Acute appendicitis occurs in approximately 10% of the general population. In this thesis, I found that the incidence of appendicitis has declined by almost 30% in Finland between 1987 and 2007. It is affected by improved diagnostic accuracy, seasonal variation of temperature, but not by the outpatient antibiotic use. To date, neither clinical findings nor laboratory tests have been able to distinguish reliably the patients with appendicitis from the patients with nonspecific abdominal pain.
Epidemiological and Clinical Studies of Acute Appendicitis
Epidemiological and Clinical Studies of Acute Appendicitis

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Mikpolisali of Mikkeli University of Applied Sciences, Patteristonkatu 2, Mikkeli, January 27th 2017, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 394

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Kuopio
2017
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ABSTRACT

Acute appendicitis (AA) and nonspecific abdominal pain (NSAP) are the two most frequent diagnoses for a patient with abdominal pain. AA has been recognized as a clinical entity for over 125 years. It is a microbiological inflammation of the appendix vermiformis with a clinically typical migration of mid-abdominal pain to the right lower part of abdomen. The incidence of AA differs significantly in the world, and has shown a declining trend in many countries during the last decades. Interestingly, the incidence is almost ten-fold lower in developing countries than that in the western world.

Three national register studies were utilized to investigate the incidence trends of AA in Finland, and to analyse the influence of some etiological parameters of AA. In the first investigation during a period of 21 years (1987 – 2007), the incidence of AA also declined in Finland. The decrease in the incidences of AA was most pronounced in age groups less than 30 years. At study time, diagnostic accuracy improved.

The possible influence of seasonality on the incidence of the AA was studied in a second investigation. The mean annual temperature, but not relative humidity, showed clear geographical variations. The incidence of AA decreased significantly during the cold months of the year. Additionally, there was a correlation between humidity and the incidence of NSAP. Temperature had no impact on the incidence of NSAP.

To investigate whether antibiotic use has an effect on incidence of the AA, a third study was performed. Although an evident decrease in the incidence of AA was detected during the study period, the total outpatient use of antibiotics did not increase during the same period. No correlation was found between the incidence of AA and the use of different groups of antibiotics.

Classically, the diagnosis of AA has been based on clinical examination and laboratory findings. During the last decades, diagnosis has increasingly been based on imaging studies. CT has become the gold standard imaging modality for suspected AA with a high sensitivity and positive predictive value. A final study was performed to evaluate whether patients with clinically suspected AA, but a negative CT scan, had different clinical or laboratory characteristics from patients with a positive CT finding for acute appendicitis. Patients with AA had a significantly higher white blood cell (WBC) level that those without AA, but the CRP level did not differ between the two groups. If both WBC count and CRP was normal, AA was very unlikely. According to receiver-operating curves (ROC), there were no markers, combination of markers, or any clinical characteristic that could accurately differentiate between patients with AA and those without.

Finally, the incidence of the AA is decreasing in Finland. It is influenced by temperature differences, but not by humidity or increased use of outpatient oral antibiotics. Both clinical findings and laboratory tests are unable to reliably distinguish between patients with AA
and those without. The current results emphasize the role of CT imaging in patients with suspected AA.

National Library of Medicine Classification: WI 535, WI 147, WH 20, WN 206, QV 350, QT 160, QT 162.H8,
Medical Subject Headings: Appendicitis; Appendix; Acute Disease; Appendectomy; Abdominal Pain; Incidence; Seasons; Temperature; Humidity; Anti-Bacterial Agents/therapeutic use; Tomography, X-Ray Computed; Leukocyte Count; Leukocytes; Clinical Laboratory Techniques; Follow-Up Studies
TIIVISTELMÄ

Akuutti appendisiitti ja epäspesifi vatsakipu ovat kaksi yleisintä diagnoosia vatsakipuisella potilaalla.

Akuutti appendisiitti on tunnettu 125 vuotta. Kyseessä on umpilisäkkeen bakteeritulehdus, jossa tyypillisesti keskivatsan kipu siirtyy oikealle alavatsalle. Taudin esiintyvyys vaihtelee eri maissa ja on tutkimuksen perusteella viime vuosikymmenen aikoina ollut laskusuuntainen. Taudin esiintyvyys kehitysmaille on yllättäen jopa kymmenen kertaa pienempi, kuin länsimaisissa.


Avohoidon antibioottien käytön vaikutusta appendisiitin esiintyvyyteen tutkittiin kolmannessa osatyössä. Yllättäen antibioottien käyttö ei tutkimusaikana nousut vaikka selvä laskeva trendi appendisiitin insidenssissä todettiinkin. Appendisiitin ja eri antibioottiryhmien välillä ei todettu minkäänlaista korrelaatiota.


Umpilisäkseen tulehdusdiagnostiikan insidenssi on laskenut Suomessa. Appendisiitin insidenssiin vaikuttavat lämpötilan muutokset, mutta ei suhteellisen kosteus eikä antibioottien käyttö. Klinisillä testeillä tai laboratorioparametreillä ei pystytä erottamaan appendisiittipotilaat muista vatsakipuisista potilaista. Tutkimus suositaa CT-tutkimusta potilaalle, jolla epäillään akuuttia umpilisäkseen tulehdusta.

Luokitus: WI 535, WI 147, WH 20, WN 206, QV 350, QT 160, QT 162,H8, Yleinen Suomalainen asiasanasto: umpilisäkkeetulehdus; leikkaushoito; vatsa; kipu; ilmaantuvuus; ilmasto; lämpötila; lääkehoito; antibiootit; diagnoosi; tietokonetomografia; seurantatutkimukset
Acknowledgements

The work of this thesis was conducted at the Department of Gastrointestinal Surgery, University of Eastern Finland in collaboration with the Department of Gastrointestinal Surgery, University of Turku in 2006-2016.

First, I am very thankful to my principal supervisor Professor Hannu Paajanen, M.D., Ph.D. for his enormous scientific enthusiasm. His invaluable ideas, and approach to simplifying the most challenging problems made it possible for me to complete this thesis.

I wish to express my deepest gratitude to Docent Pekka Miettinen, M.D., Ph.D. who inspired me to start this thesis. I am very grateful for his continuous professional guidance and his constructive criticism during this work. I appreciate his patience in teaching me scientific thinking and writing, and for his outstanding philosophical thoughts about medicine and life in general.

I want to express my gratitude to Professor Karl-Heinz Herzig, M.D., Ph.D. for his practical advice and guidance in early phases of the study.

My warm thanks to all my co-authors: Anne Fagerström M.D., and Docent Petri Juvonen M.D. Ph.D. for their support and practical advice; Professor Pentti Huovinen M.D., D.Sci., Jarkko Alajääski D.Sc.(Tech.), M.Sc., Lic.Sc. (Math.) and Jenny Alajääski M.D for their help in collecting data, and for their valuable advice regarding statistical analysis, which was necessary for the successful writing of article III.

Especially I want to express my appreciation to my co-authors from Turku Professor Juha Grönroos, M.D., Ph.D., Docent Paulina Salminen M.D., Ph.D., Elina Liezen, M.D. and all co-authors from the APPAC-study for their kindly help in writing paper IV.

I am very grateful to Tapani Liukkonen M.D., Ph.D. for his support and exhortation to complete this study.

I am deeply grateful to Marja-Leena Hannila, Hanna Wiksten, and Tomi-Pekka Tuomainen for their indispensable help and advice concerning statistical analysis throughout this thesis.

I wish to express my deepest thanks to the official referees of this thesis, Professor Jyrki Mäkelä, M.D., Ph.D. form Oulu and Docent Markku Luostarinen M.D., Ph.D. from Lahti for careful reviews and valuable and constructive advice for preparing this study.

My warmest thanks to my parents, Aime and Alari, for their love, encouragement and belief in me. Also I like to give a big warm hug to both of my sisters Helen and Evelyn, with whom I have spent many happy moments.

Finally, I want to give my deepest gratitude to my family: my beloved wife Tiina and my children Ingrid and Anders for their love. Their support has been irreplaceable to me, giving me strength and inspiration to complete this thesis.

Mikkeli, January 2017

Imre Ilves
List of the original publications

This dissertation is based on the following original publications:


* These authors contributed equally to this work

The publications were adapted with the permission of the copyright owners.
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<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>acute appendicitis</td>
</tr>
<tr>
<td>AD</td>
<td>acute diverticulitis</td>
</tr>
<tr>
<td>AE</td>
<td>appendectomy</td>
</tr>
<tr>
<td>AUC</td>
<td>area under curve</td>
</tr>
<tr>
<td>APPAC</td>
<td>Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis. The APPAC Randomized Clinical Trial.</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DDD</td>
<td>defined daily dose</td>
</tr>
<tr>
<td>IA</td>
<td>interval appendectomy</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>J01A</td>
<td>tetracyclines</td>
</tr>
<tr>
<td>J01C</td>
<td>beta-lactam antibacterials, penicillins</td>
</tr>
<tr>
<td>J01D</td>
<td>other beta-lactames, cephalosporins</td>
</tr>
<tr>
<td>J01E</td>
<td>sulfonamides, trimethoprim</td>
</tr>
<tr>
<td>J01F</td>
<td>macrolides, lincosamides, streptogramins</td>
</tr>
<tr>
<td>J01M</td>
<td>quinolones</td>
</tr>
<tr>
<td>LA</td>
<td>laparoscopic appendectomy</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>NSAP</td>
<td>non-specific abdominal pain</td>
</tr>
<tr>
<td>OA</td>
<td>open appendectomy</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RLQP</td>
<td>right lower quadrant pain</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>UHD</td>
<td>university hospital districts</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>US</td>
<td>ultrasonography</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale (pain score system)</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cells</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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1 Introduction

Acute abdominal pain is a daily challenge for a physician dealing with hospital emergencies. The spectrum of diseases causing acute abdominal problems is large and varied between the different specialities of medicine. In 13-35% of cases – even up to 70% in a paediatric population, a specific reason could not be confirmed and the diagnosis is non-specific abdominal pain (NSAP) (1-4). It is crucial for the physician on duty to distinguish patients with an acute abdomen and the need for prompt surgical care.

Acute appendicitis (AA) is still one of the most common reasons for right lower quadrant pain (RLQP) (2,4-6). The diagnosis of AA has traditionally been made mainly according to patient history and clinical signs. Typically, blunt central abdominal pain followed by vomiting and migration of the pain to the right iliac fossa is present. Because of variation in anatomical location of the appendix in the abdominal cavity and the degree of the inflammation process, clinical signs and symptoms can simulate other abdominal or pelvic diseases, and appendicitis is defined as atypical appendicitis (20-30%) (7,8). In these cases diagnosis of AA can be challenging and can cause delay in treatment. Imaging studies, such as computed tomography (CT) or ultrasonography (US) may be as useful tools for not only making a positive diagnosis of AA but also for ruling out other intra-abdominal pathology.

The etiology of the appendicitis is not clearly known and is supposed to be multifactorial. The mostly accepted theory is that AA is caused by obstruction of the lumen of the appendix (fecoliths, lymphoid hyperplasia, parasites, tumors etc.) (9). This leads to faecal stasis and to rising intraluminal pressure with mucosal ischemia and invasion of the bacteria into the appendiceal wall. For over 125 years, AA has been an emergent abdominal condition that requires immediate diagnosis and prompt operation to prevent perforation or other complications. Nevertheless, it is also known that perforated and non-perforated appendicitis are separate entities (10), and not all cases lead to perforation. Furthermore, resolution of appendicitis without surgical intervention has been reported to be possible (7,11).

The lifetime risk of developing AA is approximately 7%, and about 13-17% of abdominal pain patients have AA (12,13). The incidence of AA has a large geographical disparity, but does not differ significantly among Scandinavian countries (7,14,15). Nevertheless, the incidence rate in developing countries is almost tenth than that in developed countries (16,17). Reasons for the geographical variety of AA have been a topic of debate. A differential diagnosis on clinical grounds between AA and NSAP can be challenging for even the most experienced surgeon. Many patients with NSAP are referred with a possible diagnosis of AA, and a number of these may erroneously undergo operation. Surgical exploration for suspected appendicitis is one of the most common acute abdominal operations in the world. There are few studies about the epidemiological variables of the appendicitis and of NSAP in Finland.
2 Review of the Literature

2.1 ANATOMY AND PHYSIOLOGY OF THE VERMIFORM APPENDIX

Embryologically, the vermiform appendix develops from the midgut (18). It is a 2-20 cm long blind-ended diverticulum arising from the posteromedial side of the caecum, 1.7-2.5 cm below the terminal part of the ileocaecal junction. The position of the vermiform appendix is not consistent and this can be explained by the development and growth of the ascending colon and cecum. Two of the most frequent positions of an appendix are retrocaecal (40%) followed by pelvic (35%), paracolic (6%), and a pre- or post-ileal (16%) position. It is possible, that the final reposition of the appendix into the retrocaecal region occurs during the growth period due to helicoidal torsion of the caecum (Figure 1). This can explain the more common position of an appendix in the pelvic region in foetuses and infants. The blood circulation of the appendix arises from the ileocaecal artery. In many patients, there is in addition an accessory appendicular branch from the posterior caecal artery that supplies the base of the appendix at its junction with the caecum (19-22). While placement of the distal part of the appendix varies, the base of the appendix to the caecum is constant and is situated approximately one-third the distance from the right anterior superior iliac spine to the umbilicus, which is known as MyBurney’s point. The final location of the appendix is determined by the location of the caecum, and can vary in cases of malrotation or maldescent of the caecum (20). In addition, the gradual upward displacement of the caecum and appendix has been seen during the course of pregnancy due to the gravid uterus (23).

Figure 1. Various locations in which the tip of the appendix can be found.

