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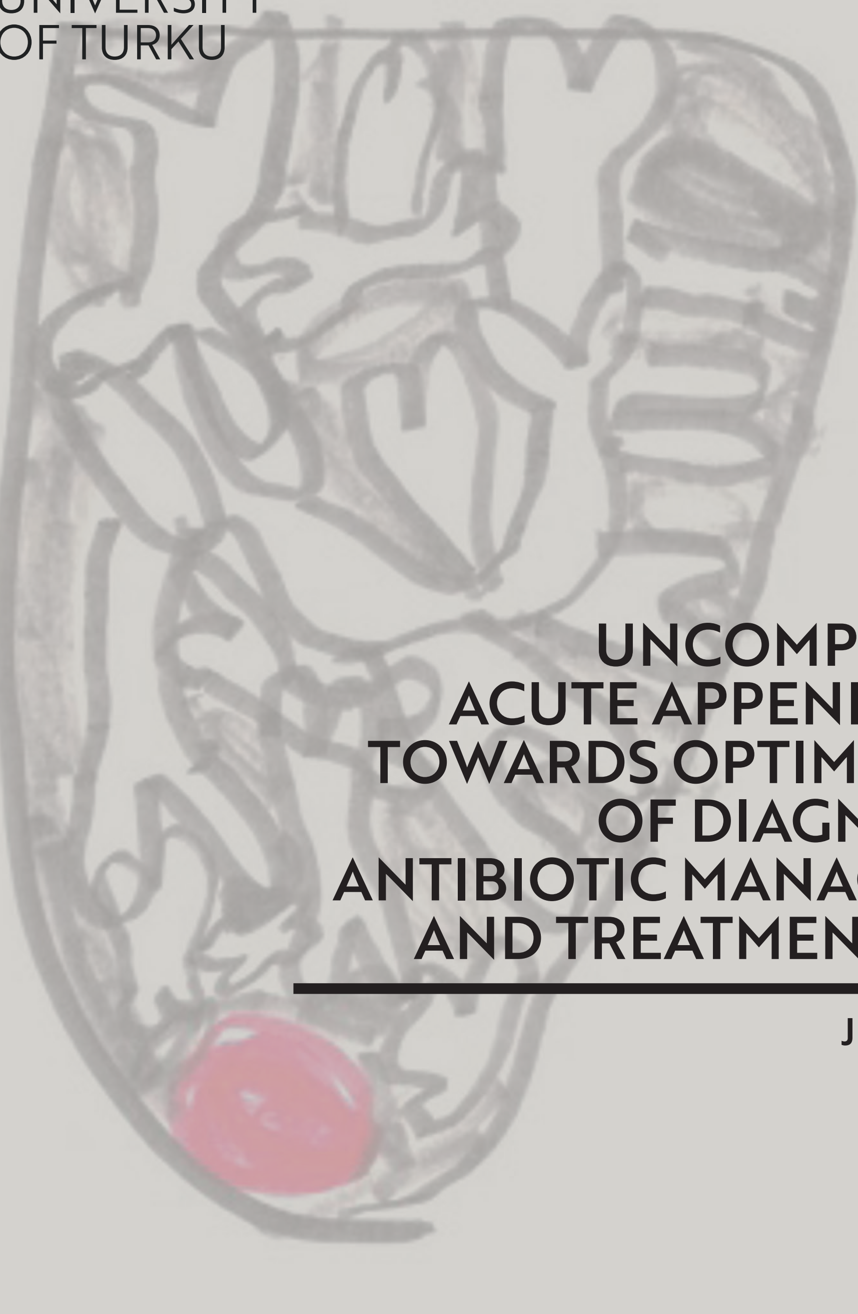

UNCOMPLICATED ACUTE APPENDICITIS – TOWARDS OPTIMIZATION OF DIAGNOSTICS, ANTIBIOTIC MANAGEMENT AND TREATMENT COSTS

Jussi Haijanen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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ABSTRACT

Acute appendicitis is the most common reason for acute abdominal pain, currently known to present in two different forms: uncomplicated and complicated acute appendicitis. This difference in appendicitis severity between these two forms can be quite accurately differentiated prior to treatment assessment using computed tomography (CT) imaging. Complicated acute appendicitis most often requires emergency appendectomy. However, recent accumulating evidence has shown antibiotic treatment to be a safe and feasible treatment alternative for uncomplicated acute appendicitis. Furthermore, in uncomplicated acute appendicitis, the overall treatment costs of antibiotics at short-term follow-up are lower compared to surgery.

The main aim of this thesis was to evaluate oral (p.o.) antibiotic monotherapy as a first-line treatment for CT-confirmed uncomplicated acute appendicitis by comparing p.o. antibiotic monotherapy to a combination of intravenous (i.v.) followed by p.o. antibiotics in a randomized multicenter non-inferiority clinical trial (APPAC II). The second aim of this study evaluated the overall costs of surgical and antibiotic treatment for uncomplicated acute appendicitis at long-term follow-up of the APPAC randomized controlled trial (RCT) comparing antibiotics with appendectomy. The third aim of this study was to determine whether the radiation dose of the diagnostic CT imaging could be significantly lowered without compromising diagnostic accuracy by using low-dose CT imaging.

In the treatment of CT-confirmed uncomplicated acute appendicitis, p.o. antibiotic monotherapy had similar clinical treatment efficacy as a combination of i.v. and p.o. antibiotics with 1-year success rates of 70.2% and 73.8%, respectively. At 5-year follow-up antibiotic treatment resulted in significantly lower overall costs compared with appendectomy. The accuracy of low-dose CT and standard CT was comparable in diagnosing acute appendicitis as well as in differentiating uncomplicated and complicated acute appendicitis. The low-dose CT was associated with a significant radiation dose reduction compared to standard-dose CT.

KEYWORDS: acute appendicitis, antibiotic treatment, appendectomy, complicated acute appendicitis, CT, computed tomography, low-dose CT, uncomplicated acute appendicitis,

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TIIVISTELMÄ

Akuutti umpilisäketulehdus eli appendisiitti on yleisin akuutin vatsakivun syy. Akuuttia appendisiittia on kahta eri muotoa: lievempi komplisoitumaton ja vaikeampi komplisoitunut akuutti appendisiitti. Nykyään nämä kaksi eri muotoa voidaan erottaa toisistaan tarkasti jo ennen hoidon määrittämistä tietokonetomografiakuvauksen (TT) avulla. Komplisoitunut akuutti appendisiitti vaatii tavanomaisesti välitöntä leikkaushoitoa. Viimeaikaisten tutkimustulosten mukaan antibioottihoito on osoitettu turvalliseksi ja käyttökelpoiseksi hoitovaihtoehdoksi komplisoitumattomassa appendisiitissa. Käytettävissä olevien lyhyen seurantavälin tutkimustulosten mukaan komplisoitumattoman appendisiitin hoidosta antibiootilla aiheutuu vähemmän kustannuksia verrattuna leikkaushoitoon.

Tämän väitöskirjatyön tarkoituksena oli tutkia suun kautta otettavaa antibioottihoitoa ensilinjan hoitona komplisoitumattomassa akuutissa appendisiitissa vertaamalla tablettimuotoisen antibioottihoidon tehoa suonensisäisen ja suun kautta otettavan antibioottihoidon yhdistelmään satunnaistetussa non-inferioriteetti-monikeskustutkimuksessa (APPAC II). Lisäksi tutkimme antibioottihoidon ja leikkaushoidon kokonaiskustannuksia pitkän aikavälin seurannassa. Arvioimme myös, voiko appendisiittin diagnostiikassa käytetyn TT-kuvauksen potilaalle aiheuttamaa säderasitusta pienentää heikentämättä kuvauksen diagnostista tarkkuutta.

Komplisoitumattoman akuutin appendisiitin hoidossa tablettimuotoinen antibioottihoito oli kliinisesti yhtä tehokas kuin yhdistelmäantibioottihoito, hoidon onnistuessa vuoden seurantajakson aikana 70.2 %:lla tablettimuotoista ja 73.8 %:lla yhdistelmäantibioottihoitoa saaneilla. Viiden vuoden seurannassa antibioottihoidosta aiheutui tilastollisesti merkitsevästi vähemmän kustannuksia verrattuna leikkaushoitoon. Matala-annoksisen ja standardiannos-TT-kuvantamisen tarkkuus oli toisiaan vastaava sekä akuutin appendisiitin diagnosoinnissa että komplisoitumattoman ja komplisoituneen akuutin appendisiitin erottamisessa. Matala-annoskuvantamisesta aiheutui tilastollisesti merkitsevä sädeannoksen pieneneminen verrattuna standardiannoksiseen TT-kuvantamiseen.

AVAINSANAT: akuutti appendisiitti, antibioottihoito, appendikektomia komplisoitumaton appendisiitti, komplisoitunut appendisiitti, matala-annoksinen TT, tietokonetomografia, TT, umpilisäketulehdus, umpilisäkkeen poisto

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Abbreviations

APPAC	APPendicitis Acuta
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
i.v.	intravenous
LOS	Lenght of stay
MRI	Magnetic resonance imaging
NAR	Negative appendectomy rate
NPV	Negative predictive value
p.o.	Oral
QOL	Quality of life
RCT	Randomized controlled trial
RLQ	Right lower quadrant
SSI	Surgical site infection
US	Ultrasound
VAS	Visual analog scale
WBC	White blood cell count

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 Haijanen J, Sippola S, Tuominen R, Grönroos J, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Hurme S, Salminen P. Cost analysis of antibiotic therapy versus appendectomy for treatment of uncomplicated acute appendicitis: 5-year results of the APPAC randomized clinical trial. PLoS One. 2019;14(7):e0220202.

II Haijanen J, Sippola S, Grönroos J, Rautio T, Nordström P, Rantanen T, Aarnio M, Ilves I, Hurme S, Marttila H, Virtanen J, Mattila A, Paajanen H, Salminen P. Optimising the antibiotic treatment of uncomplicated acute appendicitis: a protocol for a multicentre randomised clinical trial (APPAC II trial). BMC Surg. 2018;17;18(1):117.

III *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. 1. 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):353–62.
* = equal contribution

IV Haijanen J, Sippola S, Tammilehto V, Grönroos J, Mäntyoja S, Löyttyniemi E, Niiniviita H, Salminen P. The diagnostic accuracy of low-dose versus standard CT in uncomplicated and complicated appendicitis: a prospective cohort study. Br J Surg. 2021 108(12):1483–1490.

1 Introduction

Suspicion of acute appendicitis is one of the most common reasons for abdominal pain related emergency department visits and the most common reason for emergency abdominal surgery incurring significant health care costs[1–4]. For more than a century, appendectomy has been the standard treatment for all patients with suspected acute appendicitis. However, both current epidemiological and clinical data show, that there are two forms of acute appendicitis differing in disease severity, i.e. uncomplicated and complicated acute appendicitis, also with different etiology and pathophysiology[5,6]. Acute appendicitis presenting with a finding of perforation, abscess, a suspicion of a tumor, or appendicolith are usually defined as complicated[7] requiring emergency surgery, with the exception of patients presenting with a restricted abscess often initially treated conservatively. The clinical course in most (65–80%) cases of acute appendicitis is uncomplicated[6,8,9].

In uncomplicated acute appendicitis, the safety and efficacy of antibiotic management compared to surgery have been thoroughly recognized in clinical trials[7,10–14] as well as endorsed in several meta-analyses[15–19] and guidelines[20–22]. The results are very consistent throughout the different trials; with antibiotics, approximately 70% of patients with imaging confirmed uncomplicated acute appendicitis can avoid appendectomy during the first year also presenting with less morbidity compared to surgery[15–18,23]. In addition, no major complications associated with undergoing delayed appendectomy for suspected recurrent appendicitis after receiving initial antibiotic treatment have been reported underlining the safety of antibiotics as a first-line treatment of CT-confirmed uncomplicated acute appendicitis[7,24].

The APPAC trial[7] was the first larger RCT comparing antibiotics with surgery in CT-confirmed uncomplicated acute appendicitis with available long-term follow-up up to 5 years. At one year follow-up, 70/257 (27.3%) patients randomized to antibiotics in the APPAC trial had undergone surgery, with additional 30 patients having appendectomy during the years 2 to 5, resulting in an appendectomy rate of 39.1% at 5 years[24]. These results suggest that most of the recurrences occur within the first two years of initial treatment after which the incidence of appendicitis recurrence markedly declines. The cost analysis of the APPAC trial at 1-year showed substantial cost savings favoring antibiotics over appendectomy[25]. Other reports corroborate the short-term cost benefits of antibiotics over appendectomy for uncomplicated acute appendicitis[11,26,27], but long-term results are lacking.

As the evidence on non-operative treatment for uncomplicated acute appendicitis has accumulated over the last years, successful outpatient management has also been reported in a pilot study[11]. Shorter hospitalization or outpatient management will presumably result in even further cost savings in the treatment of uncomplicated acute appendicitis. However, accurate pre-intervention diagnosis between uncomplicated and complicated acute appendicitis together with a feasible oral (p.o.) antibiotic regimen are both essential to enable safe outpatient management.

Due to availability and accuracy, CT is currently gold standard in appendicitis imaging in adults[9,28] providing the best ability to both diagnose acute appendicitis and to differentiate between uncomplicated and complicated acute appendicitis[29]. The inevitable disadvantage of CT is the exposure to harmful ionizing radiation[30]. Despite accurate low-dose CT imaging modalities have been developed to minimize the induced radiation[31–33], their implementation to clinical practice has been slow.

In this doctoral thesis, the aim of study I was to compare overall treatment costs of antibiotics and appendectomy in the treatment of uncomplicated acute appendicitis at long-term follow-up based on the 5-year data of the APPAC trial.

Thesis study II was the study protocol article of the thesis study III, the APPAC II multicenter, non-inferiority RCT which compared p.o. antibiotic monotherapy with a combination of intravenous (i.v.) followed by p.o. antibiotics in the treatment of CT-confirmed uncomplicated acute appendicitis aiming to optimize the antibiotic treatment administration for uncomplicated acute appendicitis. In study III, primary outcome was treatment success defined as resolution of acute appendicitis resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during 1-year follow-up. Secondary outcomes included post-intervention complications, duration of hospitalization, pain scores, and length of sick leave.

The aim of study IV was to compare the diagnostic accuracy of low-dose and standard-dose CT in patients with suspected acute appendicitis to determine whether the radiation dose resulting from the diagnostic CT imaging could be significantly lowered without compromising diagnostic accuracy.

2 Review of the Literature

2.1 Anatomy and physiology of the appendix

The vermiform appendix is a small tubular-shaped blind-ended diverticulum, typically located in the right lower quadrant (RLQ) of the abdomen[34]. The appendix arises from the posteromedial side of the cecum, with its proximal end opening to the cecum approximately 1.7 cm below the ileocecal valve[35]. The average length of the appendix is 8.2 cm, but specimens up to 33 cm in length have been reported[36]. The blood supply for the appendix is provided by the appendicular artery, which most commonly derives from the ileocolic artery[37].

The function and meaning of the appendix long remained unknown, and therefore the human appendix was for years considered merely as an evolutionary remnant. The notable amount of lymphoid tissue, termed gut-associated lymphoid tissue (GALT) in the appendiceal submucosa has been recognized for decades[38], but it was only until in the beginning of the 21st century, when first Bollinger and co-workers perceived the role of the appendix in the immune-mediated maintenance of the microbiome of the gut[39]. Together with the finding of the appendix having a more abundant concentration of the biofilm compared to other areas of the colon, the theory of the role of the appendix as a safe-house for beneficial gut bacteria has been acknowledged. This would enable the appendix, which is rather well-isolated from the other intestine due to its shape and location, to re-inoculate the gut with its normal bacterial flora; for example as a defense mechanism in case the intestine is infected with a pathogen rapidly flushing the normal fecal material from the other parts of the colon[39–41].

2.2 History of acute appendicitis

The first time the appendix is considered having been provably identified in humans, is in the 1492 drawings by Leonardo DaVinci, whereas in 1521, a physician-anatomist Berengario DaCarpi made the first documented description of the appendix[42]. In the beginning of the 18th century, physician Lorenz Heister, based on his findings in autopsy on the body of a criminal, was the first to speculate that a right lower quadrant abdominal inflammation might be originating from the appendix. In 1735, the first appendectomy was performed by Claudius Amyand operating on a 11-year-old boy with a scrotal hernia containing part of the cecum and a perforated appendix[43]. In the following decades, the idea of appendix having a role in right-sided abdominal inflammation or pelvic abscess gained ground and in 1886 Reginald Fitz was the first to introduce the term appendicitis in his paper "Perforating inflammation of the vermiform appendix: with special reference to its early diagnosis and treatment"[44]. Fitz also reported signs of spontaneous resolution of appendicitis already in the era before appendectomy and antibiotics, as some patients he examined in autopsies had evidence of periappendiceal inflammation without perforation in the appendix. These ideas have since been supported by scarce modern evidence[45–47].

Five years after Fitz's groundbreaking paper Charles McBurney described the typical symptoms and clinical signs of acute appendicitis for the first time: Acute onset of abdominal pain, relocation of pain from the whole abdomen to the right iliac fossa, the maximal pain localization over the base of the appendix, guarding, tachycardia, and fever. McBurney described the point of maximal pain in appendicitis as: "Between 1.5 to 2 inches inside the right anterior superior spinous process of the ilium on a line drawn to the umbilicus."[48] The point corresponds to the typical location of the appendix and was named the McBurney's point. Correspondingly, as McBurney later published an article describing an oblique incision for open surgery for appendicitis, it was gradually named the McBurney incision[49]. These findings together with the development of general anesthesia towards the end of the late 1800s made it possible to consider appendectomy as a viable treatment option[42].

Although the surgical procedure of appendectomy itself then remained technically rather similar for the next 100 years or so, the health care systems and the medical treatment as a whole have become significantly more advanced and accessible. As in the era of limited anesthesiologic capabilities and no antibiotics, the mortality from appendicitis and appendectomy were high, appendicitis is nowadays only very rarely a life-threatening condition[50].

