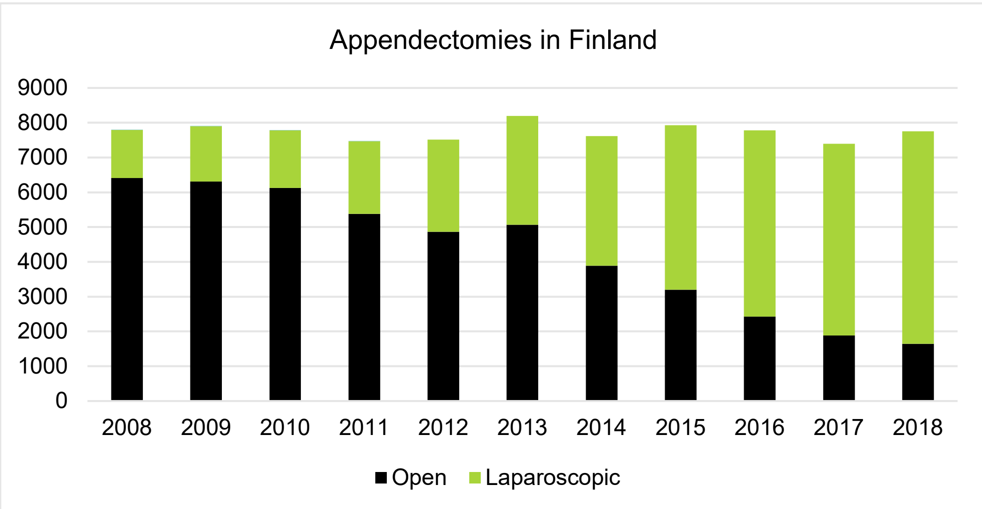

Figure 7. Trends in appendectomy approach in Finland between 2008 and 2018. Adapted from The Finnish institute of health and welfare, 2018.

Since McBurney described the muscle-splitting incision and open approach for appendectomy in 1894, it remained the gold standard treatment for nearly a century. During this time, the technique remained almost unchanged. Traditionally, the incision is made at the point of maximum tenderness of physical examination, often near McBurney's point. First the aponeurosis of the external oblique muscle is divided parallel to its fibers, after which the internal oblique is split similarly. The transverse fascia and peritoneum are opened to reveal the cecum and the appendix is found near the ileocecal fold and delivered for removal. The mesentery of the appendix is divided, and the vessels ligated. The appendix is divided from its base, and the stump of the appendix is ligated. The wound is closed in layers, except nowadays it is not mandatory to close the peritoneum.[208]

With advancements in surgical technique and the emergence of minimally invasive techniques, laparoscopic appendectomy has replaced open appendectomy during the last decade as a treatment of choice for a surgical approach in acute appendicitis. First, a camera port is placed above the umbilicus at midline and a pneumoperitoneum is created. The videoscope may be straight or angled. The status of all four quadrants is checked. Under direct visualization, the two additional ports are placed in the abdomen, one suprapubically in the midline and the other in the left lower quadrant. The appendix is visualized and mobilized. The mesoappendix can be divided with monopolar, electrocoagulation, bipolar, metals clips, Ligasure or Harmonic ultrasound scalpel. Closure of the base of the appendix can be performed with clips, loop-sutures, or an endoscopic stapler. The removed appendix is placed in a plastic bag and removed through the abdominal wall.[208] No differences have been shown in terms of outcomes, length of stay, and complication rates between the different methods of mesoappendix dissection.[209] In a Cochrane review, no differences in total, intraoperative, or postoperative complications was demonstrated between the methods to close the appendiceal stump.[210]

The open and laparoscopic appendectomy techniques have been widely studied and compared. Both have been deemed safe and effective procedures to treat acute appendicitis.[211] The proportion of laparoscopic appendectomies has greatly increased, for example from 43% in 2004 to 75% in 2011 in the United States.[212] In recent years, rates have been as high as 94–98%.[213,214] As experience with laparoscopy has increased, also the conversion rates to open appendectomy have decreased. In the United States, the conversion rate decreased surprisingly slowly from 7.2% in 2004 to 5.6% in 2011.[212] In Sweden, the rate of conversion decreased from 75% in 1992 to 20% in 2008.[215] Conversion rates as low as 0.9% in 2017 have been reported.[216]

Operation duration has been reported to be longer for laparoscopic appendectomies (by 7.6 to 18.3 minutes), but on the other hand, laparoscopic appendectomy results in significantly shorter hospitals stay.[216,217] One study found the median length of stay after appendectomy for nonperforated acute appendicitis to be 1 day after laparoscopy compared to 2 days after open procedure. The corresponding times for perforated cases were 4 days after laparoscopic compared with 5 days after open appendectomy.[212]

The feasibility of laparoscopy has been studied in specific populations. Focusing only on complicated acute appendicitis, Quah et al stated that complicated acute appendicitis at laparoscopy is not an indication for conversion, and laparoscopy should be preferred over open appendectomy due to reduced morbidity, mortality and shorter hospital stay.[218] In obese patients, laparoscopic appendectomy been shown to be superior over open appendectomy in terms of overall complication rate, mortality, mean hospital charges and shorter hospital stay, and should be considered as the primary approach in both nonperforated and perforated cases of acute appendicitis.[219] A meta-analysis by Wang et al concluded laparoscopy to be safe also in elderly patients, and to be related to shorter hospital stay, decreased morbidity and mortality. If there are no contraindications to laparoscopy, it should be the selected approach.[217]

Single incision laparoscopic appendectomy (SILA) was first described by Pelosi et al as a new advancement in appendectomy techniques.[220] When compared with the traditional laparoscopic approach, no differences in safety, complication rates, length of hospital stay, return to work and postoperative pain were found with the SILA technique. However, it is related to clearly longer operation durations, greater need for analgesia, and greater risk of wound infection and incisional hernias, so the traditional laparoscopic approach is recommended.[209,221,222] Natural orifice trans-luminal endoscopy surgery (NOTES) is another adaptation of laparoscopy and its use for appendectomy is being studied, but at this time it is still experimental.[223,224]

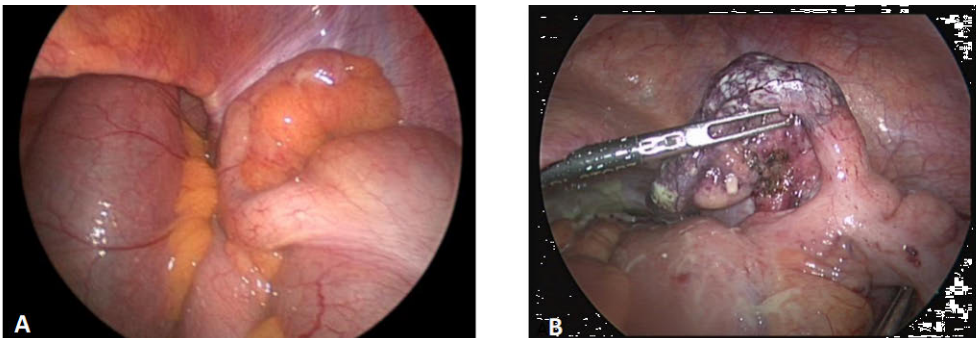

Figure 8. Intraoperative images of acute appendicitis. A) Uncomplicated acute appendicitis. B) Complicated acute appendicitis.

2.7.2 Nonoperative management

In 1956, Coldrey published his study with promising results on antibiotic treatment of acute appendicitis. Coldrey medicated pain and administered penicillin and streptomycin, and in severe cases chloramphenicol, chlortetracycline, tetracycline or sulphadimidine, and described promising results even in severe cases.[9] These results were forgotten in history and appendectomy continued as the treatment of choice.

During the last decade, the notion of antibiotic treatment for acute appendicitis has actively emerged and is currently under intense research. The major randomized clinical trials are summarized in Table 3. Earlier studies demonstrated the feasibility of antibiotic treatment for acute appendicitis, although having several significant limitations. The first pilot study by Eriksson et al concluded antibiotics to be as effective as surgery for acute appendicitis but observed a high recurrence rate.[10] This study was limited in its small number of included patients and included patients with both forms of acute appendicitis. Styrud et al reported similar findings, reporting a 14% recurrence rate at 1-year.[11] Exclusion of women from the study and no use of preintervention imaging to confirm the diagnosis limited this study. Hansson et al concluded antibiotic treatment to appear a safe first-line treatment in unselected patients with acute appendicitis, reporting a 1-year recurrence rate of 14%.[12] However, in this study, 47.5% of patients originally randomized to antibiotic treatment crossed over to appendectomy, markedly limiting the randomized nature of the study. In addition, no preintervention imaging was used to confirm the diagnosis of acute appendicitis. Vons et al was the first randomized clinical trial that used preintervention CT to identify patients with uncomplicated appendicitis to be randomized in their trial.[13] They found amoxicillin-clavulanic acid to not be noninferior to appendectomy, however they included patients with appendicoliths. The primary endpoint was postintervention peritonitis at 30 days after initiation of treatment, with 8% in the antibiotic group and 2% in the appendectomy group. In fact, had they excluded the patients presenting with an appendicolith on preintervention CT, there would have been no difference in treatment efficacy. The antibiotic used in this study has also been criticized, as E. coli, a common pathogen related to acute appendicitis, can show considerable nonsusceptibility to amoxicillin-clavulanic acid. The Finnish Appendicitis Acuta (APPAC) trial by Salminen et al also used preintervention CT to confirm the diagnosis of uncomplicated acute appendicitis.[14] Unlike Vons et al, appendicoliths were classified as complicated acute appendicitis and these patients were excluded from the study. Ertapenem, a broad-spectrum antibiotic, was chosen because of its efficacy in intra-abdominal infections, and administration of one dose daily. Open appendectomy was the recommended approach based on global generalizability as at the time of the study, laparoscopic appendectomy was not yet the gold standard globally. The APPAC trial did not meet the somewhat arbitrarily set non-inferiority limit, but it demonstrated that 73% of patients with uncomplicated acute appendicitis could successfully be treated with antibiotics at one-year follow-up. A significant finding was that none of the patients treated primarily with antibiotics who later underwent appendectomy had any major or increased complications. The APPAC trial is the only trial to publish long-term follow-up results with the finding that at 5-years follow-up, antibiotic treatment is feasible in the treatment of uncomplicated acute appendicitis in comparison to appendectomy. At five years, 39.1% patients had undergone appendectomy for suspected recurrent acute appendicitis. Based on histopathological analysis, the true recurrence rate was 32.4%.

Table 3. Summary of the major randomized clinical trials comparing antibiotic therapy with appendectomy for uncomplicated acute appendicitis in adults.

	Diagnosis	Sex (% male) Age (yrs)	Patients (Surgery: Antibiotics)	Antibiotic treatment	Initially successful antibiotic treatment	Need for surgery after successful initial antibiotics	1-year efficacy (including recurrence)
Erikson et al 1995	US	68% 18-75	20:20	I.v.: cefotaxime, tinidazole P.o.: ofloxacin, tinidazole	95%	37%	60%
Styrud et al 2006	Clinical	100% 18-50	124:128	I.v.: cefotaxime, tinidazole P.o.: ofloxacin, tinidazole	88%	14%	76%
Hansson et al 2009	Clinical (+US/CT)	53% 18-50	167:202	I.v.: cefotaxime, metronidazole P.o.: ciprofloxacin, metronidazole	91%	14%	78%
Vons et al 2011	CT	60% 18-68	119:120	I.v. and p.o: amoxicillin-clavulanic acid	88%	25%	68%
Salminen et al 2015	CT	62% 18-60	273:257	I.v.:ertapenem P.o.: levofloxacin, metronidazole	94%	27%	73%

Based on Eriksson et al 1995, Sturyd et al 2006, Hansson et al 2009, Vons et al 2011, Salminen et al 2015. Adapted from Bhangu et al 2015.

Recent meta-analyses have reviewed these randomized clinical trials and other prospective interventional studies concluding that while non-operative management is less effective than surgery, 60–85% could still successfully be treated with primary antibiotic therapy.[15-17] However, evidence suggest that antibiotic treatment is an option only in uncomplicated acute appendicitis cases. The Jerusalem guidelines updated in 2020 conclude antibiotics to be a safe and effective first-line treatment for uncomplicated acute appendicitis.[209] Currently, there is no consensus on antibiotic of choice, its administration route and duration, but antibiotics with aerobic and anaerobic coverage for typical bacteria in the bowel should be used.[42] The above-mentioned trials have been conducted with i.v. antibiotics for 1-3 days followed by p.o. antibiotics for 7–10 days. A pilot study of outpatient treatment with antibiotics has been conducted in the United States. Talan et al found promising results indicating outpatient treatment with the antibiotics-first approach could be a feasible alternative to appendectomy, warranting a multicenter trial in the United States.[225]

The trials described above have all been conducted in adult populations, but similar results have also been found in pediatric populations. In their prospective nonrandomized trial, Minneci et al found a 30-day success rate of 90% in children managed with antibiotics for uncomplicated acute appendicitis. Children in the nonoperative group had less disability days, returned to school more quickly but incurred a longer length of stay.[226] Initial success rate of nonoperative treatment ranged from 58% to 100% in a systematic review, with recurrences rates of 0.1% to 31.8%.[227]

Nonoperative management has recently been studied in a large American trial, the CODA trial, conducted in a pragmatic setting. They included 1552 patients with imaging confirmed acute appendicitis assigning 776 to receive antibiotic treatment and 776 patients to undergo appendectomy. The patient population included 414 patients with an appendicolith. Patients randomized to antibiotic treatment received varying courses of antibiotics for total of 10 days; the treatment was decided by the treating clinical team. The CODA trial found antibiotic treatment to be noninferior to appendectomy measured by 30-day quality of life scores. In the antibiotic therapy group, 29% patients underwent appendectomy within 90 days of randomization. Of the patients undergoing surgery, 41% had an appendicolith and 29% did not. This further suggests appendicolith to be of the complicated form of acute appendicitis.[65]

Spontaneous resolution of acute appendicitis has been observed and it may play a critical role in shaping the treatment of acute appendicitis in the future by questioning the need for antibiotics. Acute appendicitis has been considered similar to acute diverticulitis, and this resemblance has been illustrated in epidemiological studies.[3] The treatment of CT scan-confirmed uncomplicated acute diverticulitis has shifted towards symptomatic treatment. No benefit of antibiotic therapy in uncomplicated acute diverticulitis with low rates of complications have been widely demonstrated.[228-230] Even outpatient management without antibiotics has been demonstrated to be safe and feasible.[231] In their non-blinded study, Park et al illustrated promising initial results for CT-confirmed uncomplicated acute appendicitis; however, participants were carefully selected leading to potential selection bias. In their study, treatment failure rates at 1 month (7.3% vs. 7.5%) and 1 year (23.4% vs. 20.7%) were comparable for patients in the non-antibiotic and antibiotic group.[41] More studies on the role of symptomatic treatment and to date no blinded placebo-controlled studies have been performed.