The physiological function of the appendix is not clearly understood. The lumen of the appendix is lined by colonic epithelium. The appendix contains an abundance of lymph follicles in the submucosa – gut-associated lymphoid tissue. The amount of lymphoid follicles gradually increases in number from birth to a peak of approximately 200 follicles between the ages of 12 and 20 (20,24). The amount of nodes decline over the years and are totally absent after age 60. It has been suggested that this has a role in the human immune
system and support for the growth of beneficial or commensal bacteria in the gut. Moreover, biofilms have been found on the epithelial lining of the mucosal epithelium of the appendices. The concentration of biofilms was found to be higher in the appendix than in any other area of the intestine (25). The structure of the appendix is expected to enhance the protective effect of biofilm formation for commensal bacteria. Further, it has been proposed that such biofilm formation in the appendix not only enhances survival of normal enteric bacteria, but also avoids the adherence of the pathogenic organisms within the large bowel surface (25,26).

2.2 HISTORY

Leonardo Da Vinci demonstrated the appendix in his drawings in 1492. Later, Vesalius and DaCarpi made the first descriptions of appendix in the 16th century (27,28). At the beginning of the 18th century, Lorenz Heister speculated that the appendix might be the reason for inflammation in the right lower region of the abdomen. The first known appendectomy (AE) was done by Claudius Amyand who operated on an 11-year old boy with a right scrotal hernia and perforated appendix in the hernia sac (28). Nevertheless, AE was not a routine treatment before the development of general anesthesia. After two crucial developments in the history of surgery in the mid-1800s, nitrous oxide and chloroform anesthesia, abdominal operations become more tolerable and safe. In 1886, Reginald Herber Fitz presented a paper entitled "Perforating Inflammation of the Vermiform Appendix: With Special Reference to Its Early Diagnosis and Treatment". He deduced the sequence leading from acute inflammation of the appendix to peritonitis and other complications of appendicitis. He emphasized the importance of an accurate diagnosis and early removal of an inflamed appendix, previously known as typhilitis, before perforation occurs (29). In 1891, McBurney in his paper also emphasized the importance of early AE, and first described the muscle-splitting incision that bears his name and which is commonly used today (30). Since the end of the 19th century AE has become one of the frequent operations in a clinical practice. An enormous number of books and articles about the management of AA have been published since that period (28). In Pubmed, there were over 20,000 articles cited in September 2016.

Kurt Semm did the first laparoscopic AE in 1983 (31). He concluded that a laparoscopic technique provides faster recovery, a smaller infection complication rate and a better cosmetic result after the operation (31). Moreover, spontaneous resolution and conservative treatment of AA has been a subject of debate (32). In 1956, Coldrey et al. reported on antibiotic treatment of AA (33). Recently, several studies have been published about non-operative treatment of AA (34-36).

2.3 ETIOLOGY AND PATHOPHYSIOLOGY

For a disease that is prevalent, there is actually surprisingly little knowledge about its etiologic factors. Because of its shape and the size of the lumen the appendix is predisposed to obstruction. There are many different reasons that can participate in development of the disease.

2.3.1 Mechanical obstruction

Obstruction of the appendix may result from a variety of causes – fecolith, lymphoid hyperplasia, primary and metastatic tumors, parasites, and foreign bodies. In addition, faecal stasis might play a role in the development of AA (37). Once obstruction occurs, continuous mucus secretion leads to increased intraluminal pressure and mural edema. The patient complains of a vague and diffuse pain that is poorly localized and produced by stimulation of autonomic visceral afferent pain fibres. If the occlusion continues, the intraluminal pressure eventually exceeds capillary perfusion pressure, which leads to
venous engorgement, and this can threaten the viability of the appendiceal wall and lead to ischemia (9,28). With the ischaemic changes in the wall and compromise of the mucosal defensive system, microbes invade into the appendiceal wall leading to infection. Pain migration more closely to the appendix is a classical symptom at this stage and is related to the development of peritoneal pain, which is conducted through spinothalamic fibres to the brain. The presence of a normal functioning appendiceal mucosa is required for fluid secretion and development of the histologic picture of AA. Appendices possessing atrophic mucosa fail to exhibit evidence of fluid secretion and thereby do not develop appendicitis (38).

2.3.1.1 Fecoliths

Fecolith has been regarded as one of the most usual causative agents in mechanical obstruction. The incidence of fecolith is 11-52% in patients operated on for AA (9,39,40).

Nevertheless, fecoliths are also present in a non-inflamed appendix in 32% of cases of white people and 4% in African people. In a same study, the incidence of fecolith in an AA case was 52% and 23% in white and African blacks, respectively (41). Ramdass et al. showed that the incidence of fecolith is almost the same in an inflamed as well as in a non-inflamed appendix (42). In a study from the China the incidence of the fecolith was 9,6% in normal appendices (43). After the occlusion occurs, appendiceal intraluminal high pressure might turn obstructing material back into the caecum and evidence for a proper cause of appendicitis is missing (28). Consequently, it is possible that the real incidence of fecoliths in cases of AA is much higher.

2.3.1.2 Lymphoid hyperplasia

Lymphoid hyperplasia can develop due to an immune reaction to immunological challenges (also called lymphadenitis), mostly viruses, and can occur anywhere in the bowel, but it is often seen in the terminal ileum and appendix (44). This can cause AA, obstruction, or be the reason for chronic right lower quadrant pain (RLQP) (45,46). The significant increase in lymphoid follicles in young adults and their gradual disappearance with age suggests a pathogenic role for lymphoid tissue in the development of appendicitis (28,47,48). However, lymphoid hyperplasia without any infection can be found from a histopathologically normal appendix as well (43,46).

2.3.1.3 Tumors

Primary tumors of the appendix are a relatively rare cause of AA. An incidence of appendiceal tumors varies between the 0,4-1,7% for all appendectomies (49-53). A minority of appendiceal tumors has been diagnosed preoperatively, and in most cases diagnosis has been done intra-operatively or by a pathologist (50,54).

Carcinoid tumor is the most common primary appendiceal neoplasm. The overall incidence of appendiceal carcinoid tumors varies from 0,4% to 1% (Table 1). Within the gastrointestinal tract, the occurrence of carcinoid tumor of the appendix is 16,7% (55), and it accounts for up to two thirds of all appendiceal tumors (49,50,54,56,57). Primary adenocarcinoma of the appendix is rare with an incidence of 0.08-0.2% of all appendectomies, and accounts for 4-6% of primary malignant appendiceal neoplasms (51). The malignancy risk for patients undergoing interval appendectomy (IA) after conservative treatment of complicated appendicitis has been found to be 28-29% (58,59).

Mucocele of the appendix is characterised by dilatation of the obstructed appendicular lumen by mucinous secretions. It is encountered in 0.1-0.4% of all appendectomies with a female predominance (60,61). The etiology can be either benign (simple mucocele or retention cyst, mucosal hyperplasia, mucinous cystadenoma), or malignant (mucinous cystadenocarcinoma) (62). Of all mucoceles, 23-50% are incidental findings at surgery and should be carefully removed to prevent perforation, peritoneal contamination and the
development of pseudomyxoma peritonei (60). The extent of resection depends on histology of the mucocele (61).

**Table 1. Neoplasias of the appendix vermiformis.**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>No. of cases</th>
<th>Carcinoid</th>
<th>Benign</th>
<th>Adeno-Ca</th>
<th>Mucinous adeno-ca</th>
<th>Other malign.</th>
<th>Total</th>
<th>Comments</th>
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<td>1976</td>
<td>4107</td>
<td>30 (0,7)</td>
<td>5 (0,12)</td>
<td>3 (0,07)</td>
<td>40 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al (43)</td>
<td>1987</td>
<td>12513</td>
<td>11 (0,09)</td>
<td>50 (0,4)</td>
<td>7 (0,06)</td>
<td>42 (0,3)</td>
<td>85 (0,7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bucher et al (50)</td>
<td>2004</td>
<td>2500</td>
<td>23 (0,92)</td>
<td>12 (0,5)</td>
<td>3 (0,12)</td>
<td>14 (0,56)</td>
<td>43 (1,7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tchana-Sato et al (63)</td>
<td>2006</td>
<td>1237</td>
<td>5 (0,4)</td>
<td></td>
<td></td>
<td>Only carcinoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Donnell et al (51)</td>
<td>2007</td>
<td>2154</td>
<td>9 (0,4)</td>
<td>4 (0,2)</td>
<td>5 (0,2)</td>
<td>22 (1)</td>
<td></td>
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<td>Smeenk et al (52)</td>
<td>2008</td>
<td>167744</td>
<td>1248 (0,7)</td>
<td>211 (0,13)</td>
<td>153 (0,9)</td>
<td>1482 (0,9)</td>
<td>No carcinoids incl.</td>
<td></td>
<td></td>
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<tr>
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<td>2011</td>
<td>7767</td>
<td>44 (0,57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Carpenter et al (59)</td>
<td>2012</td>
<td>291</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td>8 (2,5)</td>
<td>Immediate op.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>18</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>2 (11)</td>
<td>1 (6)</td>
<td>(28)</td>
<td>Interval op.</td>
<td></td>
</tr>
<tr>
<td>Furman et al (58)</td>
<td>2013</td>
<td>376</td>
<td>2 (0,5)</td>
<td>3 (0,8)</td>
<td>6 (1,6)</td>
<td>3 (0,8)</td>
<td>14 (3,7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yilmaz et al (54)</td>
<td>2013</td>
<td>1621</td>
<td>6 (0,4)</td>
<td>8 (0,5)</td>
<td>3 (0,19)</td>
<td>1 (0,06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozcelik et al (56)</td>
<td>2015</td>
<td>975</td>
<td>9 (0,9)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Infection

Specific infections with viruses, bacteria and parasites have been linked to appendixitis. There are studies evaluating the role of viral etiology of appendicitis (64,65). Moreover, seasonal outbreaks of lymphotropic enteric viral or microbial infections might be the reason for a seasonal variation in AA. Although some evidence has been found (66), the level of proof is weak and further studies are needed to confirm the connection.

The role of microbes as a non-pathogenic factor inside the appendix has been found. Poole et al. isolated Streptococcus Milleri and other bacteria from both histologically normal and inflamed appendices. The incidence of enterococci was even less in appendixitis (37%) than in normal appendix (55%) (67). Bacteria can exist in the appendix in a sessile state, for example as a biofilm (25,26). It is suggested that microbes in the appendix play an important role in host immunological defence by providing a barrier to invasion by pathogenic microbes (26). Tubercular appendixitis is quite a rare entity and found mostly in developing countries, and in most cases the appendix is involved by local extension of ileocaecal or genital tuberculosis (43,68,69). Overall, one can conclude that bacteria from the
appendix may be important pathogens in appendicitis and its complications, but their initial role in the etiology of AA remains uncertain.

Parasitic infection of appendix is quite rare. This can be found everywhere in the world, but mostly in tropical countries. Different parasites are found in histopathological evaluation of appendix. Most common helminth Enterobius vermicularis or pinworms occur mostly in Southern Europe, and can be found in 4-28% of children worldwide followed by amoebae, ascaris, trichuris, and taeniae (69,70). In a study from South Africa, parasitic infection was found in an 8.6% of cases with AA (71). A majority of studies report a lower incidence of inflammatory changes, or chronic infection of appendix, in patients with appendiceal pinworms (70,72). Currently, the true role of parasites as a cause of AA has been controversial. They are found in uninflamed and histologically normal appendices, and their role in the pathogenesis of AA is unclear.

2.3.3 Dietary and hygiene habits

There are two main theories that attempt to explain the difference in the incidence of AA between countries. First – a hypothesis about high dietary fibre intake; second – a hygienic hypothesis (73,74). Appendicitis is more common in urban, industrialized societies and relatively rare in developing countries where a less-refined, high-fibre diet is typically consumed. The etiologic significance of a highly refined, low-fibre diet is not clear, but a striking variation in geographic distribution strongly suggests a dietary role in the etiology of appendicitis (75,76). It has been presumed that the diet in industrialized countries leads to a hard stool, higher intracolonic pressure, and the formation of fecolith. A study from Denmark shows no significant correlation between the long transit time in the colon or faecal load and appendicitis (77). The evidence for an association between appendicitis and dietary fibre rests on comparisons, which show that fibre consumption is high in certain countries where appendicitis is uncommon (75). Barker and Morris found in their study that appendicitis might be connected to dietary habits (73,78). They concluded that the incidence of AA was lower in areas where the consumption of non-potato vegetables, in particular green vegetables and tomatoes, and of fruit were higher. They hypothesised that cereal fibre protects against appendicitis (73,78).

In comparison, within recent years with urbanization and increasing prosperity, the energy intake of Africans has risen and fat intake has increased considerably. At the same time, their fibre intake has fallen to level that is the same or even lower than that in many western populations, but the incidence rates of AA have remaind unchanged (79-81). In addition, the incidence of the AA was as high as 227/100'000 inhabitants during the study time of 2005-2007 years in Korea, where food has a high fibre content (82). Clearly, in such a context, the level of fibre intake no longer correlates with the very low occurrence of the disease: since with a similar low fibre intake, the disease remains very infrequent in urban Africans, but is common and variable in white populations in developed countries (17,82). In the 1980s Barker et al. advanced a hygiene hypothesis, attributing the rise in appendicitis to improvements in water supplies and sewage disposal in Britain (78,83). They hypothesised that these improvements greatly reduced the exposure of infants to enteric organisms, which in turn altered children’s response to later virus infections, such that they now triggered appendicitis. The virus did this by causing appendiceal lymphoid hyperplasia, which occluded the appendix leading to microbial infection (78,83). In sum, there is no current consensus about the strong evidence between hygiene and the incidence of AA.