After the pioneer for minimally invasive laparoscopic surgery, gynecologist Kurt Semm, first described laparoscopic appendectomy in 1983[51], the laparoscopic approach has become the gold standard of operative treatment for appendicitis at least in western countries[52,53]. In recent years, attributed to the marked advances in accuracy of diagnostic imaging and understanding in pathophysiological differences between uncomplicated and complicated acute appendicitis[5,6], non-operative treatment alternatives for uncomplicated acute appendicitis have been introduced and under active research[7,10-13,26,54–56].

2.3 The epidemiology of appendicitis

Acute appendicitis is the most common cause of abdominal pain in emergency departments with a lifetime risk of 8.6% in males and 6.7% in females[57]. Although the frequency of appendicitis in older patients has slightly increased, roughly half of the cases with acute appendicitis are still diagnosed in patients aged 0–29 years with the mean age for diagnosis being 32.7 years[58]. There has been an increasing trend in the incidence of appendicitis in the newly industrialized countries in the last decades,[59] whereas in the Western countries, the incidence has peaked, declined and later plateaued during the last century. This fluctuation is suggested to originate partly from patient-related factors associated to the industrialization of the society such as increased amount of smoking[60], exposure to air pollution[61], and increasing use of low-fiber diet[62], but also factors affecting the detection of the disease such as more accurate diagnostics and documentation of cases. However, as the etiology of appendicitis is arguably multifactorial and still somewhat unknown, the exact factors inducing the chances in incidence of appendicitis are accordingly unclear[59].

The incidence of acute appendicitis in Finland has followed a similar declining trend compared to other Western countries[63] with the incidence of 9.8 per 10 000 in 2008 among the Finnish population being fairly similar to the incidence generally reported in Western countries[8,59]. Still in Finland around 8000 appendectomies are performed annually[64].

Interestingly, the decrease in the overall incidence of acute appendicitis during the last decades is unevenly distributed between nonperforated and perforated forms of appendicitis, as the two forms of appendicitis seem to have independently varying trends of incidence[6]. This divergence in the secular trends between these two subgroups of appendicitis has given further support to the hypothesis of perforated and nonperforated form actually being two different diseases with different underlying pathophysiologies[5].

2.4 The etiology and pathogenesis of acute appendicitis

Direct luminal obstruction by either lymphoid hyperplasia, appendicolith, or tumor has been traditionally suggested as the main cause for acute appendicitis[1]. According to this theory, the obstruction in the appendix lumen gradually results in increased pressure within the appendix, obstruction of lymphoid and venous drainage, ischemia and secondary bacterial infection traversing through the appendiceal wall subsequently leading to gangrene and potential perforation[65]. However, appendiceal tumors are very rare[66–68], and both appendicoliths as well as lymphoid hyperplasia have been reported to be common findings also in non-inflamed appendices[69–71], questioning the orthodox theory for pathogenesis. Thus, the current understanding suggests that at least in majority of cases, obstruction is unlikely to be the primary cause of appendicitis even though in some cases it most likely plays a major role[72]. There is, however, no clear consensus on the alternative theories on the pathogenesis other than lumen obstruction either[1]. As also the exact role of other possible factors contributing to the acute inflammation of the appendix such as viral[73], bacterial[74] and parasitic[75] infections is unknown, the precise pathogenesis for acute appendicitis remains unclear.

Because of the findings of uncomplicated and complicated acute appendicitis following different epidemiological trends, distinct underlying pathogenesis for the different disease severity have been proposed[5,6]. These arguments are further supported by recent research of uncomplicated acute appendicitis responding effectively to conservative treatment with antibiotics or even symptomatic treatment only[7,10,45]. This has added even more complexity into understanding of all factors in the pathogenesis of acute appendicitis.

2.5 The classification of acute appendicitis

Compared to the timeline of over 130 years of recognizing and treating appendicitis as a disease, the idea of classifying acute appendicitis by the disease severity into two different forms, uncomplicated and complicated, or in other words nonperforating and perforating, is relatively new. Livingston et al. compared the secular epidemiological trends of nonperforating and perforating appendicitis in children to those of nonperforating and perforating diverticulitis in adults between 1979 and 2006. They found considerable similarities in the incidence of nonperforating appendicitis and nonperforating diverticulitis as well as in the incidence of perforating appendicitis and perforating diverticulitis. They noticed that both perforated appendicitis and diverticulitis behaved very differently compared to their nonperforating counterparts. The dissimilarity in the secular epidemiological trends seemed incompatible with the traditional view of perforating appendicitis being a later manifestation of the same nonperforating disease[5,6]. Gradually, the longstanding dogma of all acute appendicitis cases eventually leading to perforation unless operated in a timely manner, has been overturned. However, although the idea of two different forms of acute appendicitis is nowadays largely accepted, the unified criteria for classification between uncomplicated and complicated acute appendicitis are missing and under active discussion and research.

Since the criteria on distinguishing uncomplicated and complicated acute appendicitis vary between studies, so do the estimations on the prevalence of these two forms. However, it is generally acknowledged that most of the acute appendicitis cases present as uncomplicated, accounting for approximately 65–80% of the cases[8,9,76].

2.5.1 Uncomplicated acute appendicitis

Uncomplicated acute appendicitis is defined as acute inflammation comprising of either a part of or the entire appendix. Initially, the mucosa is inflamed and usually ulcerated. Thereafter, neutrophilic infiltration in the submucosa and muscularis propria can be seen at histopathology, together with subsequent transmural inflammation, vascular thrombosis, and intramural abscesses[72]. Along with this histopathological verification of acute inflammation, the definition of uncomplicated acute appendicitis is often supplemented with the requisite of the absence of features of complicated appendicitis usually considered as a finding of perforation, gangrene, abscess, appendicolith or a tumor[1,7].

2.5.2 Complicated acute appendicitis

Histopathologically, in addition to the findings of acute inflammation similar to the ones described in uncomplicated acute appendicitis, a heavy transmural inflammation process can generate areas of necrosis, resulting in gangrenous appendicitis, which is recognized as a form of complicated acute appendicitis as it may progress to perforation or an abscess[72]. Traditionally, only acute appendicitis cases with a surgical finding of evident perforation or periappendiceal mass / abcess / phlegmon were classified as complicated. In addition to the unequivocal cases of perforation and abscess, the recent interest and understanding of non-operative treatment of acute appendicitis has resulted in additional definitions and prognostic factors associated with a more complicated course of the disease[10,14]. These include gangrenous acute appendicitis as well as acute appendicitis with an intraluminal appendicolith. In current clinical practice and in appendicitis trials, acute appendicitis presenting with perforation, abscess, tumor, gangrene, or appendicolith are often widely acknowledged as complicated appendicitis[21].

As appendicoliths have been found in noninflamed appendices, as well as in appendices with the severity of inflammation varying from mild to gangrene and perforation[69,71], the role of appendicolith has been previously debated both in the pathogenesis of acute appendicitis as well as in classification of appendicitis severity. There is, however, accumulating evidence showing that the presence of an appendicolith in acute appendicitis is associated with a more severe form of disease[9,77], increased risk of failure in non-operative treatment[78], and an increased risk of perforation[10,79]. This was further corroborated in a recent, large, pragmatic, randomized, study by Flum et al. showing that among patients with nonperforated acute appendicitis initially treated with antibiotics, patients presenting with an intraluminal appendicolith were at a higher risk for both appendectomy and complications compared to those without an appendicolith[14]. The histopathological comparison between acute appendicitis patients with and without an appendicolith also showed more severe form of disease in patients presenting with an appendicolith[80]. However, further research on appendicoliths is needed in order to elucidate the role of appendicolith in appendicitis severity.

Periappendicular abscess is a common complication of perforated appendicitis found in 2–11% of patients with acute appendicitis[81,82]. It consists of an inflammatory mass turning into a walled-off, localized, pus-containing collection. The incidence of appendicolith in patients with periappendicular abscess was reported 24% by Otake et al.[83], but most importantly alarmingly large numbers between 6% and 20% of appendiceal tumors have been reported in this patient group with complicated acute appendicitis[84–86].

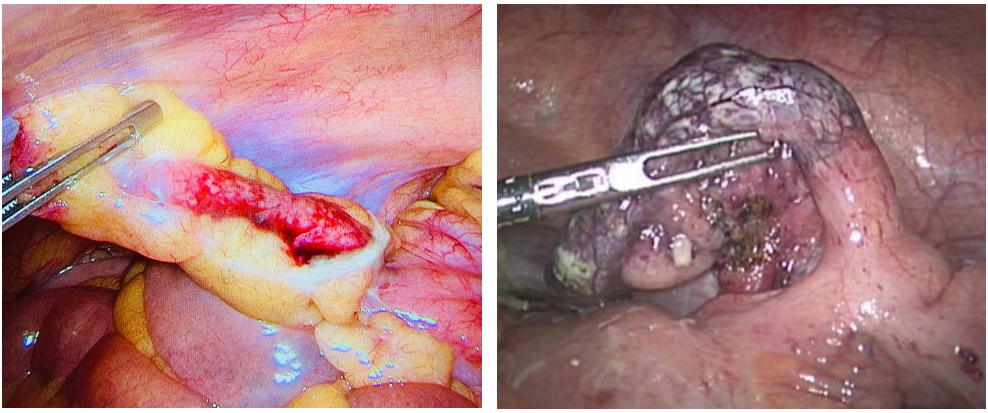


Figure 1. Intraoperative images of uncomplicated acute appendicitis (on the left) and complicated acute appendicitis (on the right).

2.5.2.1 Appendiceal neoplasms

Primary appendiceal neoplasms are rare, usually incidental findings detected in the histopathological examination of a removed appendix. In patients with acute appendicitis, the reported overall incidence in all appendicitis cases varies between 0.7–2.5%[66–68,87]. However, in a population-based registry study, Lietzen et al. reported a significantly higher rate of neoplasms associated with complicated appendicitis compared to uncomplicated acute appendicitis, with incidences of 3.24% and 0.87%, respectively. A recent RCT that enrolled adults with CT-confirmed periappendicular abscess reported even higher neoplasm rate (12/60, 20%) in patients older than 40 years[84], corroborating the earlier similar findings of Wright et al.[88] and requiring validation in future studies. Corresponding high rates of tumors have been reported by Teixeira et al. in a systematic review estimating a 10–29% risk of neoplasm among patients presenting with an appendiceal mass, highlighting the difference in tumor risk between uncomplicated and complicated forms of appendicitis[66].

The actual malignant tumors of the appendix are a histologically diverse group with complicated subclassifications. They include neuroendocrine carcinomas, adenocarcinomas, and mixed tumors containing both of these elements with goblet cells[89].

2.6 Diagnosis and differential diagnosis of acute appendicitis

For over a century, the thought of all acute appendicitis cases inevitably progressing to perforation has guided the treatment to early appendectomy with a low threshold[44]. The diagnosis previously relied mainly on clinical evaluation, later supplemented by laboratory tests, and high rates of negative appendectomies exceeding 20%, i.e. appendectomy for noninflamed appendix, were performed and accepted[90]. There are numerous symptoms, signs, and laboratory findings associated with acute appendicitis, which individually have a weak predictive value, and even when combined, the accuracy of distinguishing patients with and without appendicitis is around 70–85% unless combined as a risk score strategy with imaging[90–93].

The advances in diagnostic imaging, especially since the introduction of abdominal CT in the 1990s, together with the increased understanding on the nature and the treatment alternatives of the two different forms of acute appendicitis, have revolutionized both the diagnostic approach as well as the treatment paradigm of acute appendicitis. As appendectomy is no longer considered the only treatment alternative for every patient diagnosed with acute appendicitis[7,45], the emphasis of diagnostics has shifted from solely assessing whether the patient has appendicitis or not, towards also differentiating between uncomplicated and complicated acute appendicitis. Especially when considering patients for non-operative treatment, high sensitivity and NPV for complicated acute appendicitis are needed to accurately rule out patients with a more complicated disease, who are unsuitable for non-operative treatment[94].

2.6.1 Clinical symptoms, physical examination and laboratory tests

2.6.1.1 Clinical symptoms and physical examination

The most typical symptoms and signs of acute appendicitis are pain in the RLQ of the abdomen, relocation of the pain from the epigastrium or the periumbilical area to the RLQ, fever, nausea, and loss of appetite. As a sign of peritoneal inflammation, the pain in the RLQ is often aggravated by patient's movements or coughing[65]. According to a meta-analysis by Andersson, the most discriminative factors in physical examination were findings of peritoneal irritation (rebound, percussion tenderness, and guarding) together with migration of pain[95]. Traditionally, peritoneal irritation has been evaluated by several different methods with sensation of pain in the RLQ meaning a positive result: by suddenly releasing abdomen palpation pressure (Blumberg's sign), adding palpation pressure on the left side of the abdomen (Rovsing's sign), and hip extension or flexion against resistance (positive psoas sign). Patients often have fever, but its accuracy in diagnosing patients with and without appendicitis is poor[95].

Although several signs in physical examination have been reported to have useful predictive value in diagnosing acute appendicitis, the results have marked variation between different studies. This is probably partly due to the heterogeneous nature of study populations as the patients examined in different studies may have had varying disease severity[95]. Furthermore, the response to the physical examination is always a reflection of the patient's subjective experiences to the examination and the process cannot be standardized in terms of the physician nor the patient[96]. The accuracy of clinical examination alone in assessing appendicitis severity is evidently insufficient to aid in clinical decision-making, although, no study has apparently specifically reported these data.

2.6.1.2 Laboratory tests

In general, inflammatory response variables such as white blood cell count (WBC), C-reactive protein (CRP), and proportion of polymorphonuclear blood cells are associated with acute appendicitis. However, although they are the strongest discriminators amongst all laboratory tests, they still have low discriminative value as their own. When combined with other laboratory tests or with clinical symptoms, the discriminative power is much higher[95] and it has been reported that when WBC and CRP are both normal, acute appendicitis is highly unlikely[97]. However, Atema et al. concluded that laboratory examinations alone are still unable, even when combined, to reach sufficient positive or negative predictive value (NPV) for acute appendicitis[98]. In pediatric population, a meta-analysis reported that upon suspecting acute appendicitis, no single history, physical examination, laboratory finding, or score attained on pediatric appendicitis scoring system alone can eliminate the need for imaging studies in order to definitely either rule in or rule out acute appendicitis[99].

WBC is one of the most used laboratory tests in diagnosing acute appendicitis although it is often elevated also in patients with other causes for RLQ abdominal pain[95]. An elevated WBC can support the diagnosis of acute appendicitis when combined with other findings, but alone has limited value in clinical practice especially due to the poor sensitivity for complicated acute appendicitis[100].

The slower response to inflammation compared to the WBC[101] limits the use of CRP as it is less sensitive in the early phase of the disease and alone has very limited sensitivity in detecting complicated acute appendicitis[100].

Procalcitonin and bilirubin have also been studied in terms of feasibility in the diagnostic work-up of acute appendicitis. Both have been reported as fairly specific especially in complicated acute appendicitis, but the lack of sensitivity has so far been the main weakness for both of these markers[102,103].

There are studies suggesting that Delta-neutrophil-index as well as neutrophil-to-lymphocyte ratio could be a tool in diagnosing acute appendicitis and differentiating between uncomplicated and complicated acute appendicitis[104,105]. However, similar to many of the laboratory markers, the reported sensitivities in detecting complicated appendicitis in these studies have so far been too low to aid in clinical decision-making.

2.6.2 Computed tomography imaging

CT is an imaging method based on a series of X-ray measurements from different circular angles, generated into cross-sectional images of the body by a computer software. The major advantages of availability, accuracy, and ease of performance and interpretation together with the additional comprehensive amount of information on the whole abdomen have increased the use of CT in the diagnostic imaging for appendicitis[9,28]. Through improved preoperative diagnostic accuracy, the use of CT has been shown to decrease the NAR to as low as 1.7–3.9%[28,33,106]. Especially as it is currently known that some of the patients with acute appendicitis might not need surgical intervention, and negative appendectomies are associated with increased morbidity and mortality[107,108], past rates of negative appendectomies approximating 20%[28] can no longer be justified. Additionally, routine pre-interventional imaging results in less costs incurred by the treatment of acute appendicitis[109,110]. These findings advocating routine imaging for patients with suspected acute appendicitis, have resulted in pre-interventional CT imaging rates reported as high as 90–97.5%[9,28].

The inevitable disadvantage of CT is the exposure to ionizing radiation. The advances in the CT technology together with growing data on diagnostic imaging features have resulted in increase in the diagnostic accuracy with simultaneous major decrease in the radiation doses of CT imaging. A Cochrane review assessing the accuracy of CT in suspected acute appendicitis reported summary sensitivity and specificity of 95% and 94% with an estimated radiation doses of 8–16 mSv for 67 studies published between 1998–2015[31]. A more recent meta-analysis evaluating studies on the accuracy of novel low-dose CT modalities for suspected acute appendicitis reported a summary sensitivity of 96% and a summary specificity of 94% with a median effective radiation dose of 1.8mSv[111], highlighting the recent overall advancements in CT imaging.

In the meta-analysis by Yoon et al.[111] no difference was found in the accuracy of diagnosing patients with and without appendicitis between the low-dose and the standard CT. In the recent RCT by the LOCAT group no significant difference in the primary outcome of NAR was detected between the two groups randomized to undergo either a 2 mSv low-dose CT or a 8 mSv standard dose CT[106]. Evaluation on the lowest possible diagnostic radiation dose is ongoing together with the remarkable advancements of the CT technology. However, along with the changing treatment paradigm, also the diagnostic focus in acute appendicitis has shifted towards accurate differentiation between uncomplicated and complicated acute appendicitis.

A recent meta-analysis including 11 studies and 4427 patients with appendicitis assessing the ability of CT in detecting complicated acute appendicitis reported a summary sensitivity of 78% and specificity of 91%. The NPV for complicated acute appendicitis was estimated as 93%.[29] Kim et. al[112] recently reported 10 CT findings informative for complicated appendicitis, nine of which (extraluminal appendicolith, abscess, appendiceal wall enhancement defect, extraluminal air, ileus, periappendiceal fluid collection, ascites, intraluminal air, and intraluminal appendicolith) had high individual specificity (pooled range, 74–100%), but low sensitivity (pooled range, 14–59%). Periappendicular fat stranding was the only one found to have high sensitivity (94%), but low specificity (40%). In a follow-up study where a diagnostic algorithm considering a finding of any of the 10 previous CT findings diagnostic for complicated appendicitis was compared to a overall assessment by the radiologist, they reported pooled sensitivities of 92% and 64%, and pooled specificities of 43% and 76%, for any-of-the-10-criterion and overall assessment, respectively[113].

