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Assessing the differences between uncomplicated and complicated acute appendicitis

From accurate diagnosis to tailored treatment

Sami Sula



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ASSESSING THE DIFFERENCES BETWEEN UNCOMPLICATED AND COMPLICATED ACUTE APPENDICITIS

From accurate diagnosis to tailored treatment

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*To my family,
Jenni, Leevi, Silja and Sofia*

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SAMI SULA: Assessing the differences between uncomplicated and complicated acute appendicitis

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ABSTRACT

Acute appendicitis is one of the most common reasons for acute abdomen. Current epidemiological and clinical studies clearly suggest that appendicitis consists of a diverse spectrum of variable disease severity forms. This results in multiple treatment alternatives as uncomplicated acute appendicitis can be treated with antibiotics and even with only symptomatic treatment, while complicated appendicitis mainly requires emergency operation. Appendicitis can be broadly divided into uncomplicated and complicated appendicitis often distinguished using CT imaging. The knowledge gap is the accurate differential diagnosis with uniform definitions of appendicitis severity especially in the middle ground "grey area" between these two disease forms. Accurate differential diagnosis allows optimization of all treatment options for both patients and healthcare systems.

The main aim of this thesis was to assess the differences in blood-culture positivity rate between uncomplicated and complicated acute appendicitis and to improve the accuracy of CT imaging in differential diagnostics between the different disease severities. In addition, the longer-term outcomes of antibiotic and symptomatic treatment for uncomplicated acute appendicitis were assessed. Study I investigated blood culture positivity in patients with acute appendicitis. Studies II and III evaluated CT imaging findings to better identify and rule out complicated acute appendicitis using a large prospective patient cohort. Study II assessed the association of appendicolith CT characteristics with appendicitis severity and study III aimed to identify potential prognostic CT factors for complicated appendicitis. Study IV was a 3-year follow-up of the APPAC III randomized double-blind clinical pilot trial comparing antibiotics to placebo in adults with CT-confirmed uncomplicated appendicitis.

Complicated appendicitis was associated with higher rates of bacteremia compared to uncomplicated appendicitis, and the overall prevalence of blood culture positivity in patients with acute appendicitis was 9%. The presence of appendicolith in patients with acute appendicitis increased the risk of complicated appendicitis. CT findings associated with complicated acute appendicitis included larger appendiceal diameter, appendiceal wall enhancement defect and accumulation of fluid around the appendix. At 3 years, there was no difference between antibiotics and placebo in terms of treatment success with an overall appendectomy rate of 35%.

KEYWORDS: acute appendicitis, antibiotic treatment, appendicolith, appendectomy, blood culture, fecalith, complicated appendicitis, computed tomography, CT, uncomplicated appendicitis

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TIIVISTELMÄ

Akuutti umpilisäketulehdus eli appendisiitti on yksi yleisimmistä akuutin vatsan syistä. Uusimpien epidemiologisten ja kliinisten tutkimuksien mukaan umpilisäketulehdus koostuu vaikeusasteeltaan vaihtelevien erilaisten tautimuotojen kirjosta. Tämä on johtanut useisiin eri hoitomahdollisuuksiin, kuten komplisoitumattoman umpilisäketulehduksen hoitoon antibiooteilla tai jopa oireenmukaisesti. Komplisoitunut umpilisäketulehdus useimmiten vaatii edelleen kiireellisen päivystysleikkauksen. Umpilisäketulehdus voidaan jakaa pääpiirteittäin komplisoitumattomaan ja komplisoituneeseen muotoon, jotka ovat erotettavissa toisistaan tietokonetomografiakuvauksen (TT) avulla. Umpilisäketulehduksen vaikeusasteiden erotusdiagnoosi ongelma on näiden tautimuotojen väliin jäävä merkittävä harmaa alue. Tarkempi erotusdiagnoosi mahdollistaa eri hoitovaihtoehtojen optimoinnin, minkä avulla voidaan parantaa potilaiden saamaa hoitoa sekä sairauden ja hoidon yhteiskunnalle aiheuttamia kustannuksia.

Tämän väitöskirjatyön tavoitteena oli arvioida umpilisäketulehduksen erotusdiagnoosiin parantamista keskittyen veriviljelypositiivisuuteen sekä TT-löydöksiin. Lisäksi väitöstyössä arvioitiin komplisoitumattoman umpilisäketulehduksen antibiootti- ja oireenmukaisen hoidon pitkäaikaistuloksia. Osatyö I tutki veriviljelypositiivisuuden esiintymistä umpilisäketulehduksessa. Osatöissä II ja III arvioitiin komplisoituneeseen umpilisäketulehdukseen liittyviä TT-löydöksiä laajan prospektiivisen potilasmateriaalin avulla. II osatyö arvioi ulostekiven (fekoliitti) merkitystä ja osatyön III tavoitteena oli etsiä komplisoituneen umpilisäketulehduksen ennustetekijöitä TT:stä. Osatyö IV oli APPAC III satunnaistetun kaksois-sokkoutetun monikeskustutkimuksen 3-vuotisseurantatutkimus, jossa verrattiin antibioottia lumelääkkeeseen komplisoitumattoman umpilisäketulehduksen hoidossa.

Veriviljelypositiivisuus oli yhteydessä komplisoituneeseen tautiin ja sen esiintyvyys umpilisäketulehduksessa oli 9 %. Fekoliitti lisäsi merkittävästi komplisoituneen umpilisäketulehduksen riskiä. TT-löydöksistä umpilisäkkeen halkaisija, seinämän tehostumattomuus sekä lisääntynyt nestemäärä umpilisäkkeen ympärillä olivat yhteydessä komplisoituneeseen tautiin. 3-vuotisseurannassa lumelääkkeen ja antibiootin välillä ei ollut eroa hoidon onnistumisessa ja umpilisäkkeen poisto tehtiin 35 %:lle potilaista.

AVAINSANAT: akuutti appendisiitti, antibioottihoito, fekoliitti, komplisoitumaton appendisiitti, komplisoitunut appendisiitti, tietokonetomografia, TT, umpilisäketulehdus, umpilisäkkeen poisto, veriviljely

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Abbreviations

APPAC	APPendicitis ACuta trial
AUC	Area Under the Curve
BMI	Body mass index
CI	Confidence interval
CODA	Comparison of Outcomes of Antibiotic Drugs and Appendectomy
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CT	Computed tomography
E.coli	Escherichia coli
i.v.	Intravenous
LOCAT	Low-dose Computed Tomography for Appendicitis Trial
LOS	Length of stay
MAPPAC	Microbiology APPendicitis ACuta
MRI	Magnetic resonance imaging
NAR	Negative appendectomy rate
NPV	Negative predictive value
OPTICAP	OPTImization of Computed tomography for acute APpendicitis
OR	Odds ratio
p.o.	Peroral
QOL	Quality of life
RCT	Randomized controlled trial
ROC	Receiver Operating Characteristic
SD	Standard deviation
TT	Tietokonetomografia
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 Sula S, Han T, Marttila H, Haijanen J, Löyttyniemi E, Sippola S, Grönroos J, Hakanen A, Salminen P. Blood culture positivity in patients with acute appendicitis: A propensity score–matched prospective cohort study. *Scandinavian Journal of Surgery*. 2022;111(3):31-38.
- II Sula S, Paananen T, Tammilehto V, Hurme S, Mattila A, Rantanen T, Rautio T, Pinta T, Sippola S, Haijanen J, Salminen P. Impact of an appendicolith and its characteristics on the severity of acute appendicitis. *BJS Open*, 2024; Volume 8, Issue 5: zrae093.
- III Sula S, Kujala, M, Tammilehto V, Hurme S, Rautio T, Nordström P, Rantanen T, Pinta T, Mattila A, Grönroos J, Sippola S, Haijanen J, Salminen P. Prognostic CT-imaging Findings for Complicated Acute Appendicitis – a Prospective Cohort Study. *Scandinavian Journal of Surgery*. 2025;0(0).
- IV Sula S, Sippola S, Haijanen J, Hurme S, Nordström P, Rautio T, Sallinen V, Salminen P. Three-year follow-up of antibiotics versus placebo in adults with CT-confirmed uncomplicated acute appendicitis: a secondary analysis of the APPAC III randomized clinical trial. *British Journal of Surgery*, 2025;112(3), znaf016.

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1 Introduction

Acute appendicitis is one of the most frequent causes of abdominal pain encountered in emergency departments, with an estimated global incidence of 7–12%.¹⁻³ Even though both the incidence of acute appendicitis and appendectomy rates are declining, appendicitis remains the most common indication for emergency abdominal surgery, with over 300,000 appendectomies performed annually in the United States and around 7,500 in Finland.^{1, 2, 4}

For more than a century, acute appendicitis was considered as a single disease entity, inevitably progressing to perforation if not timely operated.⁵ This led to a treatment paradigm of mandatory appendectomy as a standard treatment for suspected acute appendicitis.⁶ New epidemiological and clinical studies have demonstrated that acute appendicitis exists in two distinct forms: uncomplicated and complicated acute appendicitis, each with different underlying pathophysiology and course of the disease.⁷⁻⁹ Most cases are considered uncomplicated, and based on available literature, uncomplicated acute appendicitis can be safely and effectively treated non-operatively with antibiotics and possibly even with only symptomatic therapy.⁹⁻¹¹ On the other hand, urgent surgical treatment is typically needed for the majority of patients with complicated appendicitis, usually characterized by perforation, or gangrene. For complicated acute appendicitis presenting with a periappendicular abscess or suspicion of tumor, the current optimal treatment is initial conservative treatment followed by interval appendectomy based on the high appendiceal tumor rate associated with periappendicular abscess, or in case of diagnosed malignancy, appendiceal carcinomas are treated similarly to colorectal cancer, often requiring a right hemicolectomy.¹²

The uniform standardized definitions of appendicitis severity outside perforation, periappendicular abscess, or tumor suspicion are under active research. In addition to these established criteria for complicated acute appendicitis, the presence of an appendicolith, is recognized as one possible complicating factor of acute appendicitis.¹³⁻¹⁶ For example, the CODA (The Comparison of Outcomes of Antibiotic Drugs and Appendectomy) trial showed that patients with acute appendicitis and an appendicolith were at a higher risk for appendectomy (41%) and for complications than those without an appendicolith (25%)¹⁷. Appendicoliths are

small calcified fecal stones in the appendiceal lumen varying in terms of size, shape and location, and it is unknown which appendicolith characteristics contribute to the demonstrated more complicated course of acute appendicitis.^{14, 15, 18, 19} Septicemia is usually considered as a sign of a severe infection. Despite the routine use of blood cultures in various infectious conditions, the prevalence and clinical significance of blood culture positivity in patients with acute appendicitis is unknown.

For decades, the diagnostics of acute appendicitis were based on clinical examination, laboratory findings, and scoring systems without imaging. This often led to unsatisfactory diagnostic accuracy resulting in high negative appendectomy rates (NARs), i.e., removal of an uninflamed appendix.^{7, 20, 21} Today, preoperative imaging, particularly computed tomography (CT), has improved diagnostic accuracy and significantly reduced the NAR²²⁻²⁶ and CT is the gold standard in diagnostics of acute abdomen. The improved diagnostic accuracy has enabled pre-interventional differential diagnosis of uncomplicated acute appendicitis and complicated acute appendicitis, which is not feasible without imaging.²⁷ Other imaging modalities, such as ultrasound (US) and magnetic resonance imaging (MRI), offer alternatives but have limitations, including lower accuracy in adults, higher costs, and limited availability.²⁸⁻³⁰

The increasing understanding of acute appendicitis has also reshaped treatment strategies. Clinical trials and meta-analyses have consistently demonstrated that antibiotic therapy is a safe and effective alternative to surgery for patients with uncomplicated appendicitis.^{10, 11, 13, 16, 31-35} Studies show that approximately 70% of patients with CT-diagnosed uncomplicated appendicitis can avoid appendectomy at the first year, and after the first year recurrences are rare even in long-term follow-up, experiencing lower morbidity and lower treatment costs compared to those undergoing appendectomies.^{32, 36-38} Moreover, delayed appendectomy in cases of recurrent appendicitis has not been associated with increased complications, reinforcing the feasibility of conservative treatment.^{10, 32} There is pilot evidence on uncomplicated acute appendicitis also resolving without antibiotics with only symptomatic care, but comprehensive data and long term-results are lacking.^{31, 39}

Despite the recent major diagnostic advancements, precise differential diagnosis between complicated and uncomplicated acute appendicitis remains a challenge. While appendectomy remains the undisputed treatment for perforated acute appendicitis, antibiotics have emerged as an alternative in selected uncomplicated cases^{13, 40} However, between these two clear entities lies the middle ground grey area of appendicitis cases with varying severity underlining the need for more accurate pre-interventional diagnosis enabling optimal treatment alternatives. Therefore, accurate diagnosis through CT-imaging and specifically ruling out complicated acute appendicitis remains essential in tailoring treatment. In the future, a more

tailored approach in treatment of acute appendicitis, guided by precise diagnostics, is needed to optimize all treatment alternatives.

The main aims of this thesis were to assess the differences of appendicitis severity regarding blood-culture positivity and to improve the accuracy of CT imaging in differential diagnostics between the different disease severities between uncomplicated and complicated acute appendicitis. With accurate differential diagnosis, uncomplicated acute appendicitis could be treated non-operatively or with symptomatic outpatient care without antibiotics. In addition, the longer-term outcomes of antibiotic and symptomatic treatment were assessed. This doctoral thesis comprises of four different studies. The aim of study I was to assess the prevalence of blood culture positivity and potential predictive factors associated with blood culture positivity in patients with acute appendicitis focusing on appendicitis severity. The aim of study II was to assess CT characteristics of appendicoliths and their association with appendicitis severity. The aim of study III was to assess the potential prognostic value of CT imaging findings predictive of complicated acute appendicitis. The aim of study IV was to assess the 3-year follow-up results of APPendicitis ACuta trial (APPAC) III double-blind RCT comparing antibiotics and placebo for uncomplicated acute appendicitis.

2 Review of Literature

2.1 Anatomy and physiology of the appendix

The vermiform appendix is a small, worm-shaped diverticulum that arises from the cecum at the convergence of the taenia coli near the ileocecal valve (Figure 1).^{41, 42} The base of the appendix is fixed at the cecum, but its tip can vary in multiple positions, of which the most common position is retrocecal, occurring in 40–65% of cases.⁴³ The most typical skin landmark for appendix tip positioning is McBurney's point, which is located one-third of the distance from the anterior superior iliac spine to the umbilicus. The appendix is typically between 5 to 10 cm in length and its diameter is normally less than 1 cm.⁴⁴ The appendix structure is composed of the four layers of the colonic wall: serosa, muscularis, submucosa, and mucosa.⁴⁵ It is supported by a small mesentery called the mesoappendix, which originates from the ileal mesentery. The blood supply of the appendix comes from the appendiceal artery, which runs inside mesoappendix, and arises from the ileocolic artery, which is a branch of the superior mesenteric artery.^{46, 47} The lymphatic drainage follows the same mesenteric pathway.

For centuries, the appendix was considered as an evolutionary remnant without a clear physiological function. Nowadays, appendix is considered to be an active immunological organ, and studies have revealed its possible role in immune defense and gut microbial regulation.^{48, 49} The appendix has a notable concentration of gut-associated lymphoid tissue within the submucosa, unlike other parts of the colon highlighting its role in the immune system.⁵⁰ The lymphoid tissue of appendix plays a role in regulating the intestinal microbiota and is an optimal site for biofilms that harbors beneficial bacteria, which may have role for example in recovery from infections and antibiotic treatments.^{48, 50-52} This indicative information challenges the century old paradigm that an appendectomy would not disturb patient physiology emphasizing the role of non-operative treatment when possible.⁵³

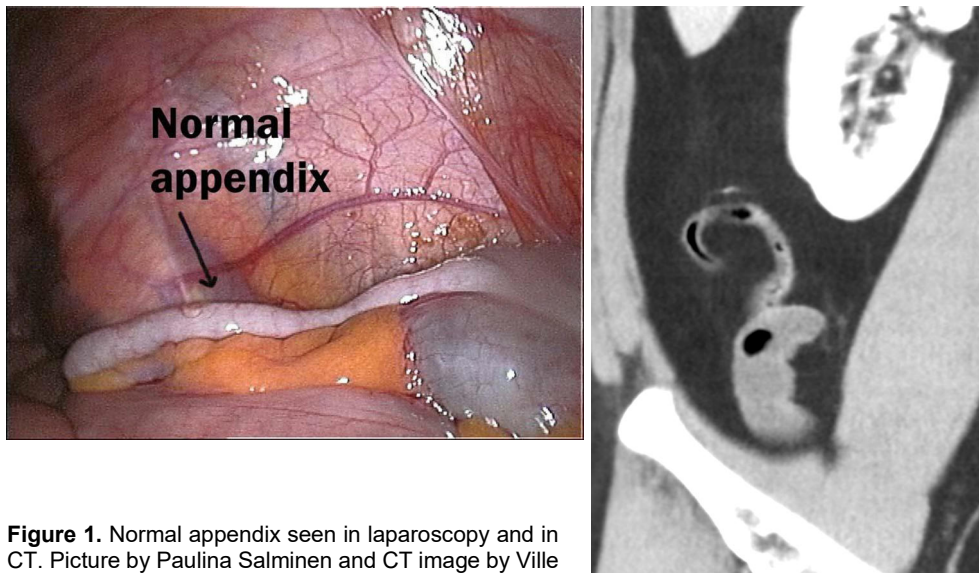


Figure 1. Normal appendix seen in laparoscopy and in CT. Picture by Paulina Salminen and CT image by Ville Tammilehto.

2.2 The epidemiology of appendicitis

Acute appendicitis is among the most common causes of abdominal pain encountered in emergency departments, with a lifetime risk of developing acute appendicitis between 7% and 12%.¹⁻³ In the Western countries its incidence rate is 100-200 patients per 100 000 residents per year.^{3, 54} The reported incidence of appendicitis appears to rise with the industrialization of society, a similar increase is now observed in both newly industrialized nations and many low- and middle-income countries^{3, 54, 55}. The highest incidence of appendicitis are in persons aged 10-19 years and males have overall incidence rate ratio of 1.4:1 to females for all age groups.¹ Nowadays, incidence and surgery rates in western countries are declining, but still appendectomy remains the most common indication for emergency abdominal surgery, with over 300,000 appendectomies performed annually in the United States and around 7,500 in Finland (Table 1).^{1, 2, 4} In a recent study in Sweden shows the incidence of acute appendicitis is about 120 patients per 100 000 residents per year, with just over 11 000 cases annually.⁵⁶ Higher rates of appendicitis have been reported in developed countries than in developing ones.^{3, 54} In addition, its incidence is 1.4 to 1.6 times higher among White individuals than in non-White populations in the United States.^{1, 3, 57} In Africa, a significant disparity exists, with less than 1% of Black individuals affected compared to 10% of White individuals.⁵⁸ This disparity might be explained by the theory that appendix is a part of the immune system that, like those immune compartments that cause allergy, is vital to life in a

"natural" environment, but which is poorly suited to post-industrialized societies, where we have high hygiene and antibiotic usage.⁴⁹

Another interesting epidemiologic trend is the change in the incidence of uncomplicated and complicated acute appendicitis. As mentioned above, the overall incidence of acute appendicitis has decreased in recent decades, but this trend is not evenly distributed between uncomplicated and complicated acute appendicitis. Several epidemiological and clinical studies have shown that complicated or perforated and uncomplicated or non-perforating acute appendicitis are different entities, each with diverse underlying pathophysiological mechanisms.^{7-9, 59} Epidemiological studies indicates that the incidence of uncomplicated appendicitis has fluctuated over the years. Between 1970 and 1995, its rate decreased but then began to rise, this happened in the same timeline as diagnostic imaging, especially CT scans and the widespread adoption of laparoscopic appendectomy occurred.⁹ This change in diagnostics and operative field has led to the detection of more uncomplicated cases that could have resolved spontaneously, which has led to seemingly increase incidence of uncomplicated acute appendicitis.^{60, 61} In contrast, the rate of perforated appendicitis has steadily increased over time. Additionally, findings from the COVID-19 pandemic supported this phenomenon and revealed a decreased incidence of uncomplicated appendicitis but an unchanged rate of complicated cases.⁶¹⁻⁶⁴ This suggests that some uncomplicated acute appendicitis resolve on their own when access to healthcare is limited, reinforcing the idea that appendicitis manifests in at least two distinct forms. Together, these epidemiological findings and observations highlight the need to consider complicated and uncomplicated appendicitis as separate conditions with different pathophysiology.