2.4 EPIDEMIOLOGY

2.4.1 Incidence

AA is a common disease all over the world. According to a study from the United States, the lifetime cumulative risk of having AA is approximately 9% for boys and 7% for girls.
Cumulative incidence is 3.2% by age 20, 5.5% by age 40, and 7.2% by age 60, in California (85).

The incidences of AA do not differ significantly among Scandinavian countries (14,86,87) (Table 2). In other European and Asian countries the incidence of appendectomies has stayed at the same level. Moreover, in United States and in Canada the incidence of AA follows the same trends. Interestingly, the incidence of the AA in developing countries is much lower than that in developed countries (16). In Ghana the incidence of AA was as low as 0,2/100’000, and in South Africa 15/100’000 (17,88).

Furthermore, a disproportion still exists among the black and white people in Africa. The incidence of AE was approximately 10% of the white population, whereas it was <1% of the black population of Africa (17). Moreover, it has been found that while whites and Hispanics have higher overall incidence rates compared to African Americans and Asians, Hispanics and Asians are at higher risk of perforation compared to whites and African Americans (85). In summary, appendicitis seems to be more prevalent in developed than in developing countries.

Table 2. Incidences of the AA and AE in different countries during the last 25 years.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Incidence/100'000/year</th>
<th>Study Years</th>
<th>No. of pt.</th>
<th>F:M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohene-Yeboah et al (88)</td>
<td>2009</td>
<td>Ghana</td>
<td>0,2</td>
<td>2000-2005</td>
<td>1266</td>
<td>-</td>
</tr>
<tr>
<td>Langenscheidt et al (89)</td>
<td>1999</td>
<td>Madagascar</td>
<td>0,8</td>
<td>1994</td>
<td>165</td>
<td>1:3,2</td>
</tr>
<tr>
<td>Ahmed et al (79)</td>
<td>2014</td>
<td>Northern-Nigeria</td>
<td>2,6</td>
<td>2001-2010</td>
<td>1 milj.</td>
<td>-</td>
</tr>
<tr>
<td>Kong et al (17)</td>
<td>2012</td>
<td>South-Africa</td>
<td>15</td>
<td>2010-2011</td>
<td>200</td>
<td>-</td>
</tr>
<tr>
<td>Al-Omran et al (93)</td>
<td>2003</td>
<td>Canada, Ontario</td>
<td>75</td>
<td>1991-1998</td>
<td>65675</td>
<td>1:1,4</td>
</tr>
<tr>
<td>Körner et al (7)</td>
<td>1997</td>
<td>Norway</td>
<td>86</td>
<td>1989-1993</td>
<td>1486</td>
<td>-</td>
</tr>
<tr>
<td>Buckius et al (95)</td>
<td>2012</td>
<td>America</td>
<td>76-94</td>
<td>1993-2008</td>
<td>4 milj.</td>
<td>-</td>
</tr>
<tr>
<td>Blomqvist et al (14)</td>
<td>1998</td>
<td>Sweden</td>
<td>107-115</td>
<td>1989-1993</td>
<td>60306</td>
<td>-</td>
</tr>
<tr>
<td>Lin et al (90)</td>
<td>2015</td>
<td>Taiwan</td>
<td>108</td>
<td>2000-2011</td>
<td>-</td>
<td>1:1,1</td>
</tr>
<tr>
<td>Addiss et al (84)</td>
<td>1990</td>
<td>America</td>
<td>110</td>
<td>1979-1984</td>
<td>561000</td>
<td>1:1,4</td>
</tr>
<tr>
<td>Andersson et al (86)</td>
<td>1994</td>
<td>Sweden</td>
<td>116</td>
<td>1984-1989</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lee et al (82)</td>
<td>2010</td>
<td>South-Korea</td>
<td>136</td>
<td>2004-2007</td>
<td>143 milj.</td>
<td>1:1,1</td>
</tr>
<tr>
<td>Sulu et al (118)</td>
<td>2010</td>
<td>Turkey</td>
<td>150</td>
<td>2004-2007</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
2.4.1.1 Trends in incidence

Recent studies from European and Asian countries report on a decreasing incidence of AA for several decades (7,14,90-92). Canada has also reported declining trends (93). Interestingly, at that time, the incidence of AA has increased in Nigeria (94). In the United States the incidence of AA has gradually increased in most recent years (10,85,95). These changes have been seen for both males and females in each ethnic group, except for black people. Additionally, AA was increasing across all ages, with the greatest percent change noted in 30–69 year old group, and with a shift towards more elderly patients being diagnosed with AA. Improved diagnostic methods have been speculated as the explanation for this increase, but a definite cause remains unclear (95).

Despite these significant changes in overall incidence rate of AA, the rate of perforated appendicitis has shown different tendencies. Only minor changes, or a reverse trend have been seen in incidences of perforated appendicitis compared to non-perforated AA (10,87,90,93).

In summary, in some countries the incidence has been decreasing and in some countries increasing. The reasons for these changing trends still remain a subject of vivid debate.

2.4.2 Age

The incidence of AA is strongly age-dependent, peaking at ages 15-24. AA is very uncommon in children younger than 5 years old and those over 70 years old everywhere in the world (82,84,96,97). About 65-70% of all patients with appendicitis are within the age group of 5-40 years old (14,98). The incidence of the AA seems to decrease after the age of 50, and remains the second most common surgical abdominal disease after biliary disorders in this age group (99). Moreover, the age distribution in several African countries follows the same trend than in developed countries (79,100-102). The rate for perforated appendicitis and complications after the surgery for AA is found to be higher at both ends of the age groups (82,99,103,104). Interestingly, Andersson et al. found that variation in the incidence between the age groups was seen mainly among non-perforated appendicitis, while for perforated disease it was almost stable at all ages (86).

2.4.3 Sex

The rates for appendicitis are higher for men than for women, and the male/female ratio varies from 1.1 to 3.2 (Table 2). The main difference has been noticed in age groups under 30 years old (82,95,105,106). The lifetime risk of undergoing an AE is 12% for men and 23% for women (84). The probability of negative appendicitis is over two times higher for women than that for men (107). Moreover, the possibility for perforated appendicitis has been reported to be 0.82 times lower in women than in men (85). The main reason for RLQP for premenopausal women is gynaecological disorder (105).

2.4.4 Familial causes

There is conflicting evidence regarding familial dependence for appendicitis (28). Familial tendency for AA may perhaps be explained by environmental factors such as a specific bacterial infection, certain food habits, or a genetic difference in resistance to bacterial infection (108). Gauderer et al. suggested that children who have developed appendicitis are twice as likely to have a positive family history than are those with RLQP (but no appendicitis) and almost three times as likely to have a positive family history than controls without abdominal pain (109). It has been found that the relative risk to have a AA is 10 times greater in a child with at least one relative with reported AE, compared with a child with no affected relatives (110). They also reported that the proportion of appendicitis varied directly with the degree of relationship: 21% in first, 12% in second, and 7% in third degree relatives (110).

Twin studies are important in regards to genetic-based studies (108). Simultaneous cases of AA are extremely rare (108). In the Swedish study they found a very weak association...
between genetics and AA (111). Overall, however, there is not sufficient literature to conclude whether genetics or coincidence is responsible for AA (108).

The common prevalence of the disease in the general population makes it difficult to prove a genetic etiology, but a polygenic inheritance pattern with substantial environmental determinants has been suggested (28). Whichever the case, because of its potential value in changing the threshold for AE, a careful family history should be obtained for every child in whom AA is suspected (109).

### 2.4.5 Ethnic causes

A wide variation in the incidence rate of AA has been reported when comparing countries and ethnical groups. In studies from the USA, appendicitis is more common in white and Hispanic people and less common in African and Asian people (85,95,106). It has been found that Hispanics and white people have higher incidences in both non-perforating and perforating appendicitis compared to Asians or blacks (85,106). In contradiction to the previous findings, Buckius et al. found no difference in term of perforated or non-perforated appendicitis between ethnical groups (95). It has been suggested that in the USA the ethnic variations in appendicitis are linked to access to healthcare and especially to insurance (85,106,112). In Scotland, where all healthcare is free of charge, the relative risk for AA has been found to be higher in white people than that in Pakistani, Indian, African black and Chinese people (112). To date it is still controversial whether ethnical differences might be attributable to cultural, environmental differences, in the ways to interact with the medical system, or whether it may truly differ by ethnicity (85).

### 2.4.6 Seasonality

Several infectious abdominal and respiratory diseases exhibit a seasonal pattern (113,114). The incidence of AA has been reported to vary substantially by country, geographic region, and season. Several studies describe high incidences of AA during the warm months of the year (84,91,93,100,113,115). Non-perforated and perforated appendicitis show similar seasonality trends, although variations in perforating appendicitis are less pronounced (85,93). Seasonality of AA for ethnic groups shows less variation for whites and blacks people than Hispanics and Asians (106).

Interestingly, in Nigeria the incidence of AA is high in the summer months, although the temperature is lower during this time of year due to the rainy season (79,94,116). It has been speculated that the rise in incidence can be associated with the onset of the rainy season and high humidity levels (94). An increase in the incidence of bacterial and viral infections (78,117) and parasitic infestations during this period might contribute to the higher incidence of appendicitis during this time (94). In sum, although, the connection of viral and intestinal infectious diseases with AA has been studied, there has been no association found (64).

In an exception from previous studies, in South Korea the incidence rate of suspected AA (diagnose of incoming patients) showed clear seasonality with higher rates in summer months. Interestingly, however, the AE rate and the incidence of perforated appendicitis did not have seasonal variability (82). Moreover, there is a publication from Turkey that found a high incidence rate of AA during winter months (118). The authors of that study speculated that the high humidity and altitude of this area was the causative reason.

### 2.5 DIAGNOSIS

#### 2.5.1 Clinical diagnosis

Traditionally, a diagnosis of appendicitis is most likely in the presence of right-lower quadrant pain, rigidity and migration of the initial periumbilical pain to the right lower quadrant (48,119). A carefully detailed history and physical examination will provide the proper diagnosis in the majority of cases (120). Typically, in the early stages of appendicitis,
autonomic visceral pain afferent fibres mediate the pain, and it begins as a midabdominal
or periumbilical ache or discomfort. Accordingly, more than 90% of patients complain of
anorexia, and 80% of patients are nauseated. When the inflammation of the appendix
extends to the parietal peritoneum, the activation of somatic pain fibers localizes pain to the
region of the appendix (121). Vomiting may occur during this time. Temperature is often
mildly elevated (<38°C). This typical presentation occurs in only 50-60% of patients.
Rovsing’s, psoas, and the obturator sign might be present, but are not specific (20,122).
Unusual presentations most likely occur when the appendix is in an atypical location, when
the patient is at an extreme in age, or when the patient is pregnant (28,123). The overall
accuracy for diagnosing AA is approximately 80%, which corresponds to a mean false-
negative AE rate of 20% (9). Diagnostic accuracy varies by sex, with a range of 78-92% in
male and 58-85% in female patients (9,84,120). In a review of medical records of 4,950
patients who underwent emergency AE, the false-negative AE rate was noted to be 9% in
male patients and 19% in female patients (124). The main three alternative diagnoses when
AA not present in operation is to be pelvic inflammatory disease or other
gynaecologic disease, mesenteric adenitis, and NSAP (125).

2.5.2 Laboratory markers
Preoperative laboratory tests often aid surgeons with decision making in patients with
suspected AA. There are many studies assessing the diagnostic accuracy of different
inflammatory markers in AA including: C-reactive protein (CRP), amount of total white
blood cells (WBC) and neutrophils, interleukine-6, phospholipase A2, bilirubin,
calprotectin, serum amyloid A, D-lactate (126-133). In addition, the value of the
radioactively labelled leukocytes (with indium-111 and technetium99m) to identify a source
of suspected intra-abdominal infection, have been studied (134,135). The value of
laboratory examination is controversial. It has been presented that only 4% of the diagnoses
were changed (78% of these to corrective direction) after assessing blood test results (136).

WBC and CRP remain the most used laboratory markers for distinguishing patients with
appendicitis from those without. WBC seems to be a very early marker of appendiceal
inflammation (128-131). When the white cell count and neutrophil count are taken together
<4% of patients with AA will have normal levels (137). CRP alone is more effective in
identifying patients with complicated appendicitis (128,138). Recent meta-analysis states
that procalcitonin has a better diagnostic accuracy (area under ROC: procalcitonin vs CRP
0.94 vs 0.75; specificity procalcitonin=94%) than CRP in diagnosing complicated AA (139).
Additionally, if all values – WBC, CRP and phospholipase A2 are within normal limits, AA
could be excluded with a 100% predictive value for an adult population (128,129,140).
Contrary to adult patients, normal WBC count and CRP value do not effectively exclude
AA in children. It has been found that 7% of children with histologically proven AA have
both normal values (130). Serum inflammatory markers seem to be age-dependent in AA
(130,141). However, Dayawansa et al recently found that 8.5% of adult patients with
confirmed AA presented with a normal CRP and WBC level on admission. Some of them
had persistently normal infection parameters on repeat testing, as well (142).

The diagnostic potential of the pro- and anti-inflammatory cytokines has been reported.
The feasibility of several cytokines as potentially involved in inflammatory process of AA
has been examined, but the improvement in diagnosis of AA has been minimal
(131,143,144). In another study, the novel plasma markers calprotectin and serum amyloid
A were significantly elevated in patients with AA, but there were no cut-off points in
observed ROC curves that could accurately discriminate between AA and other abdominal
pathology (133). In addition to inflammatory markers, it has been found that oxidative
stress markers can be used to confirm the diagnosis of AA and to determine the extent of
the disease (145). However, authors of this study concluded that these serum markers did
no have any superiority compared to ordinary diagnostic tools (145). Interestingly, a high
specificity of an increased level of bilirubin has been detected in patients with perforated
appendicitis, and the authors suggest use of this as a rule-in test on patients with RLQP, or to distinguish patients with complicated appendicitis (126,146).