In the subgroup analysis of the APPAC II trial assessing factors associated with an increased risk for complicated appendicitis among antibiotic treated patients with an initially CT-confirmed uncomplicated acute appendicitis, patients with an appendiceal diameter of 15 mm or above on pre-interventional CT were found to be at greater risk for unresponsiveness to antibiotics[4]. In a retrospective study by Hong et al. evaluating 198 patients with acute appendicitis with an appendiceal diameter of 11 mm or less, appendiceal wall enhancement defect was found to be associated with unresponsiveness to initial antibiotic therapy[114].

In the retrospective study including patients with both complicated and uncomplicated acute appendicitis, Kim et al. found appendiceal diameter of 11 mm or more the optimal cutoff to differentiate uncomplicated and complicated acute appendicitis[115]. Additionally, one prospective cohort study reported appendiceal diameter ≥ 13 mm in pre-interventional imaging associating with increased incidence of neoplasms[116], whereas a retrospective study suggested appendiceal mass, mural calcifications, a focal asymmetric wall abnormality and an appendiceal diameter of ≥ 15 mm predicting an underlying tumor[117].

These partly varying reports highlight the complexity of defining complicated acute appendicitis, but also the lack of uniform criteria for CT features predictive of complicated acute appendicitis, underlining the need for further research.

In terms of using low-dose CT to establish the assessment of appendicitis severity, potentially enabling non-operative treatment alternatives, the evidence is scarce. In the interpatient randomized OPTICAP trial enrolling 60 patients with a BMI under 30 kg/m^2, all of whom underwent both low-dose and standard CT imaging, the low-dose CT was shown non-inferior to standard CT in distinguishing between uncomplicated and complicated acute appendicitis[118]. A Recent RCT conducted in an Asian population corroborated these results[119] These are to date, however, the only studies reporting the accuracy of low-dose modalities in assessing appendicitis severity.

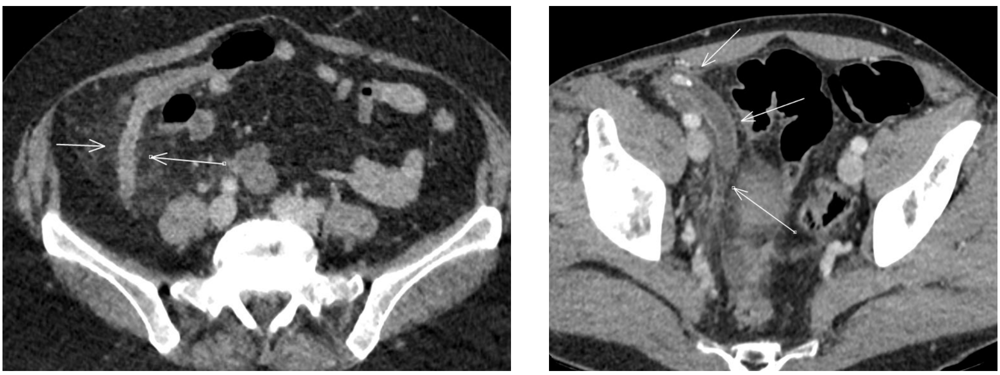


Figure 2. CT images of uncomplicated acute appendicitis (on the top left), acute appendicitis with an appendicolith (on the top right, appendicolith indicated by the top arrow), and complicated acute appendicitis with a perforation and abscess formation (bottom left).

2.6.2.1 The harms of radiation exposure

The main disadvantage of CT imaging is the exposure to ionizing radiation. This is highlighted in acute appendicitis as the majority of the population concerned are children or young adults most sensitive to the effects of radiation[120]. The estimates of the carcinogenic effects of ionizing radiation have earlier been based on studies on the atomic bomb survivors[121–123] and cohort studies on radiation workers both suggesting association between exposure to radiation and increased cancer mortality[124,125]. A recent South Korean population-based study comparing patient groups undergoing appendectomy with and without perioperative CT, reported an increased risk for hematologic malignancies (IRR 1.40), especially leukemia, in the CT-exposed group. The risk was most pronounced in the young population aged 0–15 years. There was no statistically significant difference in the incidence rate of abdomino-pelvic cancers. The average effective radiation doses used at the time of the study were substantially higher than those used in the current clinical practice. On the other hand, the median follow-up time of 8.2 years can be considered relatively short in this population of mainly adolescents and young adults[30]. These findings strongly advocate the need for lowering the radiation dose of CT in acute appendicitis imaging by utilizing low-dose CT modalities[33,106,111,118].

2.6.3 Other imaging modalities

2.6.3.1 Ultrasound

The major advantage of ultrasound (US) compared to CT is the absence of radiation exposure. However, the diagnostic accuracy of US in acute appendicitis imaging is clearly inferior to CT. A meta-analysis assessing 17 studies showed a summary sensitivity and specificity of 69% and 81% for acute appendicitis in general[126]. Another meta-analysis reported the accuracy of POCUS (point-of-care-US) in diagnosing acute appendicitis with a pooled sensitivity and specificity of 91% and 97%, respectively[127].

Data regarding US in further distinguishing between complicated and uncomplicated acute appendicitis is scarce. One retrospective cohort study based on patients all with surgical and histopathological diagnosis of appendicitis reported a sensitivity of 86% and a specificity of 60% for appendiceal perforation[128]. A prospective cohort study including patients with suspected acute appendicitis showed a sensitivity of 32% and a specificity of 93% for complicated acute appendicitis[129]. Besides the unsatisfactory accuracy, the user-dependent nature of US requiring experience to avoid frequent indeterminate examinations[130] is also an issue limiting its usability and reliability in clinical practice, whereas with CT, it has been shown that highly accurate imaging diagnoses can be achieved already with less radiological experience[131].

2.6.3.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been reported a comparable sensitivity of 96–97% and specificity of 96% to those of CT in acute appendicitis[132,133]. Besides being more time-consuming compared to US and CT impairing the feasibility in clinical practice, diagnostic imaging for acute appendicitis with MRI is limited by its availability and cost. However, as MRI does not expose patient to radiation, it can be considered an imaging alternative for pediatric and pregnant patients with a reported sensitivity and specificity of 96% and 96% for pediatric, and 92–94% and 97–98% for pregnant patients in acute appendicitis [133,134].

With respect to discriminating uncomplicated and complicated acute appendicitis, data on MRI is limited to one prospective study in adults reporting a 57% sensitivity and an 86% specificity yielding an 89% NPV for complicated acute appendicitis[129].

2.6.4 Scoring systems

In order to improve the diagnostic accuracy for acute appendicitis, several scoring systems combining clinical and laboratory findings have been created[135–137]. The New Adult Appendicitis Score developed by Sammalkorpi and collagues was able to decrease the NAR from 18.2% to 8.7%[138] following its implementation into systematic clinical use to guide diagnostic imaging in Meilahti Hospital in Helsinki. These scoring systems can aid clinicians in assessing the probability of acute appendicitis and to evaluate the possible need for imaging, when determining solely whether the patient has acute appendicitis. However, these scoring systems completely lack the diagnostic accuracy and aim for differentiating between uncomplicated and complicated acute appendicitis.

CT is currently considered the most accurate imaging method in assessing appendicitis severity[29]. Although the reported NPV for complicated acute appendicitis for CT is as high as 93%, the summary sensitivity is around 80%. When considering patients for non-operative treatment, ruling out complicated appendicitis is essential. Therefore, scoring systems combining clinical and laboratory findings and imaging features have been developed to further optimise the pre-interventional diagnostics.

Atema and collagues developed two separate scoring systems reaching NPVs up to 94–97% and 95% for complicated appendicitis, when combining clinical findings with US and CT features, respectively[139,140]. However, only the scoring system using

US has been externally validated. A scoring system combining clinical and laboratory findings with CT features has been introduced also by Avanesov et al.[141], but with the NPV of 83% for complicated acute appendicitis, the scoring system does not seem to add clinical value compared to a regular CT scan alone with an estimated NPV of 93%[29].

In the future, adequately validated scoring systems may aid in ruling out complicated appendicitis enhancing the optimal selection of patients suitable for non-operative treatment.

2.7 Management of uncomplicated acute appendicitis

2.7.1 Appendectomy

The notion of acute appendicitis progressing from mild inflammation to perforation combined with later findings of appendectomy preventing pelvic abscesses resulting from perforated appendicitis established open appendectomy as the standard treatment for all appendicitis cases for almost a century. Open appendectomy using a muscle splitting McBurney-incision was the standard treatment until laparoscopic appendectomy was introduced in 1983[51]. Laparoscopic appendectomy is currently the procedure of choice in developed countries. Despite in some reports associated with a higher incidence of intra-abdominal abscesses, the laparoscopic appendectomy has been shown to result in better overall treatment outcomes compared to the open approach. One study comparing outcomes for laparoscopic and open appendectomy among patients operated for nonperforated appendicitis reported the laparoscopic approach superior in terms of the number of surgical site infections (SSI) (0.9% vs. 4.0%), overall complications (5.3% vs 10.8%), and median hospital stay (1 day vs. 2 days). A recent meta-analysis[52] assessing patients with complicated and uncomplicated acute appendicitis reported corresponding results favouring the laparoscopic approach in terms of shorter hospital stay and fewer SSIs. The mean time of patients returning to normal activity ranged between 3.2 and 32.4 days after open appendectomy, but was on average 5.0 days shorter for patients operated laparoscopically. Two studies have evaluated quality of life; Katkhouda et al.[142] reported better scores in physical and general health at 2 weeks after laparoscopic appendectomy, whereas and Kaplan et al.[143] reported better overall gastrointestinal quality of life following laparoscopy compared to open appendectomy at 6 months following surgery.

Compared to the single and longer incision of the open procedure, three small incisions are made in the laparoscopic approach. Pneumoperitoneum is created through the first one prior to inserting the first port and the camera. After inserting two additional ports for graspers, appendix is visualized and the mesenterium divided at the base usually with a diathermy instrument. The base of the appendix is closed with clips, loop-sutures or an endoscopic linear stapler, and the resected specimen is placed into a plastic bag and removed from the abdomen through one of the ports[144]. Antibiotic prophylaxis is shown to decrease postoperative SSIs and intra-abdominal abscesses[145], with most evidence supporting administration within an hour prior to skin incision[146–148].

The current understanding of most cases of uncomplicated acute appendicitis resolving with antibiotics are in line with the results of a recent meta-analysis reporting no increased risk of complicated acute appendicitis or postoperative complications when appendectomy for presumed uncomplicated acute appendicitis was delayed up to 24 hours after admission[149]. These findings strongly suggest that when appendectomy is chosen for uncomplicated acute appendicitis, it is not an emergency procedure requiring e.g. night time surgery, but can instead be scheduled as a next available day-time operation[21,149]. This will however, increase the length of hospital stay, especially considering that reports of feasible outpatient laparoscopic appendectomy for uncomplicated acute appendicitis have been described[150].

2.7.2 Antibiotic treatment

There are reports of acute appendicitis resolving without surgery already from the 19th century, as Fitz described evidence of spontaneous resolution of earlier episodes of appendicitis in one-third of his autopsy patients. Later, in the antibiotic era, studies by Coldrey[151] (1956) and Rice[152] (1964) reported satisfactory results of antibiotic treatment of acute appendicitis diagnosed based on clinical findings. However, as at that time the pre-interventional differentiation of the cases possibly progressing to perforation carrying substantial morbidity was impossible, appendectomy remained the standard treatment for all patients with suspected acute appendicitis.

The increasing understanding of the different characteristics of uncomplicated and complicated acute appendicitis[5,6], together with the recent advances in diagnostic imaging enabling the accurate pre-interventional differentiation between the two forms, have resulted in mounting evidence and interest in the non-operative treatment of uncomplicated acute appendicitis[15–17,23,24]. The current evidence supports antibiotic treatment as an alternative to appendectomy for patients with imaging confirmed uncomplicated acute appendicitis presenting without appendicolith[21]. The effect of the COVID-19 pandemic limiting hospital resources has further increased the interest towards non-operative management and driven its inclusion into treatment guidelines[20,22] resulting in more appendicitis patients treated conservatively[153,154].

The accurate patient selection is a major factor when assessing patients most likely to succeed in non-operative treatment for uncomplicated acute appendicitis. Patients with suspected complicated acute appendicitis without an abscess should be referred to emergency appendectomy[21].

As complicated acute appendicitis has the known potential to progress to perforation over time, there are imaging features and clinical findings that might predict failure in non-operative treatment that have to be taken into account. The finding of intraluminal appendicolith predicting worse outcomes of antibiotic treatment for acute appendicitis has been reported in several studies[10,78], and corroborated by a recent large pragmatic RCT by the CODA collaborative enrolling 1552 patients. In the CODA trial, patients with acute appendicitis presenting with an intraluminal appendicolith were found to have a greater risk for adverse events (20.2% vs 3.6%) and higher 90-day appendectomy rate (41% vs 25%) compared to those patients without an appendicolith[14].

The optimal choice of antibiotic regimen for uncomplicated acute appendicitis is also unclear. The most common bacteria isolated from acute appendicitis surgical specimen is Escherichia coli, followed by Klebsiella pneumoniae, Enterococci, Streptococci and Pseudomonas aeruginosa[155]. Additionally, considerable rates of Bacteroides species have been found in peritoneal fluid cultures of patients with acute appendicitis[50]. It has been suggested that since these findings have been reported on patients most of whom have received pre-interventional antibiotic treatment, presumably affecting the results of the bacterial culture, more advanced techniques such as metagenomic sequencing should be used to assess the optimal antibiotic regimen[156]. The possible differences in the bacteria associated with uncomplicated and uncomplicated acute appendicitis also warrant further research[157].

The first large RCT comparing surgery and antibiotic treatment for CT-confirmed uncomplicated acute appendicitis by Vons et al.[10] used amoxicillin-clavulane acid associated with a notable Escherichia Coli nonsusceptibility. The APPAC study[7] conducted after the study by Vons et al. used i.v. ertapenem followed by a combination of levofloxacin and metronidazole to overcome this limitation. A recent network meta-analysis comparing the treatment efficacy of antibiotic regimens containing B-lactam/B-lactamase inhibitor, cephalosporins and carbapenem for uncomplicated acute appendicitis suggested carbapenem as the most effective regimen[158]. However, administration of broad-spectrum i.v. antibiotics such as carbapenem increases the global antibiotic resistance problem, and i.v. administration requires hospital resources prolonging the length of patient hospitalization. In the earlier studies, as antibiotic treatment was a novel and an unfamiliar treatment approach for uncomplicated acute appendicitis, extensive antibiotic coverage with extended hospital stay was evaluated necessary and stated in the study protocols to ensure patient safety[159]. To date, there are no studies comparing the efficacy of p.o. antibiotic monotherapy and i.v. antibiotics for uncomplicated acute appendicitis. In the future, we need to optimize antibiotic treatment for uncomplicated acute appendicitis in terms of treatment duration, route of administration, and antibiotic regimen regarding antibiotic spectrum, simultaneously considering the role of spontaneous resolution of appendicitis. The RCT by Park et. al[45] reported similar treatment failure rates of patients with CT-confirmed uncomplicated acute appendicitis receiving a 4-day course of antibiotics compared to symptomatic treatment alone. The double-blinded, multicenter, placebo-controlled APPAC III trial[160] is currently enrolling patients, aiming to further assess the necessity and role of antibiotics in the treatment of uncomplicated acute appendicitis.

2.8 Management of complicated acute appendicitis

2.8.1 Appendectomy

The current standard in the treatment of suspected complicated acute appendicitis in patients without a restricted periappendicular abscess, is emergency laparoscopic appendectomy[21]. Technically, the procedure is identical to the one described for uncomplicated acute appendicitis with respect to removing the appendix. In the management of peritonitis following perforation, current understanding encourages suction alone over irrigation[161] without intra-abdominal drain placement as there is no evidence demonstrating improvement in morbidity after drain placement in open[162] or laparoscopic appendectomy for complicated acute appendicitis[163]. The optimal length of postoperative antibiotic treatment after appendectomy for complicated acute appendicitis is unclear. There is evidence that continuing the antibiotic treatment after a 3- or 4-day course is unnecessary in terms of postoperative complications after source control[164–166]. Even shorter courses have been suggested optimal, with a recent RCT reporting complication rates of 21.9% in short (<24hours) and 29.3% in long (>24hours) courses of postoperative antibiotics suggesting non-inferiority of the short course[167].

2.8.2 Management of periappendicular abscess

The optimal treatment approach to complicated appendicitis with a restricted abscess is unclear. The acknowledged approach of initial conservative management with antibiotics with or without percutaneous drainage[87,168] has been recently challenged by the data suggesting that early appendectomy especially in experienced hands is also a feasible first-line treatment associated with comparable morbidity, and decreased need for readmissions compared to initial conservative management[169,170]. However, the recent reports of potential increased risk of underlying tumors[66,84,88] together with the longer operative time, increased need for conversion to open surgery, and bowel resections compared to initial non-operative management[171] further challenge the feasibility and safety of early appendectomy as the first-line approach.

Although laparoscopic appendectomy has been gaining some ground as an initial approach alternative, comprehensive evidence on its superiority is lacking, and initial non-operative management is therefore still widely used[172]. The need for interval appendectomy after successful non-operative treatment has also been a topic of discussion earlier as the reported risk for underlying tumor was previously reported low, varying between 0.7 and 3.0%[66,173]. However, the recent reported high rate of neoplasms found in patients with an appendiceal mass[68,86,88] currently supports subsequent appendectomy after initial conservative management at least in patients aged over 40 years[84].

2.8.3 Management of appendiceal neoplasms

Most primary appendiceal neoplasms are incidental findings detected in the histopathological examination of a removed appendix, leaving the clinical relevance of the finding unsure. In most cases, simple appendectomy is considered adequate treatment. However, in approximately 40% of the patients with an appendiceal tumor, additional treatments are applied[68].