Table 1. Total number of appendectomies in Finland from 2014 to 2023.⁴

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Open appendectomy (JEA00)	3 894	3 200	2 431	1 889	1 648	1 312	1 282	1 063	998	760
Laparoscopic appendectomy (JEA01)	3 724	4 729	5 353	5 502	6 105	6 519	7 132	7 286	6 736	6 727
Appendectomy and drainage (JEA10)	24	18	12	19	11	17	13	15	5	7
Total number of appendectomies [JEA]	7 642	7 947	7 796	7 410	7 764	7 848	8 427	8 364	7 739	7 494

2.3 The etiology and pathogenesis of acute appendicitis

Despite the high incidence of acute appendicitis, the detailed etiology and pathogenesis of acute appendicitis are still unclear. Historically, obstruction of the appendiceal lumen by an appendicolith, foreign body, lymphoid hyperplasia, parasites, or malignancy has been the explanation for pathogenesis and etiology behind acute appendicitis.^{65, 66} According to this theory, the obstruction eventually increases pressure within the appendix, which leads to gangrene of appendix wall and this chain leads to perforation and peritonitis.⁵ Today, this theory has been challenged as studies have shown that most acute appendicitis cases do not advance to perforation, and many cases can resolve spontaneously.^{9, 59, 64} Often no obstruction can be shown in acute appendicitis and most of the alleged causes of obstruction of appendiceal lumen are quite rare. For example, the estimated incidence of foreign body associated appendicitis is 5 per 10 000 appendectomy⁶⁷, while the risk of appendiceal tumor in uncomplicated acute appendicitis is generally 1%^{68, 69}. The risk of appendiceal tumor is increasing with higher age of the patient^{70, 71}. For patients with complicated acute appendicitis, especially if presenting with periappendicular abscess the risk for tumor is increased even as high as 14.3 %.^{12, 72-74} On the other hand, obstruction due to appendicolith or lymphoid hyperplasia is a quite common finding also in normal appendix without acute infection.⁷⁵⁻⁷⁷ Theory of obstruction behind acute appendicitis was questioned already in 1981. At that time Butler et al.⁷⁸ thought that instead of lumen obstruction, appendicitis might appear as result of mucosal injury, leading to mucosal necrosis and perforation. But as new evidence has emerged showing that acute appendicitis seems to be at least two distinct entities, with different disease progression, the theory of Butler does not appear to be comprehensive either.^{9, 63, 64}

None of the above theories fully explain the etiology and pathogenesis of acute appendicitis. It is shown in several studies that there are seasonal incidence variation and familial aggregation associating with acute appendicitis.^{79, 80} This might indicate that there are environmental, infectious, and possible genetic factors involved in etiology of acute appendicitis.⁸⁰⁻⁸² For example, positive family history of acute appendicitis has been suggested to increase the relative risk of having acute appendicitis to a nearly 3-fold.⁸³ There are also alternative theories associating hygiene, diet, and trauma in acute appendicitis, but these hold minimal significance with the current knowledge as there is lack of robust evidence. All these theories and knowledge have made understanding etiology and pathology of acute appendicitis even more complex and better understanding is needed to explain pathogenesis and etiologies of the different forms of acute appendicitis severity.

2.4 The classification of appendicitis severity and differential diagnosis between uncomplicated and complicated acute appendicitis

For two centuries, acute appendicitis has been thought to be one disease that inevitably advance to perforation if not operated in time.⁵ However, according to the current understanding, acute appendicitis seems to be more of a spectrum of different entities with varying clinical presentation and prognosis. The spectrum is wide, its mildest form seems to be localized, and self-limiting inflammation of appendicitis that resolves by-itself needing only symptomatic care.^{39, 61} Acute appendicitis can also manifest as periappendicular abscess, which are usually treated with antibiotics and possible drainage. The most severe form is free perforation of appendix, which leads to life-threatening peritonitis. This entity requires emergency surgery. Between these two entities with rather unequivocal disease severity lie different forms of appendicitis like those presenting with an appendicolith.

Conventionally the classification of appendicitis has been based on histopathological findings of inflammation, along with possible imaging and surgical observations. However, this method of classification is no longer the only way to classify appendicitis, as all patients with acute appendicitis no longer inevitably need appendectomy^{17, 84}. In this new era of acute appendicitis treatment alternatives, the diagnosis currently needs to be based on pre-interventional imaging supported by clinical symptoms and laboratory parameters. While postoperative histopathological examination confirms the definitive diagnosis, diagnosis based on CT imaging reflects the clinical assessment at a specific point in time not considering any possible disease progression. Even with a CT diagnosis of uncomplicated acute appendicitis on admission, in rare cases the disease may progress into complicated acute appendicitis. For example in the study by Bom et al.⁸⁵ the mean sensitivity for CT in discriminating complicated acute appendicitis from uncomplicated acute appendicitis was 78 % and mean specificity was 91 %, respectively. Adopting the essential knowledge that perforated appendicitis is not an advanced stage of the non-perforated appendicitis but a separate pathological process increases the awareness among the medical society on the importance of pre-interventional classification of appendicitis severity^{8, 9}. In clinical practice the classification of acute appendicitis into two different forms of uncomplicated and complicated acute appendicitis is the most practical way, and it has important implications for diagnosis, treatment, and patient management. However, despite the widespread acceptance of this classification, standardized and unified criteria to distinguish between uncomplicated and complicated appendicitis are still lacking and this remains an active area of research. The histopathological findings of normal appendix and the two forms of acute appendicitis are presented in Table 2.

Table 2. Histopathological findings of the normal appendix, uncomplicated acute appendicitis and complicated acute appendicitis. Modified from Carr et al. 2000⁸⁶, Bhangu et al 2015⁶⁶.

Normal appendix	Uncomplicated acute appendicitis	Complicated acute appendicitis
No abnormalities	Transmural inflammation, ulceration or thrombosis	Transmural inflammation and necrosis (gangrenous)
Only luminal neutrophils without mucosal abnormality	Possible extramural pus	Transmural inflammation and perforation (perforated)
Mucosal or submucosal neutrophils		Transmural inflammation with pus and possible perforation (abscess)
Possible ulceration		

2.4.1 Uncomplicated acute appendicitis

In studies and clinical practice multiple descriptions are used for the milder, less severe form of acute appendicitis. It is often referred to as non-perforated acute appendicitis, simple acute appendicitis, mild acute appendicitis, acute phlegmonous appendicitis, localized appendicitis, early-stage appendicitis, and lately the most often used terminology is uncomplicated acute appendicitis. In this thesis, the term uncomplicated acute appendicitis is used, as it is supported by multiple studies that it's not an early-stage appendicitis but rather its own entity.⁷⁻⁹ The majority of acute appendicitis cases are uncomplicated. Depending on the definition, it is estimated that 60 to 80 % of acute appendicitis cases are considered as uncomplicated.⁹

The uncomplicated acute appendicitis is characterized by a significant neutrophilic invasion of the muscular wall of the appendix, sometimes extending transmurally and causing localized peritoneal irritation. The inflammation can effect only a part of appendix or the entire appendix.⁸⁶ Macroscopic findings of uncomplicated acute appendicitis may include increased diameter, congestion, color change, pus, and exudate.⁶⁶ The CT imaging diagnosis of uncomplicated acute appendicitis enabling non-operative management is defined as acute appendicitis with absence of complicated factors, usually considered as finding of abscess, perforation, tumor, or appendicolith.^{10, 66} CT findings of the normal appendix, uncomplicated acute appendicitis and complicated acute appendicitis are presented in table 3. Laparoscopic picture of uncomplicated and complicated acute appendicitis are presented in figure 2.

The complexity in differential diagnosis is that categorization into uncomplicated and complicated forms is not always this simple as there is no clear and unified consensus on the criteria. As an example, classification of gangrenous

acute appendicitis into either uncomplicated or complicated acute appendicitis is not consistent. Gangrenous appendicitis is marked by necrosis of the appendiceal wall, likely caused by vascular thrombosis⁸⁶. Normally gangrenous acute appendicitis is considered as complicated acute appendicitis, but in many cases these kind of changes can be also seen in the uncomplicated acute appendicitis with the extent of gangrene limited to the mucosa.⁸⁶ Transmural gangrene naturally progresses into perforation without appendectomy, but gangrenous appendicitis without perforation can postoperatively be treated similarly as uncomplicated acute appendicitis without any antibiotics. The most common classification of complicated forms include the spread of the disease to the peritoneal surface. Another debated factor in differential diagnosis of acute appendicitis severity is appendicolith. Multiple studies have proven that appendicoliths are associated with a more complicated course of appendicitis.^{13, 18, 87} On the other hand, not all appendicoliths induce appendicitis or progress to perforation and appendicoliths can be found incidentally in normal uninfamed appendices.^{14, 88} However, it has now been shown that even up to 36 hours of observation and anticipating nighttime surgery to daytime operations does not lead to increased number of perforations at least in presumed uncomplicated appendicitis.⁸⁹⁻⁹⁴

Table 3. CT findings of the normal appendix, uncomplicated acute appendicitis and complicated acute appendicitis. *Findings of uncomplicated acute appendicitis are also included in findings of complicated acute appendicitis. Modified from Kim et al 2018⁹⁵, Haijanen et al 2021⁹⁶.

Normal appendix	Uncomplicated acute appendicitis	Complicated acute appendicitis*
Appendix diameter <6 mm	Appendix diameter > 6 mm	Abscess: periappendiceal walled collection
No signs of inflammation	Wall thickening > 3 mm	Appendicolith > 3 mm in diameter within the appendix lumen
	Wall enhancement	Perforation: appendiceal wall enhancement defect and major amount of fluid and/or infectious phlegmon and/or extraluminal air
	Periappendiceal oedema and/or minor amount of fluid	Acute inflammation of the appendix with suspected tumor

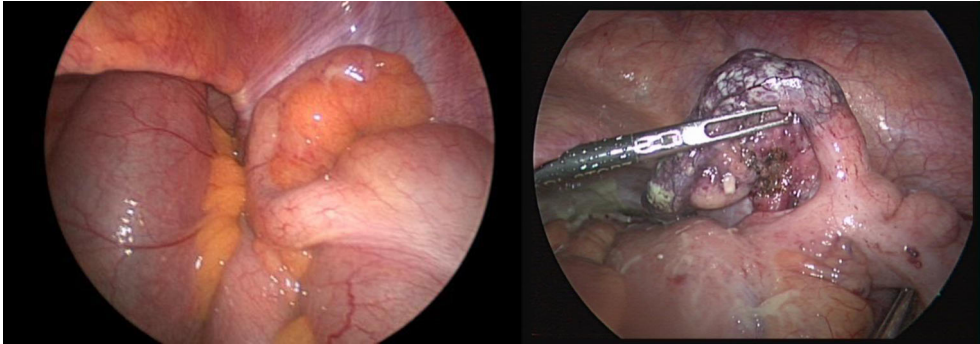


Figure 2. Laparoscopic pictures of uncomplicated acute appendicitis (left) and complicated acute appendicitis (right). Picture by Paulina Salminen.

2.4.2 Complicated acute appendicitis

As in uncomplicated acute appendicitis, the definition of complicated acute appendicitis also varies in different studies and clinical practices. Multiple terms are also used to describe complicated acute appendicitis including complex appendicitis, perforated appendicitis, severe appendicitis, or advanced appendicitis. Obvious findings categorized as complicated acute appendicitis include perforation, periappendicular abscess, and appendiceal tumor. More debated features of complicated acute appendicitis are gangrene of the appendix and presence of an appendicolith.⁹⁷ Depending on how cases presenting with an appendicolith are categorized, approximately 20 to 40 % of acute appendicitis cases are considered complicated.⁹ In this thesis, we use the term complicated acute appendicitis, referring to acute appendicitis with gangrene, perforation, abscess, appendicolith, or tumor diagnosed on pre-interventional imaging and based on the surgical finding and histopathology.¹⁰

Complicated acute appendicitis includes inflammation and vascular thrombosis leading to appendiceal wall necrosis (gangrenous appendicitis). Transmural necrosis leads to perforation causing the luminal contents leaking into the abdominal cavity. This in turn results in either diffuse peritonitis or a localized periappendicular abscess, where peritoneal defense mechanisms attempt to contain the infection. This thought of appendicitis always progressing to perforation led to the currently already discarded idea that emergency appendectomy was mandatory in all appendicitis cases. Changes in the appendix from the non-inflamed to inflamed and perforated acute appendicitis are presented in figure 3.

The gold standard pre-interventional differential diagnostics of acute appendicitis is CT imaging. Among patients with acute appendicitis, a generally agreed CT feature associated with complicated acute appendicitis is free air in abdominal cavity referring to free perforation. Another clear sign is localized

collection or mass in right lower quadrant due to periappendicular abscess as the result of a walled-off appendiceal perforation and/or concurrent presence of an appendiceal tumor. Impression of enhancement defect in CT has also been associated with complicated acute appendicitis referring to gangrenous tissue in the appendiceal wall with impaired or no circulation.⁹⁸

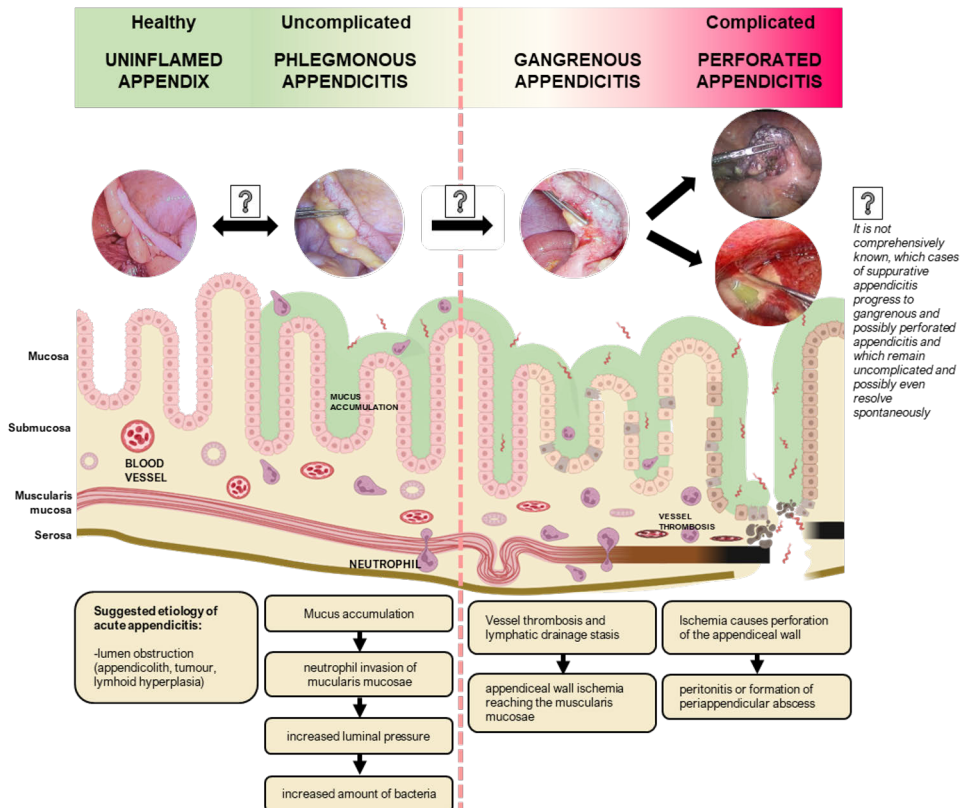


Figure 3. Changes in the appendix from the non-inflamed to inflamed and perforated acute appendicitis in longitudinal sections with corresponding cellular events.

2.5 The role of appendicolith in acute appendicitis

Appendicoliths are calcified fecal deposits in the lumen of appendix (Figure 4 and 5).⁹⁹ Other terms used for appendicolith in the literature are fecalith, faecalith, fecolith, and coprolith, but the most common terminology is appendicolith, which is used in this thesis. Appendicoliths have a role both in appendicitis pathogenesis and appendicitis severity. Appendicoliths vary in sizes, compositions, and locations.^{95, 100} Appendicoliths can be found from about 30% to over 40% of patients with acute appendicitis.^{13, 101, 102} On the other hand appendicoliths are common incidental

findings found in approximately 4% of asymptomatic patients without acute appendicitis, and there are no evidence that incidental appendicolith would elevate the risk of developing acute appendicitis.^{76, 88, 103} Ramdass et al.⁸⁸ conducted a retrospective study analyzing 1357 appendectomies, of which 186 (13.7%) patients had appendicolith. They analyzed the association of appendicolith and acute appendicitis concluding that appendicoliths might be incidental finding in acute appendicitis. Engin et al.¹⁰⁴ conducted a retrospective study including 261 patients operated with appendicolith concluding that the obstruction of the lumen is the dominant etiologic factor in acute appendicitis and that appendicoliths were the most common cause of appendicular obstruction.

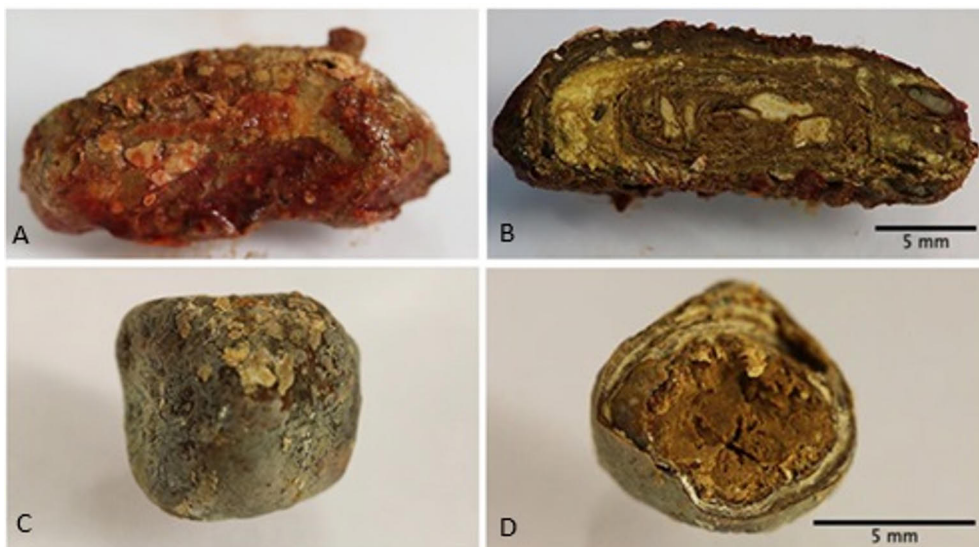


Figure 4. A+C. picture of the whole appendicolith, B+D. cross-sectional picture of the same appendicolith. Picture by Sanja Vanhatalo.

Many studies have provided robust evidence on the role of appendicolith in the severity of appendicitis showing that the presence of an appendicolith is a significant risk factor for complicated acute appendicitis and it is associated with failure of conservative treatment.^{14, 16, 17, 19, 100, 105-108} For example, in a recent large American CODA RCT comparing antibiotics with appendectomy for appendicitis, they included 1552 patients with imaging confirmed acute appendicitis assigning 776 to receive antibiotic treatment and 776 patients to undergo appendectomy.¹⁷ The patient population included 414 patients with an appendicolith. Trial showed that participants with an appendicolith were at a higher risk for appendectomy (41%) and for complications than those without an appendicolith (25%). In 2019 Mällinen et al.¹⁵ compared appendiceal histopathological parameters of patients with

uncomplicated appendicitis and patients with appendicolith appendicitis showing clear differences in the histopathological characteristics between these patient cohorts. In 2020 a retrospective study of pediatric patients with an appendicolith showed a great risk of perforation with a perforation rate of 78 % compared with 29% in patients with no appendicolith ($p<0.05$).⁸⁷ Similar findings have been reported in multiple pediatric studies regarding the association of an appendicolith with complicated acute appendicitis.^{18, 109-111}

In the RCT comparing antibiotic treatment to appendectomy by Vons et al.¹⁶, the presence of an appendicolith was the only risk factor for antibiotic treatment failure in acute appendicitis. There was a total of 239 patients, 120 in the antibiotic and 119 in the appendectomy group. In this study 30-day postintervention peritonitis was significantly more frequent in the antibiotic group (8%, $n=9$) than in the appendectomy group (2%, $n=2$ treatment difference 5.8; 95% CI 0.3-12.1). However, when they excluded patients with appendicoliths on CT imaging, there was no statistically significant difference between the appendectomy and antibiotic groups in treatment success. A recent meta-analysis comparing antibiotic therapy to appendectomy in patients with acute appendicitis by Scheijmans et al.⁸⁴ showed that among patients with an appendicolith, more complications were found in patients treated with antibiotics compared to those who had surgery. Furthermore, within the initial antibiotics group, patients presenting with an appendicolith were found to have more complications and higher risk of appendectomy compared to those without an appendicolith. On the other hand, in the CODA trial around 50% of patients with an appendicolith treated nonoperatively avoided appendectomy.¹⁷ With all this knowledge, categorizing patients with appendicitis presenting with an appendicolith as having complicated appendicitis is not completely recognized but it has gained attention through studies on nonoperative management of acute appendicitis.^{10, 13} Still after all these studies, it remains an open question which features of the appendicolith are associated with failure of conservative treatment and complicated acute appendicitis, and on the other hand which appendicoliths can be left untreated.