To conclude, there is no value for any laboratory marker that is sensitive and specific enough to be clinically useful in discriminating between AA and other abdominal pathology in a patient with suspected AA. Nevertheless, in combination they provide high discriminating power (127,133,147,148).

2.5.3 Diagnostic scoring systems
A number of clinical scoring systems have been developed in the attempt to obtain a proper diagnosis for patients with suspected AA and to separate those indicated for observation from those requiring prompt surgical intervention (149-154).

The Alvarado score is the most well-known diagnostic scoring system and is a valuable tool in ruling out a patient with AA (Table 3) (155,156). In the equivocal clinical presentation of appendicitis, as defined by Alvarado scores of 4 to 8, adjunctive CT is recommended to confirm the diagnosis in the emergency department (157,158). Additionally, in a recent study, Di Saverio et al. stated that it is not sufficiently specific in diagnosing AA (evidence level 1, grade of recommendation A) (159). Andersson et al. presented their scoring system, which had improved potential for clinical diagnosis of AA compared to an Alvarado score (154). Moreover, Sammalkorpi et al. used the novel Adult Appendicitis Score that was first to take into account the differences in diagnostics between sexes, the time passed between the onset of symptoms and taking the laboratory samples, and the score was also based on prospectively collected data of all patients with RLQP, not only those operated on for suspected appendicitis (153).

In conclusion, a good diagnostic scoring system should provide an improved positive predictive value, correctly classify the majority of patients into those who can be sent home for outpatient follow up from those that need to be operated on immediately.

2.5.4 Plain radiography
Plain radiography has been used in evaluating gastrointestinal disease since the early 1900s (28). The study may be useful in patients with atypical presenting symptoms and physical signs. The routine use of plain radiography can be misleading, and has been reported to be of little value (160). In cases of AA it may demonstrate a fecalith (with 95% accuracy and 8% sensitivity (98), localized ileus, or loss of the peritoneal fat stripe (123). This modality is not specific, and has not been useful in diagnosing patients with appendicitis, and is has been suggested that its continued routine use should be abandoned (161).

2.5.5 Ultrasonography (US)
US has been recommended when a patient presents with right upper quadrant pain (162), especially in children and in women at a reproductive age, in whom the radiation dose should be minimized (9). US can be limited by patient body habitus (obesity) as well as the position of the appendix (163). The overall sensitivity and specificity of US varies considerably ranging from 71% to 96% and from 47% to 94%, respectively (Table 3). Positive predictive value (PPV), negative predictive value (NPV) and the diagnostic accuracy of US are approximately 89-95%, 35-76%, and 71-97% respectively (9,28,163,164). The role of graded-compression US, a technique first described by Puylaert, has been studied and recommended in RLQP patients suspected to have appendicitis (9,165,166). Moreover, not only the detection of pathologic appendix on US but the identification of a normal appendix has a high diagnostic importance (163). As advantages, US is a widely available inexpensive modality; examination is quick and relatively painless and does not involve the use of ionizing radiation. Moreover, it also is highly useful in identifying an alternative diagnosis, for example, cholecystitis, which can sometimes mimic AA (9). Common false-positive diagnoses that can mimic AA include Meckel’s and right colonic
diverticulitis, acute enterocolitis and mesenteric lymphadenitis, ureteral calculi, inflammatory bowel disease, and various gynaecological conditions (167).

2.5.6 Computed tomography (CT)
CT has been used for more than 20 years as a valuable diagnostic tool for improving diagnosis of AA. Different protocols of the CT have been described – unenhanced, oral and intravenous contrast material enhancement, and rectally instilled colon contrast material with or without oral contrast material enhancement (168). As the most cost-effective strategy, computed tomography (CT) is recommended for evaluating adults with acute right lower quadrant pain (RLQP) (162,169). Moreover, the negative AE rate among patients undergoing preoperative CT is less than that among patients undergoing AE without preoperative CT: 7.4% versus 20.8% (p=.005) (170). It is a highly accurate and effective cross-sectional imaging technique for diagnosing and staging AA, with use preoperatively up to 98% of accuracy (9,171,172). With the use of CT in diagnosis of patient with RLQP the negative AE rate has decreased to 3-6% without a change in the rate of perforation (170,171). A one-way sensitivity analysis showed that ultrasound is better than CT only when its sensitivity is greater than 88% (169).

2.5.7 Magnetic resonance imaging (MRI)
MRI is being investigated as a suitable diagnostic modality especially in children and in women in childbearing age and during pregnancy because of its lack of radiation (173). It has been suggested that MRI may be performed in selected cases with US-negative, but clinically suspected AA to obtain a proper diagnosis (174). According to meta-analysis, sensitivity, specificity, positive predictive value and negative predictive value of MRI examination in the diagnosis of AA were 97% (92-99%), 96% (89-98%), 96% (92-99%), 96% (91-98%), respectively (175), and effectiveness remains excellent in cases of pregnancy (176).

Diagnostic sensitivity and specificity for both CT and MRI are excellent (Table 3) for the entire spectrum of disease manifestations and do not decrease in the presence of perforation or aberrant appendiceal location (9,173,176). Due to fact that antibiotic treatment appears to be a safe first-line therapy in patients with uncomplicated AA (34), it is desirable that in this clinical situation surgeons would ensure of clinical diagnosis by utilizing the advantages of CT or MRI (141).

To conclude, the optimal imaging technique for AA should have several key characteristics. It must be accurate, quick, safe, technically non-challenging, readily available, cost efficient, and capable of being performed with little risk or discomfort to the patient (28). Radiologic imaging usually is requested in patients with atypical or confusing clinical findings. The choice between CT and US in this clinical setting largely is dependent on institutional preference and on available expertise, although patient age, sex, and body habitus are important influencing factors (9). The goal of radiological studies is proper diagnosis and avoiding unnecessary operation. With improved diagnostic imaging, the negative AE rate has decreased from 19% in 2008 to 5% in 2011 in Dutch hospitals (177).

Table 3. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Alvarado score, ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis of acute appendicitis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peck et al (178)</td>
<td>2000</td>
<td>CT</td>
<td>92,8</td>
<td>99,6</td>
<td>99,0</td>
<td>96,9</td>
<td>Non-contrast</td>
</tr>
<tr>
<td>Kim et al (300)</td>
<td>2008</td>
<td>CT</td>
<td>97,8</td>
<td>95,5</td>
<td>96,7</td>
<td>97,0</td>
<td></td>
</tr>
<tr>
<td>Pacharn et al (163)</td>
<td>2010</td>
<td>US</td>
<td>81,0</td>
<td>67,0</td>
<td>93,0</td>
<td>36,0</td>
<td></td>
</tr>
<tr>
<td>Inci et al (174)</td>
<td>2011</td>
<td>Alvarado</td>
<td>84,2</td>
<td>66,7</td>
<td>94,1</td>
<td>40,0</td>
<td></td>
</tr>
</tbody>
</table>
Despite different modern diagnostic methods used for improving diagnosis of AA, there is still a negative AE rate of up to 10-20% (180,181). Therefore, an invasive method, diagnostic laparoscopy has been developed and offers a good possibility for use in diagnosis and to treat intra-abdominal and intrapelvic pathology. The procedure has been suggested especially for woman of reproductive age with an atypical presentation of AA (182,183). However, due to it’s invasive nature and high costs, using laparoscopy solely as a diagnostic method has so far played a minor role in Finland.

## 2.6 DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of appendicitis relies on a detailed history and thorough physical examination. The differential diagnoses for AA is lengthy (Table 4) (20,99,123,182,184). In comparison, appendicitis is in the differential diagnosis of virtually any patient with acute abdominal pain. It is good to remember that appendicitis is very unusual in children younger than 5 years old (11,66,84). In young men, the diagnosis of appendicitis is most readily apparent. The highest percentage of misdiagnosis in patients who appear to have appendicitis occurs in women of childbearing age. Gynecologic problems are frequently mistaken for appendicitis and the negative AE rate in young women ranges from 15% to 40%. In an elderly patient, malignancies of the gastrointestinal tract, and colonic diverticulitis should be in the ordinary differential diagnosis of appendicitis (20,28,123).

### Table 4. Differential diagnosis of AA.

<table>
<thead>
<tr>
<th>In all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial/Viral enteritis</td>
</tr>
<tr>
<td>Mesenteric adenitis</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Hernia</td>
</tr>
<tr>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Caecal or sigmoid diverticulitis</td>
</tr>
<tr>
<td>Caecal volvulus</td>
</tr>
<tr>
<td>Testicular torsion, epididymitis (in males)</td>
</tr>
</tbody>
</table>
Urolithiasis
Crohn’s disease and ulcerative colitis
Omental infarction
Tumors and malignancies

**In female patients**
Pelvic inflammatory disease (PID)
Ruptured ovarian follicle
Tubo-ovarian abscess
Ovarian torsion
Ectopic pregnancy

**In children**
Necrotizing enterocolitis
Intussusception
Mesenteric lymphadenitis
Lower lobe pneumonia
Meckel diverticulitis

### 2.6.1 Perforated appendicitis
The average rate of perforation at presentation has been recently reported to be between 15 and 30% (95,103,185-188). It rises to over forty percent in the youngest and oldest age groups (7,85,103,186,187). Historically, it has been stated as a fact that the delay in care is the major factor resulting in perforation (103,187). Nevertheless, several studies have found that perforation is often a pre-hospital occurrence that is not affected by time, and does not lead to an increased complication risk and mortality (188-191). It has been suggested that perforated and non-perforated appendicitis have different pathophysiologies, and that the amount of perforations is not an indicator of the quality of care (192,193). Terlinder et al. found that negative AE was mainly positively associated with non-perforated appendicitis, whereas the inverse association with perforated appendicitis was weak (193). Moreover, according to a large historical cohort study, a perforated appendix during childhood does not seem to have a long-term detrimental effect on subsequent female fertility (194).

Ethnicity has been implicated as a risk factor for perforation. At presentation, 31% of Hispanic children, followed by African-American with 27%, and Caucasian children with 23%, presented with perforated appendicitis (195). Anderson et al. found that Hispanics and Asians had higher odds of perforation compared to whites (85). Furthermore, lower household income and patients with the public insurance, or no insurance at all, have increased odds of perforation (85,196).

### 2.6.1.1 Free perforation
Delay of either operative care or antibiotic administration may permit the pathologic process of appendicitis to proceed toward perforation. In these patients, the need for urgent intervention is more obvious, and care varies from that of the non-perforated form of AA. Young and older age groups seem to have higher rates of perforation compared to adults (7,10,197). The relationship between the duration of symptoms and perforation of the appendix has been studied, but clear consensus is still missing. Some studies suggest that
the rate of perforation increases with duration of symptoms (187,198-201), whereas others negate this relationship (188,189,191). Nevertheless, Hansson et al. found that patients with perforated AA had a significantly longer duration of pre-hospital pain compared to those without perforation (198). Moreover, they found that risk of perforation is up to three times higher in the age group >50 years old, and over five times higher for those with a pain duration >72 hours (198).

2.6.1.2 Periappendicular mass (abscess or phlegmone)
Appendix mass is the result of a walled-off perforation of the appendix that localises, resulting in a mass. This walled-off perforation varies in nature from a simple inflammatory mass (an appendiceal phlegmon) to a pus-containing collection (an appendiceal abscess) (202). A periappendicular mass is reported to develop in 2-10% cases (203). Patients with an appendiceal abscess or phlegmone have a tender mass with a swinging pyrexia, tachycardia, and leucocytosis (204), but it can present with no clinical signs at presentation (203). The diagnosis is usually done by ultrasonography or computed tomography scanning (203).

2.6.2 Recurrent and chronic appendicitis
Although many patients with an uncomplicated appendicitis can be treated conservatively, operative treatment is still needed for recurrent cases. Salminen et al. found that 27,3% of patients initially treated without surgery had a recurrent hospitalisation and underwent surgical intervention within one year (34). Tanaka et al. found that recurrence of appendicitis occurred on 21% of non-operatively treated pediatric patients during an average of one-year follow-up (205).

The diagnosis of chronic appendicitis should be considered if the patient has had chronic RLQP of at least 3 weeks duration with no alternative diagnosis. After AE, a complete relief of symptoms occurs (206). The histopathological analysis should reveal a chronic active inflammation of the appendiceal wall, or a fibrosis of the appendix, partial to complete obstruction of the lumen with evidence of old mucosal ulceration and scarring (20,206). Usually patients with recurrent or chronic appendicitis are able to recall at least one episode of acute abdominal pain consistent with AA that was managed non-surgically (206). Characteristically, between attacks, patients are symptom-free or they are mild and self-limited; physical examination is normal unless the patient is examined while symptoms are present (20,207).

Nevertheless, the diagnosing of chronic appendicitis is not always so straightforward. It has been detected, in randomized controlled trial that there is significant pain relief after AE in patients with chronic RLQP (208). Although the clinical improvement was convincing, there was no correlation between pain and histological findings (208). In another study, laparoscopic AE was done to patients with chronic RLQP. All patients reported resolution of pain and the histological pathology was demonstrated in 70% of patients (209). There is still lack of explanation, why removing of the appendix (even pathohistologically normal) resolves RLQP.

2.6.3 Periappendicitis
A histologically detected inflammatory change on appendiceal serosa without involvement of mucosa, and macroscopically unaffected appendiceal lumen, constitutes the condition known as periappendicitis (210,211). It has been published that periappendicitis, affecting mostly females between the 17 and 21 years old, or boys under the 12 years (M:F 1:4.4), is found in 1-5% of appendices removed for AA (212,213). The frequency of periappendicitis is reported to vary 1.9-2.5%. It is crucial to understand that the periappendicitis is often a sequel of extra-appendiceal infection with a different origin leading to peritonitis, a gynaecological most commonly (68,210,212,214). If periappendicitis would be verified postoperatively, or if intra-operatively appendix is found to be normal, periappendicitis
should always be considered and such patients need proper diagnostics and should be treated appropriately (211).