2.7.3 Treatment of periappendicular abscess

Periappendicular abscesses are a special type of complicated acute appendicitis presenting with a perforation followed by restricted abscess formation. Nonsurgical treatment of periappendicular abscesses comprises of antibiotic therapy and drainage, if accessible and necessary, and allows for the acute inflammation to recede in over 90% of cases.[92] Abscesses smaller than 3 cm will often resolve with antibiotics, but in cases greater than 3cm percutaneous drainage is more efficient.[232] Percutaneous drainage is associated with fewer complications and shorter hospitalization than surgical drainage.[233] Interval appendectomy may follow. A meta-analysis showed that nonsurgical treatment was related to significantly fewer overall complications (including ileus, intra-abdominal abscesses, wound infections, and re-operations), similar length of antibiotic treatment and hospitalization.[234] Conversely, some studies have shown nonsurgical management to fail in 25-30% of patients, needing to undergo subsequent surgery.[95,235] Early appendectomy is indicated patients showing signs of sepsis, bowel obstruction, fever, persistent pain, and elevation of inflammatory markers unresponsive to treatment with antibiotics.

A Cochrane Review in 2017 concluded that when comparing early appendectomy to delayed appendectomy for appendiceal abscesses, it is unclear whether early operation is beneficial in terms of complications. Recent studies have indicated early laparoscopic appendectomy to be a safe and feasible first-line approach to treating periappendicular abscesses. Early appendectomy has been shown to be associated with lower incidence of bowel resection[235], fewer readmissions (7 % vs. 27%) and fewer reinterventions (7% requiring drainage vs. 30% requiring appendectomy) than nonsurgical management[95].

The role of interval appendectomy after successful initial nonsurgical treatment is under debate. The risk of recurrence of periappendiceal abscess has been shown to be between 5 and 25%.[96,236] The reported risk of underlying malignant appendiceal neoplasms has previously been reported to be low, varying between 0.7 and 3%.[74,76] Recent studies have reported alarmingly high incidences of malignancy at interval appendectomy in patients with previous periappendiceal abscess. Wright et al found a total rate of 28% of appendiceal neoplasms following interval appendectomy, with a rate of 16% in patients older than 40 years and 4% in patients under 40 years.[237] Carpenter et al found a rate as high as 28% of appendiceal malignancies following interval appendectomy.[97] The only randomized controlled trial on this topic (the PeriAPPAC trial) comparing interval appendectomy and follow-up with MRI was prematurely terminated due to an alarmingly higher neoplasm rate of 20% in patients over 40 years of age.[238] Teixeira et al recommend all patients initially treated nonoperatively to undergo interval appendectomy.[76] The recently updated Jerusalem guidelines recommend against routine interval appendectomy in patients under 40 years, but it is recommended for patients with recurrent symptoms. For patients 40 years or older, this guideline suggests colonic screening with colonoscopy and interval full-dose contrast-enhanced CT.[209] This issue needs to be addressed in future prospective cohort studies to evaluate the tumor rate before guidelines can be set.

2.8 Short-term treatment outcomes

2.8.1 Treatment success

Treatment success of appendectomy is defined as a successful appendectomy in which the inflamed appendix is removed.[14,239] It can be performed either laparoscopically or with the open technique. Treatment success for appendectomy is considered to be close to 100%, with meta-analyses reporting 99.4% to 99.6%.[15,16] A reoperation rate of 0.6%, a NAR of 6%, and a complication-free treatment success rate of 89.8% were reported.[15] Length of primary hospital stay was shorter in patients undergoing appendectomy than patients treated with antibiotics.[15,16]

Definition of treatment success for antibiotic treatment of uncomplicated acute appendicitis varies markedly between studies in terms of time point and meaning, but can be summarized as primary antibiotic treatment not requiring subsequent appendectomy during primary hospitalization or follow-up period, and no recurrent appendicitis treated conservatively.[239] During a follow-up period of 1-year, the treatment success of antibiotic therapy were 72.6%, 73.5% and 77.4% in meta-analyses.[15-17] Salminen et al reported 5.8% (15/257) of patients randomized originally to antibiotic therapy undergoing appendectomy during primary hospitalization, 2.7% having complicated acute appendicitis at surgery and 3.1% having uncomplicated acute appendicitis at surgery.[14] In the study by Hansson et al, 47.5% (96/202) of patients first randomized to antibiotic treatment ended up undergoing appendectomy during primary hospitalization due to patient preference (30%), surgeon's decision based on clinical assessment (17%), and need for surgery without description of rationale for the decision (41%), and other reasons (12%).[12] These patients did not differ by their baseline characteristics from those who successfully completed antibiotic therapy, suggesting greater primary success rates, if the patients had been able to complete their randomized treatment. Vons et al included patients with appendicolith in their antibiotic treatment group. Had they classified appendicolith as complicated acute appendicitis, and excluded these patients, they would have found no difference between appendectomy and antibiotic therapy.[13] In their meta-analysis, Sallinen et al stated antibiotic treatment to be favorable over appendectomy in terms of major complications, minor complications, rate of appendectomy within one month, and length of sick leave.[16]. Appendectomy was favorable in terms of appendicitis recurrence and length of hospital stay. At short-term, antibiotic therapy has shown to be safe and efficient for uncomplicated acute appendicitis.[15,16,240]

2.8.2 Treatment complications

Short-term outcomes between laparoscopic and open appendectomy have been compared in terms of overall complication rate, morbidity and mortality. For nonperforated acute appendicitis, overall complication rates vary from 4 to 5% for laparoscopic appendectomy and 6 to 11% for open appendectomy, and for perforated acute appendicitis treated laparoscopically between 19 and 20% to between 27 and 28% treated with open approach.[38,212] Surgical site infections are more common after open appendectomy (0.4% vs. 0.1%) than after laparoscopic appendectomy for uncomplicated acute appendicitis. The corresponding rates are 3.6% after open and 1.6% after laparoscopic appendectomy for complicated acute appendicitis.[212] Several studies have found intra-abdominal abscesses have to be more common after laparoscopic surgery[215,216,241] but other studies report no significant difference in intra-abdominal abscess after the two operative approaches[242,243]. Masoomi et al found intra-abdominal abscesses to be significantly less common after laparoscopic appendectomy than open appendectomy both in nonperforated (0.3% vs. 1.2%) and perforated (14% vs. 16%) cases of acute appendicitis.[212] Both laparoscopic and open appendectomies are associated with mortality. Mortality at 30 days post-appendectomy was 2.1/1000 in a Finnish population and was associated with negative appendectomies and complicated acute appendicitis, and increased in patients over 60 years of age.[244] In-hospital mortality for patients with uncomplicated acute appendicitis treated laparoscopically varies from 0.03% to 0.07% and from 0.05% to 0.17% for patients treated with open appendectomy.[38,245] For patients with complicated or perforated acute appendicitis, in-hospital mortalities from 0.06% to 0.13% for laparoscopic and from 0.31% to 1.03% for open appendectomies have been reported.[38,245] In the Finnish APPAC trial the suggested surgical approach was open appendectomy, and they found an overall complication rate of 20.5% in the appendectomy group and a 8.8% rate of surgical site infections.[14] A Cochrane review updated in 2018 concluded laparoscopic appendectomy to be superior to open appendectomy.[246]

Short-term complications of antibiotic therapy have been compared in terms of need for appendectomy, overall complications, morbidity, and mortality. Primary treatment failure was reported to be 8.5%.[17] The need for appendectomy within 1 month varied from 8.2% to 13.4%.[15,16] The overall complication rate for antibiotic therapy is 8.2% compared to 15.9% for appendectomy.[17] Sallinen et al assessed major and minor complications separately. They found 4.9% of antibiotic therapy patients experiencing major complications (appendiceal perforation, adhesive bowel obstruction, death) compared to 8.4% appendectomy patients experiencing major complications (appendiceal perforation, deep infection, incisional hernia, adhesiolysis, and death). In terms of minor complications, 2.2% of patients treated with antibiotics had superficial wound infections, abdominal or incisional discomfort, or other unspecified minor complications compared to 12% of appendectomy patients experiencing abdominal or incisional discomfort or diarrhea. Mortality related to antibiotic therapy is a rare complication, with only 1 death identified in a meta-analysis.[16]

2.9 Long-term treatment outcomes

2.9.1 Appendicitis recurrence

The risk of recurrent appendicitis after initial nonoperative management has been widely assessed. At 1-year follow up, recurrence rates ranging from 14% to 35% have been reported.[10-14] In their meta-analysis, Harnoss et al reported a recurrence rate of 27.4% within one year.[15] Only Salminen et al have reported recurrence data from longer follow-up. The study found a late recurrence rate (within 5 years) of 39.1% when appendectomy was performed based on recurrent symptoms per protocol and a 5-year true recurrence rate of 32.4% when uncomplicated acute appendicitis was confirmed by histopathology.[247] The cumulative recurrence rates from one to five years are shown in Table 4. It illustrates that most recurrences occur within the first year after randomization, some between years one and two, with individual cases between years three and five. Reliable factors predicting recurrence have not yet been identified.

Table 4. Cumulative incidence of recurrence of appendicitis after initial nonoperative treatment in a randomized controlled trial.

Year	Cumulative incidence of recurrence
1	27.%
2	34.0%
3	35.2%
4	37.1%
5	39.1%

Based on Salminen et al 2018.

2.9.2 Quality of life and patient preference

With increasing evidence for the efficacy of nonoperative management for uncomplicated acute appendicitis, the aspects of patient QOL, patient preference and satisfaction to treatment have been acknowledged and the notion of joint-decision making has been recognized.[16,248] A study in a pediatric population showed that when chosen by the family, nonoperative management was effective in treating US or CT confirmed uncomplicated acute appendicitis.[226] Another study in children demonstrated that patients treated with antibiotics had higher patient QOL and health care satisfaction as well as similar parental satisfaction between the treatment groups.[249] In an online survey, Hanson et al asked adult respondents to imagine that they or their child had an uncomplicated acute appendicitis. They then asked the patients to select their preferred treatment choice after offering them information about laparoscopic and open appendectomy as well as antibiotic therapy. The majority of respondents chose surgery, but 9.4% chose antibiotics, highlighting the importance of patient perspective.[248] Another survey on the perceptions on antibiotic and operative treatment was conducted in a population of US medical students with similar results.[250] The studies concluded that providing patients with unbiased information regarding all treatment alternatives is challenging.

2.9.3 Treatment complications

The most common long-term treatment complications relating to appendectomy are small bowel obstruction and incisional hernias, and rare cases of stump appendicitis have been described. Also remaining symptoms of incisional or abdominal pain are possible. Potential connections to inflammatory bowel disease (IBD) and infertility are also considered complications. Long-term complications related to antibiotic therapy are not well-known, but possible effects in gut microbiota and potentially missed malignancy are speculated.

Small bowel obstruction or ileus postoperatively after appendectomy is also quite rare. One study reported an overall rate of 2.8% at about 4-year follow-up and identified risk factors for developing small bowel obstruction as perforated acute appendicitis, nonappendicitis pathology, and midline incisions with no difference between the open and laparoscopic approaches.[4] Andersson et al also showed no difference between open and laparoscopic appendectomy in terms of small bowel obstruction with risks of 1.5% and 1.4%, respectively.[215] Swank et al reported no small bowel obstructions in a study with 755 patients.[241] The most recent study found risks of 0.8% and 1.2% after laparoscopic and open appendectomy, respectively.[251] Less severe symptoms of abdominal or incisional pain including possible adhesion-related problems have been reported in 15% (38/246) after appendectomy.[247]

Incisional hernias relating to open appendectomy and the McBurney technique as well as for laparoscopic appendectomy are rare but may require hernia repair. Risk factors of incisional hernias include patent-related factors such as diabetes, obesity, and female gender, as well as disease-related factors such as abscess, phlegmon, superficial surgical site infection, and postoperative seroma as well as technique related factors such as interrupted suture of the aponeurosis.[252] In a study by Beltran at el, 93% of patients underwent appendectomy through McBurney's incision. Of these, 0.7% developed incisional hernia.[252] Other studies have reported incidences up to 2% and consider oblique incisions low-risk for incisional hernias.[253,254] No trocar site hernias were reported by Swank et al[241] and a prevalence 0.7% over five years was reported by Rasmussen et al[251].

Stump appendicitis is defined as the interval inflammation of remaining appendiceal tissue after primary appendectomy.[255] Stump appendicitis is a rare complication after appendectomy, and can be due to anatomical (retrocecal position) or technical factors (inadequate dissection and lack of experience of the surgeon).[256] It presents as symptoms and clinical findings similar to acute appendicitis, but the diagnosis is often delayed due to knowledge of previous appendectomy. Delay in diagnosis may result in delay in treatment and thus increase in morbidity. The incidence of stump appendicitis is most likely underreported in literature and partially due to difficulty of diagnosis. One study reported an incidence of 0.2%.[256] Stump appendicitis can follow either initial open (59% to 63%) or laparoscopic (37% to 38%) appendectomy with time to reoperation ranging between 2 weeks and 60 years with a median of 2 years.[255,257] Manatakis et al reported 87.7% of patients undergoing completion stump appendectomy, 77% requiring ileocecotomy or right hemicolectomy and 1.3% undergoing drainage and cecotomy. Lengths of the removed stumps varied between 0.5 and 10 cm, concluding that stump appendicitis may occur when a stump of greater than 0.5 cm is left.[255]

Acute appendicitis and appendectomy have been implicated in causing scarring which in turn may lead to infertility and ectopic pregnancy. In a meta-analysis, Elraiyah et al found appendectomy to be associated with the risk of ectopic pregnancy but not with future infertility.[258] Another study observed an increase of pregnancy rates after appendicitis in comparison to controls, challenging the relationship between appendectomy and infertility.[251] Appendectomy is not related to tubal pathology, but can affect fertility through other mechanisms.[259]

Antibiotic treatment of uncomplicated acute appendicitis is a relatively novel development, and long-term follow-up data is not widely available. Patients undergoing later appendectomy after primary antibiotic treatment seem to face similar risks as patients undergoing primary appendectomy. The only study reporting results at five-year follow-up is the APPAC trial, which reported an overall complication rate of 6.5% in the antibiotic group compared with 24.4% in the appendectomy group. In the appendectomy group, 2 patients had complications requiring reoperation, but all other patients in both groups had less-severe complications (including surgical site infections, and abdominal or incisional pain or obstructive symptoms). Also, there were no significant complications in patients randomized to primary antibiotic treatment who underwent later appendectomy for recurrence and no appendiceal tumors in patients operated on between years 1 and 5.[247]

2.9.4 The risk of missed appendiceal malignancy

The risk of missed malignancy after nonoperative treatment for uncomplicated acute appendicitis must be considered as a complication. After appendectomy for acute appendicitis, an appendiceal tumor is confirmed in 0.9% to 1.4% of patients.[76] If these patients were treated with antibiotics, the diagnosis of malignancy would have been missed and treatment would have been delayed with potentially fatal consequences.[15] Enblad et al analyzed 13 959 patients with nonoperatively treated acute appendicitis, identifying 2.6% of patients diagnosed with small bowel, appendiceal, or colorectal cancer. While the majority of patients with cancer had complicated acute appendicitis with abscess (63%), the incidence of bowel cancer, especially appendiceal and right-sided colon cancer, was increased for acute appendicitis without abscess. The most common histopathology was adenocarcinoma. In 44% of patients, the time to diagnosis of cancers was less than three months. The study concluded that both in the short- and long-term, patients treated nonoperatively for acute appendicitis have an increased risk of bowel cancer.[260] Lietzén et al had contradictory findings in their population based study, concluding that appendiceal tumors were related to complicated acute appendicitis, especially periappendicular abscesses, and that the risk of missed malignancy due to antibiotic treatment for uncomplicated acute appendicitis was low.[113] They reported an overall prevalence of 1.2% for appendiceal tumors among patients with acute appendicitis.