A few studies have evaluated the effect of appendicolith characteristics on appendicitis. Yoon et al.¹⁰⁹ found in multivariate risk factor analysis that appendicolith diameter of 5 mm or more was a significant risk factor for perforation. Ishiyama et al. conducted a study assessing the significance of size and location of appendicoliths as an exacerbating factor of acute appendicitis.¹¹² They reported that appendicoliths larger than 5 mm and location in the root of appendix were associated with gangrenous appendicitis. Kubota et al. conducted a retrospective study on treatment for appendicitis with appendicolith by the stone size and serum c-reactive protein (CRP) level.¹⁰¹ In their study the conclusion was that appendicoliths under 5 mm and patients with a low CRP concentration might be treated conservatively,

while the diameter of appendicolith over 10 mm had a high risk of appendiceal perforation requiring appendectomy. However, further research on appendicoliths is needed to clarify the role of appendicolith in appendicitis severity.

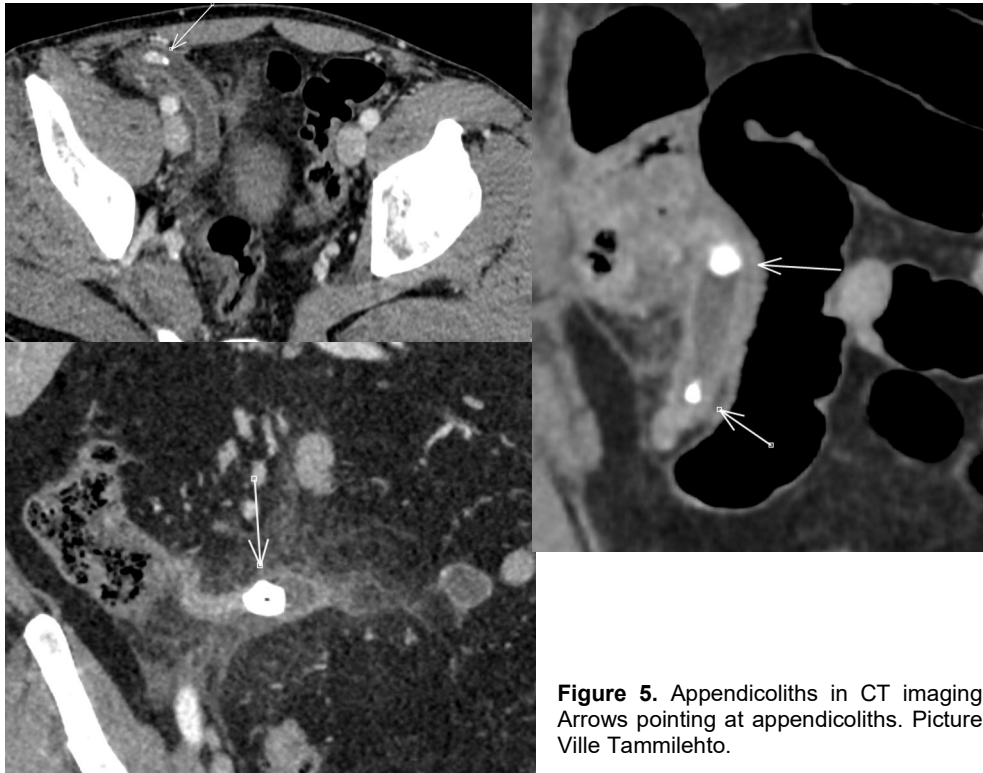


Figure 5. Appendicoliths in CT imaging. Arrows pointing at appendicoliths. Picture: Ville Tammilehto.

2.6 Clinical diagnosis of acute appendicitis

Traditionally, the diagnosis of acute appendicitis has been based on typical patient history, clinical symptoms, and laboratory tests. These findings have been used to distinguish patients with acute appendicitis from patients with some other etiology for acute abdomen. The earlier belief of all appendicitis cases inevitably progressing to perforation previously led to high rates of negative appendectomies when the appendectomy decisions were based on clinical diagnosis only. This issue was most prominent in women of fertile age, in whom alternative gynecological etiologies for abdominal pain are common potentially resembling the symptoms of acute appendicitis. These high negative appendectomy rates were accepted at the time as this was thought to reduce the risk of perforated appendicitis^{113, 114} Later, due to the poor accuracy of clinical diagnosis for acute appendicitis¹¹⁵, clinical scoring systems based on the same features were created to assess the risk of acute appendicitis.¹¹⁶

However, clinical diagnosis even with scoring systems lack the accuracy to distinguish between uncomplicated and complicated acute appendicitis underlining the importance of imaging.²⁷ The use of physical examination, laboratory markers, and scoring systems without imaging have been developed aiming to aid clinicians to select those patients most benefiting from imaging.^{117, 118}

2.6.1 Symptoms and clinical findings

Diagnosing acute appendicitis based solely on clinical assessment has limitations as mentioned above. In literature sensitivity ranges from 76% to 85% and specificity between 82% and 87%.^{119, 120}

A thorough patient history is important in the diagnosis of acute appendicitis.¹²¹ The most typical clinical features in adults include right lower quadrant (RLQ) or right iliac fossa (RIF) pain, nausea, vomiting, abdominal tenderness, and migration of pain from the periumbilical region to the RLQ.¹²²⁻¹²⁵ In children, signs of peritoneal irritation hold a high positive predictive value for acute appendicitis.¹²² However, the classic triad of RLQ pain, tenderness, and pain migration occurs in only 50–60% of cases. Furthermore, only 6% of patients with suspected appendicitis exhibit this textbook presentation.^{115, 126} If the appendix is atypically positioned, localized symptoms may be absent. Other supporting clinical factor and systemic signs as acute appendicitis progress are fever and loss of appetite.¹²⁷ Among patients with appendicitis, body temperature over 38°C has also been associated with complicated acute appendicitis, helping clinicians also in differential diagnosis of acute appendicitis.^{96, 120, 128}

Physical examination remains an essential diagnostic tool, although these findings lack satisfactory specificity. Key findings include tenderness at McBurney's point, rebound tenderness, muscular guarding, and signs of peritoneal irritation. Certain signs, such as the Psoas sign (pain with right hip flexion against resistance), Rovsing's sign (RLQ pain when palpating the left lower quadrant), and the Obturator sign (pain with internal rotation of the right hip), may suggest that patient has acute appendicitis. Additionally, Blumberg's sign—pain upon sudden release of abdominal pressure—can indicate peritoneal inflammation.^{115, 123, 129}

While several studies have identified useful clinical signs, their predictive value varies due to differences in patient populations and different entities of acute appendicitis. The subjective nature of patient responses to physical examination and symptoms further complicates standardization. Despite these challenges, clinical surgical assessment remains an essential step in diagnosing acute appendicitis, but it needs to be supplemented with laboratory tests and imaging studies for greater accuracy.¹²³

2.6.2 Laboratory tests

Acute appendicitis triggers an inflammatory response. Mostly used laboratory markers in clinical practice are white blood cell count (WBC), proportion of neutrophils, and CRP. These traditional laboratory tests are general inflammatory markers with no specificity for appendicitis; hence the sensitivity is limited. Despite their limitations, they can be used to aid in clinical diagnosis and differential diagnosis of acute appendicitis. Other inflammatory markers that have been suggested to be used with patients suspected of having acute appendicitis include procalcitonin and interleukin-6.^{130, 131} However, these markers do not improve in clinical diagnosis of acute appendicitis and are not commonly used.

In a meta-analysis in 2004, Andersson et al.¹²³ reported high discriminatory power for individual laboratory test including WBC, CRP, and proportion of neutrophils with reported area under the curve (AUC) values ranging from 0.75 to 0.78. When combined with patient history and physical examination, the reported diagnostic value increased.¹²³ Grönroos et al. showed that when both WBC count and CRP are normal, acute appendicitis is very unlikely.¹³² Despite these findings, laboratory tests are generally unable to reliably distinguish between patients with acute appendicitis and those without acute appendicitis.²⁷ One problem with laboratory markers, especially with CRP compared to the WBC, is its slow response, which limits the use of CRP as it is less sensitive in the early phase of the disease.¹³³ CRP is an acute phase protein, that usually rises after 8-12 hours from the beginning of an inflammatory process and its peak is around 24-48 hours. For WBC count, studies have shown that acute appendicitis is likely at a WBC count of $> 15 \times 10^9$ cells/l and unlikely at a WBC count of $< 8 \times 10^9$ cells /l, counting that other clinical factors refers to acute appendicitis.^{28, 124, 134}

Some studies have shown better results for CRP as a marker in differentiating uncomplicated acute appendicitis from complicated acute appendicitis. As mentioned before, CRP should not be considered as an indicator for uncomplicated or early acute appendicitis but when it is markedly elevated, it is a strong marker for complicated acute appendicitis.^{27, 132, 135, 136} For example, study by Van den Worm et al.¹³⁵ suggest that a CRP cut-off value of 215 mg/l is statistically significant in diagnosing complicated acute appendicitis. Also, procalcitonin has shown diagnostic value in identifying complicated appendicitis with a pooled sensitivity of 62 % (33 to 84) and specificity of 94 % (90 to 96).¹³⁰ However, the lack of sensitivity has prevented widespread implementation of procalcitonin in clinical use.

Recent guidelines recommend diagnostic scores such as Adult Appendicitis Score (AAS), the Appendicitis Inflammatory Response Score (AIRS), and Alvarado score for management of acute appendicitis^{20, 137}. Such scoring systems are highly effective in identifying patients at low risk of appendicitis, with several studies reporting negative predictive values exceeding 90% in ruling out acute

appendicitis¹³⁸. However, their performance in correctly identifying (ruling in) appendicitis is more variable and potentially suboptimal, which may contribute to an unnecessarily high rate of negative appendectomies¹²⁰.

In conclusion, individual laboratory markers have a limited role in diagnosing and differentiating acute appendicitis. However, CRP might aid in differential diagnosis of appendicitis severity. Combining patient history, clinical symptoms, and laboratory markers gives more accurate results, and should be included in the diagnostic workup for patients suspected of acute appendicitis. However, existing results on the unsatisfactory accuracy of laboratory and clinical findings underline the role of imaging in patients with suspected acute appendicitis.^{27, 123, 139}

2.6.2.1 Blood culture positivity in patients with acute appendicitis

The incidence of blood culture positivity in patients with acute appendicitis is unknown. There are studies reporting swab specimens from luminal contents of the appendix, suppurative peritoneal fluid, or periappendicular abscess¹⁴⁰⁻¹⁴². There are multiple studies on postoperative bacteremia after appendectomy, but there are only few case reports and studies about blood culture positivity in patients with appendicitis.¹⁴³⁻¹⁴⁵ The only studies reporting blood culture positivity in patients with acute appendicitis have been performed in pediatric populations. A prospective study of children with acute appendicitis aimed to determine frequency of systemic bacteremia with 42 patients, of whom three (6%) had systemic bacteremia.¹⁴⁵ Thompson et al. made a 2-year retrospective health record review for children to determine the proportion of true-positive blood culture in patients with appendicitis.¹⁴⁶ In their study, 1315 children were evaluated for having acute appendicitis, of which 288 (22%) had blood cultures taken. Of these 288 patients, there was only 1 (0,35%) true positive.

In conclusion, studies regarding the overall incidence of blood culture positivity in adult patients with acute appendicitis are lacking as blood cultures are clinically taken only from patients with high fever and suspicion of sepsis.

2.7 The role of imaging in diagnosis and differential diagnosis of acute appendicitis

Pre-interventional differential diagnosis of acute appendicitis has become utmost important as most patients with uncomplicated acute appendicitis can be treated with antibiotics or even symptomatic therapy without surgical intervention. Negative appendectomies are associated with increased morbidity and mortality.^{147, 148} After widespread use of CT, NARs has lowered from 20 % to as low as 1.7–3.9 %.^{23, 149, 150} For example in the Netherlands, the NAR decreased from 19% to 5% after

including a mandatory preoperative imaging of all suspected acute appendicitis patients into a guideline.^{22, 151} Nowadays, clinicians are highly dependent on imaging modalities to confirm the diagnosis and severity of acute appendicitis.^{27, 120, 126, 152} Excluding complicated acute appendicitis is the cornerstone in the diagnosis and treatment of uncomplicated acute appendicitis. In the differential diagnostics of acute appendicitis, limited sensitivity or a low negative predictive value (NPV) may result in conservative treatment and discharge of patients with complicated acute appendicitis from the emergency department. Such missed diagnoses can lead to delays in treatment. While a delay in patients with uncomplicated appendicitis does not appear to increase the rate of complications, delayed surgical intervention in cases of complicated appendicitis is associated with a higher risk of complications.¹⁵³ Therefore in differentiating between uncomplicated and complicated acute appendicitis, ruling out complicated acute appendicitis is more important than ruling it in. When considering non-operative management, it is critical to exclude complicated acute appendicitis. For this reason, diagnostic tools must demonstrate high sensitivity and NPV for detecting complicated cases. On the other hand, the ability to definitively rule in complicated appendicitis is less critical, as patients incorrectly classified as complicated would receive surgical treatment, which still remains the standard care of acute appendicitis.

To adjust the optimal treatment according to severity of the disease, predictive factors for complicated acute appendicitis are needed. Despite this fact, many limitations, such as cost, radiation, and availability are present when utilizing different imaging modalities in clinical practice. The gold standard is computed tomography (CT), and other imaging modalities include ultrasound (US) and magnetic resonance imaging (MRI). These other modalities can be used, when exposure to radiation must be avoided, mainly with children and pregnant women.

2.7.1 Computed Tomography (CT)

CT is an imaging modality that acquires a series of X-ray measurements from multiple rotational angles, which are subsequently reconstructed into cross-sectional images of the body using specialized computer software. In Finland, typical abdominal CT study is performed by scanning the patient from the xiphoid process to the symphysis. Usually, i.v. contrast medium is used if a patient's kidney function is sufficient and there is no allergy to iodine contrast. I.v. contrast agents aid both in differential diagnosis of various causes of abdominal pain as well as in distinguishing uncomplicated and complicated acute appendicitis, as it helps to identify possible perforations and enhancement defects of the appendiceal wall.^{154, 155} The widespread utilization of CT in the diagnostic evaluation of acute abdomen, including acute appendicitis, is widely attributed to its high availability, diagnostic accuracy, ease of

execution and interpretation, and its capacity to provide detailed anatomical information of the entire abdomen.^{23, 107} One advantage of CT is that, it is rarely affected by bowel gas, severe abdominal pain, or massive obesity, all of which are problematic in diagnostic US.¹⁵⁶ The CT diagnosis of acute appendicitis is very accurate across the spectrum of appendicitis severity and possible alternative diagnoses such as acute diverticulitis.¹⁵⁷ In different studies, CT's diagnostic accuracy to identify appendicitis has been shown to be quite high, with sensitivities ranging from 95% to 99% and specificities from 96% to 98%.^{158, 159} Multiple studies have demonstrated that diagnosing acute appendicitis without CT imaging leads to high NAR^{160, 161}, but on the other hand, mandatory CT imaging may be associated with potential over-diagnosis of mild appendicitis that would have had spontaneous resolution⁶⁰. CT images of different forms of acute appendicitis are shown in Figure 6.

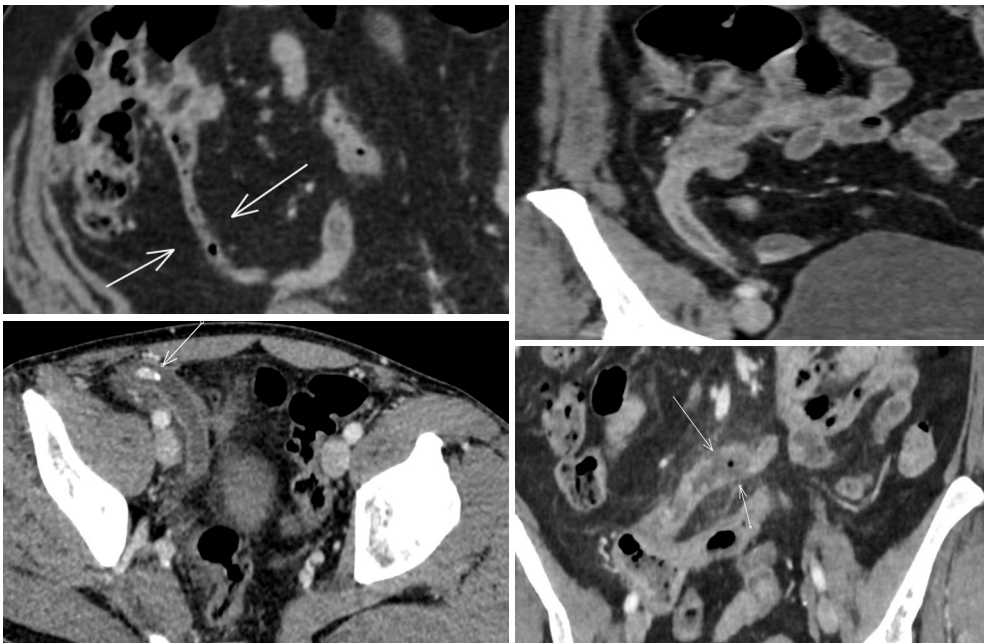


Figure 6. CT images of patients suspected of having acute appendicitis. Normal appendix (on the top left), uncomplicated acute appendicitis (on the top right), acute appendicitis with appendicolith (on the bottom left) and complicated acute appendicitis with appendiceal wall enhancement defect (on the bottom right).

The first studies describing CT in the diagnosis of acute appendicitis were published in the 1980s.¹⁶²⁻¹⁶⁴ After the introduction of CT among patients with inconclusive diagnosis based on clinical status, preoperative CT imaging has been widely implemented in clinical practice in order to reduce NAR.^{26, 151} After major

developments in CT technology and software, the accuracy has further improved and radiation dosages have decreased, which have significantly enhanced the overall feasibility of CT imaging. This in part enabled a diagnostic paradigm to change in acute appendicitis from merely diagnosing acute appendicitis (yes/no) into distinguishing between uncomplicated and complicated acute appendicitis. The ability to distinguish between the different appendicitis severity forms has markedly influenced the modern treatment strategies of acute appendicitis. CT has become the gold standard imaging modality in diagnostics of acute abdomen and/or suspected acute appendicitis. In some reports, routine imaging for patients with suspected acute appendicitis has been reported as high as 90–97.5 % in current medical practice.^{23, 107} The earlier concerns of CT causing a delay in diagnosis of acute appendicitis and therefore increasing the risk for appendiceal perforation has been refuted in multiple studies.^{23, 160, 165-167}

2.7.1.1 CT Findings associated with acute appendicitis

Findings visualized on CT associated with acute appendicitis can be divided into appendiceal findings and inflammatory changes in periappendicular area and adjacent organs. These findings include appendiceal diameter over 6 mm, appendiceal wall enhancement, appendiceal wall thickening, intramural gas, and periappendiceal fat stranding (Table 3). Additionally, CT may show secondary signs such as cecal changes, mesenteric lymphadenopathy, and the presence of phlegmon or abscess.^{95, 155, 168, 169} One of the most specific findings on CT with high sensitivity for acute appendicitis is appendix diameter over 6 mm, together with periappendiceal fat stranding, as this combination occurs in 93% of appendicitis CT cases.^{169, 170}

2.7.1.2 CT findings used in distinguishing complicated and uncomplicated acute appendicitis

The very important role of CT is to distinguish complicated and uncomplicated acute appendicitis. The more accurate the differential diagnostics are, the easier it is to identify patients with complicated acute appendicitis requiring emergency appendectomy, potential non-responders to non-operative treatment as well as the ones optimal for antibiotics. Findings such as extraluminal gas, abscess formation, wall enhancement defects, and periappendiceal fluid collections are suggestive of complicated disease, with varying sensitivity and specificity.^{95, 171, 172} Kim et al.⁹⁵ performed a systematic review and meta-analysis in 2018 assessing CT features in differentiating complicated and uncomplicated appendicitis. In all the studies, reference standard was histopathologic diagnosis, with or without surgical records. They identified ten CT features associating with complicated appendicitis:

extraluminal and intraluminal appendicolith, abscess, appendiceal wall enhancement defect, extraluminal air, ileus, periappendiceal fluid collection, ascites, and intraluminal air (Table 4). In two other studies one important factor that could indicate for more severe path of appendicitis seems to be periappendiceal fat-stranding.^{173, 174}

In the APPAC II trial³³, a subgroup analysis evaluating factors associated to an increased risk of complicated appendicitis in patients treated with antibiotics for CT-diagnosed uncomplicated acute appendicitis, showed that an appendiceal diameter of ≥ 15 mm on pre-interventional CT was associated with a higher risk of antibiotic treatment failure. Additionally, in a retrospective study by Hong et al. appendiceal wall enhancement defect was found to be associated with unresponsiveness to initial antibiotic therapy with odds ratio of 5.5 (95% CI 1.5–19.8).⁹⁸ A meta-analysis from 2021 including 11 studies, showed that CT has sensitivity of 78% and specificity of 91% in detecting complicated appendicitis, but still the predictive value of individual CT features remains inconsistent.⁸⁵ All this data highlights the importance of establishing standardized criteria in interpreting CT findings to enable optimization of all treatment alternatives for both uncomplicated and complicated acute appendicitis.^{10, 13, 17, 31}

Table 4. Individual CT features associated with complicated acute appendicitis. Data in parentheses are 95% CIs. Modified from Kim et al 2018⁹⁵.