The incidence of neuroendocrine tumors was reported 1.1–1.9 per 100 000 persons by Singh et al[174]. For patients with an incidental finding of neuroendocrine carcinoma with a diameter of less than 1 cm, appendectomy is usually adequate treatment. However, right hemicolectomy is recommended for tumors exceeding 2 cm as well as for smaller tumors with positive resection margins, high proliferative rate, or lymphovascular, mesoappendiceal, or angional invasion[89,175]. Right hemicolectomy is the recommended treatment also for tumors of all size with a mixed phenotype: goblet cell tumors and mixed adeno-neuroendocrine carcinoma (MANEC)[175].

Appendiceal carcinomas can be divided into mucinous-type and colonic-type tumors. Among patients aged under 50 years, the overall incidence was estimated 0.1–0.6 per 100 000 persons in a population-based study conducted in Canada and the United States, but the incidence increased significantly with age[174]. Mucinous neoplasms are further subdivided into mucinous adenoma, low-grade appendiceal mucinous neoplasm (LAMN), and appendiceal mucinous adenocarcinoma. Despite the last-mentioned being the only one of the three considered malignant in terms of histology, they all have the potential to progress to pseudomyxoma peritonei in case mucin and epithelial cells from inside the appendix end up into the abdominal cavity following an appendiceal perforation[176]. As a result, the treatment of appendiceal mucinous neoplasms extends from simple appendectomy to right hemicolectomy and hyperthermic intra-peritoneal chemotherapy (HIPEC) depending on the histopathology and the possible peritoneal involvement[89].

The colonic-type adenocarcinoma of the appendix is rare, with an incidence of less than 0.1% of all appendectomies[177]. The staging and treatment mirrors that of colon cancer, with right hemicolectomy being the standard surgical procedure[89].

2.9 Treatment outcomes of uncomplicated acute appendicitis

2.9.1 Treatment success

The fundamental difference of the surgical and non-operative treatments result in the challenge of determining the optimal outcome definition of treatment success for unbiased comparison of the two treatments. Treatment success of appendectomy defined as the success rate of appendix removal is practically 100%. There are some reports of stump appendicitis following an incomplete resection of the appendix in initial appendectomy, but the incidence of stump appendicitis is extremely low[178,179]. This means, that with relatively low risk of complications using the laparoscopic approach, surgery has the major benefit that the patient does not have to worry about a possible recurrent appendicitis in the future. Appendectomy also eliminates the small risk of missing an underlying neoplasm within the inflamed appendix. As in non-operative treatment the appendix remains intact retaining the possibility of recurrence, it is obvious that by solely comparing treatment success defined by the risk of recurrent appendicitis, surgical approach will always maintain superiority over non-operative management.

To overcome this dilemma of determining the comparable outcome for these two treatments, recent studies have focused on evaluating both treatments more comprehensively, including several outcomes such as QOL, treatment costs, length of stay (LOS), time to recovery, post-intervention pain, complication rate, and patient preference.

The treatment efficacy of antibiotic management for uncomplicated acute appendicitis has been thoroughly recognized in clinical trials[7,10–14] as well as in several meta-analyses[15–19]. The results show consistently that with antibiotics approximately 70% of patients with imaging confirmed uncomplicated acute appendicitis can avoid appendectomy during the first year after treatment[15–18,23]. The table 1 shows all the RCTs comparing antibiotics and surgery for uncomplicated acute appendicitis.

The first RCTs comparing surgery with antibiotics conducted by Eriksson et al. in 1995[54], Styrud et al. in 2006[13], and Hansson et al. in 2009[12] had only clinical diagnosis without imaging as the base for pre-interventional diagnosis. The study by Styrud et al. included only male participants and in the study by Hansson more than 50% of patients randomized to antibiotics crossed over to the surgery arm compromising the randomized setting of the trial[12,13]. Vons et al. was the first RCT to have a CT-confirmed diagnosis of uncomplicated acute appendicitis as an inclusion criterion. Regarding the primary outcome of postintervention peritonitis within 30 days of initial treatment, they reported a peritonitis occurrence of 2% among patients in the appendectomy group compared to 8% in the amoxicillin-clavulanic acid group. The study has been criticized besides for the used antibiotic regimen, also for including patients with an intraluminal appendicolith and the somewhat equivocal definition of the primary outcome. If the patients presenting with an appendicolith would have been excluded from their study, no difference between the primary outcome of post-intervention peritonitis would have been found between the antibiotic and surgery group[10].

The APPAC trial[7] is the first large RCT comparing antibiotics with surgery for CT-confirmed uncomplicated acute appendicitis with available long-term follow-up available up to 5 years. After the first year, 70/257 (27.3%) patients randomized to antibiotics in the APPAC trial had undergone surgery, with additional 30 patients having appendectomy during the years 2 to 5, resulting in a cumulative appendectomy rate of 34.0% at 2 years, 35.2% at 3 years, 37.1% at 4 years, and 39.1% at 5 years[24]. As all operated patients did not have true appendicitis at histopathology, the true appendicitis recurrence rate at 5 years was 32.4%. These results suggest that most of the recurrences occur within the first two years of initial treatment after which the prevalence of appendicitis recurrence markedly declines. The major limitation of the APPAC study was the open approach used as the surgical intervention, especially as laparoscopic appendectomy has since widely replaced open appendectomy as the standard operative treatment.

In 2017, the first pilot RCT on outpatient management of imaging confirmed uncomplicated acute appendicitis was carried out in the US. In this study by Talan et al. 16 patients were randomized to antibiotics with only 1 patient having appendectomy within the first year of treatment[11]. Compared to the length of hospitalization reported to be between 3 and 4 days in the earlier studies, the mean hospitalization was decreased to 0.7 days using outpatient management[7,10–13].

The recent largest pragmatic RCT conducted by the CODA collaborative in the US enrolled 1552 patients with imaging confirmed appendicitis to either appendectomy or antibiotics[14]. The trial had a primary outcome of general health status at 1 month assessed with a QOL questionnaire, based on which antibiotics were found inferior to appendectomy. Some patients randomized to antibiotics in the

CODA trial were discharged from the emergency room after a short follow-up to outpatient management resulting in similar mean length of hospitalizations of 1.3 days between the antibiotic and appendectomy groups. However, the CODA trial was carried out with a pragmatic approach, only excluding patients with peritonitis, consequently including also patients presenting with complicated acute appendicitis. This presumably explained the higher overall appendectomy rate of 40% in the antibiotic arm at 1 year compared to other trials with more selective inclusion criteria[180]. The study found patients presenting with an appendicolith to have a significantly higher risk for complications and appendectomy compared to patients without an appendicolith. Corroborating the earlier results, the CODA trial established the role of appendicolith associating to a more complicated form of appendicitis and an increased risk of failure in non-operative treatment[10,14,78].

The COMMA trial[26] randomized 186 patients to treatment with either appendectomy or with antibiotics. At 1-year, the patients having initial appendectomy had better scores in QOL -measurements, whereas initial antibiotics were associated with less sickness days and less mean total treatment costs.

Table 1. Based on Eriksson et al. 1995, Styrud et al. 2006, Hansson et al. 2009, Vons et al. 2011, Salminen et al 2015, Talan et al. 2017, Ceresoli et al. 2019, Davidson et al. 2021, O'Leary et al. 2021.

Study	**Diagnosis**	**No. of Patients (Surgery: Antibiotics)**	**antibiotics used**	**Successful initial antibiotic treatment at 1-year**	**complication rate at 1-year, (Surgery: Antibiotics), %**	**LOS (Surgery: Antibiotics), days**	**Treatment costs at 1-year**
Eriksson 1995	US	20:20	iv + po	60%	not available	3.1:3.4	not available
Styrud 2006	clinical diagnosis, and CRP>10mg/L	124:128	I.v. cefotaxime plus tinidazole P.o. ofloxacin plus tinidazole	76%	14.0:3.1	2.6:3	not available
Hansson 2009	Clinical diagnosis (+US/CT)	167:202	I.v. cefotaxime plus metronidazole P.o. ciprofloxacin plus metronidazole	52%	10.8:5.4	3:3	Surgery: 36400SEK: Antibiotics: 26000SEK
Vons 2011	CT	119:120	I.v. amoxicillin plus clavulanic acid P.o. amoxicillin plus clavulanic acid	63%	1.7:1.7	3:4	not available
Salminen 2015	CT	273:257	I.v. ertapenem P.o. levofloxacin plus metronidazole	73%	20.5:2.8	3:3	Surgery: 5989€ Antibiotics: 3744€
Talan 2017	US/CT	14:16	I.v. ertapenem, P.o. cefdinir and metronidazole	87%	not available, 30-day complication rate 14.%:6.3	1.8:0.7	at 1 month: surgery: 12447$ antibiotics: 5145$
Ceresoli 2019	clinical (+/-US/CT)	24:21	I.v. ertapenem P.o. amoxicillin plus clavulanic acid	83%	12.5:0.0	3.5:4.1	not available
Davidson 2021	US/CT	776:776	I.v. antibiotics (unspecified) P.o. antibiotics (unspecified)	60%	4.2:7.3	1.3:1.3	not available
O'leary 2021	US/CT	89:91	I.v. amoxicillin clavulanic acid P.o. amoxicillin clavulanic acid	75%	5.6:1.1	2.3:2.8	Surgery 4816€, Antibiotics 3077€

2.9.2 Morbidity and mortality

The data on morbidity related to uncomplicated acute appendicitis is limited by the fact that most large studies assessing morbidity for appendicitis do not distinguish uncomplicated and complicated acute appendicitis. The morbidity following appendectomy varies besides due to disease severity, also due to geographical location and complication definitions, but overall complication rates of 8.2–31.4% have been estimated, with wound infection rates of 3.3–10.3%[181,182]. However, Masooni et al. reported a separate complication rate of 5.3% for patients with uncomplicated acute appendicitis after laparoscopic appendectomy[183]. In operative treatment for uncomplicated acute appendicitis, the laparoscopic approach has the advantages of less SSIs, fewer pain, shorter length of hospital stay and return to normal activity, and better QOL compared to open appendectomy[52,183].

In the RCTs comparing antibiotics with appendectomy for uncomplicated acute appendicitis, the complication rate has consistently been higher in surgical treatment.[16–18,23] In addition, a large portion of the complications reported in the antibiotic groups consists of procedure-related adverse events related to subsequent appendectomy either for appendicitis or suspected appendicitis.[7] There is, however, a great challenge on determining corresponding definitions for complications allowing unbiased comparison between the two fundamentally different approaches of non-operative and operative treatment. Regarding non-operative treatment, there is a lack for generally accepted and unified complication grading corresponding to the Clavien-Dindo classification[184] for postoperative complications. The complication rates reported in the RCTs comparing antibiotics and appendectomy for uncomplicated acute appendicitis are shown in Table 1.

As the prolonged or extensive use of antibiotics is known to associate with gut microbiota impairment subsequently predisposing patients to harmful conditions such as Clostridium difficile infections[185] and potentially slightly increased risk for some cancers[186], concerns of adverse effects associated with antibiotic management of appendicitis have been raised. Most of the earlier studies assessing antibiotics for uncomplicated acute appendicitis have failed to report the number of patients with clostridium difficile colitis[16]. The recent CODA trial[14] reported 0.6% of patients treated with antibiotics as well as 0.6% of patients treated with surgery diagnosed with clostridium difficile colitis. However, all these patients initially presented with an appendicolith limiting the comparability of those results to patients with an uncomplicated disease.

The risk of missing an underlying appendiceal malignancy following non-operative treatment of uncomplicated acute appendicitis must also be considered as a complication. Lietzén et al. concluded that the overall prevalence for appendiceal tumors among all patients with acute appendicitis is 1.2%, but as the majority of neoplasms are associated with complicated acute appendicitis, the risk of missed malignancy due to non-operative treatment for uncomplicated acute appendicitis is low[68]. However, based on their population-based study, Enblad et al. suggested patients treated non-operatively for appendicitis both with and without an abscess having an increased risk for bowel cancer compared to the general population[187]. However, this study was considerably limited by issues regarding diagnostic accuracy as Enblad et al. used diagnose codes from the hospital register to determine the diagnoses and data was retrieved ever since from the 1980s, at a time when diagnostic accuracy in general was considerably inferior compared to the modern era.

Mortality for uncomplicated acute appendicitis is low both in operative treatment as well as in non-operative treatment[16]. In a worldwide observational study, including 4282 patients with acute appendicitis of whom 95% underwent appendectomy, the overall mortality rate was 0.28%[50]. The study included both patients with uncomplicated and complicated acute appendicitis and showed similarly to the Finnish study by Kotaluoto et al. that mortality was associated with complicated appendicitis, patient comorbidities and age, and negative appendectomy.[50,107] A study on frail geriatric (aged over 65 years) patients reported increased mortality in patients with a delayed appendectomy after initial non-operative treatment for uncomplicated acute appendicitis compared with primary appendectomy[188]. However, the study was not randomized, and also unexpectedly reported an increased tumor risk among the geriatric patient population with the increased mortality, suggesting that those patients initially were poor candidates for non-operative management.

2.10 Treatment costs of uncomplicated acute appendicitis

The treatment costs of antibiotic or surgical management for uncomplicated acute appendicitis consist of the costs of both the initial treatment and the treatment costs of possible readmissions for either complications or suspected recurrence. Subsequently, the success rate of the initial treatment and the rate of recurrence have a major impact on the total treatment costs incurred[189].

There is little data on the costs of non-operative treatment of uncomplicated acute appendicitis as the approach is relatively novel. Also, there is great variety in health care systems and in their economic structure, making the comparison between different studies extremely difficult.

The economic analysis based on the APPAC RCT found that at 1-year follow-up, the overall costs incurred by initial approach of appendectomy were 1.6 times higher than of those originating from initial antibiotic treatment[25]. In the APPAC trial, however, the operative approach was mainly open appendectomy, mostly nowadays replaced by the laparoscopic approach, and the antibiotic group patients underwent a 3-day hospital follow-up dictated by the protocol to ensure patient safety of what was at that time a novel treatment approach. Corresponding results of antibiotics incurring less costs compared with laparoscopic appendectomy, however, were reported also by O'Leary et. al in an RCT on adults[26], as well as by Minneci et. al in a study on pediatric population with a 1-year follow-up[27]. Lee and colleagues reported comparative costs for laparoscopic and non-operative approaches in pediatric patients, but they included patients with appendicoliths in their analyses, presumably increasing the failure rate and subsequently the overall costs of the non-operative management group[190].

A US pilot RCT comparing outpatient management and laparoscopic appendectomy in adults with uncomplicated acute appendicitis found hospital charges to be significantly lower in the antibiotics-first group at 1-year[11].

As the long-term data on the treatment costs of initial antibiotic management is lacking, predictive statistical models have been created to assess future outcomes. Wu and colleagues used a decision tree model comparing three management strategies of initial laparoscopic appendectomy, and non-operative management with and without an interval appendectomy at three months. They concluded initial antibiotic treatment without interval appendectomy as the least costly alternative, with initial appendectomy becoming the preferred strategy in case of combined failure and recurrence rate of antibiotic management exceeded 56%. In the 5-year follow-up of the APPAC trial, the combined failure and recurrence rate assessed by the number of patients undergoing appendectomy, was 39.1%. Of those patients, only 30/100 patients with suspected recurrence had appendectomy between years 1 and 5[24].

The only assessment to date suggesting appendectomy incurring less costs compared to antibiotics in uncomplicated acute appendicitis was the predictive model study by Sceats et. al, who used a Markov model in the US context to assess lifetime costs and outcomes of a patient with uncomplicated acute appendicitis treated with initial laparoscopic appendectomy, outpatient antibiotic therapy or inpatient antibiotic therapy. They included the small possibility of a missed underlying neoplasm turning into cancer in a patient receiving non-operative treatment as a factor causing added costs in the future. In most scenarios, they found initial appendectomy the preferred approach, and in none of the scenarios was the inpatient antibiotic treatment the preferred approach. They concluded appendectomy as preferred over outpatient antibiotic management when the probability of finding an incidental appendiceal malignancy at index appendicitis presentation was greater than 0.59%[189]. When considering a situation where all failures and recurrences were uncomplicated and proceeded directly to appendectomy instead of requiring initial percutaneous drainage followed by interval appendectomy, the initial laparoscopic approach was no longer cost-effective compared to outpatient antibiotic management. In the 5-year follow-up of the APPAC trial, none of the patients with initial antibiotic treatment failure or recurrence required percutaneous drainage, instead all underwent emergency appendectomy[24].

3 Aims

The aim of this thesis was to provide clinicians with further information on optimization of diagnostics, antibiotic management, and treament costs of uncomplicated acute appendicitis. The spesific aims were as follows:

1) To compare the long-term overall costs of appendectomy versus antibiotic therapy for CT-confirmed uncomplicated acute appendicitis.

2) To compare the treatment efficacy of oral antibiotic monotherapy to a combination of intravenous followed by oral antibiotics and also to assess antibiotic therapy as the first-line treatment modality for CT-confirmed uncomplicated acute appendicitis.

3) To compare the diagnostic accuracy of low-dose and standard-dose CT in identifying patients with and without appendicitis and differentiating between uncomplicated and complicated acute appendicitis.

4 Materials and Methods

4.1 The APPAC and APPAC II trials

The analyses of study I were based on the data of the APPAC randomized multicenter study, conducted at six Finnish hospitals from November 2009 until June 2012. The study compared antibiotic therapy with open appendectomy in 530 adult patients with CT-confirmed uncomplicated acute appendicitis. Despite the APPAC study being unable to show non-inferiority of the antibiotic treatment compared to appendectomy, 72.7% of the patients initially treated with antibiotics did not need appendectomy within the first year and furthermore, 64.1% had not undergone appendectomy at 5 years. In addition, no major complications were attributed to the possible delay in the operative treatment of uncomplicated acute appendicitis in patients initially treated with antibiotics and the economic analysis at 1-year showed substantial cost benefits in favour of the antibiotic treatment.

The APPAC II was a randomized multicenter study designed based on the results of the APPAC study to optimize the antibiotic treatment of uncomplicated acute appendicitis and to assess antibiotic treatment as the first-line treatment for uncomplicated acute appendicitis in a large patient cohort. The analyses of studies III and IV were based on the data of the APPAC II patients, whereas the study II was a protocol for the APPAC II study without data analyses.