2.9.5 Other potential long-term outcomes

The appendix has mostly been seen as a vestigial organ, which has lost its original function, but more recently the appendix has been speculated to be “safe house” for normal gut flora, which may aid in the restoration of microbial diversity after intra-abdominal infections.[261] Appendicitis and appendectomy are speculated to have a role the development of IBD. IBD (ulcerative colitis and Crohn’s disease) are chronic idiopathic inflammatory diseases affecting the gastrointestinal tract.[262] The etiology behind IBD is multifactorial, involving both genetic and environmental factors.[262] Rasmussen et al showed a total prevalence of 0.15% for ulcerative colitis after appendectomy and 0.19% in controls; for Crohn's disease a total prevalence of 0.2% after appendectomy and 0.1% in controls was described.[251] These findings were not statistically significant but concur with findings from other studies.

Appendectomy seems to have a protective effect in the development of ulcerative colitis, especially if appendectomy was performed for appendicitis before the age of 20.[263] Appendectomy for non-appendicitis did not have a similar risk reducing effect on ulcerative colitis. For Crohn's disease, appendectomy seems to have the opposite effect, increasing its prevalence.[262]

Other potential long-term outcomes involve antibiotic treatment. Antibiotic agents are known to affect gut microbiota and its balance[264,265] and the dysbiosis of gut microbiota is related to various disorders such as diabetes, obesity, and many types of cancers, especially colorectal cancers[266]. Especially broad-spectrum antibiotics affect the gut microbiota with long-lasting effects. Use of antibiotics can lead to increased antibiotic resistance.[267] The specific effect of antibiotic treatment for uncomplicated acute appendicitis on gut microbiota is not known; an ongoing study focuses on identifying the effects of antibiotic and placebo treatment on the gut microbiota and its recovery.[268] Also, most trials have not observed or described adverse effects of antibiotic treatment such as diarrhea or allergic reactions after antibiotic treatment for uncomplicated acute appendicitis.[16] Hansson et al reported 2.5% and 11.4% cases of diarrhea, 0.5% and 0.5% with clostridium infection, and 2% cases of fungal infection within in one year in their intention-to-treat analysis in the antibiotic and operative groups, respectively.[269] Antibiotic treatment is known to be a key factor in the development of *Clostridium difficile* infection and colitis as antibiotic treatment alters conditions in the intestine making the environment more hospitable for the growth of *Clostridium difficile.*[270]

Additionally, the relationship between gut microbiota and cancer, especially colorectal cancer, is under intense research. Recent studies have demonstrated that antibiotic-induced changes in dysbiosis and recovery of the gut microbiota occur over time.[271,272] These disturbances in the microbiota may alter the course of carsinogenesis as microbes seem to have a role in promoting dysplasia, clonal expansion, tumor growth and invasive cancer. [273] For example, A positive relationship between ß-lactam antibiotics and colon cancer development has been observed.[274] However, much more research is needed to assess this relationship, and additionally consider other related factors such as diet (the intake of processed foods and excess carbohydrates).

2.10 Economic evaluation of different treatment options

The complete assessment of surgical and antibiotic therapies for uncomplicated acute appendicitis must also consider and compare short-term and long-term costs related to each treatment option. Costs related to actual treatment include hospital charges resulting from both treatment for primary appendicitis and for possible appendicitis recurrence (laboratory costs, imaging costs, pharmacy costs, pathology costs, food, specialist fees, ward costs, and operation related costs among others), and also indirect costs of productivity losses in the form of sick leave.[275,276] Considering sick leave and following reduced productivity is important as acute appendicitis largely affects the working age population, and it has been suggested that these indirect costs can result in significant economic burden to society.[277]

In their decision tree analysis, Wu et al estimated that even at combined nonoperative treatment failure and recurrence rates up to 56%, initial treatment of uncomplicated acute appendicitis with antibiotic therapy would be the more cost effective modality of primary treatment.[278] Similar findings of nonoperative management being more cost effective than laparoscopic appendectomy in treating pediatric uncomplicated acute appendicitis have also been made.[279] However, Sceats et al found contradicting results when using a Markov model to compare laparoscopic appendectomy, outpatient antibiotic treatment, and inpatient antibiotic treatment. They found appendectomy to be cost-effective in the long-term.[280]

Most cost analysis studies have been performed using different modelling techniques, and relevant data from randomized clinical trials comparing antibiotic treatment with appendectomy are limited. According to their intention-to-treat analysis, Hansson et al found that patients treated with antibiotics had significantly shorter sick leaves than patients who underwent appendectomy with 7 days compared with 11 days. Additionally, primary hospital costs were found the be 25% less after antibiotic treatment compared with appendectomy.[12] The long-term results of the APPAC trial at 5-year follow-up considered total costs including all significant cost sources resulting from the initial treatment, hospitalization and treatment for possible appendicitis recurrence. This study found total costs resulting from treatment with primary appendectomy to be 1.4 times higher than costs resulting from primary antibiotic treatment with both costs resulting from hospital charges and productivity losses being higher in the appendectomy group. At long-term costs resulting from productivity losses comprised a slightly bigger proportion of the total costs in both groups.[276]

Hospital stay is a significant cost source. The randomized trials studying antibiotic treatment for uncomplicated acute appendicitis had set a fixed length of hospital stay per protocol to ensure patient safety. Treatment of uncomplicated acute appendicitis with for example peroral antibiotics, not requiring long hospital stay or even as outpatient treatment, could further significantly lower the overall treatment costs.

3 Aims

This study aimed to evaluate the diagnosis of acute appendicitis with low-dose CT imaging, compare open appendectomy and antibiotic treatment in terms of treatment costs and patient-related factors, and assess the treatment of uncomplicated acute appendicitis with only peroral antibiotics. We also aimed to create a study protocol to compare placebo with antibiotics in the treatment of uncomplicated acute appendicitis. The specific aims of the studies presented in this thesis were:

1. To compare the overall societal and treatment costs of antibiotic therapy and appendectomy in the treatment of uncomplicated acute appendicitis in a randomized clinical trial.
2. To compare the diagnostic accuracy of an optimized contrast-enhanced low-dose CT protocol to standard CT in patients with a high suspicion of acute appendicitis.
3. To compare the long-term QOL, patient satisfaction, and treatment preference after antibiotic therapy and appendectomy in the treatment of uncomplicated acute appendicitis in a randomized clinical trial.
4. To compare p.o. antibiotic monotherapy with a combination of i.v. followed by p.o. antibiotic therapy in the treatment of CT-confirmed uncomplicated acute appendicitis in terms of treatment efficacy, post-intervention complications, and length of hospital stay in a randomized clinical trial at 1-year follow-up.
5. To design a double-blind placebo controlled randomized clinical study protocol to compare antibiotic therapy to placebo to evaluate the effect of antibiotics in the treatment of uncomplicated acute appendicitis.

4 Patients and Methods

4.1 The APPAC trial

Studies I and III are based on the Appendicitis Acuta (APPAC) trial. The APPAC trial was a multicenter, open-label, noninferiority randomized clinical trial performed in three Finnish university hospitals (Turku, Oulu, and Tampere) and three central hospitals (Mikkeli, Seinäjoki, and Jyväskylä). The APPAC trial aimed at comparing antibiotic therapy with emergency appendectomy for the treatment of uncomplicated acute appendicitis, and the study hypothesis was that antibiotic therapy is noninferior to appendectomy.

Patients aged 18 to 60 years admitted to the emergency department for a clinical suspicion of acute appendicitis and who were diagnosed with uncomplicated acute appendicitis on CT scan were enrolled in the study. Exclusion criteria included age younger than 18 or older than 60 years, pregnancy or lactation, allergy to contrast or iodine, renal failure or serum creatinine exceeding upper reference limit, type 2 diabetes and metformin medication, suspicion of peritonitis, severe systemic illness, history of appendectomy, and inability to cooperate and give informed consent for participation in the study. The radiological diagnosis of uncomplicated appendicitis was defined as appendiceal diameter > 6 mm and thickening of the appendiceal wall with at least one of the following: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix in addition to the absence of criteria for complicated acute appendicitis. The radiological diagnosis of complicated acute appendicitis was defined as periappendiceal abscess, perforation (free peritoneal fluid, extraluminal gas), appendicolith, or appendiceal tumor.

Patients enrolled in the study were randomized to undergo open appendectomy or receive antibiotic therapy by a closed envelope method in a 1:1 allocation ratio. Open appendectomy was recommended with prophylactic antibiotics (1.5 g of cefuroxime and 500 mg of metronidazole) administered about 30 minutes before the incision in the surgery group. Appendicitis was confirmed by histopathological examination. The primary endpoint of treatment success was defined as successful appendectomy. Patients randomized to antibiotic therapy received i.v. ertapenem 1 g daily for three days followed by p.o. 500 mg once daily of levofloxacin and 500 mg three times daily of metronidazole for seven days. The primary endpoint of treatment success for patients receiving antibiotic therapy was defined as the resolution of acute appendicitis (discharge from the hospital without need for surgical intervention and no recurrent appendicitis during 1-year follow-up). If a patient initially treated with antibiotics was suspected of having recurrent appendicitis, they always underwent appendectomy based on clinical symptoms without repeat imaging. The diagnosis of recurrent appendicitis was confirmed by surgical and histopathological findings. Secondary outcomes included overall postintervention complications, late recurrence of acute appendicitis, length of hospital stay, duration of sick leave, postintervention pain evaluated by pain scores, and the need for pain medication. The patients are followed-up by telephone interview at one week, two months, and one, three, five, and ten years.

The APPAC trial is noninferiority study. The success rate of appendectomy was assumed to be 99%. A success rate of 75% for antibiotic therapy was estimated based on prior studies finding success rates between 70–80%[11,12]. A 24% (95% CI, 75–99%) noninferiority margin was set. The main analyses were based on the intention-to-treat principle.

The APPAC trial, as well as studies I and III, were approved by the Ethical Committee of the Turku University Hospital District.

4.1.1 Study I

Study I focused on evaluating the economic effects of antibiotic therapy and surgical treatment for uncomplicated acute appendicitis in the APPAC trial. This study compared costs between the two treatment options with regard to all secondary outcome measures and the effect on the overall societal costs. The cost estimates used were based on the cost levels of the final quarter of 2012. All costs were recorded whether related to the primary hospital visit and the subsequent treatment or later treatment due to possible recurrent appendicitis during the 1-year follow-up. Information on the costs originating form laboratory tests and imaging were gathered from three large participating hospitals and used to estimate the role of these cost components in addition to the total hospital charges from all the hospitals. Information on the medicines used during the hospitalization period were collected separately from the patient records and corresponding costs were used. For medications prescribed to be used at home postintervention, corresponding retail prices were applied to each medicine. The human capital approach was used in estimating the costs resulting from absence from work. Sick leave days covered days spent in the hospital in addition to sick leave given upon discharge. Average monthly gross salaries for working Finnish adults (2891€ for women, 3520€ for men) were used to estimate the costs of productivity losses. Productivity loss per day was estimated by dividing the monthly gross salary by the number of working days per month (21 days). Sensitivity analyses were performed to see if the final outcome was sensitive to specific factors. Based in this, the effects of sick leave and salary costs were analyzed separately as they represent the total cost of absence from work. Sick leave days were decreased, and salary costs were increased by intervals of 10% to 50% lower and higher values.

Statistical analysis of means costs was performed using Student's t-test. The distribution of the overall societal costs was nearly normal, so linear regression models were used to test the effect of background factors (age, sex, hospital) on the dependent variables.

4.1.2 Study III

Study III focused on evaluating the QOL, patient satisfaction, and patient preference in hindsight after treatment for uncomplicated acute appendicitis by either appendectomy or antibiotic therapy. The study aimed to compare QOL, patient satisfaction, and treatment preference at long-term follow-up as post-hoc outcomes of the APPAC trial. Assessment of QOL and patient satisfaction and treatment preference in hindsight was conducted by unmasked, structured telephone interviews conducted by three researchers not involved in the original APPAC trial or patient treatment.

QOL was evaluated using the validated EQ-5D-5L questionnaire.[281,282] The descriptive questions cover five dimensions of everyday life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and categorize them into five levels ranging from no problems to extreme problems (numerical scoring from 1-5). The numerical scores for the five dimensions were then combined into a single 5-digit number defining the respondent's health state. These were then converted into a single index value ranging from 0 (death) to 1 (full health).[77] Country specific validation tools were used for specific populations, but because this validation was not available for Finland, the validation for Denmark was used according to the recommendation of the EuroQOL group, as the Danish population closely resembles the Finnish population. The resulting value represents the patients QOL. We slightly modified the questionnaire to better suit our patient population by asking specifically about abdominal pain/discomfort. Additionally, the EQ-5D-5L reflects the patient's self-rated health using a vertical visual analogue scale ranging from 0 (worst health imaginable) to 100 (best health imaginable).