Ct feature	Pooled Sensitivity (%)	Pooled Specificity (%)	Pooled Diagnostic odds ratio
Extraluminal appendicolith	14 (8,24)	100	-
Abscess	30 (29, 48)	99 (98, 100)	65.0 (28.0, 151.0)
Appendiceal wall enhancement defect	59 (40, 75)	96 (90, 99)	36.0 (13.8, 95.0)
Extraluminal air	30 (25, 37)	99 (97, 100)	41.0 (13.8, 121.9)
Ileus	23 (8, 51)	95 (90, 98)	5.9 (2.1, 16.6)
Periappendiceal fluid collection	42 (24, 61)	79 (70, 86)	2.7 (1.5, 5.0)
Ascites	38 (26, 51)	81 (68, 89)	2.6 (1.5, 4.5)
Intraluminal air	28 (21, 35)	84 (81, 87)	2.1 (1.4, 3.0)
Intraluminal appendicolith	43 (24, 53)	74 (67, 80)	2.0 (1.7, 2.5)
Periappendiceal fat stranding	94 (86, 98)	40 (23, 60)	11.0 (6.4, 18.7)

2.7.1.3 Limitations of the usage of CT imaging in acute appendicitis

Despite all the diagnostic benefits of CT, it is not without limitations. The main limitation is the exposure to ionizing radiation, traditionally delivering doses up to 8–16 mSv per scan.²⁴ However, advancements in CT technology have enabled the development of low-dose protocols with significantly reduced radiation exposure—often as low as 1.8–2 mSv—without compromising diagnostic accuracy.¹⁷⁵ Recent randomized controlled trials and meta-analyses confirm the non-inferiority of low-dose CT compared to standard-dose imaging for both detection and severity assessment of appendicitis.^{175, 176} Trials such as Low-dose Computed Tomography for Appendicitis Trial (LOCAT)¹⁵⁰ and OPTimization of Computed tomography for acute APpendicitis (OPTICAP)¹⁶¹ have shown comparable NAR and diagnostic accuracy between low- and standard-dose protocols, even in distinguishing between uncomplicated and complicated disease. The LOCAT group conducted a multicenter, randomized controlled non-inferiority trial and reported that the radiation dose of appendiceal CT for young adults can be reduced to 2 mSv without impairing clinical outcomes and that use of low-dose CT could prevent a sizeable number of radiation-associated cancers.¹⁷⁷ Even though the radiation doses are getting lower and many studies suggest that the cancer risk associated with CT radiation is quite small, it is not zero.¹⁷⁸⁻¹⁸¹ Based on study from Brenner et al.¹⁸¹ they estimated that with current use of CT, 1.5 to 2% of all cancers in the United States might be consequent from radiation due to CT imaging. This is overestimation as the estimated radiation dose of CT imaging in this study was 20 to 40 mSv, which is almost 10-fold compared to modern CT imaging. When this risk is combined with the fact that incidence of acute appendicitis is high in adolescents and young adults, it emphasizes the need for reduction of the radiation dose as low as possible, and clinicians must understand that the imaging should always be clinically justified. Using AIR or AAS scores can be helpful in excluding patients with low risk of acute appendicitis, thus these patients can avoid unnecessary imaging studies^{20, 117, 137}.

2.7.2 Ultrasound

Even though CT outperforms ultrasound imaging (US) and magnetic resonance imaging (MRI) in both sensitivity in diagnosing appendicitis and distinguishing complicated acute appendicitis from uncomplicated acute appendicitis, there are still some applications and cases that may benefit from these other imaging modalities.⁸⁵

Graded compression technique with US was introduced in 1986 in the diagnosis of acute appendicitis.¹⁸² In some studies US sensitivity has been reported to be 68–88% and 78–100% specificity in diagnosing acute appendicitis.^{30, 183, 184} Characteristics of acute appendicitis seen on US are mainly same as on CT; appendiceal diameter >6 mm, periappendiceal fluid, local sonopalpation tenderness

and no compressibility of the appendix, periappendiceal inflamed fat, mural hyperemia, and possible appendicolith.^{115, 185} The major advantage of US is the lack of radiation exposure. It is also quite rapid and noninvasive study, with low costs and it does not require iv contrast agents in diagnosing appendicitis.^{115, 186} For these reasons, US is the preferred imaging test for children and pregnant women with suspected acute appendicitis, and it is still widely used even in adults in some regions.^{187, 188} Despite these advantages, many disadvantages occur regarding US usage in diagnosis and differential diagnosis of acute appendicitis. First, the accuracy is unsatisfactory as following a diagnostic US negative appendectomy rates are quite high varying from 6 –9 %.^{189, 190} Secondly, US is highly user-dependent, requires experience, and the accuracy can be effected by patients characteristics such as body mass index (BMI) and excess bowel gas.^{191, 192} Thirdly, the reported ability to differentiate appendicitis severity is far from perfect, and the evidence on this area is very scarce. One retrospective cohort study regarding diagnosis of appendicitis with US reported a sensitivity of 86% and a specificity of 60% for appendiceal perforation.¹⁹³ A meta-analysis by Giljaca et al.¹⁹⁴ concluded that US should not be routinely included in the general diagnostic pathway for acute appendicitis, as its sensitivity and specificity are not superior to clinical examination or validated clinical scoring systems. However, US remains a safe and generally effective imaging modality and should be considered as the first-line option, particularly in children and pregnant women, where minimizing radiation exposure is essential.¹⁹⁵⁻¹⁹⁷

2.7.3 Magnetic resonance imaging

MRI has been used to diagnose acute appendicitis mainly in children and pregnant women to avoid the harms of radiation of CT imaging, following an inconclusive US.¹⁹⁸ MRI findings associated with acute appendicitis are similar to CT or US.^{199, 200} Compared to CT, MRI is comparable in sensitivity and specificity, but MRI is more dependent on the expertise of the radiologist and commonly clinicians aren't as familiar with MRI as they are with CT images.²⁰¹ One meta-analysis assessing MRI in the diagnosis of acute appendicitis showed sensitivity of 95% and specificity of 92%.²⁰² The most acknowledged disadvantages preventing MRI of becoming routine in diagnosing acute appendicitis are the long imaging-time, limited availability, high cost, and the fact that MRI may be less accurate than CT in differentiating uncomplicated and complicated acute appendicitis.^{192, 203, 204} In some studies the accuracy of diagnosing perforation is shown to be 53 to 56 %, which would make it impossible to select patients potentially suitable for conservative management.²⁰³

2.7.4 Scoring systems including imaging features

As mentioned above, CT is considered as the most accurate imaging method in differential diagnostics of acute appendicitis.⁸⁵ The negative predictive value for complicated acute appendicitis has been reported as high as 93 %, but the summary of different studies for CT's sensitivity is around 80 %. In differential diagnostics of acute appendicitis, excluding complicated appendicitis is essential, as false negative diagnosis may result in peritonitis and increase of morbidity and even mortality.¹²⁰ For this reason, different scoring systems combining clinical findings and imaging features have been developed to further optimize differential diagnostics of acute appendicitis. These scoring systems usually include clinical features such as age, body temperature, duration of symptoms, WBC, CRP, and CT parameters like appendiceal diameter, periappendiceal fluid, extraluminal air, appendicolith, and abscess.

Avanesov et al.²⁰⁵ introduced a scoring system combining clinical findings and CT features, but its negative predictive value was only 83 %, adding no value to clinical decision making compared to normal clinical practice⁸⁵. The Scoring systems for Appendicitis Severity (SAS) by Atema et al.⁷ showed first high sensitivity and negative predictive value (94-97 %) to rule out complicated acute appendicitis, but in follow-up study for external validation SAS demonstrated limited accuracy in distinguishing complicated from uncomplicated acute appendicitis²⁰⁶. In this external validation study of SAS, Scheijmans et al.²⁰⁶ developed SAS 2.0 that was able to assess an individual patient's probability of having complicated appendicitis with high accuracy and SAS 2.0 could be helpful when considering nonoperative treatment of acute appendicitis.¹²⁸ Variables examined in SAS 2.0 score were patient related factors (age, sex, body temperature, numerical pain rating scale score, vomiting, duration of symptoms, WBC, CRP), and imaging factors on CT or US (appendiceal diameter, free intra-abdominal air or fluid, intra-abdominal abscess, appendicolith, fat infiltration, and appendiceal wall destruction). In the future, scoring systems combining imaging and objective clinical findings may aid in distinguishing complicated and uncomplicated acute appendicitis. Also artificial intelligence may be useful in the future for differentiating uncomplicated and complicated acute appendicitis²⁰⁷.

2.8 Treatment of acute appendicitis

The treatment of acute appendicitis has been in turbulence for the last decade. For over a century, appendectomy was the standard treatment for all acute appendicitis cases. The novel understanding of two different forms of appendicitis severity⁷⁻⁹ has revolutionized treatment of uncomplicated acute appendicitis, with multiple studies showing that conservative management of uncomplicated appendicitis with

antibiotics is effective and safe.^{10, 16, 32, 35, 208-213} Recent studies even suggest that supportive care alone could be enough for patients with uncomplicated acute appendicitis.²¹³ After the knowledge that uncomplicated acute appendicitis can be treated without appendectomy for the majority of patients, there are multiple perspectives to be considered, i.e., health care providers, clinicians and patients. Patients' preferences and wishes should be discussed, as these might impact on the decision-making process. Concerns like previous surgical experience, work and family responsibilities, travel plans or whether patients prefer definitive treatment to avoid recurrence must be taken account. For example, does one favor a quick return to work or avoiding surgery, or is it more important to avoid the risk of recurrence? And what are the treatment costs of each approach as this is of crucial importance with limited health care resources. All these factors need to be considered when making treatment decisions regarding patients with uncomplicated acute appendicitis.

2.8.1 Treatment of uncomplicated acute appendicitis

Treatment of uncomplicated acute appendicitis has changed in past decades as conservative management of uncomplicated acute appendicitis has become feasible and safe treatment of choice¹³⁷. Professional Society guidelines on the treatment of uncomplicated acute appendicitis is presented in table 5.

Table 5. Professional Society guidelines on the Treatment of Acute Uncomplicated Appendicitis. Modified from David et al. 2021²¹⁴.

Professional Society	Year	Guideline
American Association for the Surgery of Trauma	2018	Laparoscopic appendectomy and nonoperative treatment are both acceptable
National Institute for Health and Care Excellence	2023	Laparoscopic appendectomy is the standard treatment, but nonoperative treatment may be an alternative. There is an increasing body of evidence in support of nonoperative treatment.
World Society of Emergency Surgery	2020	High-quality evidence supports nonoperative treatment and it should be discussed with selected patients without appendicolith.
American College of Surgeons	2020	High-quality evidence indicates that most patients can be treated with antibiotics rather than appendectomy. However, patients with appendicolith are at higher risk of complications than those without appendicolith.

2.8.1.1 Appendectomy

Appendectomy was first described by McBurney in 1894.²¹⁵ After being introduced, it became one of the most common surgical emergency operations and was performed without major changes until laparoscopic appendectomy was introduced in 1983.²¹⁶ After adaptation of laparoscopic techniques, laparoscopic appendectomy has replaced open appendectomy, and nowadays almost every appendectomy, according to some studies 94-98 %, is performed with mini-invasive techniques, with conversion rates reported even as low as 0.9%.^{107, 217, 218} Studies have shown that laparoscopic appendectomy is superior to open surgery, as it significantly reduces morbidity, mortality, and length of hospital stay compared to open appendectomy.²¹⁹⁻²²¹

In laparoscopic appendectomy, three small incisions are used, offering a less invasive alternative to the single, larger incision used in open surgery. Pneumoperitoneum is first established through an incision above the umbilicus, where the camera port and videoscope are inserted. The abdominal quadrants are inspected, and under direct visualization, two additional ports are placed, traditionally one suprapubic at the midline and another in the left lower quadrant. Once the appendix is visualized and mobilized, the mesoappendix is divided, commonly using diathermy, but alternative tools such as metal clips, or high energy devices may also be employed. The appendiceal base is then closed using clips, loop-sutures, or an endoscopic stapler. The resected appendix is placed in a retrieval bag and removed through one of the port sites.^{222, 223} Studies have shown no significant differences in outcomes, length of hospital stay, or complication rates between different techniques for mesoappendix division or stump closure.^{40, 224} Prophylactic antibiotics are recommended to be administered within one hour before skin incision, as it is shown that this procedure is effective in reducing postoperative surgical site infections and intra-abdominal abscesses.²²⁵⁻²²⁸

There are multiple reasons to consider operative management for patients with CT confirmed uncomplicated acute appendicitis. Firstly, appendectomy is considered the appropriate management for patients, who do not respond to antibiotics, symptoms persist or worsen during conservative treatment, or patients who experience a recurrence of appendicitis. However, the need for appendectomy in a recurrent acute appendicitis may also be unnecessary, as it is shown that recurrent appendicitis after initial antibiotic treatment of uncomplicated acute appendicitis are mostly uncomplicated as well.³² Secondly, there is only a limited amount of data regarding the risks and benefits of non-operative management among pregnant women and elderly patients and these populations might be candidates for appendectomy even in cases of uncomplicated acute appendicitis.^{229, 230}

In case there is suspicion of possible complications, patients should be operated on, and always when considering conservative treatment, clinicians must be as

certain as possible of the diagnosis of uncomplicated acute appendicitis. On the other hand, results from different studies report that delaying appendectomy up to 24 hours after admission does not increase risk of complicated acute appendicitis or postoperative complications, which should be taken account, when planning appendectomy for patients with suspected uncomplicated acute appendicitis.⁹⁴ These findings strongly indicates that if appendectomy is chosen for uncomplicated acute appendicitis, it is not an emergency procedure requiring nighttime surgery, but can instead be scheduled as a daytime operation.^{40, 94} Lastly, the role of the appendix in the gut microbiota is under active research as current evidence supports its importance in maintaining a resilient and healthy gut microbial community. Some studies have reported an association between appendectomy and an increased risk of intestinal cancer, but findings are inconclusive.²³¹ There might be potential beneficial effects of the appendix on gut microbiome, which are lost if the appendix is removed.²³²⁻²³⁴ On the other hand, some studies, such as the ACCURE RCT²³⁵ have reported the better treatment response in ulcerative colitis after appendectomy.

2.8.1.2 Antibiotic treatment

Evidence and reports of acute appendicitis resolving without surgical intervention date back to the 19th century. First mention of appendicitis resolving without appendectomy was by Fitz, who noted evidence of spontaneous resolution in approximately one-third of his large autopsy patient cohort, who had experienced earlier episodes of appendicitis.⁵ In the antibiotic era, studies by Coldrey²³⁶ (1956) and Rice²³⁷ (1964) demonstrated favorable outcomes with antibiotic treatment in clinically diagnosed acute appendicitis cases. However, in those days, surgery was considered as the only possible treatment modality due to the idea of progression to perforation. Accurate patient selection is the key to succeeding in non-operative treatment of uncomplicated acute appendicitis.

Today, antibiotic or even symptomatic treatment could be more often considered according to recent study results.^{10, 13, 16, 17, 31, 39, 210, 238} Study results of the APPAC (RCT comparing antibiotic therapy and open appendectomy for treatment of uncomplicated acute appendicitis in patients with 18-60 years of age) and CODA trials and the recent individual patient data meta-analysis of Scheijmans et al., in which majority of the patients was driven from APPAC and CODA trials, have shown that the risks of complications and adverse events among those receiving antibiotics were similar to the risks among those who underwent appendectomy.^{10, 13, 84} Recent Cochrane review by Doleman et al.²³⁹ have suggested that antibiotic treatment may result with higher rates of unsuccessful treatment, although this difference was not clinically significant. This review also suggest that antibiotics may lower the risk of wound infections, and approximately one-third of patients

initially managed with antibiotics required appendectomy within one year. This indicating that two-thirds avoids surgery during that time; however, the certainty of this evidence remains low. Similar results have been seen also in long-term results. At 5 years, the incidence of complications in the APPAC RCT was similar among those who had initial appendectomy and those who had been treated with antibiotics but subsequently had appendectomy showing that antibiotics were not associated with increased complications.³²

The main disadvantages of non-operative treatment are the possibility of appendicitis recurrence, and the potential of missed neoplasms. The number of patients who undergo appendectomy after initially treated conservatively with antibiotics varies depending on the patient's population, study protocol, threshold for proceeding to appendectomy, and the duration of follow-up. In APPAC trial¹⁰ 27 % underwent appendectomy within 1 year, and 39% within 5 year. While in study by Minneci et al²³⁸ with children, the number was 33 %, respectively. In the CODA trial¹³ where they included patients with appendicolith to the study. In the antibiotic group, altogether 29% of patients had undergone appendectomy within 90 days. Among patients with appendicolith the appendectomy rate was 41% and in patients without appendicolith the rate was 25%. This highlights the importance of appendicolith as a complicating factor, and appendectomy may be the best alternative for patients presenting with an appendicolith. The risk of missed malignancy in case of CT confirmed uncomplicated acute appendicitis is very rare, in some studies tumors in appendixes it is estimated to be up to 1 %.^{68, 73, 240, 241} The risk of appendiceal tumor is also clearly associated with complicated acute appendicitis, especially to periappendicular abscess in patients over 35 years.^{69, 73, 74, 242}

There are many benefits favoring antibiotic treatment instead of appendectomy. Antibiotic therapy is associated with decreased morbidity and disability related to surgical recovery^{16, 17, 243}. Antibiotic therapy was associated with major cost and health care resource savings compared with operative treatment.^{38, 244} The recent study results have shown that outpatient management of patients with uncomplicated acute appendicitis is a safe and feasible option. In the CODA trial¹⁷ 47% of the patients treated with antibiotics were discharged directly from the emergency department and no increased rate of complications was found compared to the patients with hospital follow-up. In the pilot study allowing outpatient antibiotic management by Talan et al²⁴³, there were 30 patients out of which 15 adult patients were treated with antibiotics. Of these patients 14 were discharged from the emergency department and had resolution of all symptoms. Outpatient management of uncomplicated acute appendicitis will be also assessed in on going Finnish study²⁴⁵. When patients are discharged directly from the emergency department without need for surgery or ward surveillance in the hospital, the economic burden for the healthcare system is greatly decreased.

On the other hand, there are disadvantages in antibiotic treatment. For example, the increase in antibiotic resistance represents a significant global public health challenge. Antibiotic therapy may lead also to significant alterations in the gut microbiota, thereby increasing the risk of opportunistic infections such as *Clostridium difficile* infections. The optimal choice of antibiotic regimen is still undetermined. The most common bacteria isolated from appendix after acute appendicitis from surgical specimen is *Escherichia coli*, other possible bacteria species are *Klebsiella pneumoniae*, Enterococci, Streptococci and *Pseudomonas aeruginosa*.²⁴⁶ In the major RCT's comparing antibiotic treatment to operative treatment antibiotics has been quite large in spectrum and with the newest results of possible spontaneous resolution of uncomplicated acute appendicitis, more evidence is needed of the right choice of antibiotic regimens.^{10, 13, 39} The APPAC II RCT³³ compared effect of oral moxifloxacin and i.v. ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis. In this RCT oral antibiotics were not inferior to i.v. antibiotics followed by oral antibiotics. The major RCT's comparing antibiotics and appendectomy are summarized in Table 6.