2.6.4 Non-specific acute abdominal pain (NSAP)
Both AA and NSAP are of the most frequent causes of admission to emergency rooms (1,4). The differential diagnosis between AA and NSAP may be challenging. NSAP is defined as acute abdominal pain that lasts less than 7 days and for which the diagnosis remains uncertain after baseline examination and diagnostic tests (215). It has been said that NSAP is a condition to describe cases with atypical expression, and for which no specific reason for abdominal pain could be found (216). The amount of NSAP patients of all patients with the acute abdominal pain has varied from the 10% up to 67%, and it seems to be higher in a younger age groups (1,99,217-219). Moreover, it seems that the amount of the NSAP patients is higher in wintertime (220). Ferlander et al. found that 2.2% of patients with NSAP were assigned a cancer diagnosis (most commonly of the pancreas and colon) within 12 months. The majority were 60 years or older (221). According to some studies approximately 30-40% of the patients with the initial diagnosis of NSAP require an operation during the follow-up (222,223). On the other hand, less than 1% over the young, and 10% over the adult patients with discharge diagnosis of NSAP has been reported to require further invasive investigations or operative procedures (218,222).

Different techniques, including the use of structured data sheets, laboratory tests, ultrasound, CT scanning and diagnostic laparoscopy have been used to improve diagnostic accuracy. CRP as an infection marker is not useful in differentiating a NSAP from other important surgical causes of acute abdomen (13). Abdominal ultrasound done in emergency rooms appears to have a positive impact on decision-making and proper diagnosis for patients presenting with NSAP (224). Early routine CT offers an advantage over standard local practice in terms of improved diagnostic certainty, and could identify significantly more serious diagnosis than standard practice (225-227). Nevertheless, improvements in the length of hospital stay and mortality at 6 months do not differ significantly (226). On the other hand, 5.4% of patients aged 60 years and older were diagnosed with a malignant disease, and elderly patients especially with diffuse abdominal pain and comorbidities would to be more liberally referred for follow-up (221). The usage of early laparoscopy as a diagnostic tool for NSAP is also controversial. In their systematic review Dominiquez et al. concluded that early laparoscopy performs better in establishing a final diagnosis, but it cannot be recommended as a routine strategy in clinical practice (217). The observation of a patient with an initial diagnosis of NSAP is a safe option since patients do not have a high incidence of complication (218,228).

2.6.5 Pylephlebitis
Pylephlebitis is septic thrombophlebitis of the porto-mesenteric veins with the mortality up to 30-50% (229,230). It is a rare complication of AA, but also of other intra-abdominal infections, such as diverticulitis, pancreatitis, cholecystitis, etc. (229,231). It is a secondary infection in the region drained into the portal system. The diagnosis is challenging. The clinical presentation is nonspecific and can vary from the mild symptoms with fever and nausea to a serious manifestation of acute abdomen and sepsis (230,232). Blood samples are nonspecific, but positive blood cultures are found in 50 to 88% of patients (229,230). A contrast enhanced CT scan is useful for diagnosing the extent of pylephlebitis and also the primary source of infection (229,230). In most reported cases the treatment of pylephlebitis includes intravenous broad-spectrum antibiotic therapy with anticoagulation sepsis (229-232).
2.7 AA DURING SPECIAL CONDITIONS

2.7.1 Pregnancy
The most common non-obstetric emergency needing surgery in pregnancy is appendicitis, with an incidence of 0.05% to 0.2% (233,234). However, it has been suggested that pregnancy has a protective effect on the development of an AA, especially in the third trimester (235). Due to displacement of the appendix by the gravid uterus (Figure 2) the presentation is often atypical (42%) or may be mistaken for the onset of labour (233). Nausea and vomiting are often present, with associated tenderness located in a typical place in 75%, and on the right upper quadrant of the abdomen in 20% of cases, mostly in the third trimester. Also, nausea and vomiting, fever and leucocytosis with a left shift are often present (236). The initial method of choice for imaging the appendix in pregnancy is ultrasound sonography followed by MRI if US is inconclusive. CT scanning is not preferable because of its radiation exposure to the fetus (237,238). It has been reported that in cases of uncomplicated appendicitis the risk for fetal loss is less than 5%. Perforation represents a major risk to both mother and the fetus with reported fetal mortality ranges of 20-35% in cases of perforation and up to 35% with generalized peritonitis (233,239). Both laparoscopic and open accesses are accepted for operative care of appendicitis in pregnancy. According to meta-analysis the risk of preterm delivery and fetal loss might be higher after laparoscopic surgery (240).

2.7.2 Inflammatory bowel disease
Ulcerative colitis (UC) and Crohn’s disease (CD) are idiopathic chronic inflammatory conditions involving the large intestine or small and large bowel, respectively. Cigarette smoking is a well-known environmental factor affecting the course of inflammatory bowel disease, having been shown to increase the risk and severity of CD while protecting against the development of UC (241). There is reported an inverse association between prior AE and subsequent development of UC (242). Furthermore, it has been suggested that the inflammatory condition preceding the AE, rather than the AE itself, is inversely related to the subsequent development of ulcerative colitis (15). Additionally, the protective effect of the AE to the UC is more pronounced if the operation has been done before a 20 years of age (243,244). However, in the most recent national cohort study from Denmark the previous hypothesis about direct mucosal protective influence of AA on IBD has been challenged. They suggest instead that genetic and/or environmental factors may explain the inverse association between AA and IBD (245).
Among the patients with CD it is the other way round – there is an increased risk of disease among patients with a history of AE (246). There are differences between the sexes after a non-perforated appendicitis with a positive association for women, but not for men. Moreover, CD has been reported to be more aggressive in patients with a history of perforated appendicitis (246).

2.8 TREATMENT

2.8.1 Operative treatment
Historically, the best and most acceptably treatment for appendicitis has been an early AE. An AE is an effective, universally accepted procedure performed more than 300'000 times annually in the United States (247). The lifetime risk of AE is 12% for males and 23.1% for females (247). Moreover, AE is a safe procedure with a very low mortality rate of 0.08 to 0.4% for uncomplicated appendicitis (248). The decision to operate without delay is based on suspicion that AA as an invariably progressive inflammatory condition that will lead to perforation. The difference between the open and laparoscopic operative techniques is rather small and seems to be strongly dependent on patient characteristics and the treating surgeon’s expertise.

2.8.1.1 Open appendectomy (OA)
Treatment of AA has remained essentially unchanged since the description by Charles McBurney in 1891 (30,249). He described the nature of appendicitis and emphasized the need for fast operative care for AA (30). Some surgeons still favour OA when operating for appendicitis (250). Recovery after the operation is normally fast with a length of hospital stay of 1-3 days (251-253). In addition, it has been found that OA has advantages compared to laparoscopic appendectomy (LA): a shorter operation time and a shorter learning curve (254). Although some disparities exist, it has been reported that infection complications (i.e., wound infections, intra-abdominal abscesses) are more frequent after OA than after LA. The wound infection rate varies from 1 to 10%, and the abscess rate varies from 2-6% (251-253,255). Although the trends in operation techniques are toward the laparoscopic approach, open surgery still has a place in the treatment of AA.

The OA technique with an appendix stump invagination is in common use. The superiority of invagination has been the subject of investigations, and it seems that simple ligation is a sufficient procedure. In a two prospective study from Finland, the authors concluded that simple ligation of the appendiceal stump is safe, preventing deformation of the caecal wall and possibly reducing the risk of postoperative ileus (256,257). Moreover, in meta-analysis with 2634 patients found that patients with simple ligation of the stump had a lower incidence of postoperative ileus and quicker postoperative recovery (258). Additionally, the operation is simpler and the operation time is shorter (256-258).

2.8.1.2 Laparoscopic appendectomy (LA)
LA, was first described by Kurt Semm in 1983 (249), and the procedure has gradually gained acceptance for treatment of AA (259). Short hospitals stay, faster recovery and earlier return to full activity, decreased postoperative pain, improved wound healing, and lower wound infection rates have been reported as benefits of LA (254,260). Additionally, the laparoscopic approach allows a better assessment of other intra-abdominal pathologies. Although a theoretical concern is that elevated intra-abdominal pressure may promote bacteraemia and systemic inflammatory response, the laparoscopic surgery is increasingly used for intra-abdominal disease complicated by inflammatory processes and peritonitis (253,261). Although there are advantages, there are some discrepancies between results,
and there is some evidence of a possible higher risk of fetal loss in pregnancy compared to OA (240). AE in patients with peritonitis caused by AA was associated with a significant stress response, measured by the biochemical markers, but the laparoscopic group was superior to the open group in terms of postoperative systemic inflammation as well as intraperitoneal abscess formation (261). Additionally, LA reduced the number of postoperative analgesics and visual analogue scale (VAS) compared to OA with similar length of hospital stay, operative time, and postoperative complications (249,251,253,259). The mean operative cost of LA is higher compared to OA (249,262,263). An additional benefit of the laparoscopy is the possibility to evaluate the intra-abdominal condition, especially in women of childbearing age (264). To conclude, LA provides good clinical results with slightly increased operation time and cost of surgery (249,262).

2.8.2 Treatment of periaappendicular mass (phlegmone or abscess)

The optimal management of AA complicated by an inflammatory phlegmone of abscess remains controversial. It has been proposed that the most effective approach to treat periaappendicular abscess is a primary intravenous antibiotic treatment with or without percutaneous radiological drainage followed by interval appendectomy IA to prevent recurrent appendicitis and to exclude malignancy (202,203,265,266). The failure rate for primary nonsurgical treatment is 7.2% (CI: 4.0-10.5) (265). Simillis et al. concluded in meta-analysis that immediate appendectomy in case of abscess is associated with greater incidence of ileus (OR 0.35; CI: 0.17-0.71; P=.004), abdominal or pelvic abscess formation (OR 0.19; CI: 0.07-0.58; P=.003), and wound infection rate (OR 0.28; CI: 0.13-0.60; P=.001) compared with the nonsurgical group (266). In contrast, Mentula et al. reported that more aggressive treatment with immediate appendectomy and surgical drainage of the abscess as an option for conservative treatment. They found that advantages of acute surgery include fewer readmissions (3% vs 27%) and lower additional interventions rates (7% vs 30%) than that after primary conservative treatment. Uneventful recovery was 90% in the primary operative group and 50% in the group treated conservatively (267). WSES Jerusalem guidelines recommend that non-operative management is a reasonable first line treatment for appendicitis with phlegmone or abscess (evidence level 1, grade of recommendation A) (268).

2.8.2.1 Interval appendectomy

There is debate whether the interval AE, that provides a tissue diagnosis when diagnostic uncertainty exists, is essential after the successful conservative treatment of appendiceal mass or not (203,265). The main reason is the risk of recurrent AA, which is reported to occur in 21-37% of the cases (203). Another reason is a possibility of malignant disease, which was detected during follow-up in 1.2% (CI: 0.6-1.7) of cases, and risk was related to age (265). In some studies, the risk of malignancy is found to be as high as 28-29% (58,59). A cost-effectiveness study from Taiwan concluded that routine IA increased the cost to patients and institutions by 38%, and therefore, was not routinely recommended (269). In comparison, a large cohort study by Wright et al. found that IA is strongly considered in patients over the age of 40 (270). Conversely, a recent study found that the most cost-effective strategy varies with patient age, and they concluded that IA should be considered for patients younger than 34 years of age (269). WSES Jerusalem guidelines for treatment of AA proposed that routine indication for IA is justified only in case of persistent or recurrent symptoms, and should be avoided in asymptomatic patients (268). They stated that IA is not routinely recommended both in adults and children with appendicitis (evidence level 1, grade of recommendation A) (268).

2.8.3 Conservative treatment

Despite over 100 years of experience, surgeons still weigh the risks and benefits of early AE. Surgeons who decide to operate despite subsiding symptoms will find their decision
justified by a pathologist who confirms AA, whereas surgeons who decide to remain conservative will find their decision justified by the spontaneous relief of symptoms (271). The ultimate goal in treating suspected appendicitis is to minimize the number of unnecessary laparotomies without increasing the incidence of perforated appendixes (86). Luckman et al. proposed in their meta-analysis of studies examining the epidemiology and natural history of appendicitis that perforating and non-perforating appendicitis are separate entities (11). The incidence of perforated appendicitis is independent of time, place, age, and rate of removal of appendix, and is unrelated to diagnostic accuracy (86). In contrast, the incidence of uncomplicated appendicitis differs widely, correlates strongly with the incidence of removal of a normal appendix, and is inversely related to diagnostic accuracy (86).

In the recent review by Flum it is stated that the conservative treatment with antibiotics should be considered as the first-line therapy in uncomplicated AA (272). Additionally, conservative treatment in pediatric patients is safe and does not increase morbidity in failed cases (35). The recurrence rate for AA treated non-operatively varies between studies from 7% to 27% (34,205,268,273,274), and average time from primary treatment to recurrence varies between three and seven months (274). In addition, the WSES Jerusalem guideline for treatment of AA recommends antibiotics as a first-line therapy for selected patients with uncomplicated appendicitis (evidence level 1, grade of recommendation A) (268).