4.2 Patients and methods

4.2.1 Study I

Information of the included patients in each study is shown in Table 2. The details of the APPAC study protocol, the 1-year and the 5-year follow-up results, and the economic analysis at 1-year have been published earlier[7,24,25,159]. The APPAC study randomized 530 adult patients aged 18 to 60 years with CT-confirmed uncomplicated acute appendicitis to appendectomy or antibiotic treatment. The randomization was performed with a 1:1 equal allocation ratio using 610 opaque, sealed, and sequentially numbered randomization envelopes that were shuffled and then distributed to each participating hospital.

CT criteria for acute appendicitis were defined as appendiceal diameter exceeding 6 mm with wall thickening accompanied with at least one of the following features: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or minor fluid collections around the appendix. Exclusion criteria included complicated acute appendicitis defined as the presence of an appendicolith, perforation, abscess, or suspicion of a tumor on CT. Other exclusion criteria were contraindications for CT, peritonitis, unable to cooperate and provide informed consent, and the presence of serious systemic illness. For patients randomized to surgery, open appendectomy was the predefined surgical treatment in the trial protocol. For patients randomized to antibiotic treatment, i.v. ertapenem sodium 1 g daily was administered for three days followed by seven days of p.o. levofloxacin 500 mg once daily and metronidazole 500 mg three times daily. The study was performed from November 2009 until June 2012, with 5-year follow-up completed in September 2017.

Table 2. Patient data used in each original study.

Study	**Number of patients**	**Study hospitals**	**Details of patient population included in the study**
Study I	530	6 Finnish hospitals (Turku, Oulu, and Tampere University Hospitals and Mikkeli Seinäjoki, and Jyväskylä Central Hospitals)	All patients randomized to the APPAC trial (enrollment from November 2009 to June 2012)
Study III	603	9 Finnish hospitals (Turku, Oulu, Tampere, and Kuopio University Hospitals and Pori, Seinäjoki, Jyväskylä, Mikkeli, and Rovaniemi Central Hospitals)	All patients randomized to the APPAC II trial (enrollment from April 2017 to November 2018)
Study IV	856	Turku University Hospital, Turku, Finland	All patients admitted to the emergency department with suspected acute appendicitis during the APPAC II trial enrollment period (April 2017–November 2018)

4.2.1.1 Cost analysis

Treatment costs analyzed in study I were a predefined secondary outcome in the APPAC study protocol. The analyses included all major hospital costs, whether generated by the initial visit and subsequent treatment or possible complications or recurrent appendicitis during the 5-year follow-up. Cost levels of 2016 were used in all cost estimates. In the base case of analyses, annual discount rate of 5 per cent was applied to all costs. Hospital charges were recorded based on diagnosis-related group codes as overall hospital costs and registered separately in all participating hospitals, thus representing the true costs used to charge the final payer. The human capital approach was applied to evaluate the costs of absence from work. The length of hospitalization was included in the sick leave days and additional sick leave prescribed by the attending surgeon at discharge or during the 5-year follow-up was also recorded. The recommended lenght of sick leave following appendectomy or antibiotics was not predefined in the study protocol. The costs of productivity losses were based on the average monthly gross salaries for working Finnish adults in 2016, £2409 for women and £2880 for men. The per day productivity loss estimate was computed by dividing the gross monthly salary by 21, the number of average monthly working days.

Two patients initially treated with antibiotics subsequently having appendectomy lacked comprehensive data regarding surgical treatment and productivity loss. They were included in the analyses after estimating the follow-up costs by using age and sex standardized linear regression models based on complete operation and productivity loss data from the hospital district where they were initially treated. The cost for laboratory, imaging, and medicine used during hospitalization or prescribed at hospital discharge were evaluated marginal and non-significant at 1-year follow-up[25]. As omitting these cost components was not expected to have any influence on the comparison outcome of the two treatment alternatives, they were not collected for the 5-year analyses.

4.2.2 Studies II and III

The study II was a protocol article reporting the rationale and methods of the study III, the APPAC II RCT, carried out at nine Finnish hospitals; four university hospitals (Turku, Tampere, Oulu, and Kuopio) and five central hospitals (Pori, Seinäjoki, Mikkeli, Jyväskylä, and Rovaniemi). From April 2017 to November 2018 a total of 603 patients were randomized to antibiotic treatment of uncomplicated acute appendicitis with either p.o. antibiotic monotherapy or i.v. followed by p.o. antibiotics.

The inclusion criteria for the study were age 18 to 60 years and the diagnosis of CT-confirmed uncomplicated acute appendicitis defined by the following criteria:

Appendiceal diameter exceeding 6mm with thickened and enhancing wall and periappendiceal edema and/or minor fluid collection, and the absence of the criteria of complicated appendicitis. Exclusion criteria were: Age under 18 or over 60 years, pregnancy or lactation, allergy to contrast media or iodine, allergy or contraindication to antibiotic therapy, renal insufficiency or serum creatinine value exceeding the upper reference limit, type 2 diabetes mellitus and use of metformin medication, severe systemic illness (e.g. malignancy or medical condition requiring immunosuppressant medication), inability to cooperate and give informed consent, or complicated appendicitis based on CT findings. Acute appendicitis was radiologically classified as complicated when presenting with any of the following CT features: perforation, appendicolith, periappendicular abscess, or a suspicion of a tumor. The CT findings were evaluated by the on-call radiologist using a standardized CT scan report sheet (Table 3).

Table 3. Structured radiological report including radiological criteria and categorization of acute appendicitis in the APPAC II trial

1) **Appendix Visualization**
   Report one of the following:
   Not visualized/ Partly or unclearly visualized/ Completely visualized

2) **Appendix transverse diameter** (mm):

3) **Probability of appendicitis**
   Report one of the following:
   Not likely/ Rather unlikely/ Rather likely/ Very likely

4) **Categorization of the appendicitis**
   Report either I or II, if any:

   I Uncomplicated appendicitis: transverse diameter > 6mm with typical findings
   -wall thickening and enhancement
   -periappendiceal edema and/or minor amount of fluid

   II Complicated appendicitis: Above-mentioned criteria for appendicitis with at least one of the following:
   -Appendicolith: > 3mm stone within appendix
   -Abscess: periappendiceal walled of collection with enhancing walls
   -Perforation: appendiceal wall enhancement defect and periappendiceal excess of fluid and/or infectious phlegmon and/or extraluminal air
   -Tumor: tumor-like prominence of appendix

5) **Other diagnosis:** Report if any
   Diverticulitis/ Complicated ovarian cyst/ Pelvic inflammatory disease/ Colitis/ Ileitis /Intestinal obstruction or ileus/ Ureter stone/ Hydronephrosis/ Tumor/ Other diagnosis

Among patients excluded from the study, patients diagnosed with complicated acute appendicitis were referred to emergency appendectomy, whereas patients with other diagnoses on CT were treated according to the discretion of the surgeon. To prevent selection bias and to collect a comprehensive recording of the patient population with suspected acute appendicitis, the data was recorded for all patients with acute appendicitis on CT and the aim was also to record data for all patients who underwent CT for suspicion of acute appendicitis. Data was recorded in an online database.

4.2.2.1 Randomization and interventions

Patients were randomized with a 1:1 equal allocation ratio with random permuted blocks of 10 to either p.o. antibiotic monotherapy or to i.v. followed by p.o. antibiotics. After written informed consent, the surgeon on call opened the randomization using the online database and the randomized treatment was initiated in the emergency room.

Patients randomized to p.o. antibiotic monotherapy were treated with seven days of p.o. moxifloxacin with a 400 mg once daily dose. Patients randomized to i.v. followed by p.o. antibiotics were treated two days with i.v. ertapenem sodium 1 g daily followed by p.o. levofloxacin 500 mg daily and metronidazole 500 mg three times daily for five days.

4.2.2.2 Outcomes and follow-up

The primary outcome for both groups was treatment success at one year defined as resolution of acute appendicitis during primary hospitalization without the need for surgical intervention and no recurrent appendicitis during one-year follow-up. Secondary outcomes were post-intervention complications, late recurrence (after one year) of acute appendicitis after antibiotic treatment, length of hospital stay, VAS (visual analog scale) scores, QOL, length of sick leave, and treatment costs.

After randomization, the minimum hospital follow-up was 20–24 hours. In case progression to complicated appendicitis was suspected during hospitalization, laparoscopic appendectomy was performed. The criteria or means of evaluating patients' responsiveness to antibiotics were not prespecified, but left on the discretion of the on-call surgeon. Postinterventional outcomes were assessed at discharge and by a telephone interview at one week, two months, and one year, with the follow-up planned to continue up to ten years (one, three, five, and ten years).

4.2.3 Study IV

In study IV, all patients aged 16 years or older presenting with a suspicion of acute appendicitis in the emergency department of Turku University Hospital during the enrollment period of the APPAC II trial were included in the study. In order to ensure thorough inclusion of all suspected acute appendicitis patients, the online database data used in the prospective APPAC II trial was retrospectively supplemented after a search for ICD-10 diagnosis codes for appendicitis (K35.0, K35.1, K35.9) and procedure codes for open and laparoscopic appendectomy. Additionally, referrals to CT scans due to suspected acute appendicitis were electronically checked among all on-call abdominal CT scans by searching for words: “appendicitis” and ”appendix”. Upon a patient presenting with suspected acute appendicitis, the physicians on-call were instructed to carry out the diagnostic CT-imaging according to the APPAC II protocol. The protocol stated that a low-dose contrast enhanced abdominal CT should be performed for patients with a BMI under 30 kg/m^2 and a standard contrast enhanced abdominal CT for patients with a BMI over 30 kg/m^2. The dose length product (DLP) was recorded separately for each CT examination and the effective dose calculated based on the individual patient DLP and the coefficients described by Huda et al.[191]

The radiological criteria for acute appendicitis assessment were identical to the one used in the APPAC II trial and described in the Table 2. Based on the evaluation of the radiologist on-call, the patients were classified into three groups; having either uncomplicated acute appendicitis, complicated acute appendicitis, or no appendicitis. After receiving treatment according to the discretion of the surgeon on-call or based on possible enrollment to the ongoing RCTs and completing a 30-day follow-up, the final clinical diagnosis was determined as one of the three alternatives correspondingly to the CT diagnosis groups. Three researchers assessed the final clinical diagnosis based on the diagnostic CT, possible operative and histopathological findings (in case of surgical treatment), and patient recovery. Patients who presented with an intraluminal appendicolith either on CT or at surgery were classified as having complicated acute appendicitis.

The CT diagnosis evaluated by the on-call radiologist was compared to the final clinical diagnosis set by the investigators. In assessing the accuracy of CT modalities in identifying patients with and without appendicitis, all patients were included, whereas when assessing the differential diagnostic accuracy for uncomplicated and complicated acute appendicitis, only patients with a final clinical diagnosis of appendicitis were included.

Subgroup analyses were conducted to evaluate the effect of BMI on diagnostic accuracy by comparing patients with BMI under 30 kg/m^2 and over 30 kg/m^2. Additionally, subgroup analyses were performed to assess the effect of possible appendicolith on CT accuracy, where only patients without a finding of appendicolith were included as well as a subgroup analysis in which the possible finding of an appendicolith was disregarded and both the radiological and the final clinical diagnoses were based on all other predefined criteria.

4.3 Statistical analysis

4.3.1 Study I

Categorical variables were described using frequencies and percentages, and continuous variables with means and 95% confidence intervals 95% (CI) or in case of skewed variables medians with 95% CIs. Statistical analysis of the data on average costs was performed using Student's t-test. The data on hospital charges, productivity costs and overall costs had very acceptable skewness and kurtosis values and the Student's t-test was evaluated robust enough to minor violation of the normality assumption. Differences between groups in sick leave and length of hospital stay were tested using Mann-Whitney U-test because of very skewed distributions.

Sensitivity analyses were performed to determine whether the final outcome was sensitive to certain crucial factors. The role of the costs of absence from work days was determined in two directions, i.e. by decreasing the days of prescribed sick leave and increasing the salary costs with 10% intervals up to 50% lower and higher values. The effect of discount rate was evaluated by performing the analyses using also 0%, 3%, 7% and 10% annual rates. Two-sided p-values less than 0.05 were considered statistically significant. All analyses were performed using SPSS software version 23 (IBM, Armonk, New York, USA).

4.3.2 Study II and Study III

Sample size calculations were based on non-inferiority test for binomial proportion. Sample size was calculated from an estimated success rate of 73% for i.v. + p.o. antibiotic group during the 1-year follow-up of the APPAC trial[7]. The difference between groups ((i.v. + p.o.) – p.o.) was set to zero and non-inferiority margin to 6 percentage points. It was estimated that a total of 469 patients would yield a power of 0.9 (1-β) to establish whether p.o. antibiotic therapy was non-inferior to i.v. + p.o. using a one-sided significance level (α) of 0.05. Based on an estimated dropout rate of 15% of the total of 552 patients, 276 patients per group was needed to be enrolled in the study. Targeted minimum sample size per study hospital was 20 patients.

After 250 patients were enrolled in the study, an interim analysis was carried out. The point estimate of the success rate at discharge was calculated by study statistician and evaluated in each group. As the proportion was above 70% in both groups, the study was allowed to continue.

All randomized patients were included in the analyses according to the group they were randomized into, excluding the patients randomized erroneously with initial CT-confirmed complicated acute appendicitis and early dropouts. The baseline comparison included also all early dropouts.

In order to assess the possibility of study site effects, a post hoc analysis was conducted using a binomial generalized linear model with study group as fixed effect and study center as random effect. Additionally, a post hoc Kaplan-Meier curve of time to appendectomy in both study groups was drawn.

The APPAC II trial was a non-inferiority study with a primary outcome of treatment success evaluated in two stages: It was first evaluated if the treatment success rates in both groups was greater than or equal to 65%, judged with the lower limit of 95% CI, and secondly, whether the difference of treatment success rates was less than 6% based on 1-sided 95% CIs. The CIs were calculated using the Wald method. Survival analysis with Wilcoxon test was performed to compare the time from randomization to possible appendectomy between the study groups. Two patients were lost to follow-up and consequently excluded from the primary outcome analyses.

Secondary outcomes between treatment groups were analyzed using Fisher exact tests for categorical variables and independent samples t-tests or Mann-Whitney U-tests for continuous variables. All continuous variables were presented as mean with standard deviations when normally distributed and otherwise as median with 25th and 75th percentages or range. Assumptions for t-tests were checked with studentized residuals. For the secondary outcomes, two-tailed P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS system for Windows, version 9.4 (SAS Institute, Inc).

4.3.3 Study IV

Resulting from the study protocol guiding the diagnostic imaging based on patient BMI, the patient groups imaged with low-dose and standard-dose differed notably in terms of BMI. Therefore, formal statistical analyses were performed only for the subgroup of patients with BMI under 30 kg/m^2, whereas in the whole study group, the data were presented as descriptive. Continuous variables were presented using median with range or interquartile range (IQR). Categorical variables were presented with frequencies and percentages, age as mean with range. Wilcoxon rank sum test was used for radiation dose. For patients with BMI under 30 kg/m^2, accuracy comparison (accuracy defined as the percentage of correct diagnoses) was performed using Fisher's exact test and 95% CIs were calculated for accuracies. All tests were two-tailed and P-values < 0.05 were considered statistically significant. Analysis was performed with SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

4.4 Ethics

Study I was based on the 5-year follow-up results of the APPAC study, initially approved by the ethics committees of all participating hospitals. The trial was registered in clinicaltrials.gov:NCT01022567. As antibiotic management for uncomplicated acute appendicitis was a novel approach at the time of the APPAC study initiation, a 3-day hospitalization with daily clinical assessment was included in the study protocol to ensure patient safety in the antibiotics arm. As the optimal antibiotic regimen was unknown, a rather long 10-day course of wide spectrum antibiotic treatment with a 3-day initial i.v. administration was used to ensure efficacy against a wide spectrum of bacteria. The benefits of such potent antibiotic treatment had to be weighed against its disadvantages; the prolonged hospitalization and potential antibiotic related adverse effects concerning the individual patient, and above all the possibility of contributing to the antibiotic resistance problem in general. Regarding preinterventional diagnostics, CT was already widely used for diagnostic imaging despite of its disadvantage of radiation exposure. Routine CT imaging for patients with suspected acute appendicitis was therefore not considered to greatly differ from the standard clinical practice at the time.