Table 6. The major randomized clinical trials comparing antibiotic therapy and appendectomy for uncomplicated acute appendicitis.

Study	Diagnosis	Number of patients (surgery: antibiotics)	Antibiotics used	Successful antibiotic treatment at 1-year
STYRUD 2006³⁵	clinical, and CRP>10mg/L	124:128	I.v. cefotaxime + tinidazole & p.o. ofloxacin + tinidazole	76 %
HANSSON 2009²⁰⁹	Clinical diagnosis (+US/CT)	167:202	I.v. cefotaxime + metronidazole & p.o. ciprofloxacin + metronidazole	52 %
VONS 2011¹⁶	CT	119:120	I.v. amoxicillin + clavulanic acid & p.o. amoxicillin + clavulanic acid	63 %
SALMINEN 2015	CT	273:257	I.v. ertapenem & p.o. levofloxacin + metronidazole	73 %
FLUM 2020¹⁷	US/CT	776:776	I.v. antibiotics (unspecified) & p.o. antibiotics (unspecified)	60 %
O'LEARY 2021²⁴⁷	US/CT	89:91	I.v. amoxicillin clavulanic acid + P.o. amoxicillin clavulanic acid	75%

2.8.1.3 Symptomatic treatment

New evidence of spontaneous resolution of uncomplicated acute appendicitis is further changing the treatment paradigm of appendectomy for all^{31, 39}. As these pilot

studies have shown that even symptomatic therapy may be sufficient also challenging the necessity of antibiotics in the treatment of uncomplicated acute appendicitis. In the future, larger trials are needed to assess symptomatic care in patients with uncomplicated acute appendicitis. Acute appendicitis has many similar features to acute diverticulitis, a similarity supported by epidemiological studies.⁸ Recent studies show that CT diagnosed uncomplicated diverticulitis can be managed with symptomatic treatment alone and there is no added benefit from antibiotic therapy in uncomplicated diverticulitis.²⁴⁸⁻²⁵¹

The first pilot study on symptomatic management of uncomplicated acute appendicitis was conducted by Park et al.³¹; a single-blinded study reporting encouraging preliminary results for CT diagnosed uncomplicated acute appendicitis managed without antibiotics. However, the study's careful patient selection introduces the possibility of selection bias. There was no difference in treatment failure rates in non-antibiotic and antibiotic groups at 1 month or 1 year: 7.3% versus 7.5% and 23.4% versus 20.7%, respectively. The APPAC III³⁹ study was the first randomized double-blind superiority trial comparing antibiotic treatment to placebo treatment. In the APPAC III study adults with CT diagnosed uncomplicated acute appendicitis were randomized to receive antibiotic therapy (intravenous ertapenem followed by oral levofloxacin and metronidazole) or placebo. The primary endpoint was treatment success at 10 days showing that antibiotics were not superior compared to placebo for treatment success defined as resolution of appendicitis resulting in discharge from the hospital without appendectomy during the follow-up. There were only 66 patients in the APPAC III study population, but results corroborate the findings of Park et al. Long-term results are still lacking with no studies reporting results after more than one year of symptomatic care.

2.8.2 Treatment of complicated acute appendicitis

2.8.2.1 Appendectomy

The treatment of complicated acute appendicitis has not changed much after the introduction of laparoscopic appendectomy, which is the standard treatment for complicated acute appendicitis, excluding periappendicular abscess and appendiceal neoplasms.⁴⁰ In addition to removal of the inflamed appendix, possible intraperitoneal pus and bowel contents are evacuated using suction, preferably without irrigation or drainage placement.^{252, 253} The optimal length of postoperative antibiotic treatment is still unclear, but consensus has been that no longer than 3 to 4 day course is needed, and even shorter courses have been suggested to be optimal in treatment of complicated acute appendicitis after source control.²⁵⁴⁻²⁵⁶ Recent RCT by Wijkerslooth et al.²⁵⁷ showed that 2 day postoperative antibiotics were non-

inferior to 5 days of antibiotic after laparoscopic appendectomy in patients with complicated acute appendicitis. This finding could reduce adverse effects of antibiotic treatment and shorten the length of hospital stay after appendectomy.

2.8.2.2 Treatment of periappendicular abscess

A periappendicular abscess represents a complication of acute appendicitis, where the perforation is contained locally. Incidence of appendiceal abscess is around 3-10% of adult patients with acute appendicitis.^{258, 259} While the overall incidence of appendiceal tumors are up to 1%, the highest risk of tumors are presented with periappendicular abscess.²⁶⁰ In a recent prospective cohort study in Finland an overall tumor rate in patients with periappendicular abscess was 14.3%.¹² The traditional initial treatment approach in most cases is non-operative management, particularly in clinically stable patients. This typically includes i.v. antibiotic therapy and supportive care, such as fluid resuscitation, pain management, and monitoring for signs of systemic infection or clinical deterioration. If the abscess is large, typically over 4 cm, or the patient remains symptomatic despite antibiotic therapy, percutaneous drainage under radiologic guidance may be needed. This approach has been shown to effectively control infection, and minimize the need for emergency surgery.²⁶¹

After the initial treatment, the need for interval appendectomy is underlined by the recent reports of high appendiceal tumor rate associated with periappendicular abscess.^{12, 69, 73, 74, 262} Interval appendectomy refers to a preplanned surgical removal of the appendix following initial conservative management, performed after the acute inflammation has been resolved. Historically interval appendectomy was routinely performed to prevent recurrence despite many studies suggesting that recurrence rates are relatively low^{40, 263}. Instead, recent reports show that periappendicular abscess is associated with a risk for appendicular neoplasms as high as 14.3%.¹² Salminen et al. suggests in their study that at least, all patients older than 35 years with periappendicular abscess should undergo routine interval appendectomy.¹² Some studies prefer immediate surgery²⁶⁴, but this might compromise long-term results for patients having malignancy as spreading the otherwise contained appendiceal tumor perforation in the emergency appendectomy is naturally against the principles of surgical oncology.^{260, 265, 266} However, in young patients under the age of 35, immediate appendectomy may be considered appropriate due to the low risk of underlying malignancy. In some cases, emergency appendectomy may still be necessary, for example if patient has generalized peritonitis indicating rupture of the abscess, clinical deterioration despite adequate antibiotic therapy, or failure of percutaneous drainage.

2.8.2.3 Treatment of appendiceal neoplasms

The treatment of appendiceal neoplasm depends on the type of tumor, size, and extent of its possible spread. The most common types include neuroendocrine tumors, mucinous neoplasms (Figure 7), and adenocarcinomas. In a large prospective cohort study conducted by Salminen et al.¹² with 6165 patients with acute appendicitis, there were 370 patients included in the study, presenting with periappendicular abscess. Of these patients with periappendicular abscess, there were 53 appendiceal tumors (21 were mucinous neoplasms, 20 adenocarcinomas, 8 adenomas, and 5 neuroendocrine tumors). For local small tumors, which are usually incidental findings after appendectomies, simple appendectomy is adequate treatment.²⁶⁷ Mucinous neoplasms, if ruptured, may need cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC).²⁶⁸ Appendiceal adenocarcinomas, neuroendocrine carcinomas and goblet cell carcinomas are treated similarly to colorectal cancer, often requiring a right hemicolectomy and possible adjuvant chemotherapy depending on staging and lymph node status.²⁶⁸

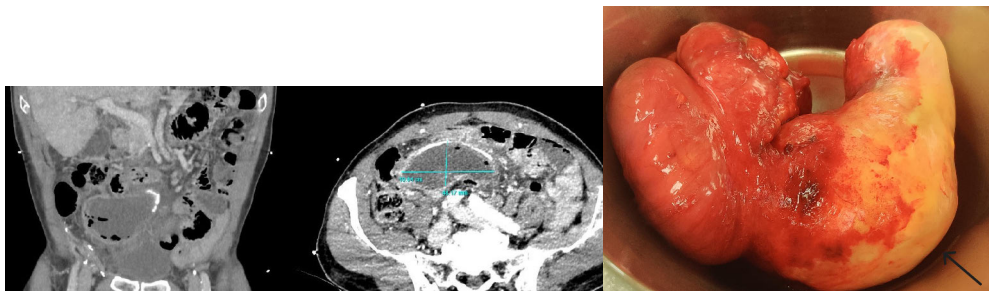


Figure 7. Mucinous cystadenoma of appendix. On the left CT images and on the right removed appendix and cecum after operation.

2.8.3 Long-term treatment outcomes of nonoperative treatment of uncomplicated acute appendicitis

As evidence of nonoperative treatment success and feasibility as initial treatment choice of uncomplicated acute appendicitis has become part of common clinical practice^{10, 13, 40}, authors and clinicians must consider long-term results, advantages and disadvantages of this treatment alternative. As nonoperative treatment of uncomplicated acute appendicitis has been adapted to international guidelines quite recently, we still lack evidence on long-term results, even though some long-term studies have been conducted.^{32, 269} The advantages and disadvantages can be divided between patient related and health care system related matters. In health care system loss of resources must be considered, as the lower cost of successful nonoperative treatment has been proven and should be taken account when discussing different treatment outcomes.³⁸

²⁴⁴ Patient related outcomes to be considered include for example late recurrences, QOL, and treatment complications. It also needs to be informed that most of the recurrences occur during the first year and long-term recurrences are rare.^{32, 269}

2.8.3.1 Appendicitis recurrence

The most investigated long-term outcome is the recurrence rate of acute appendicitis after the initial nonoperative management. The recurrence rates vary in different studies depending mostly on the patient population studied as well as on the definition of recurrence. Some studies categorize recurrence as an appendectomy performed for any reason, while the true appendicitis recurrence should perhaps be determined after histopathological confirmed diagnosis of acute recurrent appendicitis. Nowadays, there are many studies with 1-year follow up, the recurrence rates in different studies ranges from 14% to 35%.^{10, 16, 35, 270, 271} The most comprehensive data on recurrence after initial antibiotics are based on the APPAC study reporting a follow-up of five years.³² At 5 years, the study found an appendectomy rate of 39.1% and a true recurrence rate, meaning histopathology confirmed acute appendicitis, of 32.4%. The long-term recurrence rates of APPAC study population are shown in Table 7. As seen in the table, most recurrences occur within the first year after nonoperative treatment, some between years one and two, and only individual cases after two years of initial treatment. Similar results have been seen also in three-year follow-up of APPAC II RCT, in which treatment success at year 3 was 63.4% in the oral antibiotic monotherapy group and 65.2% in the combined i.v. and oral antibiotics group.³⁶ In Swedish long-term registry-based study of two earlier RCTs with follow-up time of 19 to 26 years, 60% (82 of 137) of patients had not undergone appendectomy at the end of follow-up.²⁶⁹

Table 7. Long-term appendectomy rate after initial nonoperative treatment in APPAC and CODA rct populations. Based on Salminen et al 2018³² and Flum et al 2021²⁷².

Year	Cumulative appendectomy rate after initial antibiotic management in APPAC RCT	Cumulative appendectomy rate after initial antibiotic management in CODA RCT
1	27.3 %	40 %
2	34.0 %	46 %
3	35.2 %	49 %
4	37.1 %	49 %
5	39.1 %	

2.8.3.2 Quality of Life and patient preferences

One consideration when deciding between treatment options is the patient's overall quality of life (QOL) in the short- and long-term. Sippola et al.²⁷³ conducted an observational follow-up of the APPAC RCT population to assess patient satisfaction and QOL after antibiotic therapy and appendectomy for the treatment of uncomplicated acute appendicitis. QOL was assessed with EQ-5D-5L. Of the 530 patients enrolled in the trial, 423 (80%) were available for phone interview at a median follow-up of 7 years. Results of this long-term follow-up were that QOL was similar in both groups. Patients who underwent antibiotic treatment and later underwent appendectomy were less satisfied than patients with successful antibiotic treatment or initial appendectomy. This highlights the importance of patient selection and accurate patient information of possible long-term results of different treatment choices. This aspect has become acknowledged and shared decision making with patients has become a norm in treating uncomplicated acute appendicitis. Before deciding on the treatment option, patient preference and long-term outcomes has to be discussed with patients.^{274, 275} Hanson et al.²⁷⁴ conducted an online survey of 1728 participants, where they asked adult respondents to imagine that they or their child had an uncomplicated acute appendicitis. In survey patients had to select their preferred treatment choice after information about laparoscopic appendectomy, open appendectomy, and antibiotic therapy. Most respondents chose surgery, but 9.4% chose antibiotics. In questionnaire study by Scheijmans et al.²⁷⁶ made to patients who had undergone appendectomy without being offered antibiotic treatment, 25.2 % (185/734) of patients preferred antibiotics as the treatment for uncomplicated appendicitis versus 69.5 % (510/734) of whom would have chosen appendectomy, 2.5% (39/734) of patients had no preference to the treatment choice. On another survey conducted by Rosen et al.²⁷⁷ for patients with no appendicitis in history, the result was opposite. In their survey 83.1 % (1045/1257) were willing to try antibiotic treatment, and even when informed about 60 % risk of failure in the initial management, 75 % were willing to attempt antibiotic treatment. These results highlight the importance of patient perspective and shared decision making.

2.8.3.3 Treatment complications

Complications related to the treatment of uncomplicated acute appendicitis vary depending on whether the approach is appendectomy, antibiotic treatment or symptomatic care.

Mortality associated with uncomplicated acute appendicitis is low with both treatment options. A large global observational study found a 0.28% overall mortality rate, mostly related to complicated cases, older age, comorbidities, and negative appendectomies.²⁷⁸ Delayed surgery in elderly or frail patients after initial

non-operative management may be associated with higher mortality, likely reflecting pre-existing health risks and further lower tolerance for complications.^{147, 278, 279}

The overall complication rates after appendectomy vary in different studies. Postoperative morbidity has been reported between 8.2 % and 31.4 %, depending on disease severity, surgical approach and definition of complications.^{220, 280} However, complications in patients with uncomplicated acute appendicitis treated with laparoscopic appendectomy is reported to be as low as 5.3 %.²⁸¹ The complication rate in the RCTs evaluating management of uncomplicated appendicitis has been consistently higher in surgical compared to nonoperative treatment.²⁸²⁻²⁸⁵ Also, most complications in antibiotic groups are appendectomy related complications due to subsequent appendectomy after non-responsiveness to initial antibiotic treatment rather than being related to the initial antibiotic treatment itself.¹⁰ Long-term complications after appendectomy include small bowel obstruction, incisional hernia, stump appendicitis, possible changes in infertility, and persistent abdominal or incisional pain. Small bowel obstruction is relatively rare but significant postoperative complication, with incidence ranging from 0.7 % to 2.8 %.²⁸⁶⁻²⁸⁹ Incisional hernia rates reported after appendectomies vary between 0.7 % to 2 %.²⁹⁰⁻²⁹² Risk factors include obesity, diabetes, surgical site infections, and open approach. Stump appendicitis is quite rare but potentially serious complication due to incomplete removal of the appendix with similar clinical presentation to acute appendicitis but is often diagnosed later, because patients have history of appendectomy.²⁹³ In some studies, the incidence has been 0.2 %, but this condition might be underreported.²⁹⁴ Acute appendicitis treated with appendectomy has been linked to the formation of pelvic adhesions, which have been associated with infertility and an increased risk of ectopic pregnancy. A meta-analysis by Elraiyah et al.²⁹⁵ found an association between appendectomy and ectopic pregnancy, but no significant link to long-term infertility. Persistent abdominal or incisional pain is also a quite common complication after appendectomy. It's been reported in up to 15% of patients and is possibly caused by adhesions or nerve involvement.³²

Potential complications specific to antibiotic therapy include allergic reactions, tendinitis, adverse effects on gut microbiota and potentially missed malignancy. Prolonged antibiotic use may disrupt the microbiome, potentially predisposing patients to conditions such as *Clostridium difficile* colitis.²⁹⁶ Although rare, the CODA trial reported *C. difficile* infection in 0.6% of patients treated with antibiotics, the same rate as in the surgical group.¹⁷ Missed malignancy of CT diagnosed acute appendicitis is rare but potentially significant risk factor, that must be taken account when treating acute appendicitis nonoperatively. The overall prevalence of appendiceal neoplasms is about 1.2%, with most associated with complicated appendicitis.⁷³ But in uncomplicated cases, the risk is much lower. In the study conducted by Salminen et al¹², appendiceal tumor rate in patients with

periappendicular abscess was 14.3%, while in patients with uncomplicated acute appendicitis tumor rate was 1.5 %, and in patients with complicated acute appendicitis without periappendicular abscess this rate was 2.4%, respectively. Moreover, the likelihood of underlying appendiceal tumors increases with age.

However, several challenges remain comparing the two approaches objectively. Unlike surgery, non-operative treatment lacks a standardized classification system for complications like the Clavien-Dindo grading used postoperatively. Also, the long-term data is scarce. The APPAC RCT remains the most comprehensive study, reporting five-year follow-up data of 6.5% complication rate in the antibiotic group compared to 24.4% in the surgery group. The major limitation of the APPAC study was open appendectomy, since nowadays laparoscopic appendectomy is the treatment of choice if the operative treatment is warranted and the complication rates with this approach are lower.³² Notably, patients who later underwent appendectomy after initial antibiotic therapy experienced complication rates similar to those treated with initial surgery, with no major adverse events or missed tumors reported during follow-up.³² Albeit these patients with later appendectomy were the group with least satisfaction regarding to treatment²⁹⁷.

3 Aims

The main aims of this thesis were to assess the differences of appendicitis severity regarding blood-culture positivity and to improve the accuracy of CT imaging in differential diagnostics between uncomplicated and complicated acute appendicitis. In addition, the longer-term outcomes of antibiotic and symptomatic treatment were assessed.

1. To assess the prevalence of blood culture positivity and clinical features associated with blood culture positivity in adult patients with either complicated or uncomplicated acute appendicitis.
2. To assess the association of appendicolith and its CT-characteristics with appendicitis severity among patients with acute appendicitis.
3. To identify pre-interventional CT characteristics that could be associated with complicated acute appendicitis.
4. To evaluate 3-year results of the safety and efficacy of symptomatic therapy compared to antibiotics for CT-confirmed uncomplicated acute appendicitis.

4 Materials and Methods

4.1 The APPAC II and III trials

Studies of this thesis are based on APPAC II³³ and APPAC III³⁹ RCTs. Study IV was a predefined 3-year follow-up study of the APPAC III trial, and materials and study population were based entirely on APPAC III study. Data of studies I, II and IV were based on the prospectively collected patient data of patients evaluated for enrolment in APPAC II and APPAC III multicentre RCTs between 1.4.2017 and 27.11.2018.

APPAC II (NCT03236961) was a multicentre, open-label, noninferiority RCT comparing oral moxifloxacin with intravenous ertapenem followed by oral levofloxacin and metronidazole in the treatment of CT-confirmed uncomplicated acute appendicitis. The study aimed to demonstrate the noninferiority of oral antibiotics compared with intravenous followed by oral antibiotics and the feasibility of oral antibiotics alone in the treatment of uncomplicated acute appendicitis.

APPAC III (NCT03234296) was a multicentre, double-blind, placebo-controlled, superiority RCT comparing antibiotic therapy (intravenous ertapenem followed by oral levofloxacin and metronidazole) with placebo in the treatment of CT-confirmed uncomplicated acute appendicitis aiming to evaluate the role of antibiotics in the resolution of uncomplicated acute appendicitis.

Inclusion and exclusion criteria for both APPAC II and III trials are identical.

Inclusion criteria:

1. Signed informed consent
2. Age 18 – 60 years
3. CT-diagnosed uncomplicated acute appendicitis.

Exclusion criteria:

1. Age <18 or > 60 years
2. Pregnancy or lactating
3. Allergy to contrast media or iodine
4. Renal insufficiency

5. Allergy or contraindication to antibiotic therapy
6. Metformin medication
7. Severe systemic illness (for example malignancy, medical condition requiring immunosuppressant medications)
8. Complicated acute appendicitis in a CT scan (appendicolith, perforation, abscess, suspicion of a tumor)
9. Inability to co-operate and give informed consent.

The trial protocols for the RCTs were approved by the ethics committee of Hospital District of Southwest Finland and all patients gave written informed consent.