2.8.4 Conservative vs operative treatment

There is no doubt that the treatment for the complicated appendicitis with peritonitis is operative. Meanwhile, there is evidence that uncomplicated AA often resolves, either spontaneously or with antibiotic therapy, and has outcomes equivalent or better to those of appendectomy (10,34,36,275). In one study, the AE rate among patients in the operation group was 39% compared with only 13% among those treated expectantly with operation if needed. Appendicitis was confirmed histologically in all patients having surgery, providing supporting evidence for spontaneous resolution of AA (223). Furthermore, it has been found that delaying surgery does not impact perforation rate and can be fairly tolerated (276). Additionally, patients after negative AE had longer hospitalization, more complications, and higher mortality rates than patients with appendicitis (277). These observations rebut the argument of surgeons that appendicitis is a progressive disease and that delaying AE is unacceptable (247).

The role of antibiotics might be to control local inflammation in this end-artery organ while mucosal repair and healing take place. In meta-analysis of four randomized controlled trials (RCT) (36,275,278,279) antibiotic therapy was associated with a 63% success rate and a 31% reduction of relative risk of complications compared with operative treatment (280). Recently, Salminen et al. in their so far largest multicentre, open-label, noninferiority RCT found that 186 of 256 patients (72%) with uncomplicated AA (and no fecolith seen in CT scan) were successfully treated with antibiotic therapy alone (34). They couldn’t to demonstrate the noninferiority of antibiotic treatment, and they concluded that most patients with uncomplicated AA do not require an operation. Additionally, none of the antibiotic-treated patients experienced severe complications, suggesting that not only is acute uncomplicated appendicitis a non-surgical emergency, but that delay in surgical treatment when preceded by a course of antibiotics has only a few consequences (34).

2.9 POSTOPERATIVE COMPLICATION

The overall complication rate differs a little between open and LA, and is reported to vary between 8.3% to 13.2% and 2.9% to 7.4% for open and laparoscopic surgery, respectively (259,281). The main advantages of laparoscopic over open surgery are decreased risk of wound infection (OR 0.43; CI 0.34-0.54), and lower incidence of postoperative pain, whereas
a rate of intra-abdominal abscesses is higher in laparoscopic surgery (OR 1.87; CI 1.19-2.93) (264).

In addition, length of hospital stay and readmission rates is reported to be lower after LA compared to OA, even in a patient with perforated appendicitis (253,282).

A large register complication study from Finland reported that two most common claims for complications were wound infection (27%) and abscess (12%) for open surgery, and abscess (21%) and intestinal perforation (13%) for laparoscopic surgery (283). The most common claim for intraoperative complication for both groups was bleeding, 15% and 29% for OA and LA, respectively (283). The rate of infection complications increases in cases of perforated appendicitis (263,282). In addition, the duration of preoperative symptoms over the 36h, and the age of a patient seem to correlate positively with the incidence of postoperative septic complications (284).

2.9.1 Mortality
Appendectomy is a relatively safe operation. Although, AE for non-perforated appendicitis is not an entirely harmless procedure, with 2.5-fold excess in the 30-day mortality rate compared with the general population (285). The rate of mortality and morbidity is related to the stage of disease, and patient age (125,248,285,286). Emergency appendectomies are still considered the most common approach for treating AA, with mortality rates of 0.5-2.4% and 0.07-0.7% for patients with and without perforation, respectively (14,99,248,287).

Mortality is higher in older age groups. Kraemer et al. found that mortality for patients <50 and >50 years old was 0.2% vs 2.9% for uncomplicated AA, and 1.8% vs. 2.8% for complicated appendicitis, respectively (99). In Finland, the post-AE mortality rate was found to be 0.21% with a rapid increase in age groups older than 60 years of age (288).

2.9.2 Morbidity
Overall postappendectomy complication rates are typically around 5-15% for AA without perforation and reach up to 30% for perforated AA (99,185,286). The morbidity rate rises to over 70% in elderly patients with perforated appendicitis (289).

In a study from Sweden, they showed that if the diagnosis at the time of surgery, done for suspected appendicitis, was not related to appendix, there was a higher morbidity. This finding led to the conclusion that greater diagnostic effort is warranted for elderly patients before subjecting them to an urgent AE (248). Moreover, there were no significant differences noted in the overall morbidity and mortality in patients operated at <12h, 12-24h, and >24h from time of surgical admission (199). Interestingly, black people, supposed to be an independent predictor of morbidity after AE, are reported to have a 1.5 times higher risk of postoperative complications (290).

Published results indicate that there is no difference in the overall morbidity rate for the removal of a normal appendix in patients suspected of having AA (124,125). Hale et al. found that the overall complication rate after AE was 5% and there was no difference in complication rates between removal of normal appendix or inflamed (4% vs. 3%, respectively), whereas the complication rate associated with perforated appendicitis was 12% (124).

2.9.2.1 Wound infection
The rate of postoperative wound infection is determined by intraoperative wound contamination. Rates of infection vary from < 5% in simple appendicitis to 20% in cases with perforation and gangrene (291,292). The use of perioperative antibiotics has been shown to decrease the rates of postoperative wound infections (292). According to large meta-analyses the incidence of the wound infection after the open surgery is significantly higher than that of laparoscopic surgery (262,293). The method of the wound closure with
absorbable or not-absorbable sutures does not seem to have an effect to incidence of wound infection (294).

2.9.2.2 Abscess

Nevertheless, the rate of intra-abdominal abscesses is reported to be higher after a laparoscopic operation (253,291). The incidence is found to be less than 2%, and it is not affected by the length of post-operative antibiotic treatment (291,295). A surgical site abscess may form in the postoperative period after removal of an infected appendix especially after perforation. The patient presents with swinging pyrexia, and the diagnosis can be confirmed by ultrasonography or computed tomography scanning (203,204). Antibiotic treatment combined with a radiologically guided drainage of collection with a pigtail drain is recommended. Additionally, open or per rectal drainage may be needed for a pelvic abscess (296).

2.10 SUMMARY

AA can occur at any age, although it is quite rare in infants and in the elderly. There are remarkable variations in the incidence of the disease among various ethnic groups and countries. The clinician must appreciate that the anatomic location of the appendix determines the presentation of symptoms and signs during an episode of appendicitis. The close contact with the parietal peritoneum determines the ordinary clinical picture of appendicitis. The organ may provide immune-mediated maintenance of gut flora within the organ, especially during episodes of severe diarrhea. Increased use of advanced diagnostic techniques such as laparoscopy, CT and US have led to a significant reduction (from 20-30% to 5-10%) of unnecessary operations and have also reduced the mortality rate. According to the latest findings, an antibiotic treatment can be considered a safe first-line therapy in patients with uncomplicated AA and with no signs of peritonitis. Consequently, the treatment principles of AA may need a re-evaluation to determine whether it should be individualized based on which form of the disease is present.
3 Aims of the Study

The purpose of the current study was to analyse epidemiological and clinical patterns of AA and non-specific abdominal pain. The specific aims of the studies were:

I To evaluate the possible changes in the incidence of AA and of NSAP during the last two decades in Finland and to detect any connections between the incidence rates of AA and NSAP;

II To determine whether the incidence of AA and NSAP could be explained by seasonal changes in temperature and humidity;

III To study whether changes in overall antibiotic use have an influence on the incidence of AA and AD;

IV To investigate clinical and laboratory findings in patients with clinically suspected AA in conjunction with computed tomography (positive/negative).
4 Patients and methods

Studies I, II and III were all population-based register studies. The study population was recruited from the National Institute for Health and Welfare registry, a research and development institute of the Finnish Ministry of Social Affairs and Health. The data was retrieved for the whole country and subdivided separately for every university hospital district (UHD) of Finland. Diagnoses were classified according to the World Health Organization International Classification of Diseases, versions 9 and 10 (ICD-9 and ICD-10). We retrieved the data on the discharge diagnoses of AA, NSAP and colonic (uncomplicated) acute diverticulitis (AD) (ICD-9: 562.11 and ICD-10: K57.3) as well as surgical procedures of AE. Data on complicated appendicitis, i.e., perforation with abscess or peritonitis (ICD9: 540.0, 540.1 and ICD10: K35.0, K35.1), were also recorded. Additionally, we gathered data on age, sex distribution, and duration of hospital stay. Data was retrieved from the year 1987 to 2007 for Studies I and II, and from 1990 to 2007 for Study III. The choice of the time period in studies I and II was based on the introduction of ICD-9 in 1987 in Finland (use of ICD-10 began in 1996 in Finland) The time period for study III was based on availability of data on outpatient use of antibiotics from the year 1990. Population data from 1987 to 2007 and mortality were retrieved from the Official Statistics of Finland. Study IV was based on data of surgical and antibiotic treatment for uncomplicated AA (APPAC trial) (34).

4.1 STUDY I: CHANGING INCIDENCE OF AA AND NONSPECIFIC ABDOMINAL PAIN

Data was divided into three groups to assess changes in the number of AA and diagnostic accuracy and to compare trends in AA to NSAP (Table 5). Group A consisted of patients with a discharge diagnosis of AA. Group A was identified by combining the diagnosis of AA and the surgical procedure of AE, including both laparoscopic and conventional appendectomies. Group B consisted of all patients who were operated on and for whom AE was performed. From group B we excluded all patients with a diagnosis of benign (n=220; starting from 1996, ICD10: D12.1) and malignant (n=2563; ICD9: 153.5, 209.11, 230.3; ICD10: C18.1) tumors. To rule out the possible bias caused by these tumors, their incidence was calculated. Group C consisted of patients with a hospital discharge diagnosis of NSAP. It was not known whether these patients were operated on or not. The diagnostic accuracy for AA was calculated as the proportion of cases of appendicitis to the total number of appendectomies performed.

Table 5 Groups of the study.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Diagnosis code</th>
<th>Operation code</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients with appendicitis</td>
<td>540-542 (ICD-9)</td>
<td>6421 (ICD-9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K35-K37 (ICD-10)</td>
<td>JEA00, JEA01, JEA10 (ICD-10)</td>
</tr>
<tr>
<td>B</td>
<td>Patients with appendectomy</td>
<td>-</td>
<td>6421 (ICD-9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>JEA00, JEA01, JEA10 (ICD-10)</td>
</tr>
<tr>
<td>C</td>
<td>Nonspecific abdominal pain</td>
<td>7890 (ICD-9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R10.0-10.1, R10.3-10.4 (ICD-10)</td>
<td>-</td>
</tr>
</tbody>
</table>
4.2 STUDY II: SEASONAL VARIATIONS OF AA AND NONSPECIFIC ABDOMINAL PAIN

Weather data for the years 1987 to 2007 were retrieved from the Finnish Meteorological Institute (297) for each of the five university hospital districts (UHD). In Finland, five geographically-different University Hospital Districts (UHD) serve as a good base for comparing incidences and investigating various seasonal impacts on diseases. Temperature and humidity levels were obtained from the main measurement points in each of the UHD, and were expressed as mean values for each month. Moreover, the temperature of the whole country was calculated as mean temperature value for each of UHD. The mean temperature over the 21-year study period was below zero degrees from November to March (-4.1; SD 1.44°C), and above zero degrees from April to October (10.6; SD 0.72°C). According to that, the period from April to October was defined as a “warm period”, and from November to March as a “cold period”.

4.3 STUDY III: OUTPATIENT ANTIBIOTIC USE AND THE INCIDENCE OF AA IN FINLAND

Data on outpatient use of antibiotics from 1990 to 2008 were collected through the Finnish Medicines Agency. We obtained data for the use of oral outpatient antibiotics grouped according to the drugs’ active constituents from the anatomic therapeutic chemical (ATC) classification with defined daily dose (DDD) measurement units (WHO, version 2003) (298). To study more specifically the demographic variables of AA and NSAP, and the relationship of antibiotic use to the incidence of AA, we also conducted a sub-analysis for geographic areas with high incidences of AA (Oulu University Hospital; North Finland) and low incidences of AA (Tampere University Hospital; South Finland) for the years 2005–2007.

4.4 STUDY IV: CLINICAL AND LABORATORY FINDINGS AND COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF RIGHT LOWER QUADRANT ABDOMINAL PAIN

Data was collected from patients that underwent a CT scan according to an APPAC trial protocol. Details of the APPAC study protocol and one-year follow-up results have been previously published (34). There were six Finnish hospitals participating in the study: three university hospitals (Turku, Tampere and Oulu) and three central hospitals (Mikkeli, Jyväskylä and Seinäjoki). All patients aged 18-60 years old admitted to emergency departments with a clinical suspicion of uncomplicated AA were examined by the surgeon on call. Age, gender, body temperature, pain scores (VAS) and the duration of symptoms (<12 hours, 12-24 hours or >24 hours) before admission to hospital were recorded. If AA was suspected on the basis of clinical history and physical investigation, blood hemoglobin (Hgb, g/l), white blood cell count (WBC, upper limit of the reference interval 8.2 E9/l), plasma C-reactive protein (CRP, reference <10 mg/l) and creatinine (mol/l), serum human chorionic gonadotropin (U/l) and urine analysis were undertaken. A total of 1,379 patients were evaluated for enrolment in the APPAC trial. In this present study, all the patients (n=1321) who underwent a CT scan were included.

The patients were divided into two groups according to CT findings. In the first group (n=970) patients either had uncomplicated or complicated AA. All patients with false positive CT findings (diagnosis other than AA at operation) were excluded (n=19). In patients not undergoing surgery, the CT finding was considered accurate. In the second group (n=351) patients did not have AA on CT. This group was further divided into four subgroups for subsequent analyses: non-specific abdominal pain (NSAP) with no CT findings or lymphadenitis only, acute diverticulitis, gynecological disorders and other
diagnoses. The APPAC trial protocol was approved by the ethics committees of all participating hospitals.