Patient satisfaction to the treatment they received was evaluated by asking the patients to rate their satisfaction on a 5-point Likert scale (very unsatisfied, unsatisfied, indifferent, satisfied, very satisfied). Knowing the course and outcome of the received treatment, patients were also asked whether they would reselect the randomized treatment again.

Analysis was performed according to the intention-to-treat principle, but also a subgroup analysis was used after categorizing the patients into three clinically interesting subgroups: the appendectomy group, the successful antibiotic treatment group, and the primary antibiotic treatment followed by later appendectomy group. Continuous variables were described using means or medians and the range of values or 95% confidence intervals (95% CI) of medians for nonnormally distributed variables. Percentages and frequencies were used for categorical variables. Treatment satisfaction was analyzed with multivariable cumulative logistic regression adjusted for age and sex. Treatment preference was analyzed with multivariable, multinomial, logistic regression adjusted for age and sex. The results from the cumulative regression analyses were quantified using odds ratios or cumulative odds ratios (COR) with 95% CIs. Two-sided tests were used. P-values less than 0.05 were considered statistically significant. Statistical analyses were carried out using SAS system for Windows, version 9.4 (SAS Institute Inc, Cary, NC).

4.2 The OPTICAP trial

Study II was based on the clinical phase of the OPTICAP (OPTImization of Computed tomography for acute APendicitis) trial. The OPTICAP trial was an interpatient noninferiority randomized trial conducted at Turku University Hospital. The trial hypothesis was that contrast-enhanced low-dose CT protocol is noninferior to standard contrast-enhanced CT protocol in radiologically diagnosing acute appendicitis. The clinical phase of the trial was preceded by the preclinical phase in which several CT protocols were optimized by a phantom model for imaging accuracy and radiation dose. The low-dose protocol selected for this study was the best performing in the phantom study phase.

Patients aged 18 to 60 years with a body mass index (BMI) under 30 kg/m^2 with a clinical suspicion of acute appendicitis who were admitted to the emergency department were evaluated by a senior research surgeon, and if they confirmed the clinical suspicion, the patient was recruited to participate in the study after informed consent. The target population for enrollment consisted of patients with symptoms varying in the degree of severity to include patients with both forms, uncomplicated and complicated, of acute appendicitis. The exclusion criteria were otherwise the same as in the APPAC trial (studies I and III), with the addition of a BMI over 30 kg/m^2.

All patients enrolled in the study were randomized to undergo CT imaging of the abdomen by both the contrast-enhanced standard and the contrast-enhanced low-dose protocols in a randomized order to allow for direct comparison of the images in regard to diagnostic accuracy, quality, and readability. Randomization of the sequences was performed using random permutated block randomization with a block size of 8. Patients were imaged during the early and late portal venous phase with routine patient weight-adjusted intravenous Iodinated contrast media (1.5mL7kg; concentration 350 mgI/mL; injection rate 3 mL/s) from the diaphragm to the symphysis. Randomization of the imaging protocol order was performed to avoid bias resulting from the timing of intravenous contrast media in the consecutive protocols. The primary outcome was the accuracy of the low-dose protocol in diagnosing acute appendicitis. Secondary outcomes included radiation dose incurred by the patient from each protocol, appendiceal visualization, accuracy of differential diagnosis between the forms of appendicitis, NAR, APR, and the interval between imaging and appendectomy.

Imaging was performed at the emergency department of Turku University Hospital (Aquilion One, Toshiba Medical Systems, Otawara, Japan). The standard CT protocol used for reference was the protocol currently used for abdominal imaging at Turku University Hospital and used 120kV, standard iterative reconstruction and had a noise index of 12.5. The low-dose protocol was selected based on the preclinical phase of the OPTICAP trial[198] and used 100kV, standard iterative reconstruction and had a noise index of 14.5.

The radiologist on-call reviewed the images and made the radiological diagnosis according to which the patient was treated in the clinical setting. The criteria for the radiological diagnosis of uncomplicated and complicated acute appendicitis were identical to the APPAC trial (studies I and III).

Later, blinded review was performed primarily by an abdominal radiologist and also by an emergency radiologist for comparison. The images were assessed in a randomized order to avoid direct comparison between the two images from each patient, consequently minimizing bias in protocol evaluation. The radiologists described appendiceal visualization, the likelihood of appendicitis, and the criteria for uncomplicated and complicated acute appendicitis. Due to a limited sample size diagnostic accuracy was chosen to illustrate how well the protocols performed. Diagnostic accuracy was measured using the overall proportion of correct acute appendicitis diagnoses (no appendicitis, uncomplicated acute appendicitis, complicated acute appendicitis) in each protocol for both of the radiologist separately. All patients with a diagnosis of acute appendicitis, either uncomplicated or complicated, underwent laparoscopic appendectomy. The diagnosis as well as the differential diagnosis between the forms of appendicitis was confirmed by operative findings and histopathological analysis of the appendix. Patients with a radiological diagnosis of something else than appendicitis were treated according to that diagnosis. This primary diagnosis was concluded as correct if the patient did not have recurring symptoms requiring a new visit to the emergency department and treatment within 6 months of the initial visit.

Radiation dose was illustrated by volume CT dose index ($CTDI_{vol}$) because it reflects the radiation dose released from the CT machine. The estimation of effective dose was calculated based on the $CTDI_{vol}$, the mean imaging length, and the coefficients described by Huda et al[283].

The study was approved by the Ethical Committee of the Turku University Hospital District.

Statistical analysis

Sample size calculations were based on a noninferiority test for binomial proportion. We anticipated an 85% success rate in diagnosis with the standard protocol. A noninferiority margin of -15 percent for the difference between success rates of the protocols was used for the sample size calculations. We estimated that 108 images would yield a power of 0.9 ($1-\beta$) to establish whether the OPTICAP low-dose CT protocol was inferior to the standard protocol using a significance level α of 0.05. With an estimated dropout rate of 10%, a total of 120 images were needed and 60 patients were necessary for study enrollment.

Categorial variables were characterized using frequencies and percentages. Continuous variables were characterized using means and standard deviations (SD), or if the data were skewed as medians with a range of values. Missing values were excluded from the analyses. Noninferiority of the proportion of correct acute appendicitis diagnosis was evaluated using the 95% CI of the difference between protocols. The predefined noninferiority margin difference of 15% points was used in the evaluation. Weighted kappa with 95% CIs was used to evaluate the agreement in diagnosis of the two protocols. The analyses of radiation dose were performed using linear model with repeated measurements where protocol was used as a repeated measure. The final model included protocol, sex, BMI, and age, and also interactions of protocol and BMI (protocol × BMI) and sex and BMI (sex × BMI). The interactions were also evaluated, but statistically nonsignificant interactions were excluded in the final model. Residuals were checked to justify the analyses. The results were quantified using slopes with 95% CIs and the model-based estimates for differences between the protocols with 95% CIs in BMI values 20 kg/m^2, 25 kg/m^2, and 30 kg/m^2. Regression plots were used for illustrative purposes to describe the differences. P-values less than 0.05 were considered statistically significant. Statistical analyses were carried out using SAS system for Windows, version 9.4 (SAS Institute Inc, Cary, NC).

4.3 The APPAC II trial

The APPAC II trial was a multicenter, open-label, noninferiority randomized controlled trial conducted at nine Finnish Hospitals: four university hospitals (Turku, Oulu, Tampere, and Kuopio) and five central hospitals (Pori, Jyväskylä, Mikkeli, Seinäjoki, and Rovaniemi). The aim of the study was to compare p.o. antibiotic monotherapy with i.v. followed by p.o. antibiotic therapy for CT scan confirmed uncomplicated acute appendicitis in terms of treatment efficacy, post-intervention complications, length of hospital stay and treatment costs. The study hypothesis was that p.o. antibiotic monotherapy is noninferior to the combination of i.v. followed by p.o. antibiotics.

Similar to the APPAC trial, patients aged 18–60 years with the suspicion of acute appendicitis underwent CT imaging, and if the diagnosis of uncomplicated acute appendicitis was confirmed, they were enrolled into the study. Based on the OPTICAP trial, patients with a BMI of under 30 kg/m^2 are imaged with a low-dose CT protocol, and patients with a BMI of over 30 kg/m^2 with the standard CT imaging protocol. In some centers, CT with tube current modulation was used. The exclusion criteria were similar to those of the APPAC trial with the additional of contraindications for the use of antibiotics (allergy to the antibiotic agent or auxiliary substance of the drug, or interaction with other medications of the patient). In the case of moxifloxacin, additional contraindications included electrolyte imbalance, liver failure, and heart condition. In terms of quinolones, additional contraindications included epilepsy and previously diagnosed tendon rupture, or tendinitis related to quinolone use. The radiological criteria for the diagnosis of uncomplicated and complicated acute appendicitis were also identical to the criteria used in the APPAC trial. However, in the APPAC II trial, a structured reporting template for abdominal CT findings was implemented and used (Table 5).

Table 5. Structured reporting template for CT imaging and diagnosis of acute appendicitis.

Descriptive part	Structured report of appendiceal findings
Technique and overall findings of the whole abdomen	Appendix visualization *Not visualized* *Partly or unclearly visualized* *Completely visualized*
	Appendix transverse diameter (mm)
	Probability of appendicitis *Not likely* *Rather unlikely* *Rather likely* *Very likely*
	Appendicitis categorization *Uncomplicated acute appendicitis** *Complicated acute appendicitis**
	Other diagnosis *Diverticulitis* *Pelvic inflammatory disease* *Complicated ovarian cyst* *Ileitis* *Colitis* *Ileus or intestinal obstruction* *Hydronephrosis* *Ureter stone* *Tumor* *Other diagnosis*

* The specific criteria are the same as reported in the APPAC trial.
Adapted from Sippola et al 2018, Haijanen et al 2018.

Patients were randomized by an online database (BCB Medical) in a 1:1 allocation ratio to receive either antibiotics as p.o. monotherapy or i.v. followed by p.o. combined therapy. Patients in the p.o. only group received moxifloxacin 400 mg once daily for a total of seven days with the first two doses administered in the hospital. Patients in the i.v. followed by p.o. first received i.v. ertapenem sodium 1 g once daily for two days, followed by p.o. levofloxacin 500 mg once daily and metronidazole three times a day for five days. The primary outcome was defined as treatment success of the randomized treatment at 1-year follow-up as in the antibiotic therapy group of the APPAC trial: the resolution of uncomplicated acute appendicitis resulting in discharge from the hospital without need for appendectomy during the primary hospitalization and no recurrent appendicitis for one year. Secondary outcomes included post-intervention complications, length of hospital stay, late recurrence (after one year) of acute appendicitis, QOL, length of sick leave and treatment costs. If the patient was suspected of having recurrent appendicitis, they underwent appendectomy based on clinical symptoms and findings without repeat CT imaging. Follow-up by telephone interview was performed at one week, two months, and one, and will continue at three, five, and ten years.

The trial was approved by the Ethical Committee of the Turku University Hospital District.

Statistical analysis

The APPAC II trial was a noninferiority study with the primary outcome evaluated by first assessing if treatment success was over 65% with lower limit 95% CI and secondly by assessing if the difference of proportions for success was less than the 6% inferiority margin based on 95% CIs. Categorical variables were characterized using frequencies and percentages and means and standard deviations or means with range and 25th and 75th percentages were used for continuous variables. Secondary outcomes were analyzed using chi-squared test, independent samples t-test or Mann-Whitney U-test. The assumptions of the tests were checked for justifications of the analyses. P values less than 0.05 were considered statistically significant. Statistical analyses were carried out using SAS system for Windows, version 9.4 (SAS Institute Inc, Cary, NC).

4.4 The APPAC III trial

The APPAC III trial was a multicenter, placebo-controlled, double-blind, superiority, randomized trial conducted at all five Finnish University Hospitals (Turku, Tampere, Oulu, Kuopio, and Helsinki). The APPAC III trial aimed at assessing the role of antibiotic therapy in the resolution of CT-confirmed uncomplicated acute appendicitis and the possible spontaneous resolution of uncomplicated acute appendicitis by symptomatic care by comparing i.v. followed by p.o. antibiotic therapy and i.v. followed p.o. placebo. The study hypothesis was that antibiotic treatment is necessary in the resolution of uncomplicated acute appendicitis.

The APPAC III trial was partially ongoing simultaneously with the APPAC II trial, so the inclusion and exclusion criteria were identical. Only senior surgeons were allowed to enroll patients in the APPAC III trial. Enrollment into the APPAC III trial was dependent on hospital pharmacy hours, as the pharmacy delivered the randomized, placebo-controlled, medications by order. The hospital pharmacy hours differed between the participating centers but, generally, randomization was possible between 8 am and 2 pm between Monday and Thursday. During hospital pharmacy hours, patients are first asked to participate in the APPAC III trial and if they declined, they had the opportunity of participating in the APPAC II trial in participating centers except for Helsinki University Hospital. Outside hospital pharmacy hours, patients were enrolled in the APPAC II trial. Identical to the APPAC II trial, the diagnosis of uncomplicated acute appendicitis was confirmed by either low-dose CT for patients with BMI <30 kg/m^2 or standard protocol CT for patients with BMI >30kg/m^2.

An online database (BCB Medical) was used to randomized patients into the two treatment groups in a 1:1 equal allocation ratio. Patients randomized to the antibiotic treatment group will receive i.v. 1 g ertapenem sodium once daily for three days followed by p.o. 500 mg levofloxacin once daily and p.o. 500 mg metronidazole three times a day for four days. This is the same antibiotic regimen as studied in the original APPAC trial. Patients randomized to the placebo group will receive i.v. and p.o. placebo in an identical schedule. The trial is double-blinded. After randomization, the surgeon informed the hospital pharmacy of the randomization number provided by the database and manufacturing of the drug begun. The hospital pharmacy manufactured the drugs to appear exactly identical for blinding the treatment from the patient, and the nurses and surgeons when caring for the patient. The intravenous antibiotic and placebo were delivered in similar intravenous bags to the surgical ward, where the randomized treatment was initiated. The p.o. antibiotic and placebo were manufactured into identical colored gelatin capsules; thus, the capsules do not have a specific smell and the characteristic metallic taste of metronidazole was simultaneously hidden. Colored capsules were selected as levofloxacin tablets have characteristic red spots, which could possibly be seen through other kinds of capsules. Patients received the p.o. treatments in two similar plastic bottles with labels and dosage instructions, one containing levofloxacin or placebo and the other containing metronidazole or placebo, upon discharge from the hospital. If a patient was suspected of having an adverse reaction to the randomized treatment (antibiotic or placebo), a safety copy of the randomized code was located in the hospital pharmacy and was only opened in such cases.