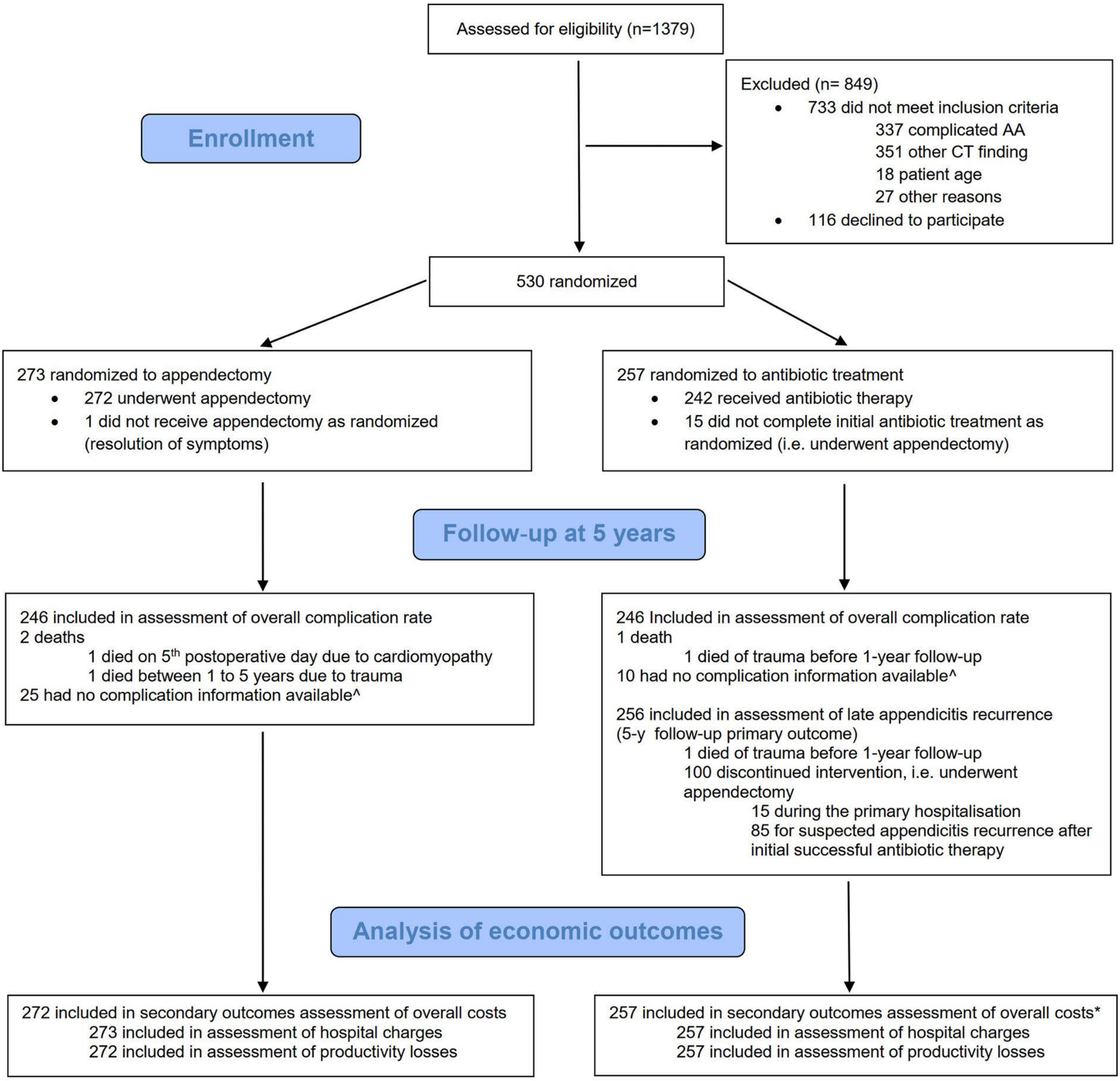
The APPAC II trial (studies II–IV) was approved by the ethics committee at the Hospital District of Southwest Finland and by institutional research boards at each participating site. The trial was performed in accordance with the Declaration of Helsinki. Trial was registered in clinicaltrials.gov: NCT03236961. After the results of the APPAC study[7] demonstrated antibiotics as safe and feasible treatment for uncomplicated acute appendicitis, the follow-up study III (APPAC II trial) aimed to optimize the antibiotic treatment. Subsequently, based on the earlier data, shorter hospitalization was included in the study protocol. To decrease possible harms related to the prolonged use of antibiotics, especially regarding the antibiotic resistance problem, shorter duration of antibiotic treatment was used. Furthermore, as the accuracy of low-dose CT was reported non-inferior to standard dose CT among patients with a BMI under 30kg/m^2 in the OPTICAP trial, low-dose CT was included as the diagnostic imaging for patients with a BMI under 30kg/m^2 in study III. Study IV was conducted to further corroborate the findings of similar diagnostic accuracy of low-dose and standard dose CT in order to encourage implementation of low-dose CT modalities in clinical practice to avoid unnecessary radiation of the patient population with suspected acute appendicitis.

5 Results

5.1 The 5-year cost analysis of antibiotic therapy versus appendectomy for uncomplicated acute appendicitis

Out of the 530 patients enrolled in the study, 273 patients were randomized to appendectomy and 257 patients to antibiotic treatment. Figure 3 shows the trial profile. At 5-year follow-up, 495/530 (93%) patients were reached by telephone, and hospital records were checked for all patients. 529 out of the 530 patients were included in the economic analysis, with one patient excluded due to death of trauma before the 1-year follow-up point. One hundred patients (38.9%) out of the initial 257 patients underwent appendectomy during the 5-year follow-up period, of which 85 (31.1%) after the initial hospitalization.

At five years, the overall costs in the appendectomy group were significantly ($p<0.001$) higher (€5716; 95% CI 5510 to 5925) than in the antibiotic treatment group (€4171; 95% CI 3879 to 4463). The overall costs in the operative group were 1.4 times higher at 5-years, with a cost advantage of €1545 per patient (95% CI 1193 to 1899, $p<0.001$) for antibiotic therapy. The median length of hospital stay was 3 days in both groups (95% CI, 3 to 3). More sick leave was prescribed to the patients in the operative group compared to those in the antibiotic group (median 22 (95% CI 19 to 23) versus 11 (11 to 12) days, respectively; $p<0.001$).



^ I.e. patient could not be reached by phone at 5-year follow-up and did not have a complication at any previous follow-up timepoint.
* Two antibiotic group patients operated abroad during long term follow-up due to suspected recurrence and they were lacking sufficient data on hospital costs and productivity losses. Their cost related data was estimated using age and sex standardized linear regression models.

Figure 3. Flow of patients in the APPAC trial.

The detailed distribution of costs is presented in Table 4. The costs in the surgical group were found higher for both hospital charges and productivity losses. In both groups, productivity losses formed slightly higher proportion of the overall costs compared with hospital charges. The relative differences in the costs between the two study groups were found nearly equal in terms of hospital charges, productivity losses as well as in overall costs.

Table 4. Average hospital charges, productivity losses and overall costs in Euros for appendectomy and antibiotic therapy group patients with uncomplicated acute appendicitis at five-year follow-up.

	Appendectomy Group € (95% CI, €)	**Antibiotic therapy Group € (95% CI, €)**	**Difference € (95% CI, €)**	**P <**
Five-year follow-up				
Hospital charges	2730 (2645–2817)	2056 (1861–2251)	674 (465–883)	0.001
Productivity losses	2986 (2822–3149)	2115 (1950–2280)	871 (639–1104)	0.001
Overall costs	5716 (5510–5925)	4171 (3879–4463)	1545 (1193–1899)	0.001

No changes in the findings of this study were detected in the sensitivity analyses. The differences in the sensitivity analyses of the costs between the two groups at 5-year follow-up are presented in Table 5. The costs remained 1.3 to 1.4 times higher for operative group, even when applying the most extreme value options.

Table 5. Sensitivity analyses of mean overall costs of appendectomy and antibiotic therapy group patients with uncomplicated acute appendicitis in Euros per patient at five-year follow-up.

	Appendectomy Group € (95% CI, €)	**Antibiotic Therapy Group € (95% CI, €)**	**Difference € (95% CI, €)**	**P <**
Discount rate				
10%	5716 (5510–5922)	4137 (3853–4423)	1579 (1229–1926)	0.001
0%	5720 (5511–5928)	4212 (3911–4513)	1508 (1145–1870)	0.001
Sick leave days				
30% fewer	4951 (4784–5119)	3728 (3460–3995)	1223 (911–1534)	0.001
50% fewer	4438 (4296–4581)	3406 (3158–3653)	1032 (752–1313)	0.001
Salary costs				
30% higher	9335 (9030–9638)	6538 (6102–6972)	2797 (2271–3321)	0.001
50% higher	9932 (9599–10265)	6964 (6506–7422)	2968 (2407–3527)	0.001

5.2 Oral antibiotic monotherapy versus intravenous followed by oral antibiotics for uncomplicated acute appendicitis: The APPAC II randomized clinical trial

Figure 4 shows the trial profile. Out of the 3512 evaluated patients with clinically suspected acute appendicitis, 603 patients were randomized to receive either p.o. moxifloxacin or i.v. ertapenem followed by p.o. levofloxacin and metronidazole. After randomization, 20 patients were excluded from analysis for the following reasons: complicated acute appendicitis stated on CT prior to randomization (randomization protocol violation, n=4) and early patient withdrawal of consent (n=16) without receiving actual allocated treatment leaving altogether 583 patients (p.o. antibiotic monotherapy group, n=295, i.v. followed by p.o. antibiotics group, n=288) in the primary analyses.

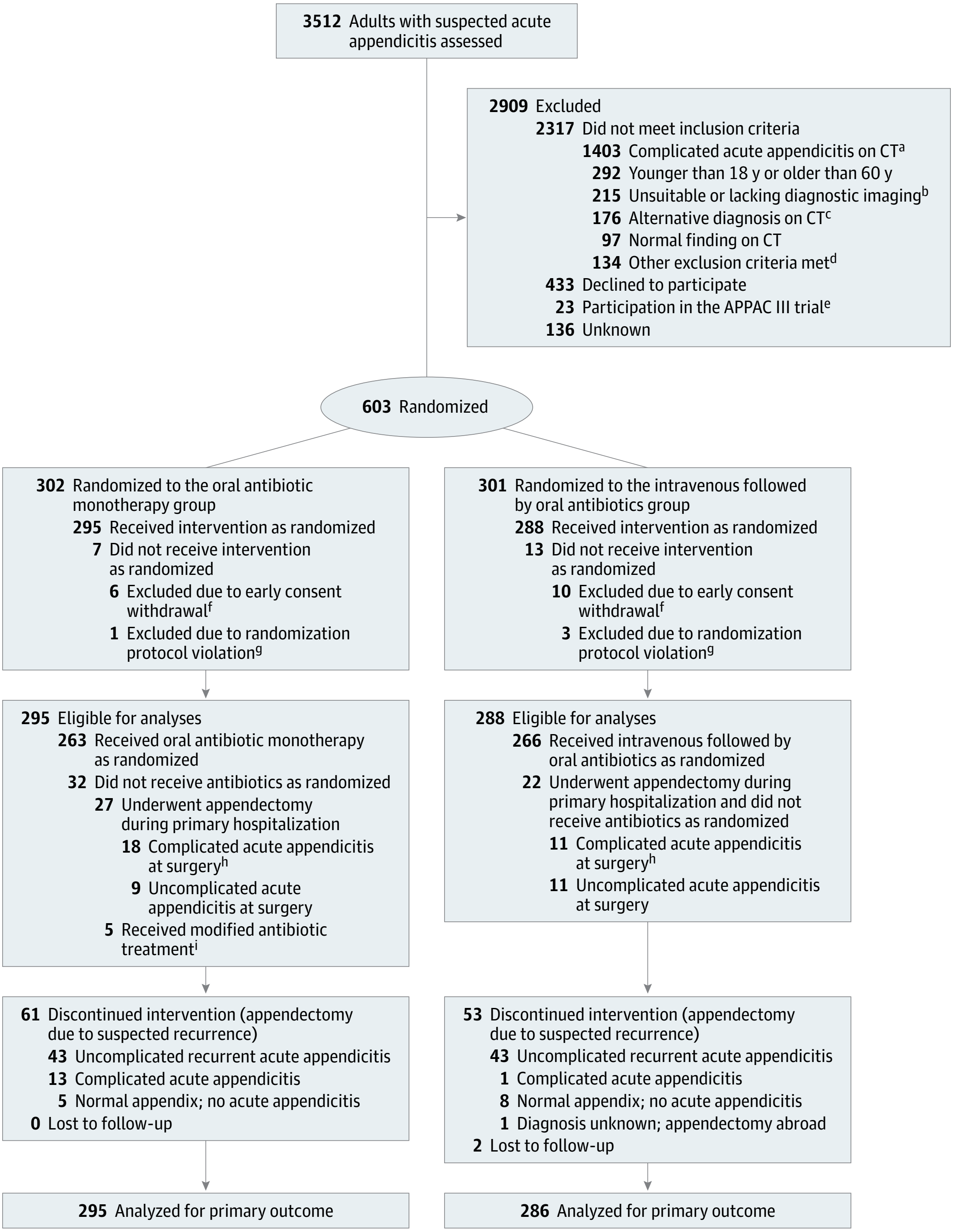


Figure 4. Flow of participants in the APPAC II trial. Reproduced with the permission of the copyright holders. Footnotes included in the next page.

[a] Includes appendicolith, perforation, abscess, or suspicion of tumor.
[b] The majority of these patients underwent ultrasound examination, magnetic resonance imaging, or non-contrast-enhanced CT. 12 patients were operated on without diagnostic imaging.
[c] The alternative diagnoses were as follows: Diverticulitis 36, ovarian mass/cyst 25, colitis 24, pelvic inflammatory disease 12, mesenterial lymphadenitis 11, pyelonephritis 8, kidney/ureteral stone 4, bowel obstruction 1, and 55 other miscellaneous pathological findings or suspicion of such.
[d] Additional exclusion criteria were pregnancy, lactation, allergy to contrast media, kidney insufficiency, use of metformin, systemic illness, and inability to consent.
[e] A randomised placebo-controlled double-blind multicentre trial comparing antibiotic therapy with placebo in the treatment of uncomplicated acute appendicitis. Sippola S, Gronroos J, Sallinen V, et al. A randomised placebo-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.
[f] Patients who withdrew consent within 24 hours of randomization having received a maximum of 1 dose of randomized treatment were excluded from the analyses. Two patients, who withdrew their consent 5 and 7 days after randomization, respectively, were included in the analyses.
[g] Patients erroneously randomized despite a finding of complicated acute appendicitis initially seen on CT were excluded from the analyses according to the study protocol.
[h] Operative or histopathological findings of appendicolith, gangrene, perforation, abscess, or tumor were classified as complicated acute appendicitis.
[i] One patient in the po arm mistakenly received the iv + po arm antibiotic treatment. Four patients received 1 dose of moxifloxacin and thereafter cephalexin and metronidazole; 2 patients due to suspected reactions to moxifloxacin, 1 due to lactation, and 1 in order to prevent a possible adverse interaction with the patient’s antidepressant.

Baseline characteristics were similar in the two groups and are presented in Table 6. The mean age of the patients was 36 years, and 43.9% of the patients were female.

Table 6. Baseline patient characteristics in the APPAC II trial.

Characteristics	Oral antibiotic monotherapy group (n=301)	Intravenous followed by oral antibiotics group (n=298)
Patients[a]		
Female sex, n, (%)	137(45.5%)	126(42.3%)
Male sex, n, (%)	164(54.5%)	172(57.7%)
Age, median (IQR), years	34(26-45)	33(26–43)
Visual analog scale (VAS) score for pain on admission, mean (SD)[b]	5.2(2.3)	5.2(2.4)
Body temperature, mean (SD), °C	37.2(0.6)	37.2(0.6)
Leukocyte count, median (IQR), x109/l (3.4–8.2 x109/l) [c]	12.5(9.4–14.9)	12.2(9.1–14.9)
C-reactive protein, median (IQR), mg/l (<10 mg/l) [c]	29.9(11.0–61.0)	34.0(13.0–62.6)
Neutrophil count, median (IQR), x109/l (1.5–6.7 x109/l) [c]	9.4(6.6–11.9)	9.4(6.1–11.9)
Body mass index, median (IQR), kg/m^2 [d]	26.8(24.2–30.1)	26.4(23.6–30.2)
Appendiceal diameter on CT, mean (SD), mm [e]	10.9(2.6)	10.7(2.4)
Duration of symptoms on admission, median (IQR), h	18.0(10.0–30.0)	22.0(12.0–30.0)

Abbreviation: IQR, interquartile range;
SI conversion factor: To convert C-reactive protein to mg/dL, divide by 10.
[a] Includes all randomized patients excluding erroneously randomized patients with complicated appendicitis initially seen on CT.
[b] Score range 0–10; a score of 0 indicates no pain and 10 indicates the worst possible pain. 324/599(54.1%) of patients had received some form of analgesic prior to pain scale score assessment.
[c] The range presented in brackets is the reference range
[d] Body mass index is the weight in kilograms divided by the square of the height in meters.
[e] Defined as the outer-to-outer surface appendiceal diameter measured from the widest part of the appendix on the axial plane (i.e. perpendicular to the longitudinal axis). A diameter of 6mm or smaller was considered normal, whereas a diameter exceeding 6mm together with signs of acute inflammation (thickened and enhancing wall and periappendiceal edema and/or minor fluid collection) was considered pathological.
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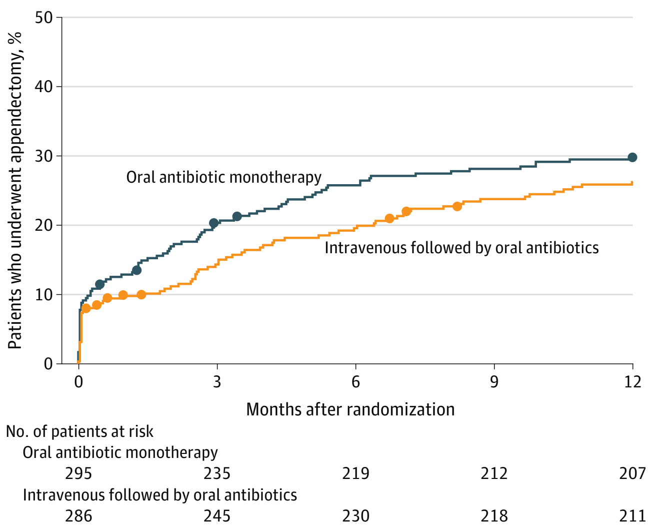
Out of the 1195 patients with CT-confirmed uncomplicated acute appendicitis, 569 patients meeting all inclusion criteria were either not evaluated for study enrollment or declined to participate and 23 patients took part in a concurrent appendicitis trial (APPAC III)[160], i.e. 51.5% (603/1172) of the eligible patients were randomized.

The follow-up rate for primary outcome was 99.7% (581/583); two patients moved abroad and were lost to follow-up, and subsequently excluded from the primary outcome analysis at 1-year. 72 patients could not be reached by telephone and information about possible appendectomy for the primary outcome analysis was obtained from hospital district electronic medical records.

5.2.1 The primary outcome of treatment success in the APPAC II trial

The predefined margin of 65% for treatment success was exceeded in both groups. The treatment success in the p.o. antibiotic monotherapy group at 1-year was 70.2% [one-sided 95% CI from 65.8% to ∞] consisting of 88 out of the 295 patients undergoing appendectomy, 27 patients (9.2%) during primary hospitalization and additional 61 patients (20.7%) during 1-year follow-up. The treatment success in the i.v. followed by p.o. antibiotics group was 73.8% [one-sided 95% CI from 69.5% to ∞] resulting from 75 out of the 288 patients undergoing appendectomy, 22 patients (7.6%) during primary hospitalization and 53 patients (18.5%) during the 1-year follow-up. For the primary outcome of treatment success between the groups, the analysis yielded a difference of -3.6% [one-sided 95% CI from 9.7% to ∞] (P=0.26), with CI of the difference exceeding the predefined non-inferiority definition of lower limit of -6%. The cumulative incidence of appendectomy during the 1-year follow-up is shown in Figure 5.