4.2 Patients and methods

4.2.1 Study I

Blood culture data was retrieved at Turku University Hospital during enrolment for ongoing concurrent APPAC II, APPAC III, and MAPPAC (Microbiology APPendicitis ACuta)²⁹⁸ studies. All patients evaluated for enrolment in these trials between 1.4.2017 and 27.11.2018, with either CT or histopathological confirmed diagnosis of uncomplicated or complicated acute appendicitis with available blood culture samples, were included in this study (Table 8.). Appendicitis was diagnosed based on computed tomography among patients treated nonoperatively and based on histology of removed appendix among patients treated with surgery.

Study patients were divided according to blood culture results (positive or negative). In addition, all patients with appendicitis were analyzed using propensity score matching to assess the prevalence of blood culture positivity in this large prospective patient cohort. Patients were informed about the study and asked for written informed consent to participate. The trial protocol was approved by the ethics committee of Turku University Hospital district.

The primary aim was to assess the prevalence of blood culture positivity in a large prospective patient cohort with CT or histopathological confirmed complicated or uncomplicated acute appendicitis. Antimicrobial treatment and all microbes found in blood cultures were documented. Other characteristics evaluated in this study were age, sex, body mass index (BMI), body temperature, C-reactive protein (CRP), leukocyte count and clinically significant comorbidities. The medical reports for all patients were examined to register all comorbidities potentially impacting the patient's immune system. These comorbidities included ulcerous colitis, Crohn's disease, diabetes, coronary heart disease, malignancy and systemic

immunosuppressive medicine for any reason; multiple sclerosis, Addison's disease, polymyalgia rheumatica and rheumatoid arthritis.

4.2.2 Study II

Study II was a retrospective subgroup analysis of the patient data collected within the APPAC II and APPAC III trials. In this study the medical records of all patients who had been evaluated for enrollment for these RCTs and had given written consent were analyzed. Medical records for patients presenting with an appendicolith were reviewed for available CT images to a retrospective review. Patients with available original CT images and appendicolith in CT at re-evaluation by senior consultant radiologist were included in the main analysis of this study (Table 8.). CT images of the included patients were reassessed by abdominal radiologists, and appendicolith diameter, location, pressure effect, and enhancement defects to the appendiceal wall were assessed and recorded. The impact of appendicolith characteristics on the final clinical diagnosis, which was determined by two researchers in blinded manner as complicated versus uncomplicated acute appendicitis, was evaluated. Final diagnosis were determined by histopathology of the removed appendix after surgery if patient was operated, and if treated non-operatively from CT imaging and patient history. In addition, the entire population of patients with appendicitis was divided into two categories based on the initial CT scan diagnosis either having appendicitis and an appendicolith or appendicitis with no appendicolith. In this initial analysis, the final clinical diagnoses of these two cohorts were assessed and compared to evaluate the overall association of CT-diagnosed appendicolith to complicated appendicitis.

The aim of this study was to evaluate the role of appendicolith and its characteristics, potentially associating with a more severe path of acute appendicitis. The primary variables evaluated were the diameter and the location of appendicolith. The location of appendicolith was divided into four categories: the base, the middle, and the apex of appendix, and free peritoneal space. Secondary variables evaluated were the potential pressure effect of appendicolith to the appendiceal wall, and the enhancement defects of the appendiceal wall around appendicolith. Aim was to find a cut off point for the diameter of appendicoliths to distinguish which appendicoliths have clinical relevance.

4.2.3 Study III

Study III was a retrospective analysis of the prospectively collected patient data of patients evaluated for enrolment in APPAC II and III trials (Table 8.). The medical records of all patients evaluated for eligibility in the APPAC II or APPAC III RCTs with suspected acute appendicitis were evaluated for this current substudy (N=3512).

Reference standard for patients included in this study was CT confirmed appendicitis and available histopathologic diagnosis after surgery. Main aim of this study was to evaluate CT characteristics that could associate with complicated acute appendicitis. The evaluated characteristics were appendiceal diameter, fluid and swelling around the appendix, and the appendix wall enhancement defect. As appendicolith is a known risk factor for complicated appendicitis, a subgroup analysis was conducted for patients without appendicolith. In this subgroup analysis CT characteristics (appendiceal diameter, fluid, and swelling around the appendix, and the appendix wall integrity) were analyzed for possible association of complicated acute appendicitis.

The primary CT variable was the diameter of appendix. The aim was to find a cut-off value potentially predicting complicated acute appendicitis, recurrence of appendicitis, and failure of non-operative treatment. Secondary CT variables included appendiceal wall enhancement defect, accumulated fluid, and swelling around the appendix.

Patients were included in this study only if they had CT-diagnosed appendicitis and available histopathologic diagnosis after appendectomy. The final clinical diagnosis was determined by two researchers based on both surgical and histopathological findings. The surgical finding of perforation was evaluated as complicated acute appendicitis as well as gangrene of the appendix, if supported by both surgery and histopathology. The finding of transmural neutrophil invasion involving the appendiceal muscularis layer of the removed appendix was required for the histopathological diagnosis of acute appendicitis. Appendiceal neoplasm, and/or abscess was classified as complicated acute appendicitis.

4.2.4 Study IV

Study IV was a predefined 3-year secondary analysis of APPAC III trial, which was a prospective randomized double-blind, placebo-controlled, superiority multicenter trial to compare antibiotic therapy with placebo in the treatment of acute uncomplicated appendicitis (Table 8.). In the APPAC III trial the primary endpoint of treatment success was assessed at 10 days and for this 3-year predefined secondary analysis, the primary endpoint was late appendectomy rate and appendicitis recurrence. The predefined secondary endpoints at 3 years included possible appendectomy (timing and histopathology) for suspected late appendicitis recurrence after 10 days, treatment adverse events, the length of sick leave and hospital stay, assessment of abdominal symptoms, and quality of life (QOL) using the validated EQ-5D-5L (EuroQol-5Dimension-5levels) questionnaire. The 30-day time point was added as a post-hoc outcome to enable comparison with other large RCTs^{17, 299}. All outcomes were evaluated by phone interviews at 3 years. For patients

who were not reached for follow-up by phone (n=4), electronic hospital records were searched for possible appendectomy or emergency department visits.

Table 8. Patient data used in different studies of this thesis.

Study	Number of patients in main analyzes	Study hospitals	Details of inclusion criteria of the study population
Study I	271	Turku University Hospital	All patients enrolled in APPAC II and III studies with correctly taken blood culture samples
Study II	380	7 Finnish hospitals (Turku, Oulu, and Kuopio University Hospitals, Jyväskylä, Mikkeli, Pori, and Seinäjoki Central Hospitals)	All patients enrolled in APPAC II and III studies with acute appendicitis, appendicolith and available CT images
Study III	3085	9 Finnish hospitals (Turku, Oulu, Tampere, and Kuopio University Hospitals, and Pori, Seinäjoki, Jyväskylä, Mikkeli, and Rovaniemi Central Hospitals)	All patients enrolled in APPAC II and III studies with CT-diagnosed appendicitis and available histopathology after surgery.
Study IV	66	Turku University Hospital	All patients included in APPAC III RCT

4.3 Statistical analysis

4.3.1 Study I

Categorical variables were summarized with counts and percentages, continuous variables with mean and standard deviation (SD). In addition, range was reported for age. Association between blood culture positivity (positive or negative) versus type of appendicitis, sex, comorbidities and antibiotics (categorized) was examined using Fisher's exact test. Comparison of age, body mass index, body temperature, CRP and leukocyte count between the blood culture positivity groups was performed using one-way analysis of variance. Square root transformation was used to CRP and white blood cell count to fulfill the assumption of normality. Normality assumption was checked from studentized residuals.

Prevalence of blood culture positivity was calculated directly from those (n=271) whom blood culture test was analyzed. Furthermore, propensity scoring was used to match this subpopulation to those who did not have blood culture test taken. Matching was done with sex, age, body mass index, CRP (categorized below and above reference limit), leukocyte count (categorized below and above reference limit), body temperature (categorized below or above 37.5).

Confidence intervals (CI) of 95% were calculated. All statistical tests were performed as 2-sided, with a significance level set at 0.05. The analyses were programmed using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

4.3.2 Study II

Continuous variables were described using means and standard deviations (SD) for normally distributed variables and for non-normally distributed variables medians with range of values or interquartile range (Q1, Q3) are used. For categorical variables frequencies and percents were used. Univariate analyses for the association of categorical variables and complicated appendicitis were performed using Pearson's χ^2 -test or Fisher's exact test when needed. For continuous explanatory variables binomial logistic regression was used for univariate analyses.

Receiver operating characteristic (ROC) curve was used to evaluate a possible cut-point value for diameter of appendicolith to predict complicated acute appendicitis. Area under the ROC-curve (AUC) with 95% confidence intervals (95% CI) was presented as the result of the analysis. Complicated appendicitis was further analyzed using multiple binomial logistic regression analysis. All variables which were statistically significant in the univariate analyses were included in the first model and then non-significant variables were excluded from the model one by one. The final model included only the variables that were statistically significant. As the duration of symptoms had many missing values, it was not included in the model selection procedure (first model). Instead, an additional multiple logistic regression analysis was performed to evaluate the association of diameter of appendicolith and duration of symptoms to complicated appendicitis. This additional model also included the interaction of diameter of appendicolith and duration of symptoms. The results of logistic analyses were quantified using odds ratios (OR) with 95% CI.

Two-sided tests were used and p-values less than 0.05 were considered as statistically significant. Statistical analyses were performed using SAS System for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA) and figure was drawn with R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

4.3.3 Study III

Categorical variables were characterized using frequencies and percentages and continuous variables were described using medians with range or quartiles. Differences between groups were evaluated using Pearson's Chi-squared -test for categorical variables and non-parametric Kruskal-Wallis -test for continuous variables. Univariate binomial logistic regression was used to analyze associations

of explanatory variables (appendiceal diameter, fluid, and oedema around the appendix, and the appendix wall enhancement defect) to complicated appendicitis and results were quantified using odds ratios (OR) with 95% confidence intervals (CIs). In addition, a multivariable binomial logistic regression analysis was conducted in further analyses of complicated appendicitis. Model included CT variables (appendiceal diameter, fluid, and oedema around the appendix, and the appendix wall enhancement defect) and baseline characteristics (sex, age, body mass index, temperature, white blood cell count, and C-reactive protein). Receiver operating characteristics (ROC) curve was used to evaluate a possible cut-off point value for appendix diameter to predict complicated appendicitis and area under the ROC-curve (AUC) with 95% CIs is presented as a result. Sensitivity and specificity of possible cut-off points with 95% CIs are also presented. In the subgroup analysis among patients without an appendicolith, CT characteristics (appendiceal diameter, fluid, and oedema around the appendix, and the appendix wall enhancement defect) were analyzed for possible association for complicated acute appendicitis similarly to the main analysis. Two-sided tests were used and 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, Cary, NC, USA).

4.3.4 Study IV

The differences between groups in appendectomy rate at 10 days, 30 days, 1 year, and 3 years along with 3-year recurrence rate were tested using one-sided Fisher's exact test. The two-sided 90% confidence interval for the difference in proportions was calculated to estimate the treatment difference. The secondary outcomes were analyzed using chi-squared test, independent samples t-test or Mann-Whitney U-test in concurrence with the primary endpoint analysis. Statistical analyses were performed using SAS system for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA).

5 Results

5.1 Study I

Between April 2017 and December 2018, there was a total of 815 patients with confirmed acute appendicitis and out of these, 299 (37%) patients had blood culture samples taken. Of these 299 patients, 28 were excluded from this study for protocol violation: blood cultures taken after surgery (18/28), administration of antibiotics before blood culture (3/28), or recurrent appendicitis (7/28). After the exclusion there were 271 (33%) eligible patients for analysis. Included patients were divided according to blood culture results (positive, n=33 and negative, n=238). Patient demographics are shown in Table 9 and patients flow in Figure 8.

Of the patients with blood culture positivity (n=33), 24 patient (73%) were diagnosed with complicated acute appendicitis presenting as perforation, gangrene of the appendix, or periappendicular abscess and in addition five complicated appendicitis patients (15%) presented with an appendicolith without other signs of complicated appendicitis. Four patients (12%) were diagnosed with uncomplicated acute appendicitis. In the patient group with negative blood culture (n=238), 160 patient (67%) were diagnosed with complicated acute appendicitis, of which 34 patients presented with only appendicolith and no other signs of complicated acute appendicitis. 78 (33%) patients with blood culture negativity were diagnosed as uncomplicated acute appendicitis.

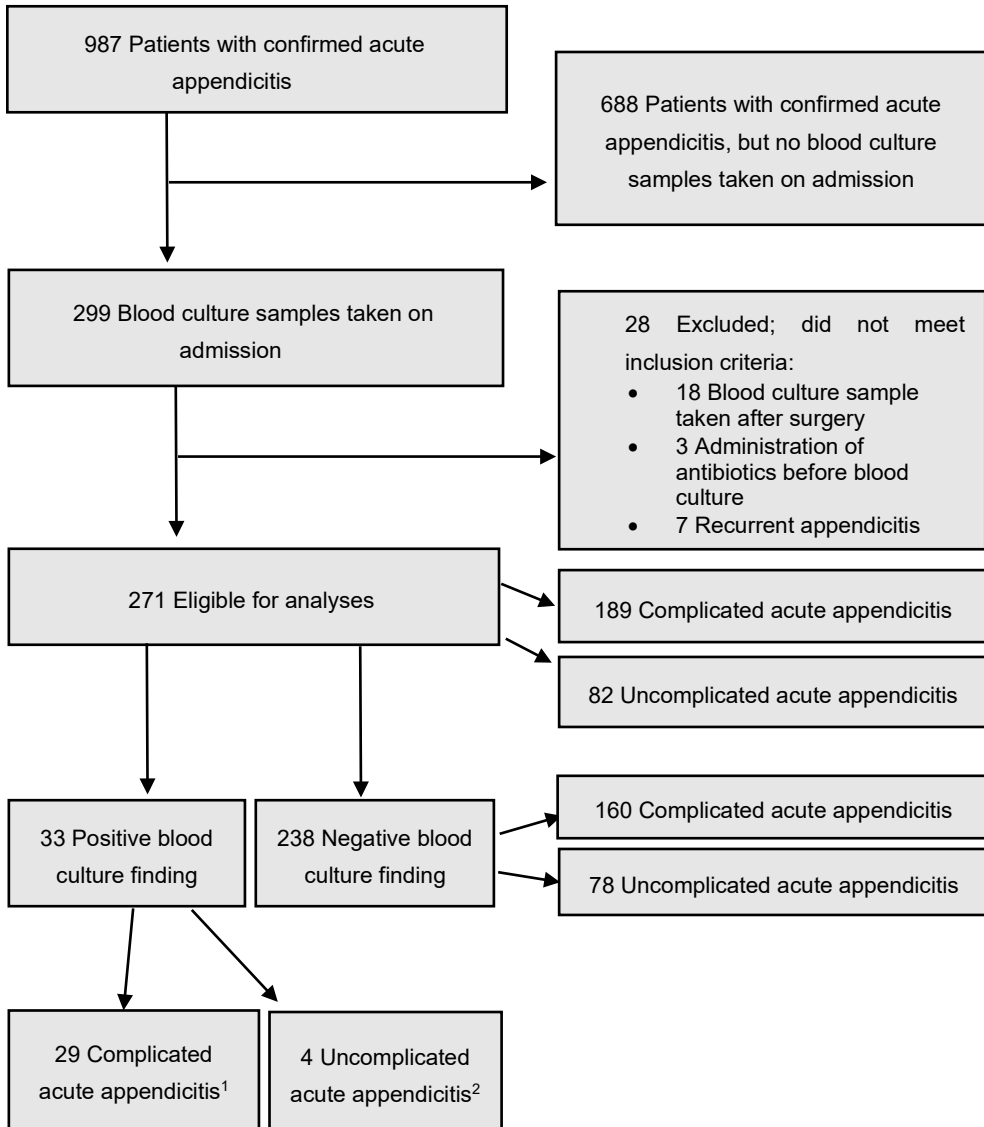
Blood culture positivity was significantly more frequent in patients with complicated acute appendicitis when compared to patients with uncomplicated acute appendicitis ($p=0.015$, Fisher's exact test). From all other measured characteristics only higher body temperature and male sex were associated with blood culture positivity in patients with acute appendicitis. Mean body temperature in blood culture positive group was 38.2°C (SD 0.9) and in blood culture negative group 37.8°C (SD 0.7) ($p=0.0044$). Out of the patients with blood culture positivity, 73% (24/33) were male and in patients without bacteremia, 50% (120/238) were male, ($p=0.024$).

Other measured characteristics had no association with blood culture positivity. These were mean BMI (kg/m^2) which was 27.7 (SD 4.7) in the group with blood culture positivity and 27.8 (SD 5.2) in the group with blood culture negativity

($p=0.87$). Median CRP was 58 (Q1:25; Q3:158) and 70 (Q1:27; Q3:137) ($p=0.76$), respectively. White blood cell count in blood culture positive group was 14.7 (Q1:9.8; Q3:18.0) and in blood culture negative group 13.8 (Q1:11.2; Q3:16.2) ($p=0.38$). Mean ages were 48 years (range, 20 to 69) and 45 years (range, 16 to 89) ($p=0.23$), respectively. In addition, the influence of comorbidities on blood culture positivity was analyzed. Medical reports of every patient were examined to see all conditions, of which those that could have impact on the patient's immune system were included. Included comorbidities were ulcerative colitis, Crohn's disease, diabetes, coronary heart disease, malignancy and given systemic immunosuppressive medicine for any reason: multiple sclerosis, Addison's disease, polymyalgia rheumatica and rheumatoid arthritis. Disorders like asthma, dementia, mental illness or hypertension were excluded. In blood culture positive group there were three (9%, 3/33) patients with significant comorbidities (two ulcerative colitis and one diabetes mellitus) and in the blood culture negative group there were 25 (10%, 25/240) patients with significant comorbidities. Comorbidities had no association with blood culture positivity in this study ($p=1.00$).

The prevalence of blood culture positivity, among 271 eligible patients with both confirmed appendicitis and available blood culture on admission, was 12 % (33/271). When the propensity score–matched prevalence of bacteremia was calculated from the large prospective patient cohort ($n = 815$), the assumed prevalence was 11.1%.

A total of 46 isolated bacteria in 33 episodes of blood bacteremia; 25 anaerobes, 13 gram-negative aerobes and 9 gram-positive aerobes. A total of 14 different bacteria were found in blood cultures. The most common bacteria were *Bacteroides fragilis* ($n=13$) and *Escherichia coli* ($n=12$).



¹All 29 patients were treated with appendectomy, and 2 patients received only preoperative dose of antibiotics. Appendicitis was considered complicated when presented with an appendicolith, perforation, periappendicular abscess, tumor, or clear intraoperative finding of gangrene supported by histopathology.

²Out of the 4 patients, 2 were treated with appendectomy and 2 were treated with antibiotics only.

Figure 8. Flow chart of study patients.

Table 9. Patient demographics and Baseline characteristics of the study I.

	Bacteraemia	No bacteraemia	Patients with available blood cultures
N	33	238	271
Complicated	29 (88 %)	160 (67 %)	189 (70 %)
Uncomplicated	4(12 %)	78 (33 %)	82 (30 %)
Sex, male	24 (73 %)	120 (50 %)	144 (53 %)
Sex, female	9 (27 %)	118 (50 %)	127 (47 %)
Age, years, mean (range)	48 (20–69)	45 (16–89)	45 (16–89)
BMI, kg/m², mean (sd)	27.7 (4.7)	27.9 (5.3)	27.8 (5.2)
Crp, mg/l, median (q1, q3)	65 (22, 158)	68 (25,144)	67 (25, 146)
WBCs, per µl, median (q1, q3)	13700 (9100,17700)	13800 (11100,16200)	13700 (11000,16400)
Temperature, °c, mean (sd)	38.2 (0.9)	37.8 (0.7)	37.8 (0.8)
Comorbidity (n)	3 (9 %)	25 (10 %)	28
Duration of symptoms (n)	32	237	269
Under 12 hours	4	49	53
12 to 24 hours	12	70	82
24 to 48 hours	10	47	57
Over 48 hours	6	71	77

5.2 Study II

A large patient cohort with suspected acute appendicitis (N=3512) in APPAC II and III trials was analyzed in this study. After exclusion of patients with no CT imaging, unverified diagnosis, or normal appendix, there were 3085 patients diagnosed with acute appendicitis for the analysis of this study. All CT statements were reviewed for appendicolith. After review, there were a total of 1101 (35.7%) patients with CT confirmed acute appendicitis and appendicolith, of which 519 (47.1% (95% CI 44.2% to 50.1%)) had complicated acute appendicitis. While in the 1984 patients with no appendicolith, 426 (21.5% (95% CI 19.7% to 23.3%)) had complicated appendicitis ($P < 0.001$). The study flow chart is presented in Figure 9.