The primary endpoint was treatment success defined as the resolution of uncomplicated acute appendicitis resulting in discharge from the hospital without need for appendectomy within 10 days after beginning of the randomized treatment. If a patient participating in the APPAC III was suspected of having recurrent appendicitis, they underwent surgical intervention based on clinical symptoms without repeat imaging. The diagnosis of recurrent appendicitis was confirmed by surgical and histopathological findings. The secondary outcomes included postintervention complications, recurrent symptoms after treatment until one-year, recurrent appendicitis, length of sick leave, length of hospital stay, cost of treatment, and QOL. Patients were followed-up by telephone at days 2-4 (depending on the discharge day), day 10, two months, and at one, three, five and ten years since randomization. Additionally, laboratory follow-up of leukocyte count and CRP will be conducted by a blood draw at 2–4 days and/or 10 days since randomization.

A pilot study of five patients was conducted at Turku and Kuopio University Hospitals to certify drug manufacturing to order at the hospital pharmacies and to ensure satisfactory blinding in real-life. The pilot did not result in changes to the study protocol. However, based on this pilot, and previously recognized challenges in conducting trials in the emergency setting, as well as factors particular to the study design (randomization only by senior surgeons, opening hours of hospital pharmacies), we created three different scenarios for study power analysis and number of patients to be enrolled, to deal with the challenges and delays in enrolment (Table 6). A power of 0.8 and one-sided significance level of 0.05 were used in the sample size calculations. The final scenario was decided based on speed of patient enrolment by a study committee consisting of the outside safety monitoring committee on June 1st, 2019, and scenario C was selected.

Table 6. Enrolment scenarios for the APPAC III trial.

	Scenario A	**Scenario B**	**Scenario C**
Clinically important difference between treatments*	15%	20%	25%
Estimated success rate in placebo group	79%	75%	69%
Patients per group	64	41	29
Total number of patients (including anticipated 10% dropout)	142	92	64

* The estimated clinically important difference between the treatment groups or rescue appendectomy rate was determined arbitrarily based on clinical relevance at the time of study planning.
Adapted from Sippola et al 2018.

An interim analysis was conducted after 46 patients have been enrolled in the trial and have been followed-up for 10 days to ensure patient safety. No statistical tests will be conducted at this time.

The APPAC trial III was approved by the Ethical Committee of the Turku University Hospital District.

Statistical analysis

The APPAC III trial is a superiority trial. The main analyses will be based on the intention-to-treat principle. Categorical variables will be characterized by treatment with frequencies and percentages. Continuous variables will be characterized by treatment with means and SD or medians with range and 25^{th} and 75^{th} percentiles. Difference in treatment success will be tested using Fisher's one-sided test. Secondary outcomes will be analyzed using x^2-test, Mann-Whitney U-test or independent samples test. P-values less than 0.05 will be considered statistically significant. Statistical analyses will be performed using SAS System for Windows (version 9.4 or later).

5 Results

5.1 The APPAC trial: cost analysis

A total of 530 patients were enrolled in the APPAC trial between November 2009 and June 2012. Out of the 530 patients, 257 were randomized to receive antibiotic therapy and 273 to undergo appendectomy. Of the 257 randomized to antibiotic therapy, 15 patients underwent appendectomy during primary hospitalization. During the 1st year of follow-up, 55 patients in the antibiotic group underwent appendectomy based on clinical suspicion of recurring symptoms. Patient demographics were similar between the study groups[14] and are shown in Table 7.

Table 7. Baseline patient demographics of the APPAC trial.

Column 1	**Antibiotic therapy group (n=257)**	**Appendectomy group (n =273)**
Sex		
Female	102 (40%)	99 (36%)
Male	155 (60%)	174 (64%)
Age (median (25th-75th percentile)	33.0 (26-47)	35.0 (27-46)
WBC count (SD)	11.7 (3.9)	12. 0 (4.0)
CRP (median (25th-75th percentile)	29.0 (11-63)	36.0 (14-61)
VAS pain score (median (25th-75th percentile)	5.0 (4-7)	6.0 (4-7)

WBC white blood cell; CRP C-reactive protein; VAS visual analogue scale; SD standard deviation.
Adapted from Salminen et al 2015.

The individual source of costs by group are presented in Table 8. The total hospital charges ($p<0.001$) and loss in productivity ($p<0.001$) were higher in the appendectomy group than the antibiotic therapy group. Costs resulting from medicines prescribed upon discharge were higher in the antibiotic group than the appendectomy group (p<0.001). The resulting overall societal costs were 1.6 times in the appendectomy group than the antibiotic group (p<0.001). Sensitivity analyses indicated that salary costs and length of sick leave had a significant effect on the overall societal costs. With 30% and 50% higher salary costs, the cost advantage for antibiotic therapy was 2918.3 € (95% CI 2522.7–3313.8) and 3367.2€ (95% CI 2910.8–3823.6) respectively. In terms of sick leave, both 30% and 50% shorter sick leave were advantageous for antibiotic therapy with savings of 1876.2 € (95% CI 1617.4–2135.0) and 1630.4 € (95% CI 1379.6–1863.8) respectively. Linear regression models, controlled for sex, age, and hospital, all showed higher costs related to appendectomy. Available independent variables explained 30.5–37% of variation in overall societal costs.

Table 8. Components of overall societal costs.

Cost	**Antibiotic therapy (€ (SD))**	**Appendectomy (€ (SD))**
Total hospital charges	1806.8 (1368.7)	2882.0 (725.6)
Imaging costs	136.3 (135.0)	110.5 (129.9)
Laboratory costs	57.2 (46.0)	78.2 (52.8)
Medicine costs	44.5 (4.6)	8.9 (9.2)
Medicines prescribed upon discharge	29.0 (8.0)	10.4 (4.8)
Loss in productivity	1937.6 (1131.2)	3112.1 (1379.1)
Overall societal costs	3744.4 (1870.3)	5989.2 (1691.1)
Salary costs		
30% more	4867.7 (2431.7)	7786.0 (2198.7)
50% more	5616.6 (2805.5)	8983.8 (2537.0)
Length of sick leave		
30% less	3313.1 (1669.3)	5189.3 (1352.3)
50% less	3025.6 (1558.8)	4656.0 (1147.6)

Adapted from Sippola et al 2017.

5.2 The OPTICAP trial

A total of 60 patients were enrolled in the OPTICAP trial between November 2015 and August 2016 and randomized to undergo two consecutive imaging protocols in a randomized order (the low-dose and standard protocols). After enrollment, 3 patients were excluded due to protocol violations (1 allergy to iodine contrast media, 1 CT scanner malfunction, and 1 treated successfully with antibiotics). The remaining 57 patients were successfully imaged with the low-dose protocol and 55 with the standard protocol (patient positioning errors leaving the appendix out of the imaging window in 2 patients). Acute appendicitis was diagnosed in 49 patients (86%) and they underwent appendectomy for histopathological confirmation of the diagnosis. The laparoscopic approach was recommended, but 5 (10%) patients were operated on via open technique. Patient demographics are shown in Table 9.

Table 9. Patient demographics of the OPTICAP trial.

Patient characteristics	**N = 57**
Sex	
Female	26 (46%)
Male	31 (54%)
BMI mean (min, max)	25.4 (16.1, 30.0)
Age in years mean (min, max)	33.3 (19.9, 60.3)
WBC count mean (min, max)	13.4 (4.7, 22.9)
CRP mean (min, max)	42.9 (1.0, 243.0)
Median VAS pain score (25th, 75th percentiles)	5.0 (4.0, 7.0)

WBC white blood cell count; CRP C-reactive protein; VAS Visual analogue scale.
Adapted from Sippola et al 2018.

Blinded analysis of the CT images was performed by two radiologists; primarily by an abdominal radiologist and secondarily by an emergency radiologist; the results are shown in Table 10. The low-dose CT protocol was not inferior to the standard protocol in diagnostic accuracy in the primary analysis by the abdominal radiologist. The diagnostic accuracy rate was 1.05 percentage points lower using the low-dose protocol than the standard protocol but based on the predefined non-inferiority margin of 15%, it was not inferior to the standard protocol. In the 55 patients successfully imaged with both protocols, all diagnoses made by the abdominal radiologist were identical between the low-dose and standard protocol (95% CI 1.0-1.0, weighted kappa 1.0). The accuracy to detect appendicitis and to differentiate between the forms of appendicitis in this analysis are also shown in Table 10.

A similar analysis was performed by the emergency radiologist. The results are shown in Table 10. In this analysis, the diagnostic accuracy rate of the low-dose protocol was 2.5% higher as compared with the standard protocol, confirming the noninferiority of the low-dose protocol when compared to the standard protocol. In all 55 patients imaged successfully with both protocols, the diagnoses were identical between the protocols in 53 cases (95% CI 0.87-1.0, weighted kappa 0.95). The accuracy to detect appendicitis and to differentiate between the forms of appendicitis in this analysis are also depicted in Table 10.

Table 20. Accuracy of the low-dose and standard imaging CT protocols.

	Low-dose protocol	**Standard protocol**
Accuracy of diagnosis		
Abdominal radiologist	79% (66-89% 95% CI)	80% (67-90% 95% CI)
Emergency radiologist	83% (70-91% 95% CI)	80% (67-90% 95% CI)
Accuracy to detect appendicitis		
Abdominal radiologist	97%	98%
Emergency radiologist	98%	100%
Accuracy to differentiate between the forms of appendicitis		
Abdominal radiologist	80%	79%
Emergency radiologist	81%	77%
Visualization of the appendix		
Abdominal radiologist	95%	100%
Emergency radiologist	98%	98%

Based on Sippola et al 2018.

The NAR was 0% (0/49). Perforation was seen in surgery in 3 patients, and 2 of these were seen on CT. The APR was 6% (3/49). The median time from image acquisition to operation was 339 minutes (75–1942 min range), and for the patients with perforations the times were 223 min, 271 min, and 255 min. The perforations were not related to delay due to imaging preoperatively.

In 3 patients, the CT scan was normal without a specific diagnosis. A differential diagnosis to acute appendicitis was detected in 5 patients imaged for suspected acute appendicitis (2 cases of diverticulitis, 1 lymphadenopathy, 1 ruptured ovarian cyst, and 1 gastroenteritis). The patient diagnosed with diverticulitis was treated with antibiotics, and the other patients with radiological diagnoses were treated symptomatically. None of these patients were readmitted to any emergency department within the hospital district during a follow-up of 6 months.

The effective radiation dose was calculated using the mean imaging length of 48 cm because the imaging length varied by patient. The effective doses were 3.32 mSv for the low-dose and 4.43 mSv for the standard protocol. The mean $CTDI_{vol}$ were

4.24 mGy (1.55 SD) for the low-dose protocol and 5.67 mGy (1.93 SD) for the standard protocol. The exact difference between the protocols varied, but at all BMI values between 20 and 30 kg/m^2 it was found to be statistically significant. The final model for radiation dose included the main effects of protocol ($p<0.001$), BMI ($p<0.001$), age ($p=0.004$) and sex ($p=0.003$), and the interactions of protocol and BMI ($p<0.001$) as well as sex and BMI ($p<0.001$). As anticipated, an increase in radiation dose was seen with increases in BMI. This association was stronger in the standard protocol (slope 0.32, 95% CI 0.23–0.42), than in the low-dose protocol (slope 0.21, 95% CI 0.12–0.30). The association of BMI and radiation dose was stronger in males than in females. The radiation doses are shown in Figure 9.

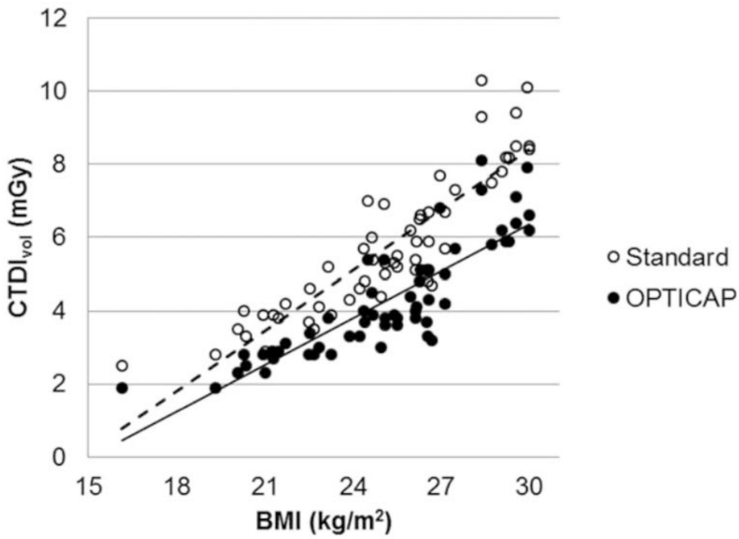

Figure 9. Radiation dose in $CTDI_{vol}$ at different BMIs. ($CTDI_{vol}$ volume CT dose index, BMI body mass index). From Sippola et al 2020.

5.3 The APPAC trial: quality of life and patient preference

The QOL and patient preference study was conducted at a median follow-up of 7 years (range 5.7–8.2 years). Out of the 530 patients originally randomized in the APPAC trial, 423 (80%) were reached and participated in the telephone interview. Of the 423 patients reached, 217 (51%) were originally randomized to the appendectomy group and 206 (49%) to receive antibiotic treatment. Of the 206 patients originally randomized to receive antibiotic, 81 (39%) patients underwent appendectomy during the follow-up period (14 (17%) during primary hospitalization and 67 (83%) for suspected recurrent appendicitis). There were no differences in response rates between the groups: 80% (217/273) in the appendectomy group and 80% (206/257) in the appendectomy group. Patient demographics are shown in Table 11.

Table 31. Patient demographics of the QOL analysis

	Appendectomy group (n=217)	**Antibiotic group (N=206)**
Sex		
Female	76 (35%)	84 (41%)
Male	141 (65%)	122 (59%)
Mean age in years (SD)	45 (12.0)	43 (12.5)

SD Standard deviation.
Adapted from Sippola et al 2020.

There was no difference in QOL between patients in the appendectomy and antibiotic groups, with a median health index value 1.0 (95% CI 0.86–1.0) in both groups (p=0.96). Self-rated health VAS values were also similar between the groups with a median health of 79.7 (95% CI 77.7–81.7) in the appendectomy group and 79.5 (95% CI 77.5–81.4) in the antibiotic group.