A total of 581 of 583 patients (99.7%) were followed up to achievement of the primary outcome or to 1 year and included in this post hoc analysis. The solid dots represent appendectomies of histologically normal appendixes.

Figure 5. Time to appendectomy after initial treatment in the APPAC II trial. Reproduced with the permission of the copyright holders.

The classification of appendicitis severity for patients who underwent surgery is presented in detail in flow chart figure 4. Complicated appendicitis was found in 29 out of the 49 patients undergoing appendectomy during the initial hospitalization, (p.o. antibiotic monotherapy group, n=18, i.v. followed by p.o. antibiotics group, n=11) resulting in true primary failure rates of 6.1% and 3.8% (P=0.25) for the two groups, respectively. In blinded retrospective radiological evaluation, 18 of the 29 (62%) patients with complicated acute appendicitis found at surgery during primary hospitalization were evaluated as having radiologically complicated appendicitis already in the initial CT.

In eight patients out of the 61 in the p.o. monotherapy group and five out of the 53 in the i.v. followed by p.o. antibiotics group who underwent surgery for suspected recurrent appendicitis the removed appendix was deemed uninflamed at histopathology. This yielded in a true recurrence rate of 20.9% and 16.7% (P=0.22) after initial successful antibiotic treatment for p.o. antibiotic monotherapy group and i.v. followed by p.o. antibiotics group, respectively. The median time to appendectomy in patients with true recurrent appendicitis was 104 days [95% CI, 84–132 days] and in all patients operated for suspected recurrence 101 days [95% CI, 82–127 days].

5.2.2 Secondary outcomes in the APPAC II trial

There was no mortality during 1-year follow-up. There was no statistically significant difference between the treatment groups regarding the overall complication rate, length of hospitalization or sick leave, or VAS scores at discharge, 1 week, and two months. The complications are presented in Table 7 and the other secondary outcomes including detailed follow-up rates for each secondary outcome in Table 8. In two patients, both in the p.o. antibiotic monotherapy group, the randomized treatment was discontinued due to suspected adverse event related to antibiotic treatment (one skin eczema with facial swelling and one patient with blurred vision). Out of all randomized patients undergoing appendectomy, four (4/163=2.6%) patients were found to have an appendiceal tumor.

Table 7. Complications in the APPAC II trial.

	oral antibiotic monotherapy group (n=295)	**intravenous followed by oral antibiotics group (n=288)**
Adverse events related to antibiotic treatment (n)[a]	6	14
Skin eczema	3	3
Other allergic reaction	1	2
Tendinitis	1	1
Blurred vision	1	0
Prolonged diarrhea[b]	0	5
Candidiasis (oral or vaginal)	0	3
Tendon rupture	0	0
Adverse events related to operative treatment (n)[a]	9	10
Abdominal pain, incisional pain, or obstructive symptoms	7	7
Surgical site infection	2	3
Incisional hernias	0	0
Other miscellaneous symptoms related to antibiotic treatment		
Nausea	23	40
Diarrhea	11	36
Metallic taste sensation	1	23
Number of patients with at least one adverse event, n, (%, 95% CI)[c]	14/295 (4.8%, 2.3–7.2)	21/286 (7.3%, 4.3–10.4)

[a] Number (%) of patients in oral antibiotic monotherapy group and intravenous followed by oral antibiotics group available for adverse event assessment at each time point: at discharge 295 (100%) and 288 (100%), at 1 week 273 (92.5%) and 255 (89.5%), at 2 months 265 (89.8%) and 253 (88.8%), and at 1 year 256 (86.8%) and 239 (83.0%), respectively.
[b] Patient still reporting diarrhea at two months.
[c] Includes adverse events reported at any time point (at discharge, 1 week, 2 months, and 1 year) and during possible re-hospitalization.
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Table 8. Secondary outcomes in the APPAC II trial.

	Oral antibiotic monotherapy group (n=295)	Intravenous followed by oral antibiotics group (n=288)	Absolute difference, mean (95% CI)	P value
Secondary outcomes				
Length of primary hospital stay, median (IQR), hours, [n][a]	28.9(23.0–41.9)	29.9(23.3–43.2)	-0.77(-3.9–2.4)	.38
Length of overall hospital stay during 1-year follow-up, median (IQR), hours, [n][a]	36.5(24.0–63.1)	35.7(24.7–58.6) [n=286]	0.68(-4.2–5.5)	.91
Visual analog scale (VAS) score for pain, median (IQR)[b]				
At discharge, [n][a]	1.0 (0.0–2.0) [n=265]	1.0 (0.0–2.0) [n=263]	NA[c]	.91
At 1 week, [n][a]	0.0 (0.0–0.0) [n=265]	0.0 (0.0–0.5) [n=252]	NA[c]	.84
At 2 months, [n][a]	0.0 (0.0–0.0) [n=262]	0.0 (0.0–0.0) [n=248]	NA[c]	.38
Length of sick leave, median (IQR), days, [n][a]	7.0 (3.0–8.0)	7.0 (3.0–9.0)	0(-0.70–0.70)	.42

[a] The number in square brackets indicates the number of patients with data available for each outcome.
[b] Score range 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain.
[c] Due to similarity of the values in the two groups, the absolute differences for VAS score for pain at discharge, 1 week, and at 2 months could not be presented.
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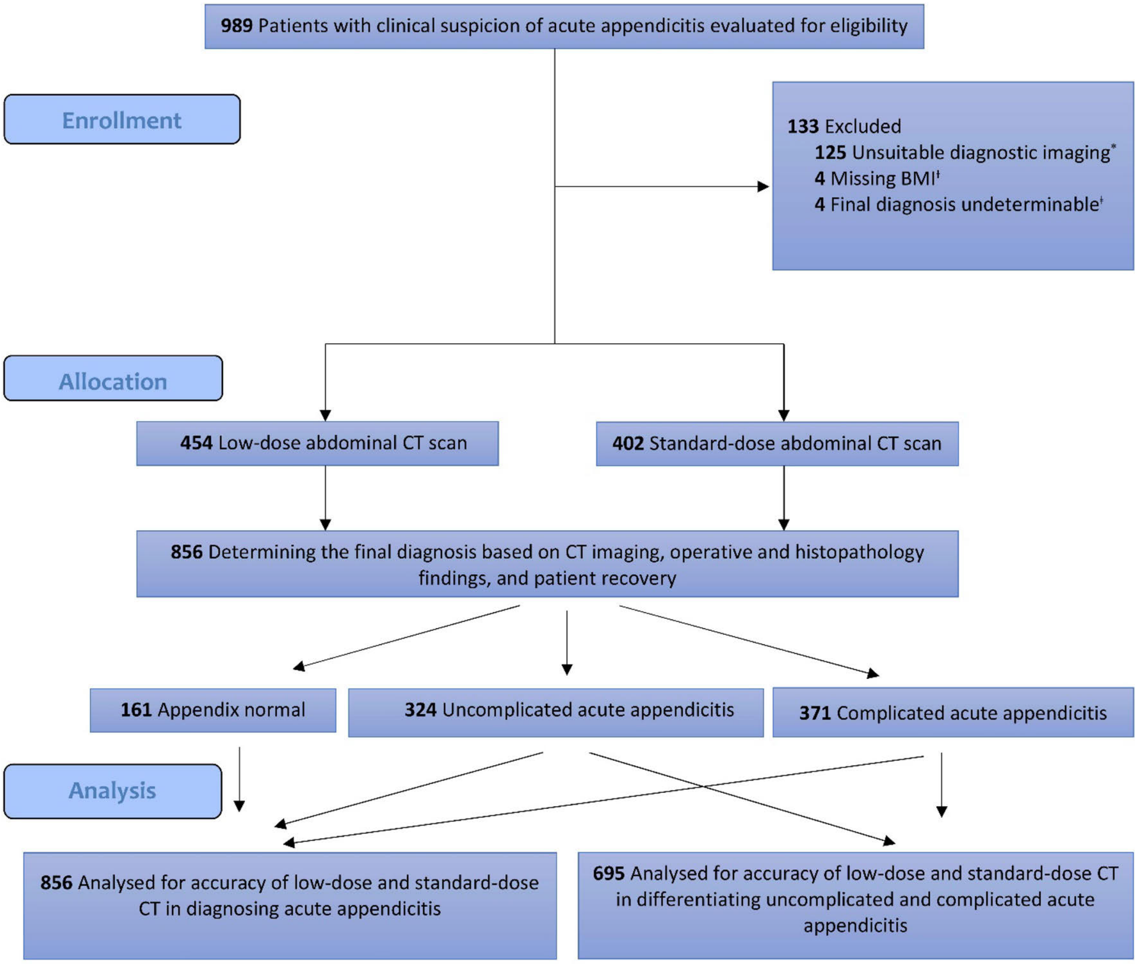
5.3 The accuracy of low-dose CT versus standard CT for acute appendicitis

The study IV patient flow is presented in Figure 6. Among the 856 included patients, 116 patients were concurrently enrolled in the APPAC II study and 10 patients in the APPAC III study. Out of the 856 patients, 52% were women and the median age was 37 years (range 16 to 87). Patient baseline demographics are presented in Table 9. Low-dose CT was performed in 53% (454/856) and standard-dose CT in 47% (402/856) of the patients.



* Majority of these patients underwent ultrasound examination, non-contrast-enhanced CT, or magnetic resonance imaging. Some patients were operated on without diagnostic imaging.

ǂ BMI is the weight in kilograms divided by the square of the height in meters. Four patients were excluded due to unknown BMI needed for the analyses.

‡ Two patients were transferred from the emergency department to another hospital for treatment. For two patients, the appendix could not be visualized on CT and no alternative pathology on CT was found. They were not operated on, but recovered with antibiotics, but the final clinical diagnosis could not be reliably determined.

Figure 6. Patient flow in the study.

Table 9. Baseline characteristics for patients included in the analyses.

Characteristics	Low-dose abdominal CT (n=454)	Standard-dose abdominal CT (n=402)
Female sex, n, (per cent)	244 (53.7)	204 (50.8)
Male sex, n, (per cent)	210 (46.3)	198 (49.3)
Age, median (range), y	31 (16–75)	47 (16–87)
BMI*, median (range), kg/m^2 BMI≥30 (n, per cent) BMI<30 (n, per cent)	24.7 (16.6–42.7) 20 (4.4 per cent) 434 (95.6 per cent)	29.5 (16.9–56.8) 192 (47.8 per cent) 210 (52.2 per cent)
C-reactive protein, median (range), mg/l	35.0 (1.0–462.0)	42.5 (1.0–418.0)
White blood cell count, median (range), $x10^9/l$	12.3 (2.7–27.3)	12.8 (2.9–30.9)

* BMI calculated as weight in kilograms divided by height in meters squared.

The accuracy of low-dose and standard-dose CT in diagnosing patients with and without acute appendicitis was 98.0% and 98.5%, and the accuracy for differentiating between uncomplicated and complicated acute appendicitis was 90.3% and 87.6%. The sensitivity of low-dose and standard-dose CT for complicated acute appendicitis was 89.6% and 84.6% and the specificity 91.0% and 91.8%. In the subgroup analyses classifying patients according to their BMI or appendicolith status, the accuracy between the two imaging modalities was comparable (Table 10). In the subgroup analysis of patients with a BMI under 30kg/m2, overall accuracy of low-dose and standard-dose CT in diagnosing patients with and without acute appendicitis was 98.2% (95% CI 96.9–99.4%) and 98.6% (95% CI 97.0–100.0%), respectively, (P=1.000), and the accuracy for differentiating between uncomplicated and complicated acute appendicitis was 89.8% (95% CI 86.5–93.1%) and 88.4% (95% CI 84.0–92.9%), respectively, (P=0.663).

Table 10. Subgroup analyses for accuracy in diagnosing acute appendicitis and in differentiating complicated and uncomplicated acute appendicitis.

Subgroup	**Accuracy in diagnosing acute appendicitis and no acute appendicitis**	**Accuracy in differentiating complicated and uncomplicated acute appendicitis**
Patients with a BMI <30 kg/m^2 (n=644)*	ld 98.2 per cent (426/434)	ld 89.8 per cent (290/323)
	sd 98.6 per cent (207/210)	sd 88.4 per cent (176/199)
Patients with a BMI ≥ 30 kg/m^2 (n=212)	ld 95.0 per cent (19/20)	ld 100.0 per cent (17/17)
	sd 98.4 per cent (189/192)	sd 86.5 per cent (135/156)
The presence of appendicolith selectively disregarded[ƚ] (n=856)	ld 98.0 per cent (445/454)	ld 80.9 per cent (275/340)
	sd 98.5 per cent (396/402)	sd 75.8 per cent (269/355)
Patients with no appendicolith[ǂ] (n=602)	ld 97.3 per cent (322/331)	ld 86.2 per cent (187/217)
	sd 97.8 per cent (265/271)	sd 81.7 per cent (183/224)

Abbreviations: ld, intravenous contrast enhanced low-dose abdominal computed tomography imaging; sd, intravenous contrast enhanced standard-dose abdominal computed tomography imaging.

* BMI calculated as weight in kilograms divided by height in meters squared.

ƚ For this subgroup the possible finding of appendicolith in CT or intraoperatively was not automatically considered a finding of complicated acute appendicitis and the diagnosis and subcategorising of acute appendicitis was based on all other findings in CT imaging, surgery and histopathology.

ǂ Including only patients with no appendicolith visible on CT scan or intraoperatively.

The median radiation dose was lower in the low-dose group compared to the standard-dose group (low-dose CT 3mSv, standard-dose CT 7mSv. In the subgroup analysis with only patients with a BMI under 30kg/m2, the median radiation dose was significantly lower in the low-dose group compared to the standard-dose group (low-dose CT 3mSv [IQR, 3–4mSv], standard-dose CT 5mSv [IQR, 4–7mSv]; P<.001).

Three patients (0.7%, 3/454) in the low-dose group had a normal appendix based on CT with a final diagnosis of acute appendicitis (two uncomplicated and one complicated appendicitis). None of the patients in the standard-dose group with normal appendix on CT eventually had appendicitis.

There were five patients (0.6%) among the 989, for whom the appendix could not be visualized by the radiologist and no alternative diagnosis was found leaving the initial CT inconclusive (four patients with low-dose imaging and one patient with initial low-dose CT followed by standard-dose CT two days later). Two of these patients underwent explorative laparoscopy with appendectomy both with a finding of a normal appendix both at surgery and histopathology and no alternative diagnosis at laparoscopy. Three out of these five patients were successfully treated with antibiotics; one patient was diagnosed with pelvic inflammatory disease during the primary hospitalization, and in the remaining two patients, no final clinical diagnosis could reliably be determined and they were therefore excluded from the analyses.

When classifying patients with intraluminal appendicolith visible on CT or at surgery as having complicated acute appendicitis, 371 patients out of 695 patients (53.4%) with appendicitis were classified as having complicated appendicitis. If the presence of an appendicolith was disregarded and complicated acute appendicitis diagnosis was based on the finding of perforation, gangrene, tumor, or abscess, 242 patients (34.8% of all patients with appendicitis) were classified as having complicated acute appendicitis.

6 Discussion

6.1 Long-term treatment costs of antibiotic treatment and surgery for uncomplicated acute appendicitis

In this study, treatment of uncomplicated acute appendicitis with antibiotics incurred significantly lower overall costs compared to surgery during a 5-year follow-up. Combined with the recent data showing that most of the appendicitis recurrences after initial successful antibiotic treatment occur during the first year[24], these results suggest that the cost-benefit favoring antibiotic treatment over appendectomy will remain even at longer-term follow-up exceeding 5 years.

Earlier studies have reported similar results of antibiotic treatment incurring less costs compared to appendectomy at short-term follow-up[11,25–27]. The APPAC trial is the only RCT comparing antibiotic treatment with appendectomy with available follow-up up to five years. Out of the total of 85 patients with suspected recurrent appendicitis undergoing appendectomy, only 13 underwent appendectomy during the years three to five showing that the recurrence rate significantly diminishes after the first year of treatment. Moreover, almost all of the appendicitis recurrences after initial antibiotic treatment were uncomplicated[24,192], underlining the importance of optimizing the initial patient selection also in terms of treatment costs.

Pre-interventional imaging has been shown to provide imperative diagnostic accuracy in both decreasing the NAR of operative treatment[28,109] as well as in differentiating uncomplicated and complicated acute appendicitis to enable possible non-operative treatment. Through increased diagnostic accuracy, routine imaging decreases the overall costs resulting from the treatment of acute appendicitis[110]. During the initiation of the APPAC study, antibiotics for uncomplicated acute appendicitis was a novel approach, and prolonged hospital follow-up was predefined in the study protocol to ensure patient safety. However, recent studies suggest that p.o. antibiotics[192] and even outpatient management[11] are feasible treatment alternatives for CT-confirmed uncomplicated acute appendicitis. Optimizing and unifying the CT criteria to accurately rule out complicated acute appendicitis enabling possible outpatient management will minimize or even omit the hospital stay, presumably resulting in even more significant cost savings and better utilization of hospital resources in the future. Similarly, efforts should be made to minimize treatment costs related to surgery. This includes optimizing the benefits of the laparoscopic approach in terms of hospital stay and sick leave, as well as evaluating possible outpatient laparoscopic appendectomy.

6.2 Optimizing the antibiotic treatment for uncomplicated acute appendicitis

In the APPAC II trial, treatment success of both p.o. antibiotic monotherapy as well as i.v. followed by p.o. antibiotics for CT-confirmed uncomplicated acute appendicitis was over 70% at 1-year. The first primary outcome criterion of treatment success ≥ 65% based on lower limit of confidence interval was met for both treatments. However, for the second primary outcome criterion of treatment success between the groups, the analysis yielded a difference of -3.6% [one-sided 95% CI from -9.7% to ∞] (P=0.26), with confidence limit exceeding the predefined non-inferiority margin of -6%. Therefore, we were unable to demonstrate non-inferiority of p.o. antibiotics for uncomplicated acute appendicitis related to the combined treatment of i.v. and p.o. antibiotics.