There were 380 (35%) eligible patients with CT confirmed acute appendicitis, appendicolith, and CT images available for retrospective evaluation by abdominal radiologists in the main analysis of this study. All patients evaluated in Turku University Hospital (n=272) together with 114 patients from other six study hospitals had available CT images and were eligible for retrospective analyses. Patients with complicated acute appendicitis were older and had higher CRP (Table 10).

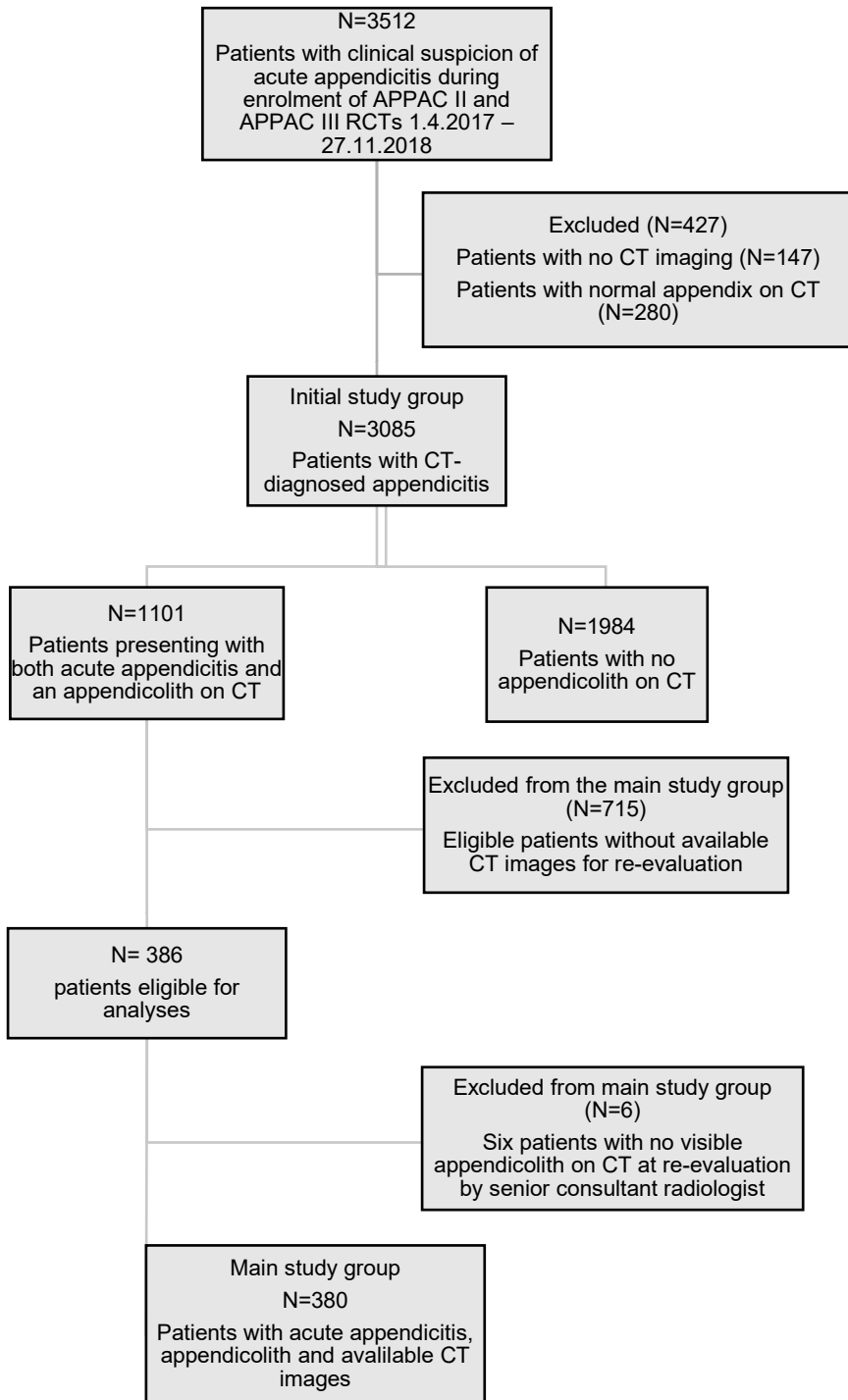


Figure 9. Flow chart of study population.

The wider diameter of appendicolith was associated with complicated acute appendicitis, even though cut of point could not be specified (OR 1.153; 95% CI 1.061–1.253). Also, the location of appendicolith in the base of appendix was associated with complicated acute appendicitis ($p=0.008$). Secondary variables were appendicolith-induced pressure and heterogeneous appendiceal wall enhancement around the appendicolith of which both were associated with complicated acute appendicitis ($p = 0.003$ and $p < 0.001$) (Table 11).

Table 10. Patient demographics and Baseline characteristics of the study II.

	N	N missing values	All	Appendicolith and complicated acute appendicitis	Appendicolith and uncomplicated acute appendicitis	P-value ⁴
Number n (%)	380	0	380	197 ¹ (51.8%)	183 (48.2%)	
Sex², male	226	0	226	115 (50.9%)	111 (49.1%)	
Sex², female	154	0	154	82 (53.2%)	72 (46.8%)	
Mean age, years (sd)	380	0	43,2 (17.0)	47,0 (17.6)	39.1 (15.4)	<0.0001
Median body mass index, kg/m2 (range)	372	8	26.1 (16.9–53.3)	26.1 (18.8–50.8)	26.1 (16.9–53.3)	0.82
Mean temperature, °C (sd)	364	16	37.6 (0.7)	37.8 (0.7)	37.4 (0.6)	<0.0001
Median wbcs*, x10⁹/l, (q1, q3)/(range)	380	0	14.1 (11.4,16.6)	14.3 (12.2–17.2)	13.6 (10.9–16.3)	0.013
Median crp#, mg/l (q1, q3)	380	0	37 (12, 111)	73 (25, 158)	18 (6, 47)	<0.0001
Median duration of symptoms to surgery³, hours, (q1, q3)	153	227	33.5 (20.7, 54.9)	37.6 (22.0, 62.3)	26.1 (17.8, 40.0)	<0.001

*WBC, White blood cell count #CRP, C-reactive protein

¹ Of these 197 patients with complicated acute appendicitis, there were 138 patients with gangrenous appendicitis, 29 with periappendicular abscess, 121 with perforation of appendix, and 7 with a tumour. The findings are not mutually exclusive, and one patient may have had several of the findings mentioned above.

² Sex of the patient had no association with complicated acute appendicitis ($p=0.64$; Chi-squared Test)

³ Duration of symptoms was counted from the first symptom onset (pain, nausea, vomiting) to surgery.

⁴ Logistic regression analysis

Table 11. Characteristics of intraluminal appendicoliths in patients with acute appendicitis.

	N	Missing information (N)	Appendicolith and complicated acute appendicitis	Appendicolith and uncomplicated acute appendicitis	P-value
Median length of appendicolith, mm (Q1, Q3)	380	0	9.0 (7.0, 12.0)	8.0 (6.0, 11.0)	0.767 ²
Median diameter of appendicolith, mm (Q1, Q3)	380	0	7.0 (5.0, 8.0)	6.0 (4.0, 7.0)	0.0008 ²
Location of appendicolith¹, n (%)	374	6	195 (52.1%)	179 (47.9%)	0.0076 ³
Base of appendix	287		158 (55.1%)	129 (44.9%)	
Middle part and Apex of appendix	81 (60 + 21)		31 (38.3)	50 (61.7%)	
Abdominal cavity	6		6 (100%)	0 (0%)	
Appendicolith causing pressure on the wall of the appendix, n (%)	276	13	155 (56.2%)	121 (43.8%)	0.0034 ³
Appendiceal wall enhancement defect around appendicolith, N (%)	212	6	145 (68.4%)	67 (31.6%)	<0.0001 ³

¹ Location of appendicolith was analysed in two groups comparing the location at the base of the appendix to a combined group of appendicoliths located at the middle, or in the apex of appendix; extraluminal appendicoliths located in the abdominal cavity were excluded.

² Logistic regression analyses ³ Chi-squared Test

5.3 Study III

Of the 3085 patients with CT confirmed acute appendicitis and available histopathological diagnosis of appendicitis, 1531 (49.6%) had complicated acute appendicitis, 1495 (48.5%) had uncomplicated acute appendicitis, and 59 (1.9%) had a normal appendix. Patient flow chart is presented in Figure 10 and patient demographics in table 12.

In the univariate analysis (Table 13), a larger appendix diameter was associated with increased likelihood of complicated acute appendicitis ($p < 0.001$) with no specified clear cut-off point. The area under the ROC curve was 0.713 (95%CI 0.695 to 0.731). Of the other assessed CT variables, appendiceal wall enhancement defect

($p < 0.001$), and accumulated fluid around the appendix ($p < 0.001$) were associated with complicated acute appendicitis. The appendiceal wall enhancement defect had an OR of 3.92 (95%CI 2.91 to 5.28) for complicated acute appendicitis.

In the multivariable analysis (Table 14) adjusted with baseline characteristics, larger appendiceal diameter was associated with complicated acute appendicitis ($p < 0.001$) and the OR for 1 mm increase in appendiceal diameter for complicated acute appendicitis was 1.27 (95%CI, 1.23 to 1.32). The appendiceal wall enhancement defect had an OR of 2.21 (95%CI, 1.35 to 3.16; $p < 0.001$) for complicated acute appendicitis. In this analysis, accumulated fluid around the appendix was not statistically significantly associated with complicated acute appendicitis ($p = 0.129$, OR 1.25 (95%CI, 0.94 to 1.67)).

For removing possible bias caused by appendicolith, known risk factor for complicated acute appendicitis, a subgroup analysis was conducted for 1965 patients with no appendicolith. Of these patients, 411 (21%) had complicated acute appendicitis, and 1495 (76%) had uncomplicated acute appendicitis, while 59 (3%) patients had normal appendix. Also, in this subgroup analysis the greater diameter of appendix ($p < 0.001$), heterogenous appendiceal wall enhancement ($p < 0.001$), accumulated fluid around the appendix ($p < 0.001$), and oedema around the appendix ($p = 0.044$) were all associated with complicated acute appendicitis.

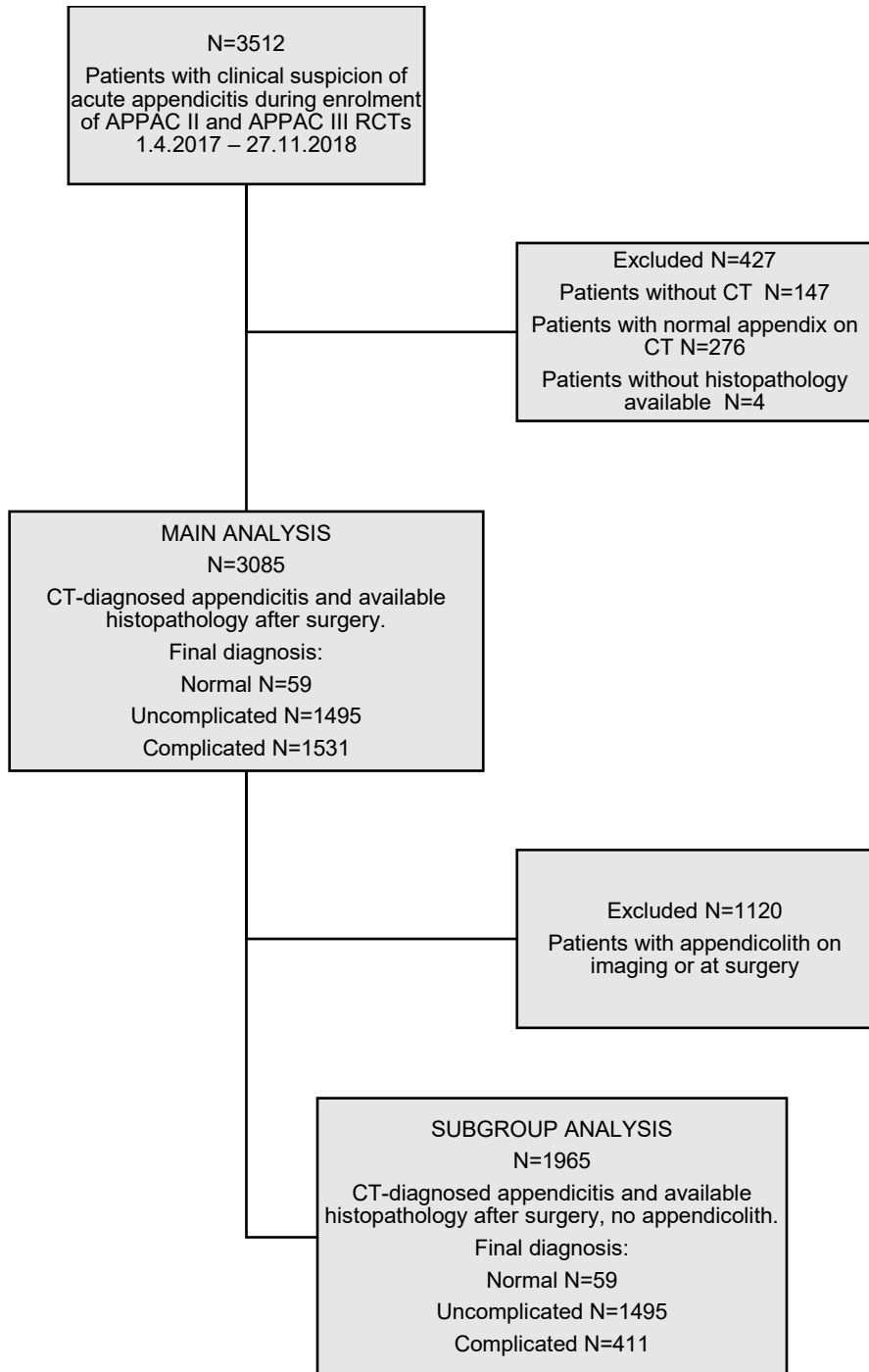


Figure 10. Flow chart of study patients.

Table 12. Patient Demographics and Baseline characteristics.

	N	N Missing	Complicated Appendicitis	Uncomplicated appendicitis	Normal appendix	All
N	3085	0	1531 (49.6%)	1495 (48.5%)	59 (1.9%)	3085
Sex, male	1636	0	854 (52.2%)	762 (44.6%)	20 (1.2%)	1636 (53.0%)
Median age, years (range)	3085	0	44 (16–95)	36 (16–92)	42 (19–77)	40 (16–95)
Median BMI¹, kg/m² (range)	2961	124	26.7 (16.5–60.5)	26.6 (16.6–62.2)	26.2 (19.3–46.5)	26.6 (16.5–62.2)
Median body temperature, °c (sd)	2839	246	37.6 (0,8)	37.2 (0,7)	37.2 (0,7)	37.5 (0,7)
Median WBCs², x10⁹/l, (range)	3076	9	13.7 (1.2–31.8)	12.2 (1.7–62.0)	10.8 (2.9–21.3)	12.9 (1.2–62.0)
Median CRP³, mg/l (range)	3072	13	48.0 (0.0–597.0)	32.0 (0.0–380.0)	61.5 (1.0–462.0)	39.0 (0.0–597.0)
Median appendix diameter, mm (range)	3012	73	13.0 (5.0–30.0)	11.0 (5.0–25.0)	8.5 (3.0–23.0)	12.0 (3.0–30.0)
Appendiceal wall enhancement defect	3085	0	208 (77.9%)	56 (21.0%)	3 (1.1%)	267
Accumulated fluid around the appendix	3085	0	218 (62.1%)	127 (36.2%)	6 (1.7%)	351
Oedema around the appendix	3085	0	923 (48.4%)	951 (49.9%)	33 (1.7%)	1907

¹ BMI, body mass index² WBC white blood cell count³ CRP, C-reactive protein

Table 13. Study results of univariate main analysis.

	Missing information (n)	Complicated appendicitis	Uncomplicated appendicitis*	P-value	Odds ratio, (95% confidence interval)
Patients (%)	0	1531 (49.6%)	1554 (50.4%)		
Median appendix diameter, mm (Q1, Q3)	73	13,0 (11,0–15,0)	11,0 (9,0–12,0)	<0.001 ¹	1.326 (1.287–1.367) ³
Appendiceal wall enhancement defect, n (%)	65	208/1511 (13.8%)	59/1509 (3.9%)	<0.001 ²	3.923 (2.910–5.288)
Accumulated fluid around the appendix, n (%)	0	218/1531 (14.2%)	133/1554 (8.6%)	<0.001 ²	1.774 (1.412–2.229)
Oedema around the appendix, n (%)	0	923/1531 (60.3%)	984/1554 (63.3%)	0.083 ²	0.879 (0.760–1.017)

¹Univariate logistic regression analysis

²Chi-Squared Test

³odds ratio for 1 mm increases in appendicolith diameter

*Patients were categorized into two groups either having complicated appendicitis or uncomplicated appendicitis/normal appendix

Table 14. Subgroup analysis of patients without appendicolith.

	Missing information (n)	Complicated appendicitis	Uncomplicated appendicitis*	P-value	Odds ratio, (95% confidence interval)
Patients (%)	0	411/1965 (20.9%)	1554/1965 (79.1%)		
Median appendix diameter, mm (Q1, Q3)	47	12.0 (11.0–14.0)	11.0 (9.0–12.0)	<0.001 ¹	1.265 (1.214–1318) ³
Appendiceal wall enhancement defect, n (%)	48	75/408 (18.4%)	59/1509 (3.9%)	<0.001 ²	5.651 (3.656–8.734)
Accumulated fluid around the appendix, n (%)	0	66/411 (16.1%)	133/1554 (8.6%)	<0.001 ²	2.044 (1.488–2.808)
Oedema around the appendix, n (%)	0	238/411 (57.9%)	984/1554 (63.3%)	0.0442	0.797 (0.639–0.994)

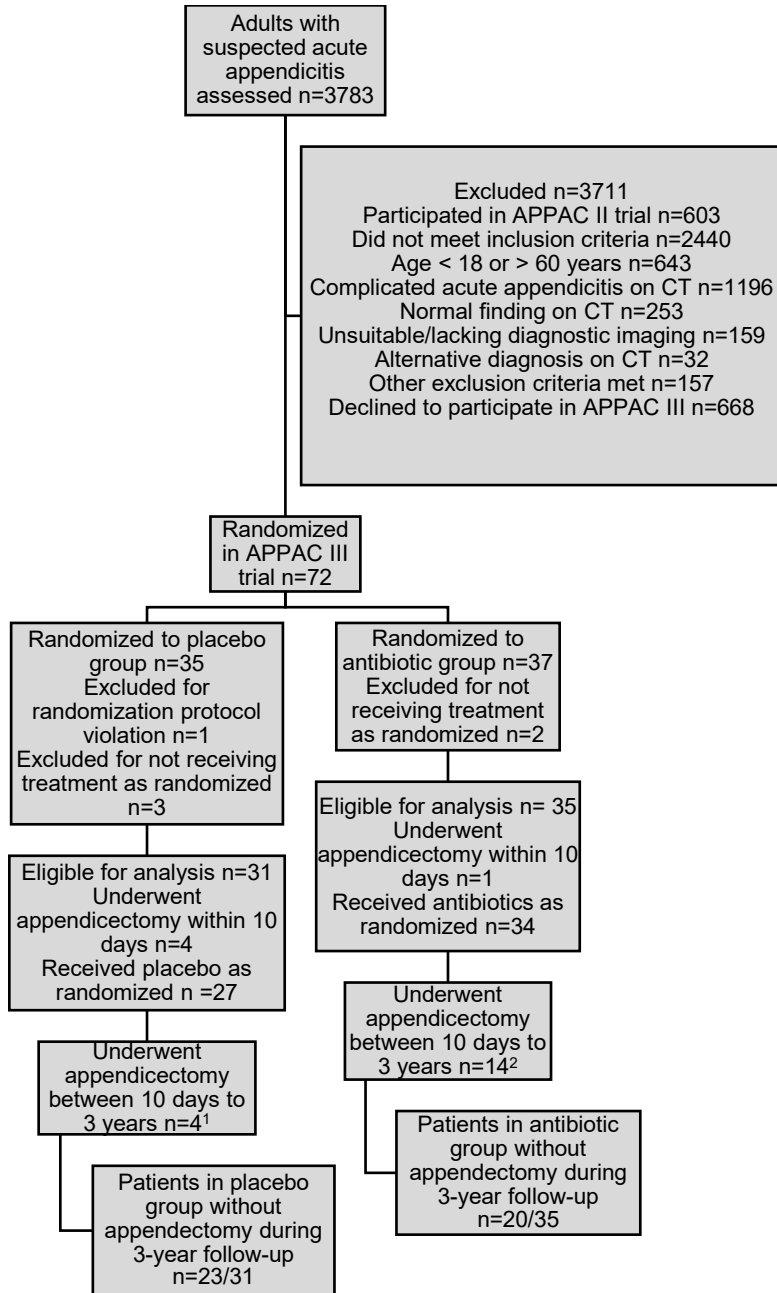
¹ Univariate logistic regression analysis² Chi-Squared Test³ Odds ratio for 1 mm increase in appendiceal diameter

5.4 Study IV

In APPAC III RCT, 72 patients, from 1 May 2017 to 21 September 2020, were assigned randomly to receive either placebo or antibiotic treatment. After randomization and exclusions, there were 66 eligible patients in the primary outcome analyses (35 in antibiotic group and 31 in placebo group). Of these 66 patients, 5 underwent appendectomy in 10 days (1 in antibiotic group and 4 in placebo group), leaving 61 eligible patients for 3 years follow-up. Study patient flow is shown in Figure 9. At 3 years, the appendectomy rate was 35% (23/66) with no difference between antibiotic and placebo groups [43% (15/35) vs. 26% (8/31), $p=0.957$]. The true appendicitis recurrence rate with acute appendicitis at histopathology was 28% (17/60) with no difference between antibiotics and placebo [39% (13/33) vs. 15% (4/27), $p=0.993$].