4.5 STATISTICAL ANALYSIS

A statistician chose and provided specific tests for calculating the association between the variables, and differences between the groups. In Study I, II and III the annual incidences for the three groups (A, B, and C) were calculated per 10’000 persons and stratified by gender and age groups (0-4, 5-9, 10-14, … , 80-84, > 85 years). Incidence was calculated for each of five UHDs of Finland (Helsinki, Turku, Tampere, Kuopio, and Oulu). Diagnostic accuracy (the proportion of appendicitis to the total number of appendectomies performed) was calculated for males and females in different age groups.

In Study I and II we used SPSS for Windows, to compare the differences between the groups. Additionally, SAS for Windows was used in Studies I, II and IV. The analysis in Study III was done with R statistical software (R Foundation for Statistical Computing, Vienna, Austria).
5 Results

5.1 STUDY I: CHANGING INCIDENCE OF ACUTE APPENDICITIS AND NONSPECIFIC ABDOMINAL PAIN BETWEEN 1987 AND 2007 IN FINLAND

During the study period of 21 years, the number of patients with a hospital discharge diagnosis of AA and who had an appendectomy (group A) was 137,528 (average of 6500 per year). The overall diagnostic accuracy of AA was lower for females but showed an increasing trend for both genders. The incidence of the AA declined 32% from 14.5/10'000 to 9.8/10'000 inhabitants. The mean incidence of complicated appendicitis was stable during the study period – 3/10'000 inhabitants, the proportion being higher for men than for women [11% (9.1-12.6%) vs. 9% (7.6-9.8%)]. The decrease of the appendectomies was 39% (19.7-12.0/10'000) (Figure 3). The rise of diagnostic accuracy from 73% to 82% was statistically significant during the 21 years (p<0.001). The incidence of AA declined for all University Hospital Districts (UHD), with no statistical or geographical difference between the hospital districts. During the 21-year period, the mean length of stay for the patients operated on for AA decreased by 40%, from 4.6 days in 1987 to 2.7 days in 2007.

Figure 3. The annual incidence of acute appendicitis (Group A), appendectomy (Group B), and nonspecific abdominal pain (Group C) per 10’000 persons. The accuracy of the diagnosis of acute appendicitis (percentage) is on the right y-axis.

The proportions of malignant and benign tumors versus all appendicitis were 2% and 0.3%, respectively. For patients with a final diagnosis of appendicitis, the mean mortality was 0.03 (0.01-0.05) per 10’000 population and showed a declining trend (from 0.04 to 0.02/10’000) during the study period.
Opposite to AA, the incidence of NSAP showed different trends. The incidence rose between the years 1987 and 1998 (from 25.2 to 39.8/10'000/year), after which it fell to 27.1/10'000/year (Fig. 3). Moreover, the incidence of NSAP differed among the UHDs being higher in the northern than in the southern UHDs (p<0.0001). We did not observe any relationship between the incidence of NSAP and the incidence of AA or AE (Figure 4).

Appendectomy (group B) was equally common in both sexes, whereas the male/female ratio of AA (group A) was 1.30, 1.25, and 1.28 in 1987, 1997, and 2007, respectively. The incidence of NSAP was clearly higher in women and the female/male ratio was 1.8, 1.6, and 1.6 in 1987, 1997, and 2007, respectively. In men, the incidence of NSAP in 1987 was even lower than that of AE.

Figure 4. The differences in the incidence of acute appendicitis in five University Hospital districts of Finland between 1987 and 2007.

Both AA and NSAP were strongly age-dependent, peaking at 15-24 and 65-85 years, respectively (Figure 5). Up to 70% of appendectomies were performed on patients aged 5-39 years and the main changes in the incidence rate of AA over the study period were due to changes within these age groups. In contrast, the incidence of NSAP changed minimally in younger age groups until the age of 65, and then it rose constantly, peaking in the age group over 80.
Figure 5. Incidences of AA and NSAP in different age groups.

5.2 STUDY II: SEASONAL VARIATIONS OF AA AND NONSPECIFIC ABDOMINAL PAIN

During the study period, the mean annual temperature and relative humidity varied from 0.4-6.3°C (mean 3.9°C) and 62-76% (mean 69%), respectively (Figure 6). Furthermore, relative humidity showed higher values during the cold months. There was a large geographical disparity between temperatures of the different UHDs. The biggest difference between annual mean temperatures were measured between the UHD of Oulu and of Tampere with the mean temperature of 2.4°C (min, -0.8°C; max, 4.5°C) vs. 5.0°C (min, 1.6°C; max, 7.55°C), p=0.006, respectively. There was no statistically significant difference in the incidence of AA between the hospital districts.

There was a clear difference in the incidence of AA between cold and warm months (Figure 7). AA incidence was higher during warm months throughout the study period. According to Poisson regression analysis, an increase of 10-Celsius degrees in temperature increased the incidence of AA by 4%, 1.04 (95% CI: 1.019-1.061). The incidence of NSAP did not change during the year, and the association between temperature and NSAP incidence was not statistically significant (Figure 7). Furthermore, humidity levels had no effect on incidence of AA, but had an effect on the incidence of NSAP. An increase of 10% in humidity decreased NSAP incidence by 0.8%, 0.992 (95% CI: 0.984-0.999).
Figure 6. Temperature, humidity and incidences of acute appendicitis, and non-specific abdominal pain in 1987-2007 in Finland. AA: Acute appendicitis; NSAP: Non-specific abdominal pain.

Figure 7. Incidences of acute appendicitis and non-specific abdominal pain during the warm compared to the cold periods of the year in Finland. AA: Acute appendicitis; NSAP: Non-specific abdominal pain.
5.3 STUDY III: OUTPATIENT ANTIBIOTIC USE AND THE INCIDENCE OF ACUTE APPENDICITIS IN FINLAND: A NATIONWIDE STUDY FROM 1990-2008

The incidences of AA and AE had linear-like downward trends, whereas the incidence of acute diverticulitis (AD) had a respective upward trend. Correlation of the incidence of AA and AD was strongly negative ($r=-0.938$, $p<0.001$), the incidence of AA and AE was strongly positive ($r=0.991$, $p<0.001$), and the incidence of AD and AE was strongly negative ($r=-0.908$, $p<0.001$). The means ($\pm$ SD) of the incidence of AA and AD during the study period were $12.3\pm1.7$ cases/10\(^{4}\) inhabitants/year and $6.2\pm1.4$ cases/10\(^{4}\) inhabitants/year ($p<0.001$), respectively.

Total outpatient antibiotic use during the study period of 1990–2007 showed a slowly declining trend in Finland, varying from a defined daily dose (DDD) per 1000 inhabitants per day of 19 in 1995 to a DDD per 1000 inhabitants per day of 15 in 2004, respectively, with a mean value of 17 (Figure 8).

The incidence curves for AA and AD were correlated positively and negatively, respectively, with the use of antibiotics. The trends in outpatient use of various antibiotics in Finland from 1990 to 2008 are shown in Figure 9. Penicillins (J01C) and tetracyclines (J01A) were the two main groups of antibiotics prescribed for outpatient use in Finland during this period. The group of beta-lactam antibiotics other than penicillin (J01D) made up more than three-quarters of all outpatient antibiotics used. All but the J01D (other beta-lactams), J01F (macrolides), and J01M (fluoroquinolones) groups showed a declining trend during the 18-year monitoring period. The reduced consumption of antibiotics was more pronounced for the J01A (tetracyclines) and J01E (sulfonamides, trimethoprim) groups than for other groups. The overall consumption of antibiotics in the J01E, J01F (macrolides, lincosamides, and streptogramins), and J01M groups remained at less than 4 DDD/1000 inhabitants/day.

A statistically significant increase was noted only in the J01F (macrolides, $p<0.039$, 1.7 to 1.9 DDD/10\(^{4}\) inhabitants) and J01M (fluoroquinolones, $p<0.001$, 0.6 to 1.3 DDD/10\(^{4}\) inhabitants). The time series of appendicitis and diverticulitis were not co-integrated with those of the antibiotics examined ($p>0.15$ for each co-integration). Moreover, there was no correlation found for geographical differences in the incidence of AA with antibiotic use.

5.4 STUDY IV: CLINICAL AND LABORATORY FINDINGS IN THE DIAGNOSIS OF RIGHT LOWER QUADRANT ABDOMINAL PAIN: OUTCOME ANALYSIS OF THE APPAC TRIAL

The diagnosis changed after CT in 27% (n=351) of the patients with suspected AA according to clinical and laboratory findings. These patients avoided unnecessary AE and 54% of them (n=191/351) had no abnormal findings on CT (NSAP). In the rest of the 160 patients (46%) with no appendicitis on CT, imaging revealed another specific diagnosis for acute abdomen. Of these 160 patients, 45 had acute diverticulitis, 39 patients had gynaecological disorders and 76 patients presented with other miscellaneous diagnosis. Patient data, clinical, laboratory and pain characteristics of appendicitis patients and those with no appendicitis are presented in Table 6.
Figure 8. Antibacterial agents prescribed for systemic use, trends in antibiotic use, and incidences of acute appendicitis and acute diverticulitis in Finland from 1990 to 2007.

Figure 9. Consumption of antibiotics in Finland from 1990 to 2007 in defined daily dose per 1000 inhabitants/day.
Table 6. Demographic, clinical, laboratory and pain characteristics of the patients with right lower quadrant abdominal pain (n=1321).

<table>
<thead>
<tr>
<th></th>
<th>Acute appendicitis</th>
<th>Other diagnosis</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Median (IQR)</td>
<td>Min-Max</td>
</tr>
<tr>
<td>Age</td>
<td>970 (35.0%)</td>
<td>35.0 (26.0-47.0)</td>
<td>17.0-64.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>600 (80%)</td>
<td></td>
<td>150 (20.0%)</td>
</tr>
<tr>
<td>Women</td>
<td>370 (64.8%)</td>
<td></td>
<td>201 (35.2%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12h</td>
<td>195 (74.4%)</td>
<td>67 (25.6%)</td>
<td>262 (20.1%)</td>
</tr>
<tr>
<td>12-24h</td>
<td>348 (88.3%)</td>
<td>46 (11.7%)</td>
<td>394 (30.2%)</td>
</tr>
<tr>
<td>&gt;24h</td>
<td>415 (63.8%)</td>
<td>236 (36.3%)</td>
<td>651 (49.8%)</td>
</tr>
<tr>
<td>Hgb (g/l)</td>
<td>144.0 (134.0-152.0)</td>
<td>84.0-193.0</td>
<td>140.0 (129.0-148.0)</td>
</tr>
<tr>
<td>WBC (E9/l)</td>
<td>12.2 (9.5-15.2)</td>
<td>2.0-33.8</td>
<td>10.0 (7.7-12.3)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>35.8 (11.2-74.0)</td>
<td>0.0-412.0</td>
<td>32.0 (6.0-77.0)</td>
</tr>
<tr>
<td>VAS</td>
<td>6.0 (4.0-7.0)</td>
<td>1.0-10.0</td>
<td>6.0 (5.0-7.5)</td>
</tr>
<tr>
<td>Temp</td>
<td>37.5 (37.1-38.0)</td>
<td>35.4-40.6</td>
<td>37.5 (37.0-38.0)</td>
</tr>
</tbody>
</table>

AA patients were older than patients with other diagnosis (p<0.0001) and the duration of abdominal symptoms was shorter in the AA group (p<0.0001). The mean age of patients with gynecological disorders was 32 years, with NSAP 30 years and with AA 37 years. Patients with acute diverticulitis were, however, significantly older with a mean age of 47 years. The risk increase (OR, Odds ratio) of having AA according to demographic, clinical and laboratory characteristics is presented in detail in Table 7.

Diagnosing AA was more accurate in males compared with females and males also had 2.17 times increased risk of having AA (Table 7). Patients, who had symptoms 12-24 hours before admission, had the highest risk of having AA. Patients with an elevated WBC had a 2.52 times higher risk of having AA than patients who had normal WBC (p<0.0001). With elevated CRP level the risk was only 1.48 times higher (p=0.005). When comparing patients who had both WBC and CRP rise with those with both values normal, the risk of having AA was 11.66 times higher in those with both values elevated (p<0.0001). When all the background factors (duration of symptoms and both WBC and CRP elevated vs. normal) were standardized, the results comparing incidence between genders remained statistically significant. The proportion of patients with both WBC count and CRP normal was significantly (p<0.0007) lower in patients with AA than in patients with other diagnosis.
Table 7. The risk increase (odds ratio, OR) of having acute appendicitis in patients with right lower quadrant abdominal pain (n=1321) according to demographic, clinical, laboratory and pain characteristics (univariate logistic regression analysis).

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0003</td>
<td>1.02</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>WBC high vs normal</td>
<td>&lt;0.0001</td>
<td>2.52</td>
<td>1.88-3.38</td>
</tr>
<tr>
<td>CRP high vs normal</td>
<td>0.005</td>
<td>1.48</td>
<td>1.13-1.94</td>
</tr>
<tr>
<td>WBC and CRP high vs normal</td>
<td>&lt;0.0001</td>
<td>11.66</td>
<td>5.41-25.12</td>
</tr>
<tr>
<td>Temperature</td>
<td>0.72</td>
<td>1.05</td>
<td>0.81-1.35</td>
</tr>
<tr>
<td>VAS</td>
<td>0.11</td>
<td>0.90</td>
<td>0.79-1.02</td>
</tr>
<tr>
<td>Hgb</td>
<td>&lt;0.0001</td>
<td>1.02</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>Men vs Women</td>
<td>&lt;0.0001</td>
<td>2.17</td>
<td>1.70-2.79</td>
</tr>
</tbody>
</table>

To discriminate the patients with AA from those without, optimal cutoff points were evaluated for the laboratory tests for clinical use. Therefore, ROC curves were calculated for the laboratory parameters and the results are presented in detail in Table 8. The area under (AUC) the ROC curve represents the overall accuracy of both WBC and CRP separately and also combined WBC and CRP in identifying patients with AA from those without. Ideal cut-off points were assessed as a maximum sum of sensitivity and specificity (Youden index). The area under the ROC curve measures accuracy of a test. According to a traditional academic point system, AUC for an excellent test is 0.90-1; a good test 0.80-0.90; a fair test 0.70-0.80; poor test 0.60-0.70, and a failing test <0.60. The results indicated that in clinical decision making even ideal cut-off points led to poor discrimination between patients with AA and those without. Results with maximum sensitivity are also shown in Table 8. None of these markers or their combination accurately differentiated between patients with AA and those with other diagnoses.