Patient satisfaction based on the intention-to-treat analysis is shown in Figure 10 and based on the subgroup analysis in Figure 11. Patients in the appendectomy group significantly more satisfied than patients in the antibiotic group (p<0.001). The subgroup analysis illustrated that this difference resulted from the patients randomized to the antibiotic group but later undergoing appendectomy for suspected recurrence. There was no difference in patient satisfaction between patients in the appendectomy group and the patients with successful antibiotics treatment (no later appendectomy) (COR 7.8, 95% CI 0.5-1.3, p=0.36). Patients with appendectomy or successful antibiotic treatment were more satisfied than the patients first randomized to antibiotic therapy undergoing later appendectomy for suspected recurrence (COR 7.7, 95% CI 4.6-12.9, and COR 9.7, 5.4-15.3 95% CI, p<0.001, respectively). Multivariable cumulative logistic regression analysis was used to adjust the results for age and sex.

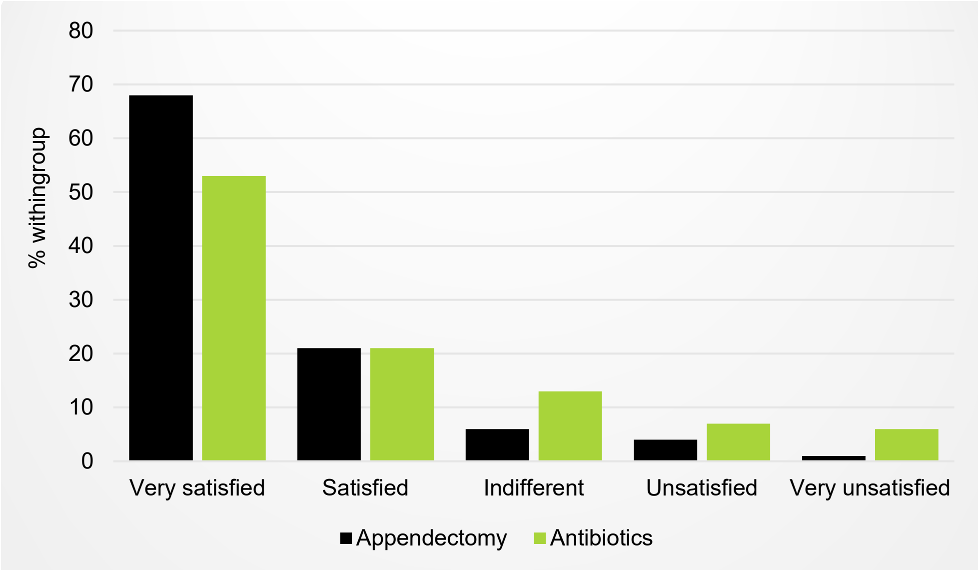

Figure 10. Patient satisfaction in the appendectomy and antibiotic groups (intention-to-treat analysis). Adapted from Sippola et 2020.

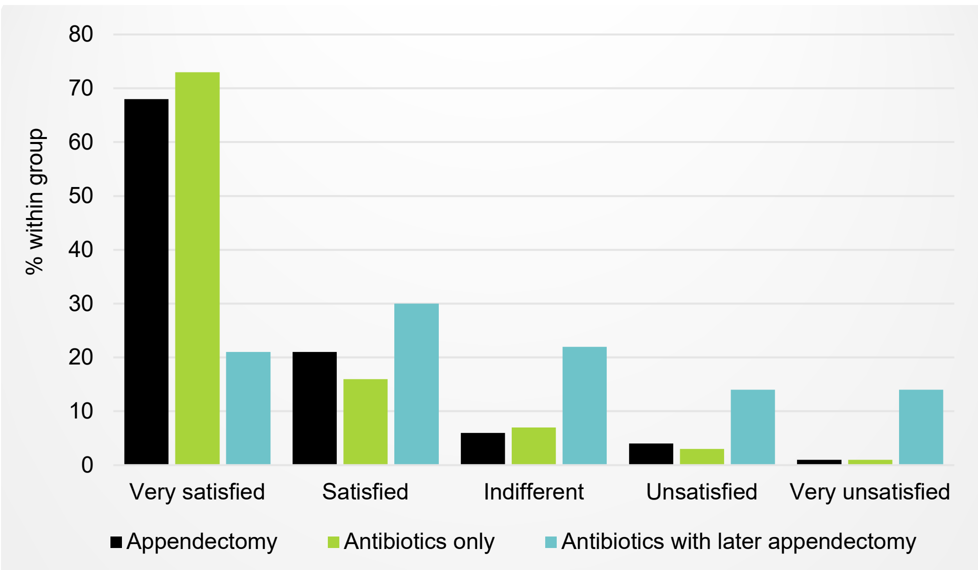

Figure 11. Patient satisfaction in the appendectomy, antibiotics only, and antibiotics with later appendectomy groups (subgroup analysis). Adapted from Sippola et 2020.

Treatment preference in hindsight based on the intention-to-treat analysis is shown in Figure 12 and based on the subgroup analysis in Figure 13. Patients in the appendectomy group would more likely choose the original randomized treatment again in hindsight as compared to the antibiotic group (p<0.001). In the subgroup analysis, patients in the later appendectomy group were statistically significantly more likely to choose the different treatment option compared than patients in appendectomy group (OR 8.8, 95% CI 4.9-15.9, p<0.001) and patients in the successful antibiotic treatment group (OR 11.2, 95% CI 5.6-22.2, p<0.001). Multivariable multinomial logistic regression analysis was used to adjust the results for age and sex.

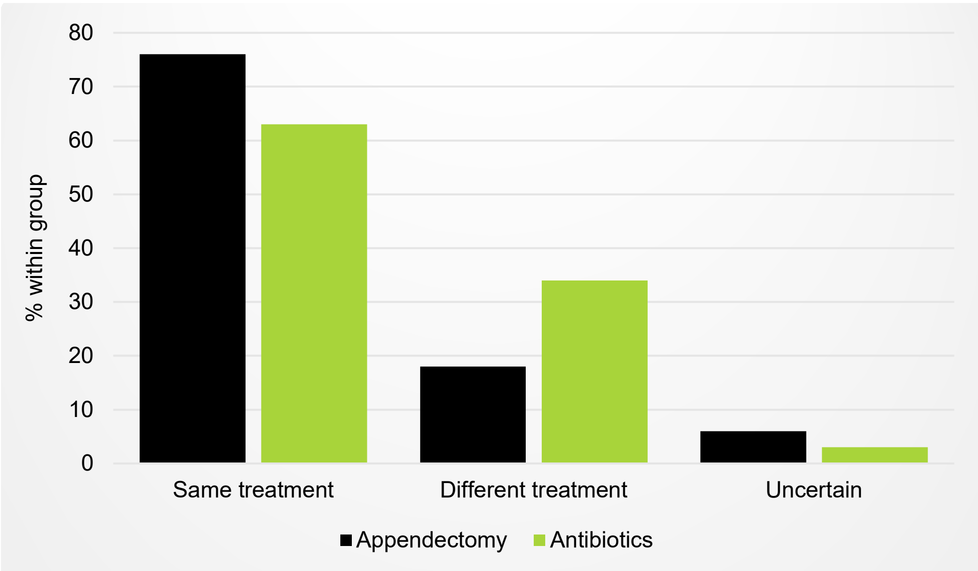

Figure 12. Treatment preference in hindsight in the appendectomy and antibiotic groups (intention-to-treat analysis). Adapted from Sippola et 2020.

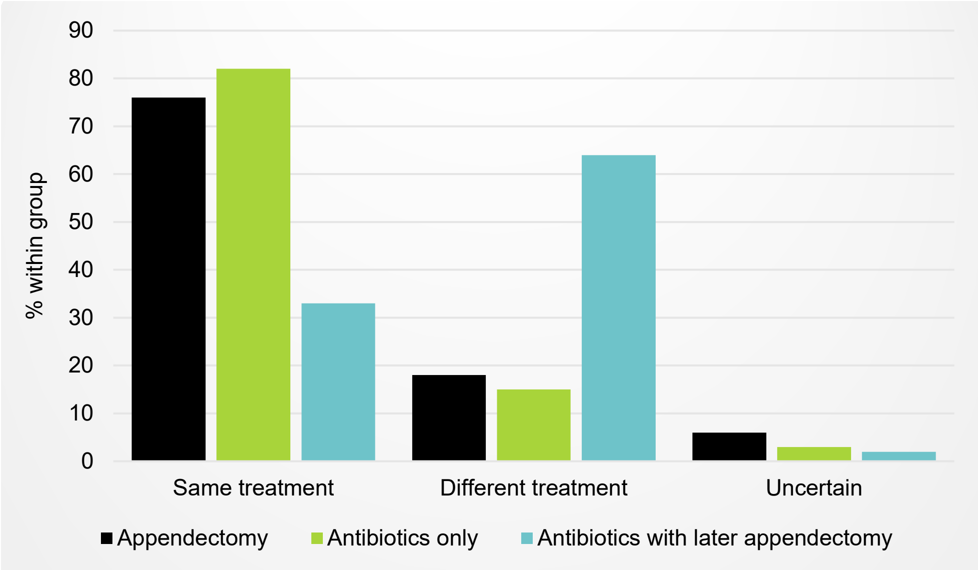

Figure 13. Treatment preference in hindsight in the appendectomy, antibiotics only, and antibiotics with later appendectomy groups (subgroup analysis). Adapted from Sippola et 2020.

5.4 The APPAC II trial

Between April 2017 and November 2018, 603 eligible patients with CT-confirmed uncomplicated acute appendicitis were identified from a total of 3512 patients with clinical suspicion of acute appendicitis, consented to participate in the study, and randomized to receive either i.v. ertapenem followed by p.o. levofloxacin and metronidazole or to receive p.o. moxifloxacin. After randomization, 20 patients were excluded from analysis due to early patient withdrawal of consent without receiving allocated treatment (16 patients) or randomization protocol violations (4 patients). A total of 583 patients were included in the primary analyses, 288 in the i.v. followed by p.o. group and 295 in the p.o. group. Patient demographics of all randomized patients (excluding patients incorrectly randomized with complicated appendicitis on CT) are shown in Table 12. The follow-up rate was 99.7% (581/583) with two patients lost to follow-up due to moving abroad.

Table 12. Baseline patient demographics of the APPAC II trial.

	P.o. group (n=301)	**I.v. + p.o. group (n=298)**
Sex		
Female	137 (46%)	126 (42%)
Male	164 (54%)	172 (58%
Age median (min-max)	34 (18-59)	33 (18-59)
BMI median (IQR)	26.8 (24.2-30.1)	26.4 (23.6-30.2)
WBC count median (IQR)	12.5 (9.4-14.9)	12.2 (9.1-14.9)
Neutrophil count median (IQR)	9.4 (6.6-11.9)	9.4 (6.1-11.9)
CRP median (min-max)	29.9 (11.0-61.0)	34.0 (13.0-62.6)
VAS pain score mean (SD)	5.2 (2.3)	5.2 (2.4)
Appendiceal diameter (mm) on CT mean (SD)	10.9 (2.6)	10.7 (2.4)

BMI body mass index; WBC white blood cell; CRP C-reactive protein; VAS visual analogue scale; CT computed tomography; IQR Interquartile range; SD Standard deviation.
Adapted from Sippola et al 2020.

In the p.o. group, out of the 295 patients randomized, 27 (9.2%) patients underwent appendectomy during primary hospitalization and 61 (20.7%) patients after primary discharge during the one-year follow-up period. Thus, the treatment success at one year was 70.2% (95% CI 65.8%–74.6%). In the i.v. followed by p.o. group, 288 patients were randomized and of these patients 22 (7.6%) underwent appendectomy during primary hospitalization and 53 (18.5%) after primary discharge during one-year follow-up. In this group, treatment success at one year was 73.8% (95% CI 69.5%–78.1%). According to intention-to-treat analysis, there was a 3.6% difference (95% CI -2.5% to 9.7%) in the primary outcome between the two groups. According to our statistical hypothesis, both groups had a higher treatment success rate than the predefined 65%. Although the point estimate for difference of treatment success between groups was below the 6% noninferiority margin, the upper limit of 95% CI exceeded this predefined margin.

The decision to proceed to appendectomy was based on the patient not recovering as suspected during primary hospitalization, or suspicion of recurrent appendicitis after primary discharge. After excluding patients with complicated acute appendicitis on CT (18 patients in the p.o. group and 11 patients in the i.v.+p.o. group), the true primary failure rates were 6.1% and 3.8.% (p=0.25), respectively. Primary treatment failure was associated with body temperature over 38°C on admission (OR 3.8, 95% CI 1.3–10.7) or appendiceal diameter 15 mm or greater on

CT (OR 6.6, 95% CI 2.6–16.4). During one-year follow-up, 61 p.o. group patients and 53 i.v.+p.o. group patients underwent appendectomy. As 5 p.o. patients and 8 i.v.+p.o. patients did not have appendicitis on histopathological examination, true recurrence rates after successful initial antibiotic treatment were 20.9% and 16.7% (p=0.22) within a year, respectively. Statistically significant prognostic factors for recurrent appendicitis could not be identified after analyzing gender, age, VAS, BMI, WBC count, neutrophil count, CRP, body temperature, symptom duration, appendiceal diameter and fluid or edema around the appendix.

Secondary outcomes of complications are presented in Table 13. There was no mortality during the follow-up period. QOL and treatment costs have not yet been analyzed and reported. Statistically significant differences were not found in terms of total complication rate (p=0.22), length of primary hospital stay (p=0.38), length of total hospital stay during 1-year (p=0.91), and length of sick leave (p=0.42).

Table 13. Secondary outcomes of the APPAC II trial.

	P.o. group (n=295)	**I.v. + p.o. group (n =288)**
Complications		
Total complication rate % (95%CI)	4.8 (2.3-7.2)	7.3 (4.3-10.4)
Related to antibiotic treatment(n)		
Prolonged diarrhea	0	5
Tendinitis	1	1
Skin eczema	3	3
Other allergic reaction	1	2
Candidiasis	0	3
Blurred vision	1	0
Related to operative treatment (n)		
Surgical site infection	2	3
Abdominal, incisional pain or obstructive symptoms	7	7
Length of hospital stay (h)*		
Primary	28.9 (23.0-41.9)	29.9 (23.3-43.2)
Overall during 1-year	36.5 (24.0-63.1)	35.7 (24.7-58.6)**
Length of sick leave (d)**	7.0 (3.0-8.0)	7.0 (3.0-9.0)

* median (Interquartile range).
** Information available for 286 patients due to 2 lost to follow-up.
Adapted from Sippola et al 2020, (submitted).