The safety and efficacy of antibiotic treatment compared to appendectomy have been thoroughly recognized in clinical trials[7,10–14] as well as endorsed in several meta-analyses[15–19] and guidelines[20–22]. Recently, the feasibility of antibiotic treatment for uncomplicated acute appendicitis has been confirmed also at long-term follow-up[24]. Therefore, this RCT was designed to compare different antibiotic therapies aiming to optimize antibiotics alone strategy for uncomplicated acute appendicitis and eventually aiming to minimize the future hospital stay and resource use using p.o. administration of antibiotics. In addition to the main aim of the study, this RCT also served as a large prospective cohort of antibiotics alone in the treatment of uncomplicated acute appendicitis and the treatment success rates corroborate the findings of the earlier RCTs in which the 1-year antibiotic treatment success was around 70%[7,10,11,14,26,56,193].

This study was designed and carried out prior to the COVID-19 pandemic. The massive burden on the healthcare systems and increased risk associated with hospitalization caused by the COVID-19 pandemic has forced re-evaluation of the true safety of different treatment alternatives especially in diseases potentially feasible to non-operative and outpatient management such as uncomplicated acute appendicitis[11]. Consequently, due to the high prevalence of acute appendicitis, the feasibility, efficacy and safety of antibiotics have been even more widely recognized in the surgical community during the COVID-19 pandemic[20,22].

Previous trials assessing antibiotics for uncomplicated acute appendicitis have reported up to 3-day hospitalizations. This was mostly related to trial protocols with i.v. antibiotics[7,11–13] and hospital follow-up ensuring patient safety at the time when antibiotic therapy was not yet established as a safe and feasible alternative to appendectomy[7,12,13,54]. The p.o. amoxicillin-clavulanic acid used by Vons et al[10] has been criticized for its possible nonsusceptibility for Escherichia coli and thus we chose a potent broad-spectrum p.o. antibiotic with both indications and efficacy for intra-abdominal infections[194,195] and advantageous once-daily administration. In this study, the median primary hospitalization was already significantly shorter with a median of 36 and 37 hours at 1 year (i.v. followed by p.o. and p.o. groups, respectively). A US pilot RCT showed promising results with outpatient treatment[11] and symptomatic treatment may also be sufficient in uncomplicated acute appendicitis[160,196]. In fact, uncomplicated acute appendicitis appears to be quite similar to uncomplicated acute diverticulitis, where recent studies have demonstrated no benefit of antibiotics compared with symptomatic treatment alone[197–202]. Management of acute appendicitis with alternative means including p.o. antibiotics or even symptomatic treatment instead of appendectomy for all, would have a profound impact in further changing the treatment paradigm for uncomplicated acute appendicitis.

There was no difference in the morbidity between the groups and there were no serious complications in this large multicenter RCT with high accuracy of pre-intervention CT diagnosis between uncomplicated and complicated acute appendicitis. When selecting patients for possible non-operative treatment with either antibiotics or even symptomatic therapy, the accurate differential diagnosis between uncomplicated and complicated acute appendicitis is of vital clinical importance requiring diagnostic imaging with a high sensitivity in detecting patients with complicated acute appendicitis. In this trial, the CT sensitivity for initial classification as complicated appendicitis was 95%. With blinded retrospective imaging assessment, this was even better as 62% of the patients undergoing appendectomy during the initial hospitalization presenting with complicated acute appendicitis at surgery, were retrospectively evaluated as having complicated appendicitis in the initial CT. A recent meta-analysis stated ten specific CT imaging features informative for complicated appendicitis[112] suggesting that large prospective cohorts are needed to assess the potential of low-dose imaging protocols[118] and to reach uniform definitions of CT findings suggestive of complicated appendicitis directing these patients to laparoscopic appendectomy. The presence of an appendicolith seems to play an important role[10,27,78] and the majority of trials nowadays have appendicolith as an exclusion criterion. The recent large pragmatic CODA trial[203] included patients with complicated acute appendicitis including patients presenting with an appendicolith corroborating the earlier findings of appendicolith being associated to a more complicated course of appendicitis and an increased risk of complications and appendectomy in non-operative treatment.

Primary non-responsiveness to antibiotics and recurrence are the factors that need to be both discussed with the patient and taken into consideration when choosing the optimal treatment alternative. With accurate patient selection using CT, antibiotic therapy has been shown to be safe regarding both primary non-responders and recurrences[24]. In this study, the primary non-responder rates were similar in both groups and in accordance to a current meta-analysis[19]. The subgroup analysis showed appendiceal diameter exceeding 15 mm and higher body temperatures on admission associating with an increased risk of primary treatment failure[4].

No prognostic factors could be identified for appendicitis recurrence in the present study and international scientific collaboration using large prospective cohorts would be beneficial in detecting potential pre-intervention parameters predictive of possible recurrence. There was no difference in the recurrence rate between the groups defined either by appendectomy during the 1-year follow-up [i.v. and p.o. 20.2% (53/263) and p.o. 22.8% (61/268), respectively], or by true appendicitis at histology [16.7% (44/263) and 20.9% (56/268), respectively]. These recurrence rates are similar to those in our previous APPAC trial[7] in which despite the similar QOL at 7 years after antibiotics and appendectomy, patients with appendectomy or successful antibiotic treatment were more satisfied than patients treated with antibiotic later undergoing appendectomy for suspected recurrence[204]. These findings highlight the notion that comprehensive assessment of all treatment alternatives requires consideration of multiple factors including patient preference and shared decision-making after receiving unbiased information of all treatment options.

6.3 Accuracy of low-dose CT for acute appendicitis

In this study, diagnostic imaging of acute appendicitis with contrast enhanced low-dose CT resulted in comparable accuracy with lower radiation dose compared with standard dose CT. These results are in line with the earlier findings on the accuracy of low-dose CT modalities in differentiating patients with and without appendicitis. More importantly, this large prospective cohort study collected in an emergency room setting representing actual clinical practice shows that low-dose CT modalities have the ability to distinguish uncomplicated and complicated acute appendicitis with similar accuracy compared to standard dose CT. To our knowledge, this finding has previously only been reported by Sippola et al. in the OPTICAP trial[118] on 60 patients with a BMI <30 kg/m^2 and by Kim et al. in an Asian population[119].

Considering the current evidence on the safety, efficacy, feasibility, and cost benefits[15–17,23–25,204] of non-operative treatment for CT-confirmed uncomplicated acute appendicitis, the current finding suggesting that the radiation dose induced by the diagnostic CT imaging can be substantially lowered is of major clinical importance as the majority of patients with appendicitis are young adults. As the availability of MRI is very limited and US is lacking the diagnostic accuracy, these findings should further encourage implementing low-dose CT protocols to everyday practice in acute appendicitis imaging.

When evaluating patients for possible non-operative treatment, ruling out complicated acute appendicitis is important. The diagnostic approach should aim to maximize the rate of detecting all patients with complicated appendicitis, although at the cost of a higher false-positive rate resulting in some appendectomies performed for uncomplicated appendicitis, which is not a major issue, as appendectomy will remain as one of the treatment options also for uncomplicated acute appendicitis.

The lack of unified and standardized criteria for CT features of complicated acute appendicitis and the complexity of defining complicated acute appendicitis altogether makes the comparison of different studies challenging[31]. A meta-analysis by Kim et al.[112] reported ten CT features associated with complicated acute appendicitis, reaching a pooled sensitivity of 92% and specificity of 43% for complicated acute appendicitis[113] comparable to our results with a sensitivity of 90% and specificity of 91% with low-dose CT. In order to avoid missing the diagnosis of complicated acute appendicitis, the future focus should be in assessing the most useful CT findings and potentially combining these with clinical features. Promising results have been reported by Atema et al.[140], who reached a 95% NPV for complicated acute appendicitis using a scoring system that combined clinical features with CT findings.

The different treatment options for the two different forms of acute appendicitis emphasize the importance of pre-interventional patient selection. The recent large pragmatic CODA trial[14] confirmed the earlier findings of appendicolith being associated with a more severe form of appendicitis and poor outcomes in non-operative treatment[10,78]. The subgroup analyses in our current study showed similar diagnostic accuracy of low-dose and standard dose CT regardless of the appendicolith status. This further supports the notion that the vitally important pre-interventional diagnostics and patient selection can be carried out with a decreased radiation dose using low-dose CT.

As evaluating the ability of the two CT modalities to differentiate between uncomplicated and complicated acute appendicitis was the main focus of this study, we aimed to reach the most accurate reference standard for the appendicitis severity. Therefore, we used blinded assessment of three investigators taking into account the surgical and histopathological findings together with imaging, laboratory tests, and patient recovery, which can be considered a major strength of the study.

In this study, the accuracy of low-dose CT and standard-dose CT in identifying patients with acute appendicitis was similar corroborating the existing evidence[33,118,205,206]. To our knowledge, this is the largest study on Western population assessing the diagnostic accuracy of low-dose CT in differentiating between uncomplicated and complicated acute appendicitis. The current results highlight the need for implementing low-dose CT protocols for appendicitis diagnosis in acute care surgery departments to avoid unnecessary radiation in the large number of patients with suspected acute appendicitis.

6.4 Limitations of this study

The main limitation in study I was the open approach used for appendectomy as the laparoscopic approach is the current gold standard shown to shorten both the hospital stay and sick leave and decrease the number of complications[52]. The open approach was chosen as the surgical intervention to maximize the standardization of the procedure and global generalizability, as laparoscopic equipment and expertise may not be available throughout the world and especially not at the time of the study initiation. However, it is uncertain if the open approach has a major impact on the cost evaluation as similar total treatment costs have been reported for open and laparoscopic approaches in a meta-analysis, despite the shorter hospitalization after laparoscopic appendectomy. This is mainly due to the significantly higher surgical costs related to laparoscopy[207]. However, comprehensive evidence describing the overall costs of the laparoscopic compared to open approach in current everyday practice is relatively scarce and would be required to assess these effects. As even successful outpatient laparoscopic appendectomy has currently been described[150], the overall treatment costs related to surgery for uncomplicated acute appendicitis could arguably be decreased in future practice.

The protocol dictated 3-day hospitalization in the antibiotic group, ensuring patient safety due to the at-the-time novel approach of antibiotic treatment for appendicitis, can also be considered a limitation. As recent evidence has shown the safety and efficacy of antibiotics for uncomplicated acute appendicitis[16–18,23,24], the length of stay for patients treated with antibiotics is constantly decreasing[192] and inevitably shifting towards possible outpatient management[11]. This will presumably result in even bigger cost savings regarding the patients treated with antibiotics.

In studies II and III there were several limitations. First, the antibiotic regimens used in the treatment arms were both broad-spectrum antibiotics adding to the risk of developing antibiotic resistant microbes. The ertapenem followed by levofloxacin and metronidazole was chosen based on the first APPAC trial[7] due to proven efficacy for CT-confirmed uncomplicated acute appendicitis and to enable comparison of the APPAC and APPAC II trial outcomes. As p.o. ertapenem was not available for clinical use, p.o. moxifloxacin was evaluated as the best alternative, due to offering a very similar bacterial coverage with proven efficacy for intra-abdominal infections[194,208] and the additional benefit of the simple once-daily administration. Also, the impact of the possible spontaneous resolution of appendicitis[45] and the true effect of the received antibiotics on the treatment outcomes of this study cannot be distinguished.

Additionally, there were four patients incorrectly enrolled in the study II despite meeting exclusion criteria. However, these patients were excluded from the analyses according to the study protocol and therefore had no effect on the outcomes of the analyses. Among the 1168 eligible patients there were also 136 patients who were not evaluated for study enrollment.

Finally, as this was the first study comparing p.o. antibiotics to i.v. followed by p.o. antibiotics for uncomplicated acute appendicitis, the predefined difference of 0% between treatments and the inferiority margin of 6% were set somewhat arbitrarily. After the study initiation however, the outbreak of the COVID-19 pandemic laid a substantial burden on the healthcare systems, limited the hospital resources around the world and made it even more beneficial to avoid hospitalization. Had such circumstances been known beforehand, a larger non-inferiority margin and difference could certainly have been used to accept larger treatment failure rate for p.o. antibiotics to compensate for the high hospitalization risk related to the pandemic.

In study IV, the diagnostic imaging was carried out according to the APPAC II and APPAC III study protocols[160] guiding patients with BMI under 30 kg/m^2 to low-dose CT and patients with BMI over 30 kg/m^2 to standard dose CT. Due to acute care surgery setting of this trial, not all patients eventually underwent the correct imaging modality predefined by the protocol, but the majority did. This resulted in patients in the standard dose CT group having a higher mean BMI compared to the low-dose CT group limiting the possibility to carry out formal statistical analysis on the whole study population. Furthermore, only 20 patients with a BMI over 30 kg/m^2 underwent low-dose CT, leaving the study underpowered to assess the accuracy of low-dose CT in the subgroup of patients with a BMI over 30 kg/m^2. The BMI 30kg/m^2 cut-off limit was based on the results of the earlier OPTICAP study[118] and the OPTICAP phantom study[209], in which the attenuation of adipose tissue in larger patients resulted in additional image noise and simultaneous unfavorable dose increase. There are however contradicting reports suggesting that higher BMI does not substantially decrease the accuracy in detecting acute appendicitis using low-dose CT[210–212].

The higher BMI in the standard dose group also limits the assessment of radiation dose, as higher BMI is associated with an increase in the radiation dose[213]. However, we conducted a subgroup analysis including only patients with a BMI under 30kg/m^2

showing a statistically significant difference in the radiation dose in favor of the low-dose CT. This corroborated the findings of the OPTICAP trial[118] in which the same patient underwent imaging with both low-dose and standard dose protocols identical to the ones in the study IV.

6.5 Future perspectives

During the last decade, robust evidence on the safety, efficacy, and cost benefits of non-operative treatment for uncomplicated acute appendicitis has made it imperative to include non-operative management as an alternative to surgery in imaging confirmed uncomplicated acute appendicitis. From now on, instead of striving to solve the superiority between these two fundamentally different treatments, they should be seen as alternatives and not rivals. It should also be noted that when facing a choice, the patients might weigh the risks and benefits of these alternatives differently than the surgeon. According to a recent study based on a sample of adult population facing a hypothesized situation of presenting with an uncomplicated acute appendicitis, around half preferred initial non-operative treatment over surgery and would have accepted a much higher risk of future appendectomy than truly expected based on the current data[214].

The future focus should be in identifying objective pre-interventional factors predicting both primary failure in non-operative treatment as well as possible recurrent appendicitis in the longer term. Identifying these factors is crucial in order to further distinguish the patients most likely to recover without surgery and being possibly suitable for outpatient management from the ones that should be referred to emergency appendectomy to avoid morbidity resulting from complicated appendicitis. From a clinical perspective, the emphasis in pre-interventional diagnostics should be in ruling out complicated acute appendicitis with high sensitivity, accepting that it might result in higher false-positive rates and subsequently some appendectomies performed for uncomplicated appendicitis instead of complicated.

The treatment paradigm shift of uncomplicated acute appendicitis mirrors that of uncomplicated acute diverticulitis, transitioning from inpatient surgical treatment towards outpatient non-operative management. This underlines the similarity of these two diseases. Uncomplicated diverticulitis has been shown to resolve without antibiotics, whereas the role of spontaneous resolution of uncomplicated acute appendicitis is still unclear. If future research demonstrates that antibiotics do not provide any advantage over symptomatic treatment alone in uncomplicated acute appendicitis, this could have a major impact not only on reducing the use of antimicrobial agents, but especially on the general opinion and century-long treatment paradigm of operative treatment for all acute appendicitis cases.

At the time, it seems evident that CT is the imaging of choice in differentiating between uncomplicated and complicated acute appendicitis. However, even more accurate, unified CT criteria for detecting features predictive of complicated acute appendicitis should be sought, preferably using large prospective patient cohorts. In addition, the accuracy of low-dose modalities in patients with BMI > 30kg/m^2 needs further evaluation, and bearing in mind the ongoing advancements in the CT technology, future studies should continue the search for the lowest possible radiation dose capable of maintaining satisfactory diagnostic accuracy in differentiating uncomplicated and complicated acute appendicitis. Additionally, it is important to continue evaluating the feasibility of MRI and US in assessing appendicitis severity as they both have the major advantage of lacking the radiation exposure altogether.

Future data on even longer-term recurrence rate after initial antibiotic treatment will provide not only a more comprehensive assessment of the non-operative treatment in general, but also aid in assessing the overall treatment costs at longer-term follow-up. However, in order to enable unbiased comparison between the different treatment alternatives regarding treatment costs, we need to have comparison of optimized treatment options, i.e. laparoscopic appendectomy and optimized non-operative treatment.

Future research assessing the treatment of uncomplicated acute appendicitis should follow the lines of the earlier trials in prioritizing patient safety within the conducted studies. The evaluation of non-operative management begun with maximizing the pre-interventional diagnostic accuracy. This was carried out using CT, which at the time generally induced radiation doses that would currently be considered very high. The non-operative treatment in turn was initiated with broad-spectrum antibiotics with prolonged hospital stay to ensure patient safety. As the evidence on the subject has accumulated, the radiation dose of diagnostic CT has been decreased, the spectrum of antibiotics is being narrowed down and only symptomatic treatment also evaluated, with hospital stay simultaneously being minimized to allow better utilization of hospital resources. These improvements were only possible after sufficient evidence on this novel management had been gradually obtained. The patient first -mentality should remain the basis when designing the upcoming studies assessing the non-operative management for uncomplicated acute appendicitis.

When tailoring the actual treatment for patients with suspected acute appendicitis in the future, efforts should focus on optimizing a selective pre-interventional evaluation. Thereafter, the patient should be offered an unbiased information on all treatment alternatives, before a shared decision-making on the best approach in that patient’s current situation.

7 Conclusions

On the basis of the present data, the following conclusions can be drawn:

1) In the long term, antibiotic therapy of CT-confirmed uncomplicated acute appendicitis results in significantly lower overall costs compared with appendectomy.

2) Oral antibiotic monotherapy is a feasible and safe treatment alternative with similar clinical treatment efficacy as a combination of intravenous and oral antibiotics in the treatment of CT-confirmed uncomplicated acute appendicitis. The treatment efficacy of antibiotic therapy was consistent with the earlier studies and the majority of patients did not require appendectomy during the 1-year follow-up.

3) Low-dose and standard-dose abdominal CT had similar accuracy in both diagnosing acute appendicitis and in differentiating between uncomplicated and complicated acute appendicitis. The radiation dose associated to low-dose CT was significantly lower compared to standard-dose imaging.

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