Table 8. The clinical value of the laboratory tests in separating patients with acute appendicitis (n=970) from those without (n=351) According to receiver operating characteristic curves.

### Diagnostic Accuracy of WBC and CRP in patients with suspected AA using ROC curves

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>9.2 (E9/l)</td>
<td>70,7% (56,9-82,0%)</td>
<td>63,7% (51,7-78,3%)</td>
<td>84,3% (81,4-88,3%)</td>
<td>44,2% (83,1-51,2%)</td>
<td>0,710 (0,679-0,742)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP</td>
<td>5 (mg/l)</td>
<td>65,0% (52,1-82,9%)</td>
<td>57,6% (39,0-71,5%)</td>
<td>80,7% (77,7-84,4%)</td>
<td>37,5% (33,3-47,3%)</td>
<td>0,635 (0,599-0,670)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WBC+CRP</td>
<td>9,0/6</td>
<td>70,2% (54,8-81,5%)</td>
<td>64,0% (53,7-79,1%)</td>
<td>84,3% (81,4-88,2%)</td>
<td>43,9% (37,3-51,9%)</td>
<td>0,711 (0,679-0,742)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The overall accuracy is represented by AUC of WBC, CRP and WBC+CRP. Ideal cutoff points were assessed as maximum sum of sensitivity and specificity (Youden index).
### Ideal cutoff Point determined by the maximum sensitivity

<table>
<thead>
<tr>
<th>Variable Point</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>3.4 (E9/l)</td>
<td>100 %</td>
<td>0.00 %</td>
<td>73.30 %</td>
<td>0.00 %</td>
<td>0.710 (0.679-0.742)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP</td>
<td>3 (mg/l)</td>
<td>100 %</td>
<td>0.00 %</td>
<td>73.20 %</td>
<td>0.00 %</td>
<td>0.635 (0.599-0.670)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WBC+CRP</td>
<td>3.4/12</td>
<td>100 %</td>
<td>0.00 %</td>
<td>73.30 %</td>
<td>0.00 %</td>
<td>0.711 (0.679-0.742)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AA=acute appendicitis; WBC=white blood cell count; CRP=C-reactive protein; PPV=positive predictive value; NPV=negative predictive value ROC=receiver operating characteristic; AUC=area under the ROC
6 Discussion

6.1 INCIDENCE

The mean overall incidence for AA, being strongly age-dependent, showed a declining trend of 32% over the 21 years of the study period (12.8/10'000 on average) (Study I). The incidence of the NSAP stayed almost unchanged during the study years, being 34.0 per 10'000 population on average. There was no relationship observed between AA and NSAP during the study period.

The mean level of the incidence of AA in Finland, presented in the first study are in accordance with reports from other Scandinavian countries, as well as in European, Asian and American countries (14,17,82,84,85,87,88,92,106,299). Higher levels of incidence were found in whites and Hispanics compared to Asians and Africans (84,85,106). In a large cohort study from Sweden, there were found high incidence rates of AA in immigrants and adoptees from South America, and lower rates in immigrants for Africa and Asia (193). Hereditary factors might play a stronger role in appendicitis than environmental factors (193). Interestingly, AA is less frequent in Africa where it has been found to be almost a 10th of that in other countries. So far, no clear explanation has been found.

A diminishing trend in incidence has been reported in studies from Norway, Sweden, England, Canada and Taiwan (7,14,86,90,92,93), while another study from Norway (87) found stability in incidence of AA, and a few studies from America and Nigeria reported increasing trends (94,95). The reasons for changes in incidence are unclear and might be multifactorial. Some authors have suggested that socioeconomic status plays a role in the pathogenesis of AA (74,74,83,90). It has been supposed that the improvement in hygiene status and decline in infectious diseases as a consequence of improved living standards could alter the response of lymphoid tissue in the appendix wall to enteric infections, indirectly affecting the frequency in AA (74,74,83,90). In addition, the dietary fibre hypothesis has been proposed as an etiological factor for AA. Although there is additional radiation exposure, the usage of CT as a diagnostic tool in a patient with abdominal pain has increased, and it has been become a golden standard imaging modality for suspected AA (177,300,301). The increased usage of CT might reduce the frequency of unnecessary AE and at least partly explain the decreasing trend in AA. CT can also help establish a differential diagnosis with regard to other conditions that might produce similar symptoms to AA, such as gynecologic or urinary tract infections. Spontaneous resolution of AA may occur in some cases, and some patients with a nonspecific clinical manifestation of AA may have been treated conservatively. Moreover, it could be that patient awareness of abdominal diseases and their course has improved, and patients with a mild manifestation may not as readily go to the doctor. Surgical education and centralization of appendectomies into larger hospitals may also reduce unnecessary appendectomies.

6.2 CLIMATE

It has been speculated that temperature and humidity have an effect on the incidence of AA. In the present study, a significant association was found between the incidence of AA and temperature, but not humidity (Study II). The incidence of AA is higher during the warm period of the year. The incidence of NSAP has a statistically significant association with humidity but not with temperature. The incidence of NSAP is higher during a period with higher levels of humidity.

The seasonality of the AA, as well as of respiratory and cardiological diseases, are well known, and have been discussed in many studies (93,115,117,302,303). The true role of
temperature on development of appendicitis is unclear. Unless the fluctuation of the temperature during the seasons of the year is over forty degrees, the true effect of a temperature on the human body core is minor. In the summertime the effect is more straightforward than in winter, when people usually dress warmly and they spend more time inside. Therefore, the true effect of temperature might be questionable, and some additional factors may play an important role. Interestingly, although the appendicitis rate is higher in the warm season of the year in most countries, the incidence of AA in African countries is still low (17,79). Moreover, a higher incidence in Africa is noted especially during the rainy season, when the humidity is significantly higher (94). There is speculation that sweating is lesser because of higher levels of humidity and therefore formation of fecoliths is lower. In Africa, the fluctuation of temperature is minimal in comparison to countries with a non-equatorial climate, and fluctuation is associated mostly with humidity and not to temperature. In addition, it is possible that people with abdominal pain do not visit a doctor so easily in Africa, and mild cases of AA might resolve spontaneously. In a study from Nigeria (94), where the temperature has high levels all year round, the incidence of the AA was reported to be higher during the cooler and rainy season than during the warmer season. It is possible that different extrinsic factors such as allergens, viral and bacterial infections might play a role during humidity changes. Nevertheless, in the present study the impact of humidity on AA was not significant.

6.3 ANTIBIOTIC USE

The quite liberal usage of outpatient antibiotics might have a prophylactic effect on development of symptomatic appendicitis. In the third investigation, a declining trend was noted in antibiotic use during the study years. It seemed that there was no clear co-integration between antibiotics usage and infection in the incidence of AA.

It has been shown that a majority of patients with uncomplicated AA may safely be treated with antibiotics (34). We presumed that increased prescriptions of antibiotics might be one reason for a decrease in the incidence of AA. Surprisingly, total outpatient antibiotic prescriptions during the study period of 1990–2007 showed a slowly declining trend in Finland. The increase was noted only in the macrolides and fluoroquinolones group. The most notable decrease in prevalence of the AA was about 2500 patients during a twelve year (form 1995 to 2007), which makes about 250 patients in one year, in Finland. Finnich Medicines Agency data indicated an increase of quinolones use during the same timeframe at about 3000 DDD, which makes 250 DDD/year, in Finland. The nationwide study in Finland indicates that the declining rate of AA is not associated with the use of outpatient antibiotics (Study III). Moreover, the incidence of AD in Finland has increased in the past several decades. The clinical pictures of AA and AD may in some cases be similar, which might partially explain the decrease in emergency appendectomies. During the period of the study, the prescription of antibiotics in primary care practice in Europe varied greatly, with the highest rate being in France and the lowest rate being in the Netherlands (304). Among the Scandinavian and European countries, a shift was noted from the use of old, narrow-spectrum antibiotics to the use of new, broad-spectrum antibiotics. The use of penicillins decreased and the use of amoxicillin-clavulanic acid increased (304). The increased use of fluoroquinolones in particular might prevent some admissions of patients with suspected AA for surgical treatment (Study III). Antibiotic use in Finland is within the same range as in other western European countries, but the situation with regard to antibiotic resistance is better (305). It may also be possible that the diminished overall use of antibiotics in Finland protects innate immunity and saves patients from acute appendicitis. However, the decrease in incidence of AA was 30%, whereas the use of antibiotics declined only by 15%. Nevertheless, the role of immunity in the decline in incidence of AA is theoretical, and future studies of this issue will be needed. There is an escalating problem
with antibiotic resistance among intestinal pathogens in patients with acute surgical infections (306).

6.4 CLINICAL AND LABORATORY FINDINGS

The diagnosis of AA has historically been based on clinical investigation. The usage of computed tomography has increased the diagnostic accuracy of AA for patients with RLQP, and it is advisable to find out possible uncomplicated AA. In the present study, for 27% of patients with clinically suspected AA, the diagnosis was altered after CT imaging and no surgical treatment was needed. In recent years, the traditional treatment for uncomplicated AA with AE has been challenged and it has been shown that the majority of patients with uncomplicated acute appendicitis may safely be treated with antibiotics (34). Several miscellaneous diseases needing no treatment or some specific treatment other than appendectomy can mimic clinical symptoms and laboratory findings of acute appendicitis. In our study, NSAP is found in 54% of patients with negative AA in CT scan followed by diverticulitis and gynecological disorders (Study IV). Similarly, in a prospective study Schellekens et al. showed the same distribution of CT-diagnoses with NSAP as the main finding followed by gynecological disorders and acute diverticulitis (133). Other studies have had similar results (300,307). It is of pivotal importance to be able to identify patients with a more complicated course of acute appendicitis needing surgery and at the same time to evaluate the optimal use of antibiotic therapy in patients with uncomplicated acute appendicitis. The diagnostic accuracy of clinical evaluation alone is about 80% in acute appendicitis (308). Imaging modalities and clinical scoring systems (i.e., Alvarado, Lintula, Adult Appendicitis Score) may increase diagnostic accuracy up to 95% (150,153,308). In the literature, there are various earlier studies on the role of laboratory tests in the diagnosis of acute appendicitis (128,129,133,148,154). WBC and CRP are useful in diagnosis, and particularly in excluding acute appendicitis (129). The elevation of WBC and CRP may be associated with various intra-abdominal infections, and the specificity of these laboratory markers alone remains low. According to our study, if both values were normal, acute appendicitis was very unlikely. In addition, there was no statistically significant difference in VAS or temperature levels between patients with acute appendicitis and those without.

To conclude, the results of our present study suggest that the current clinical or laboratory tests alone are not sufficiently reliable to diagnose AA.

6.5 STRENGTHS AND WEAKNESSES IN STUDIES

A major strength of the study was the use of population-based registries, covering all patients in different geographical areas of Finland. Additionally, in the second study, the Finnish Meteorological Institute provided high-quality observational data. As a population-based retrospective study, however, there are also weaknesses. There was use of discharge diagnoses in our analyses for studies I-III. Therefore, the data about appendicitis was without histological confirmation. In the first study, the discharge diagnosis of appendicitis is a clinical diagnosis, which is usually overestimated at operation. There is a reported 6% overestimation of appendicitis by surgeons (86). In comparison, according to Kraemer et al. (309), there was no evidence to support the assumption that the macroscopic diagnosis of appendicitis is unreliable.

In the second study, the small difference between the mean temperatures in the warm and cold period and the low mean annual temperature could be considered as a possible bias when generalizing conclusions. However, in reports from warmer countries [United States (85), Canada (93), Iran (115), and South Africa (117), a similar incidence peak of AA during the warmer period was observed.
In the third study, a weakness was that there are no exact data on the reasons for outpatient antibiotic prescription. However, the daily dose data for antibiotics is reliable because the Finnish drug reimbursement registry has nearly 100% coverage.

Study IV was limited by the relatively small number of patients, but the data was collected prospectively and was based on large, well-defined prospective multicenter patient material.
7 Conclusion

(I) There has been a decline in the incidence of AA and NSAP during a 21-year period in Finland. We did not see any connection between the incidence rates of AA and NSAP.

(II) The incidence of appendicitis, but not NSAP, was significantly higher during warm times of the year. This difference remained unchanged during the whole 21-year study period. Humidity had effect on the incidence of NSAP, but not on AA.

(III) The changes in outpatient use of antibiotics during the period of 20 years in Finland may partly explain the changes in incidences of AA and AD.

(IV) About one out of four patients with a clinical diagnosis of acute appendicitis did not have acute appendicitis on CT. The main alternative diagnosis was NSAP followed by acute diverticulitis and gynecological disorders. There are neither clinical findings nor laboratory markers reliable enough to distinguish between patients with acute appendicitis and those without.
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Acute appendicitis occurs in approximately 10% of the general population. In this thesis, I found that the incidence of appendicitis has declined by almost 30% in Finland between 1987 and 2007. It is affected by improved diagnostic accuracy, seasonal variation of temperature, but not by the outpatient antibiotic use. To date, neither clinical findings nor laboratory tests have been able to distinguish reliably the patients with appendicitis from the patients with nonspecific abdominal pain.