Of all patients who underwent appendectomy, four were diagnosed with an appendiceal tumor: 1 neuroendocrine tumor, 1 sessile serrated non-dysplastic adenoma, 1 goblet cell tumor, and 1 adenocarcinoma. For the first two cases, appendectomy was definitive treatment. The patient with the goblet cell tumor had positive margins on appendectomy and underwent subsequent right hemicolectomy with no sign of pathology in the resected colon. The patient with adenocarcinoma underwent later right hemicolectomy with subsequent hyperthermic intraperitoneal chemotherapy. In blinded retrospective evaluation of the initial CT, findings strongly indicating complicated acute appendicitis were present (diameter 21 mm, focal enhancement defect of the appendiceal wall, and significant periappendiceal edema), but no signs indicative of tumor.

5.5 The APPAC III trial

The pilot of the APPAC III trial was conducted between May and June 2017. Trial enrolment began thereafter and was concluded in September 2020. A total of 71 patients were randomized to either antibiotic therapy or placebo. The target scenario selected based on enrolment rate, was study scenario C.

6 Discussion

6.1 Diagnosis and low-dose CT imaging

As stated previously, although acute appendicitis is very common condition and one of the most common reasons for emergency abdominal surgery, the diagnosis remains challenging. Scoring systems have been created to aid in the diagnosis by considering symptoms, clinical findings and laboratory test results. These findings are scored, and the total amount of points is used to assess the possibility of acute appendicitis.[145,147,148] However, as many conditions can imitate the clinical presentation of acute appendicitis, clinical findings and laboratory tests cannot reliably distinguish acute appendicitis for differential diagnosis or evaluation the severity of acute appendicitis.[284] The role of diagnostic imaging, especially with CT, has increased with imaging utilization in up to 99.7% in patients with suspected acute appendicitis.[19] Preoperative imaging in patients with clinical suspicion of acute appendicitis is acknowledged as standard in the workup of the patients, with CT considered the gold standard outperforming other imaging modalities.[157]

In Study II, we found the contrast-enhanced low-dose OPTICAP protocol to be noninferior to the contrast-enhanced standard CT protocol used at Turku University Hospital in terms of diagnostic performance while resulting in a significantly reduced radiation dose. Comparable results have been reported by many trials.[20,193-195] Aly et al demonstrated low-dose protocols to be comparable to standard dose in regards to NAR, APR, and additional imaging needed in their systematic review.[285]

Diagnostic performance is evaluated in terms of accuracy, NAR, and APR. In Study II, the diagnostic accuracy of the low-dose and standard protocol were 79% and 80%, respectively. The NAR was 0%, which is exceptionally low compared to 1.7% after preoperative imaging that was already considered very low, and 10% to 20% in patients without preoperative imaging.[184,185] The APR in Study II was 6%, which compared to 13% to 33% reported in other trials, is very low.[20,194] The mean time to operation from image acquisition was 250 min in patients with perforated acute appendicitis. Preoperative imaging with CT does not seem to increase the APR based on the potential delay of surgery due to imaging.[154] Thus the low-dose protocol studied in Study II had comparable results to other low-dose imaging protocols.

The rationale behind developing low-dose protocols is lowering the radiation dose incurred by the patient to lower future radiation-related risks. Study II reported a radiation dose in $CTDI_{vol}$ of 4.2 mGy or effective dose of 3.3 mSv for the low-dose protocol and radiation dose in $CTDI_{vol}$ of 5.6 mGy or effective dose of 4.4 mSv for the standard protocol. The radiation authority of Finland (STUK) estimated a 12 mSv radiation dose for abdominal CT. The results for both protocols were well below the national average. There is no clear consensus on the calculations and units to report radiation dose. We used $CTDI_{vol}$, which reflects the radiation released from the CT machine. The effective dose was calculated based on the $CTDI_{vol}$, mean imaging length and the coefficients for tissue weighting factors by Huda et al[283]. For example, Kim et al used the dose-length product, which is an indicator of the integrated radiation dose of an entire CT scan.[20] Keyzer et al reported radiation doses using effective dose, which they calculated using a simulation phantom and specific conversion factors.[193]

Study II was limited in that it included only patients with a BMI under 30 kg/m^2 as determined in the preclinical phase of the OPTICAP study.[198] The BMI limit was set at 30 kg/m^2 to minimize the added noise effect of excess adipose tissue on image quality. Poletti et al concluded that the diagnostic performance of low-dose CT was equivalent to standard CT in imaging the acute abdomen in patients with a BMI over 30 kg/m^2. However, they excluded patients with suspected acute appendicitis from their study due to local protocols.[286] Seo et al demonstrated that BMI did not affect the visualization of the appendix or the radiological diagnosis of acute appendicitis. However, their study used unenhanced imaging.[197] Low-dose imaging could be feasible also in patients with BMIs exceeding 30 kg/m^2 with the added intra-abdominal fat potentially acting as natural contrast adjacent to the appendix, aiding in the visualization and evaluation of the appendix.

A key parameter of CT protocols when evaluating the feasibility of different protocols is the visualization of the appendix. Study II found visualization rates of 95% to 98% for the low-dose protocol and 98% to 100% for the standard protocol, with no significant difference. Another study also showed no significant difference in the visualization between low-dose and standard protocols, although they reported lower visualizations of 86% for their low-dose and 84% for their standard protocol as compared to the results of Study II.[287]

As antibiotic therapy for uncomplicated acute appendicitis presents as a viable treatment option to appendectomy, the differential diagnosis between the two forms of acute appendicitis is of fundamental importance. In Study II, the abilities of the low-dose and standard protocols to differentiate between uncomplicated and complicated acute appendicitis were similar at 80% to 81% for the low-dose protocol and 77% to 79% for the standard protocol. Storz et al compared standard CT images to low-dose reconstructions with 75%, 50% and 25% of the original radiation dose.

They showed that appendicitis was correctly detected in all datasets, and complications were correctly identified in the 75% and 50% low-dose sets.[288]

Additionally, in order to properly compare findings of uncomplicated and complicated acute appendicitis and the differential diagnosis between appendicitis severity, more specific and universal definitions are needed, especially for complicated acute appendicitis. In the APPAC trial, complicated acute appendicitis is defined as appendicolith, abscess, perforation, or appendiceal tumor.[14] Another study defined complicated acute appendicitis as gangrenous or perforated with or without the presence of diffuse peritonitis.[207] Vons et al included patients with appendicolith on CT into the group receiving antibiotic therapy, indicating that had these patients been diagnosed with complicated acute appendicitis and excluded, there would have been no significant difference between antibiotic therapy and appendectomy. Other CT findings highly suggestive of complicated acute appendicitis are periappendiceal fat infiltration, appendiceal wall enhancement defect, appendiceal diameter exceeding 14 mm, ascites and abscess.[289]

In Study II, the patients were treated based on the radiological diagnosis provided in the emergency department by the radiologists on-call. In our hospital, these radiologists are often less experienced, practicing at varying stages of specialization, and abdominal radiologists are not available around the clock. The blinded evaluation by the specialist radiologists was performed later, demonstrating that CT imaging with either protocol was accurate in diagnosing acute appendicitis, regardless of the experience of the radiologist. Another study also showed the experience of the radiologist resulted in no difference in the diagnostic accuracy for acute appendicitis.[290] This adds to the generalizability of the results of Study II and low-dose imaging protocols.

Low-dose CT imaging protocols have been proposed as first-line imaging tools due to the reasons described above.[196,291] Additionally, when considering the as-low-as-reasonably-achievable imaging principle, low-dose CT protocols should be implemented in emergency departments to facilitate significant reductions in radiation doses for patients with suspected acute appendicitis.[292] Still, implementation of low-dose CT in routine clinical practice has been quite slow and the use of low-dose CT protocols should be the aim of all surgical emergency departments with the appropriate CT facilities. However, it has to be noted that in all preoperative imaging, the importance of surgical decision-making based on clinical status cannot be discarded. In Study II, there was one patient with a false negative CT finding, emphasizing the role of the surgeon, especially if the clinical status and imaging findings are inconsistent.

6.2 Treatment

Appendectomy has been the gold standard treatment for acute appendicitis for over a century with reported treatment success of nearly 100%. The two approaches, open and laparoscopic, have widely been compared in terms of short- and long-term outcomes, with both approaches deemed practical but laparoscopic appendectomy considered superior to open appendectomy.[246]

The safety and efficacy of antibiotic treatment compared to appendectomy for uncomplicated acute appendicitis have been recognized in several clinical trials[10-14,293], confirmed in several meta-analyses[15-17,294], and endorsed by several guidelines.[209,295] These trials and analyses are mostly based on comparisons between open appendectomy and i.v. followed by p.o. combination antibiotic therapy.

Study IV aimed at optimizing antibiotic therapy for uncomplicated acute appendicitis by comparing p.o. antibiotics alone to a combination of i.v. followed by p.o. antibiotics. In the APPAC II trial, the treatment success at one-year follow-up was 70.2% in the p.o. group and 73.8% in the i.v. followed by p.o. group. These are very similar results to the one-year results of the Finnish APPAC trial[14] and the results summarized in meta-analyses[15,16], illustrating that the route of antibiotic administration may not be significant. In Study IV, 9.2% of patients in the p.o. group underwent appendectomy during primary hospitalization; 3.1% had uncomplicated and 6.1% had complicated acute appendicitis on histopathological examination. In the i.v. followed by p.o. group, 7.6% underwent appendectomy during primary hospitalization; 3.8% with uncomplicated and 3.8% with complicated acute appendicitis on histopathology. In the APPAC trial, results were somewhat similar with 5.8% of patients randomized to the antibiotic group undergoing appendectomy during primary hospitalization, with 2.7% having complicated acute appendicitis and 3.1% having uncomplicated acute appendicitis on histopathological examination.[14] The rates of primary failures were similar to findings in a current meta-analysis.[296] It has to be noted that the definitions of primary failure of antibiotic therapy also vary, and in the APPAC trials not all of the patients operated on during initial hospitalization had complicated acute appendicitis. The same discrepancy goes for the definition of appendicitis recurrence. Study IV found appendiceal diameter greater than 15 mm and higher body temperatures on admission to be predictive of primary treatment failure. No factors predictive of recurrence could be identified in this study. Detecting prognostic factors for recurrence would be beneficial, as it would aid in identifying the patients like to require later appendectomy after antibiotic treatment and would have great value in giving comprehensive information to the patient about treatment options.

Another aspect which must be considered is complication rate after each of the treatment alternatives. The overall complication rates at one year did not differ significantly, with 4.8% in the p.o. group and 7.3% in the i.v. followed by p.o. group.

Complications were considered minor. A meta-analysis reported a minor complication rate 2.2% in patients treated with antibiotics.[16]

Study IV was unable to illustrate the noninferiority of p.o. antibiotic therapy compared with i.v. followed by p.o. antibiotics, meeting only two out of three predefined noninferiority criteria. Both treatments met the first criterion of treatment success exceeding 65% based on lower limit of confidence interval. The second criterion of a point difference of less than 6% was also met, but the confidence interval of the point difference exceeded the noninferiority margin. If the margin had been set at for example 10%, which is still clinically acceptable, the noninferiority margin would not have been exceeded. From a clinical viewpoint, the treatments had similar success and complication rates. This demonstrates the challenge of evaluating and setting statistical limits for clinically important differences, particularly when considering matters with little clinical information to provide a good estimate for it.[297]

The difficulty of comparing two fundamentally different treatment modalities between surgery and antibiotic therapy in common outcomes such as treatment efficacy presents a possible but potentially significant bias in interpreting and comparing these studies. Unsurprisingly, appendectomy is superior to antibiotic therapy in treatment efficacy. However, it needs to be acknowledged that other factors such as overall complication rate, hospital costs, sick leave, quality of life, patient preference and patient's current life situation, are important parameters in the equation. Combining these factors would be comprehensive and patient-centered, resulting in tailored and optimal individualized treatment plans. Trials comparing optimized treatments, i.e., laparoscopic appendectomy, optimized antibiotic treatment and possibly symptomatic treatment taking into account all of these different treatment aspects are needed to sufficiently assess the available treatment options. Based on such future data, the guidelines and treatment paradigms of acute appendicitis can be evaluated.

The appendiceal tumor rate is interesting, as antibiotic treatment is criticized of this risk of missing appendiceal malignancies. In Study IV, 2.6% of patients who had appendectomy were diagnosed with an appendiceal tumor. This is in accordance with incidences reported by other studies ranging between 0.7 and 1.7%.[74-76,109,113] In the single case of adenocarcinoma detected in an appendectomy specimen of Study IV, signs implicating complicated acute appendicitis were present in a retrospective blinded evaluation of the initial CT, showing an appendiceal diameter of 21 mm, focal enhancement defect in the appendiceal wall, and a substantial periappendiceal edema. However, there was no suspicion of a tumor. In other cases of Study IV, appendiceal diameters were 16 mm, 11 mm, and 13 mm. Lietzén et al[113] found that the risk of missed appendiceal tumors related to antibiotic treatment of uncomplicated acute appendicitis is low.

6.3 Quality of life and patient preferences

QOL has been recognized as an important factor in evaluating disease burden and it provides a valuable viewpoint in assessing treatment outcomes as it reflects the patients' subjective experience of their treatment.[298] Appendectomy for acute appendicitis has been shown to have short-term and fully reversible effect on patient QOL regardless of operative approach used.[277] Varying tools for QOL assessment have been developed, but long-term QOL assessment is challenging for conditions having a shorter-term effects. In Study III, the EQ-5D-5L questionnaire was selected based on the reasonable length of the questionnaire covering relevant areas of everyday life, allowing the interview to be conducted by telephone. Additionally, Study III assessed patient satisfaction with treatment and preference.

QOL has been studied in randomized clinical trials assessing the feasibility of nonoperative management of uncomplicated acute appendicitis in pediatric patients. In pediatric patients, Minneci et al showed that when the treatment was chosen by the family, nonoperative management was effective in treating children with US or CT-confirmed uncomplicated acute appendicitis, resulting in higher QOL scores and satisfaction among the children and similar QOL among the parents than appendectomy.[226,249] Children treated nonoperatively had fewer disability days and returned to school more quickly, these factors most likely affecting their satisfaction. These results concur with our results in Study III, showing that QOL was similar between adult patients treated with antibiotics or appendectomy for uncomplicated acute appendicitis. Other studies assessing QOL have not been conducted so far in adult patients with uncomplicated acute appendicitis.