In the antibiotic group 14 patients were operated on between 10 days and 3 years. Of these patients, one had a normal appendix, one had perforated complicated acute appendicitis, and 12 patients had uncomplicated acute appendicitis. In the placebo group 4 patients with uncomplicated acute appendicitis were operated between 10 days and 3 years.

There were no differences in the length of sick leave 6 days vs 7 days ($p=0.504$), or hospital stay 56 hours vs 63 hours ($p=0.166$) between the groups. QOL data at 3 years was available for 70% (46/66) of patients with no difference in the total QOL EQ-5D-5L score between the groups ($p=0.275$). Most of the patients were satisfied with the treatment, of 46 patients answering questionnaire, 38 (83%) patients would have chosen the same treatment option despite the outcomes of the treatment choices (22/26 after antibiotics and 16/19 after placebo, $p=0.455$). A total of 8 (23%) patients treated with antibiotics reported a potential side effect related to antibiotics. Of the operated patients, there was only one reported complication. Table 15. shows the outcomes of the study.



¹ In the placebo group, 4 patients were operated on between 10 days and 3 years. All 4 patients had uncomplicated acute appendicitis based on surgery and histopathology.

² In the antibiotic group, 14 patients were operated on between 10 days and 3 years. Of these patients, one had a normal appendix, one had perforated complicated acute appendicitis, and 12 patients had uncomplicated acute appendicitis based on surgery and histopathology.

Figure 11. Study Flow chart.

Table 15. Outcomes of patients at 3-year follow-up of APPAC III RCT.

	Placebo group (n= 31)	Antibiotics group (n=35)	Difference between groups (percentage points, 90% CI)	P value
Appendectomy rate[#]				
10 d¹	4 (12.9%)	1 (2.8%)	10 (-0.9 to 21)-	0.142*
30 d	4 (12.9%)	1 (2.8%)	10 (-0.9 to 21)-	0.142*
1 y	6 (19.4%)	11 (31.4%)	-12 (-30 to 5)-	0.920*
3 y²	8 (25.8%)	15 (42.9%)	-17 (-36 to 2)	0.957*
Appendicitis recurrence rate³	4 (14.8%) excluded 4	13 (39.4%) excluded 2	-25 (-43 to -7)	0.993*
Side effects of treatment⁴	1 (3.2%)	8 (22.9%)		0.030 [□]
Median length of hospital stays at 3-year follow-up, h (q1, q3)	56 (50, 71)	63 (52, 92)		0.166 [#]
Median length of sick leave at 3-year follow-up, d (q1, q3)	6 (4, 11)	7 (4, 15)		0.504 [#]
Abdominal symptoms⁵	5 (16.1%)	13 (37.1%)		0.095 [□]

¹One-sided Fisher's exact test, [#]Wilcoxon Two-Sample test, [□] Two-sided Fisher's exact test

¹ Of the five patients that were operated within 10 days of randomization 2 had uncomplicated appendicitis, and 3 patients had complicated acute appendicitis (2 perforated, and 1 gangrenous) based on surgery and histopathological evaluation.

² Out of the 18 patients operated between 30 days and 3 years, there were 16 patients with uncomplicated acute appendicitis, 1 normal appendix, and 1 perforated complicated acute appendicitis based on surgery and histopathological evaluation.

³ Patients operated within 30 days (primary non-responsiveness) of randomization (regardless of the operative finding) and patients with initial successful conservative treatment operated for suspected recurrence within 3-year follow-up with a finding of normal appendix are excluded (n=6) from the true recurrence rate assessment but they were included in the appendectomy rate assessment.

⁴ 1 patient in placebo group had laparoscopic appendectomy 7 days after diagnosis, and a haematoma was reported in the incision area, which resolved without intervention. Histopathological diagnosis of appendix was uncomplicated acute appendicitis. 8 patients in antibiotic group reported medication side effects (5 diarrhoea, 1 tendinitis, 1 rash, 1 neurologic symptom, 1 yeast infection).

⁵ Abdominal symptoms reported at 3-year follow-up included abdominal pain (severe n=1, moderate/mild n=12) and bowel dysfunctions (n=5).

6 Discussion

6.1 Appendicitis severity, blood culture positivity and accuracy of CT for differential diagnosis of acute appendicitis

In this thesis, study I showed a significant difference in the prevalence of blood culture positivity between uncomplicated and complicated acute appendicitis. Furthermore, two studies evaluated CT findings in differentiating these two forms of acute appendicitis. Study II showed that the presence of appendicolith was associated with complicated acute appendicitis. Furthermore, the CT characteristics of appendicolith including larger appendicolith diameter and appendicolith location at the base of the appendix increased the risk of complicated acute appendicitis. Study III showed statistically significant CT characteristics associated with complicated acute appendicitis. In this study the wider diameter of the appendix and appendiceal wall enhancement defect were associated with complicated acute appendicitis. CT accuracy in the differential diagnosis of appendicitis severity has markedly improved in the last decades and its ability to distinguish between uncomplicated and complicated acute appendicitis has significantly shaped the management of acute appendicitis.¹⁵⁷ A meta-analysis including 11 studies, performed in 2019 showed that in detecting complicated appendicitis CT has a sensitivity of 78% and a specificity of 91%.^{85, 161}

As shown in meta-analysis made by Kim et al.⁹⁵ there are multiple CT features for differentiating complicated and uncomplicated appendicitis. In the APPAC II trial³³, a subgroup analysis showed an appendiceal diameter of ≥ 15 mm on pre-interventional CT been associated with a higher risk of non-responsiveness to antibiotic treatment. In study III the results were similar, even though a cut-off point could not be determined. In the study by Hong et al.⁹⁸, they found appendiceal wall enhancement defect to be associated with non-responsiveness to initial antibiotic therapy. Study III showed similar association of appendiceal wall enhancement defect to increase the risk of complicated acute appendicitis, but non-responsiveness was not evaluated in this study. In the large CODA trial¹⁷, the presence of an appendicolith was associated with higher risk for both appendectomy and higher complication rate compared to patients without an appendicolith. Study II results

were in concurrence with the CODA results as the presence of an appendicolith was associated with complicated acute appendicitis. Furthermore, study II addressed in more detail the characteristics of the appendicolith that might account for this association. Some studies have shown different cut-offs for appendicoliths diameter. For example, in the study by Kubota et al.¹⁰¹ they concluded that nonoperative management could be considered for patients with appendicoliths of 5 mm or smaller. In study II, the result was contradictory to this as even the smallest appendicoliths were associated with complicated acute appendicitis, and no cut-off point could be determined. All this data show that with imaging, acute appendicitis can be divided into uncomplicated and complicated acute appendicitis with fairly good accuracy prior to treatment decisions.

Study I showed that patients with complicated acute appendicitis had also risk for bacteremia. This furthermore highlights that pre-interventional diagnostics are in an important role when diagnosing and treating acute appendicitis. Although non-operative treatment has been deemed a feasible choice to manage uncomplicated acute appendicitis, standardized and unified criteria in interpreting CT findings and classifying appendicitis severity are still lacking. This is due to balancing between the two schools of thought regarding non-operative management: The first, emphasizing the importance of ruling out complicated acute appendicitis resulting in a very selected patient population thus optimizing the treatment success of non-operative treatment of uncomplicated acute appendicitis and the other perspective of aiming to expand the nonoperative treatment alternative to a larger patient population despite the risk of including some patients with a potentially higher risk of complicated acute appendicitis. The accuracy of differential diagnosis of acute appendicitis has become an utmost important factor in safe and optimized management of uncomplicated acute appendicitis.^{10, 13, 17, 31}

6.2 Long-term outcomes of nonoperative treatment of uncomplicated acute appendicitis

Data regarding long-term outcomes of nonoperative treatment for uncomplicated acute appendicitis is scarce. Study IV with the 3-year follow-up of the double-blind RCT showed that patients treated with antibiotics or placebo had similar results in QOL and treatment success, defined as resolution of appendicitis without appendectomy during the follow-up, and most patients were satisfied with the treatment they received even if they later underwent appendectomy for suspected recurrence. The overall recurrence rate of acute appendicitis was 28 % in three-year follow-up, with no difference between the antibiotic group 39 % versus placebo group 15 % and the majority of the recurrences were uncomplicated. These pilot results support the idea that antibiotics may not be necessary in the treatment of

uncomplicated acute appendicitis. To date and to our knowledge, the small set of patients in study III is the only one describing longer-term outcomes of patients treated with symptomatic care for uncomplicated acute appendicitis.

A few studies have reported long-term outcomes regarding antibiotic management of uncomplicated appendicitis. In 5-year follow-up of the APPAC study most recurrences occurred within the first two year after nonoperative treatment, and only few cases after two years of initial treatment.³² In the APPAC II three-year follow-up study results were similar, the treatment success at year 3 was 63.4% in the oral antibiotic monotherapy group and 65.2% in the combined i.v. and oral antibiotics group.³⁶ In these studies, recurrences were mostly uncomplicated and there were no increase in adverse events or complications after appendectomies in recurrence cases. Patkova et al.²⁶⁹ reported long-term registry-based outcomes of two RCT patient cohorts comparing antibiotic and operative management of uncomplicated acute appendicitis. Among patients treated with initial antibiotics, the rate of appendectomy was low after the first year and up to 20 years, 60% (82/137) of the patients were successfully treated without appendectomy. On the other hand, no appendiceal tumors were reported in the nonoperative patients who underwent appendectomy during follow-up, and 60% of the patients treated with antibiotics avoided surgery over 20 years.

From a health economics perspective, the lower cost of nonoperative treatment has been proven and warrant careful consideration when discussing different treatment options due to the global scarcity of the health care resources.^{38, 244} Even though study III did not evaluate treatment costs, similar population of APPAC study was evaluated for long-term treatment costs at 5 years establishing both similar treatment success and cost savings also at long-term follow-up.²⁴⁴ Presumably these results and cost savings could also be applicable in symptomatic therapy. Symptomatic management may be beneficial option also by its potential advantages in preserving the gut microbiome and reducing the contribution to global antibiotic resistance, as opposed to antibiotic-based treatment, if proven efficient and safe also in long-term results.

These long-term results indicate that nonoperative management is a safe and feasible option also in the long-term and should be considered every time when treating patients with uncomplicated acute appendicitis. Shared decision making with patient should also be made every time possible, when treating uncomplicated acute appendicitis.

6.3 Limitations of this study

There were several limitations regarding studies in this thesis. In study I the main limitation was that only 30 % of the study population had their blood culture taken

in the emergency department, which may cause bias in the results. However, we tried to overcome this limitation with propensity score matching. Second limitation is that, within this study population, male patients exhibited a higher risk of complicated appendicitis, which may partly explain the association between male sex and bacteremia. However, due to the limited sample size and the absence of blood culture data at admission for the entire study cohort, this association cannot be conclusively assessed in this study.

In study II, the main limitation was the unavailability of all CT images for reassessment. Because of this limitation, only 35 % (386/1101) of the study population could be assessed for appendicolith characteristics, which could cause selection bias. Secondly, there is some missing data, especially regarding the duration of symptoms, which is a clear limitation of this study.

In study III, the main limitation is the subjective and potentially radiologist dependent nature of some imaging features, which of course can never be completely eliminated. Secondly, the potential confounding effects of clinical parameters, such as fever and CRP cannot be overruled when assessing the independent risk factor nature of the CT findings for complicated acute appendicitis. The exclusion of patients treated non-operatively may also introduce selection bias. However, including only patients with a high accuracy reference standard of thoroughly assessed final clinical diagnosis taking into account imaging, surgical findings and histopathology is also a major strength of this study.

In study IV, the main limitation was the small number of patients. However, this was due to the pilot feasibility nature of the original APPAC III RCT.

Lastly, the patient cohort in these studies is selected and excludes for example patients over 60 years, children and pregnant individuals. Thus these findings may not be directly generalizable to other groups, such as elderly patients.

6.4 Future perspectives

In acute appendicitis, both the understanding regarding treatment options and the accuracy in pre-interventional diagnostics have increased with accelerating pace within the last 10 to 15 years. The first trials are limited by the lack of imaging^{35, 270, 271}, the following by open appendectomy¹⁰ or by broad-spectrum antibiotics or antibiotics outside the guidelines^{10, 16, 33, 39}. Another limitation is the variability of the inclusion criteria¹⁷, but this was recently mitigated by the IPDMA (Individual Patient Data Meta-Analysis)⁸⁴ using patient level data and uniform definitions. A major limitation is also the long hospital stay^{10, 16} as outpatient treatment appears to be safe³⁰⁰. All these issues have a major impact on the conclusions, and this is especially true for the cost analysis as patients with uncomplicated acute appendicitis may be treated with even symptomatic therapy and without hospitalization. In the earlier

trials of nonoperative treatment, patients were treated with a wide spectrum i.v. antibiotic courses and prolonged hospitalization to ensure patient safety. Diagnostic CT devices used higher doses of radiation with inferior accuracy and resolution compared to the current equipment. The major advances in diagnostics and treatment warrant swift implementation of up-to-date knowledge to clinical practice as current knowledge gaps are bridged by new trials.

As many studies and this thesis have shown, acute appendicitis has two different entities with different management options, both of which have their own advantages and disadvantages. Even though appendectomy is a safe procedure, it is still related to general risks of surgery and general anesthesia.²⁸¹ When considering the fact that many uncomplicated acute appendicitis cases may resolve without any specific treatment, the rationale for appendectomy for all appendicitis patients is unjustified. This issue is even more relevant today, as the accuracy and use of CT imaging have increased, and we are likely detecting milder forms of acute appendicitis that may previously have been managed with surveillance rather than surgery. For nonoperative treatment, most of the treatment complications and possible disadvantages are related to antibiotics.³⁹ If antibiotics are proven unnecessary in the treatment of uncomplicated acute appendicitis, these disadvantages can be ignored. In the future, the objective should not be to try to solve superiority between operative and non-operative management, but to see these two management choices as alternatives in different situations and tailor the best possible treatment paradigm for both the health care system and in specific cases for each individual patient with acute appendicitis. This, however, cannot be accomplished without accurate diagnostics and focus should be on identifying pre-interventional factors discriminating uncomplicated and complicated acute appendicitis.

If risk factors related to both non-responsiveness of antibiotic or symptomatic therapy and appendicitis recurrence could be identified, the treatment of acute appendicitis could be optimized for all patients and health care systems. Patients with complicated acute appendicitis and high risk for complications or non-responsiveness to nonoperative treatment could be treated with initial appendectomy, while patients with no risk factors and uncomplicated acute appendicitis could be treated with antibiotics or even symptomatic care and discharged from the emergency department. As CT is the most accurate modality in differentiating these entities, even more accurate and unified CT criteria for complicated acute appendicitis should be determined internationally. Nothing in medicine can be diagnosed or treated with absolute certainty, so ultimately every clinical decision and treatment choice involves balancing risks, guided by both the surgeon judgment and patient preference. Regardless of patient's or surgeon's preferences, the main objectives in the treatment of appendicitis should be to minimize unnecessary appendectomies, redundant antibiotic courses, excessive

costs of treatment, nonresponsiveness to nonoperative treatment, and recurrences of acute appendicitis.

Nevertheless, ongoing research is warranted to refine diagnostic thresholds—such as appendiceal diameter cutoffs and appendicolith relevance—and to validate low-dose CT protocols for broader clinical application, especially considering concerns about cumulative radiation exposure and its long-term risks. Also, the use and further assessment of the accuracy of US and MRI in appendicitis diagnostics should be kept in mind to minimize patient exposure to radiation when possible. In the future, objective scoring systems that integrate clinical findings and laboratory values with imaging modalities should be further evaluated regarding their potential to enhance differential diagnostics of acute appendicitis.

In diverticulitis it is shown that uncomplicated diverticulitis is its own entity and mostly patients having uncomplicated diverticulitis tend to have uncomplicated diverticulitis also in recurrent episodes^{301, 302}. If this same trend will be proven in the future with uncomplicated acute appendicitis, the diagnosis and treatment of uncomplicated acute appendicitis could follow the same path with uncomplicated acute diverticulitis, and patients with recurrent acute appendicitis might be treated with symptomatic care without routine CT images after the first episode.

For conclusion, after accurate pre-interventional diagnosis, patients with appendicitis should be offered unbiased information on different treatment options, including long-term results enabling a proper shared decision making. Hopefully, in the future symptomatic outpatient treatment choice will be the first line treatment in patients with uncomplicated acute appendicitis, as it is in uncomplicated acute diverticulitis.

7 Conclusions

Based on the findings of presented studies of this thesis, the following conclusions can be drawn:

1. The prevalence of blood culture positivity in patients with acute appendicitis was 15% in complicated acute appendicitis and 5% in uncomplicated acute appendicitis. Probability of having bacteremia in patients with acute appendicitis was associated with complicated acute appendicitis, male sex, and higher body temperature.
2. Among patients with acute appendicitis, the presence of an appendicolith is associated with an increased risk of complicated acute appendicitis compared to patients without an appendicolith. This risk is further increased by larger appendicolith diameter, and the appendicolith location at the base of the appendix.
3. Of the pre-interventional CT characteristics in patients with appendicitis, the wider appendiceal diameter was an independent risk factor of complicated acute appendicitis. Appendiceal wall enhancement defect was also associated with an increased risk of complicated acute appendicitis.
4. Based on a 3-year follow-up of patients with CT-diagnosed uncomplicated acute appendicitis within the APPAC III RCT, symptomatic treatment appeared to have similar treatment outcomes compared to antibiotic management. A larger noninferiority RCT is needed to confirm the safety and feasibility of symptomatic treatment alone for uncomplicated acute appendicitis.

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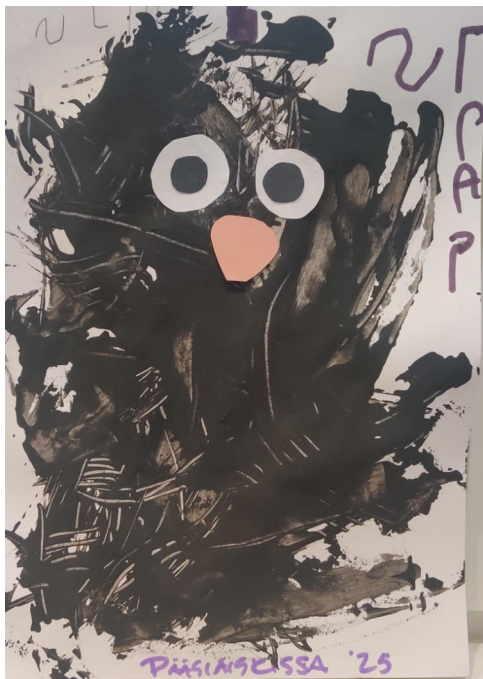


Figure 12. Easter Cat by Silja Sula 17.4.2025

September 2025
Sami Sula

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