Two survey-based studies have been conducted regarding perceptions of operative and antibiotic treatment, one in a sample of adult respondents and the other in medical students.[248,250] The results of these surveys illustrated that most respondents were inclined to select operative treatment, but a meaningful amount would select primary treatment with antibiotics. In the survey study by Hanson et al the results indicated the desirability of antibiotic treatment would be increased by improvements in short- and long-term failure rates, rather than decreases in total hospital stay or duration of antibiotic treatment.[248] This emphasizes the importance of identifying prognostic factors predicting primary failure of antibiotic treatment during hospitalization and later recurrence of uncomplicated acute appendicitis. Additionally, it illustrates the importance of providing patients with unbiased neutral information of treatment options for uncomplicated acute appendicitis. Furthermore, Study IV demonstrated that p.o. antibiotics could be used for uncomplicated acute appendicitis, which in turn would decrease hospital stay and increase QOL and patient satisfaction.

Patient satisfaction and preference have not been studied regarding antibiotic therapy and appendectomy for uncomplicated acute appendicitis. However, it is an important aspect to be considered when evaluating the different treatment options comprehensively. In Study III, we found that patients in the appendectomy group were more satisfied than patients in the antibiotic group. The antibiotic group included patients originally randomized to antibiotic treatment who later underwent appendectomy for suspected recurrence; this subgroup was treated twice for the same disease and with a standard median hospital stay of three days for the initial hospitalization. In sub-group analyses separating these patients into their own group, we found that patients undergoing appendectomy or successful antibiotic treatment were more satisfied than patients undergoing appendectomy after primary antibiotic treatment. There was no difference between the successful antibiotics and appendectomy groups. Of the patients primarily randomized to the antibiotics groups later undergoing appendectomy, 33% would still choose primary antibiotic treatment regardless of the risk for recurrence and subsequent appendectomy. A similar finding was brought up by the meta-analysis by Sallinen et al; patients averse to surgery may choose primary antibiotic treatment whereas patients averse to the risk of recurrent appendicitis would lean towards primary emergency appendectomy.[16]

Shared informed decision making involves both surgeons and patients reaching a mutual agreement for treatment by considering the risks and benefits of treatment options, as well as patient values and preferences.[299] This line of thinking emerged in regard to the treatment options of uncomplicated acute appendicitis.[296,299,300] QOL outcomes, patient satisfaction and patient preference bring light to the patient's perspective and provide new tools for joint-decision making. In the case of acute appendicitis and antibiotic treatment, the role of the surgeon is to identify patients eligible for antibiotic treatment (cases with uncomplicated acute appendicitis), give unbiased information on the disease entity, and educate the patient on the possible recurrence risk associated with antibiotic use. The role of the patient is to consider the trade-offs related to the different treatment options presented. Involving patients in making an individualized joint decision will increase patient commitment to the selected treatment.[299]

6.4 Economic effects

Study I found the overall treatment costs of appendectomy to be 1.6 times higher than after antibiotics for the treatment of uncomplicated acute appendicitis at one-year follow-up when considering all costs. This is the only study reporting cost analysis data from a randomized clinical trial at one-year, including both direct costs, such as treatment costs, and indirect costs, in the form of productivity losses. The five-year follow-up results from the APPAC trial confirmed this cost effectiveness of antibiotics, reporting still a 1.4-fold cost advantage of antibiotics over appendectomy.[247] In the APPAC trial, open appendectomy was the study protocol approach to appendectomy with 94.5% of patients undergoing open appendectomy. Compared to the laparoscopic approach, open appendectomy is related to longer hospital stay and longer sick leave.[301,302] It can be speculated, that had a laparoscopic approach been used, the cost of disability days and sick leave would have been reduced.

Hospital stay is also an important cost component, and shorter hospitalization would decrease total hospital charges. The duration of hospital stay was predefined of 3 days for patients in the antibiotic group in the APPAC trial.[14] For comparison, the non-randomized NOTA trial reported a mean hospitalization of 0.4 days after nonoperative treatment.[293] A meta-analysis showed a modestly shorter primary hospital stay after appendectomy than after antibiotics treatment.[16] Podda et al showed that in non-randomized clinical trials antibiotic treatment resulted in significantly shorter hospital stay, but in randomized clinical trials, there was no statistically significant difference.[17] It could be argued that this is due to protocols in randomized clinical trials, but interestingly a subgroup analysis showed that study design did not modify this effect. A recent prospective observational study reported primary hospitalizations of 3.6 days after antibiotic treatment compared to 4.8 days after appendectomy, but no difference in total hospital stay after one year.[239] A pilot trial comparing outpatient antibiotic treatment and appendectomy for uncomplicated acute appendicitis showed promising initial results with antibiotic patients spending 16.2 hours and appendectomy patients spending 42.1 hours in the hospital.[225] Shorter hospitalization was also indicated in Study IV, with primary hospitalizations of 28.9 hours and 29.9 hours for the p.o. and i.v. followed by p.o. groups, respectively. Total hospitalization duration at one-year were 36.5 hours and 35.7 hours.

The results of the APPAC trial are in line with Wu et al, who showed treatment with antibiotics to result in significantly lower costs in their decision-tree model. However, they assessed only direct costs in their analysis.[278] Sceats et al also used modelling techniques and assessed only direct costs.[280] They found contradictory results indicating slightly higher costs resulting from antibiotic treatment. Our study demonstrated that a large proportion of costs resulted from indirect costs in the form of sick leave. Peterson et al showed sick leave to be the most expensive cost component in general medical care.[303] Durations of prescribed sick leaves are variable[304], and practices could be unified with guidelines[305].

Laparoscopic appendectomy results in lower hospital charges than open appendectomy.[38,245] To date, laparoscopic appendectomy has differed from many other laparoscopic procedures which are done on an outpatient basis. Promising results of outpatient laparoscopic appendectomy have been published.[306,307] Patient outcomes and the use of health care resources could be improved with selecting suitable patients for outpatient laparoscopic appendectomy. If laparoscopic appendectomy is shown to be feasible in an outpatient setting, a cost-analysis comparing optimized antibiotic treatment with short hospital stay or as outpatient management should definitely be compared with outpatient appendectomy to gain insight into potential future cost savings.

6.5 Strengths and limitations of the study

Key strengths are shared by the studies comprising this work. Studies I through IV are based on randomized trials and Study V proposes a protocol for a randomized trial. Additionally, all trials with the exception of Study II are multicenter trials. The populations in each study are sufficient to allow for conclusion to be made based on the results.

Studies I and III were limited by limitations of the original APPAC study as well as factors relating specific aims of these studies. A key limitation of the APPAC trial in terms of these studies was that 94.5% of appendectomies were performed with the open approach based on aiming to standardize the technique and increase generalizability of the results.[14] Laparoscopic appendectomy results in shorter hospitalization and sick leave that decrease treatment and productivity costs. Patients after laparoscopic appendectomy may also experience a higher quality of life and higher satisfaction postoperatively. Hospital stay was defined in the protocol to allow for i.v. administration of ertapenem and status monitoring of patients receiving antibiotic therapy. Patients that recovered quickly had to stay admitted regardless of good clinical condition, which potentially increased hospitalization costs and negatively affected patient satisfaction.

For Study I, another potential limitation lies in that the imaging and laboratory costs were calculated based on data from the three largest participating centers instead of actual costs from all participating hospitals. However, a clear strength of Study I is that it is based on actual patients randomized to either antibiotic treatment or appendectomy instead of using modelling techniques.

To our knowledge, study III is the only trial reporting QOL, patient satisfaction and patient preference in adult population in a randomized trial comparing appendectomy and antibiotic treatment for uncomplicated acute appendicitis. The importance of patient related factors was not initially recognized at the time of study enrollment, so study III was carried out as a post hoc outcome, which can be seen as a limitation. Additionally, tools to measure QOL are not designed specifically for acute care conditions, so the lack of optimal tools can also be seen as a limitation. For the same reason of not identifying QOL as an important factor, QOL was not assessed before randomization, therefore preventing the comparison of long-term and baseline QOL. A clear strength is the high follow-up rate of 80% at a median follow-up of seven years. In addition, with the CT-confirmed diagnosis of uncomplicated acute appendicitis, this population accurately represents patient-related factors after uncomplicated acute appendicitis.

Study II included quite small population of patients considering the volume of patients with suspected acute appendicitis at the study hospital, and a limited population did not provide reliable information on sensitivity and specificity. Study II was also limited by only three study surgeons allowed to enroll patients into the trial. Finally, based on preclinical testing, only patients with BMI under 30 were included in the study, limiting the generalizability of these results in the whole population of patients with suspected acute appendicitis. The main strength of Study II is the inter-patient randomized imaging of participating patients with both the standard and low-dose protocols allowing for direct comparison of the images in the same patient. The randomization of imaging sequences was performed to allow for optimal administration of i.v. contrast and i.v. contrast was administered to aid in the differential diagnosis between uncomplicated and complicated acute appendicitis. An additional strength is that the assessment of the images by two radiologists was performed blinded from each other and patient information.

Studies IV and V have identical inclusion and exclusion criteria and were ongoing concurrently, so they share key limitations and strengths, but also potential for selection bias. This risk is minor, as the trials differ only in terms of office hours vs. 24-hour surgical emergency recruitment. The nature of the emergency surgical care setting includes challenges of incorrectly randomizing patients with exclusion criteria to participate in the study as well as possibly missing suitable patients for randomization. Antibiotics used in both trials, including ertapenem and moxifloxacin, are still both broad-spectrum agents, possibly related to future issues of antibiotic resistance and also potentially unnecessary hospitalization. In surgical non-inferiority trials, limits are often set based on estimations of what is clinically acceptable, especially if no previous trials exist to provide a better estimate for the predefined minimal clinical difference. In Study IV, the point difference estimate was set at 6%, and as the result was not within the confidence intervals, the noninferiority criteria were not met even though clinically the results of the treatments were comparable. Had a point difference estimate been set at for example 10%, the noninferiority criteria would have been met. This illustrates the difficulty of a trial when setting the noninferiority criteria. The 6% in this trial was set somewhat arbitrarily, but clinically 10% would also have been acceptable.

In addition to the multicenter and randomized study setting, one of the main strengths of studies IV and V is the use of CT for confirming the diagnosis of uncomplicated acute appendicitis. To our knowledge, Study IV is the only randomized clinical trial focusing on the optimization of antibiotic therapy for uncomplicated acute appendicitis by comparing p.o. monotherapy with i.v. followed by p.o. antibiotics. Study V is so far the only double-blinded randomized placebo-controlled trial investigating antibiotics and symptomatic treatment for uncomplicated acute appendicitis. A key strength is that the patient, surgeon and nurses taking part in the treatment are all blinded to the treatment received by the patient, excluding potential bias to treatment. However, double-blinded clinical trials are not easy to conduct in an emergency surgical care setting. The key limitation of Study V is the dependence on hospital pharmacy resources that enable the double blinding. As the hospital pharmacy opening hours are very limited, recruitment has been slow, as anticipated, and scenario C with 64 patients has been selected for the target patient population. In addition, only senior surgeons are allowed to recruit patients to the APPAC III trial to ensure patient safety, limiting the patient recruitment during on-call hours. The per protocol hospitalization of three days may be considered a limitation that further affects patient satisfaction to care. However, this hospitalization was set to ensure patient safety as no such trials have been previously performed. The primary endpoint in Study V was set at 10 days instead of 1 year as in the original APPAC trial and the APPAC II trial to allow for rapid analysis of the results. The setting of the study is novel and only limited suggestive results of placebo for uncomplicated acute appendicitis are available.

6.6 Future prospects

Aspects of uncomplicated acute appendicitis are under intense research and discussion. Future directions for studies are and need to widely cover diagnostics, treatment and shared decision making.

Appendicoliths show strong association to cause complicated acute appendicitis. Future studies should focus on assessing appendicoliths, their classification, and role in acute appendicitis. A generally accepted global consensus is needed on how and which appendicoliths complicate acute appendicitis.

In terms of diagnostics, future studies should focus on further optimizing low-dose CT protocols to further decrease radiation dosage without compromising diagnostic accuracy. Also, studies assessing the feasibility of low-dose protocols in patients with BMIs over $30kg/m^2$ are needed.

In terms of treatment paradigms, the key is to compare currently optimized treatments for uncomplicated acute appendicitis to gain more insight in terms of treatment success and complications. Currently optimized treatments include laparoscopic appendectomy and p.o. antibiotic monotherapy with potential outpatient treatment. If Study V provides promising results, symptomatic treatment should also be compared to the above-mentioned optimized treatments. Outpatient treatment with antibiotics has shown promising results in a pilot study[225], and the notion of outpatient treatment should be explored more widely. Optimized treatments should also be studied in terms of costs as well as QOL and patient satisfaction. In the optimal setting, pre-intervention QOL should be evaluated, and follow up at preset short-and long-term time points.

Translational research with microbiologists and immunologists is encouraged as many aspects of acute appendicitis are still unknown, such as the etiology. More studies are needed in the microbiological and immunological aspects of acute appendicitis in relation to appendicitis severity.

Major topics related to antibiotic treatment include reasons for primary treatment failure and recurrence, as the current knowledge is very limited. Future studies should focus on identifying prognostic factors for both of these issues. As the post hoc efficacy of antibiotic therapy seems to fail in approximately 25% of patients, a large prospective cohort is needed to assess these factors reliably. Information on prognostics factors would be valuable for tailored patient selection.

7 Conclusions

The following conclusions can be made from the studies and data presented:

1. The overall societal and treatment costs after appendectomy were 1.6 times higher than after antibiotic treatment taking into account all costs, whether generated by the initial visit or possible recurrent appendicitis within one year.
2. The diagnostic accuracy of contrast-enhanced low-dose CT was noninferior to standard-dose CT in both diagnosing acute appendicitis and in distinguishing between uncomplicated and complicated acute appendicitis. The low-dose CT protocol was associated with a significantly reduced radiation dose.
3. Long-term patient QOL was similar after antibiotic therapy and appendectomy for uncomplicated acute appendicitis at 7-year follow-up. Patients randomized to antibiotic treatment but later undergoing appendectomy were less satisfied than patients with successful antibiotic treatment or patients randomized to appendectomy.
4. Most patients randomized to either p.o. or i.v. followed by p.o. antibiotic treatment did not require appendectomy during the 1-year follow-up. Among patients with uncomplicated acute appendicitis, p.o. moxifloxacin did not meet all prespecified noninferiority criteria compared to i.v. ertapenem followed by p.o. levofloxacin and metronidazole. There was no significant difference in posttreatment complications or length of hospital stay.
5. The APPAC III trial protocol was designed, and patient recruitment has been completed.

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