Diagnosis and treatment of complicated and uncomplicated appendicitis

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Diagnosis and treatment of complicated and uncomplicated appendicitis

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Chapter 1

General introduction and outline of this thesis

The appendix was first depicted in an anatomic drawing 1492 by Leonardo da Vinci. [1] Several years later, Reginal Fitz first described the inflamed appendix and introduced the term appendicitis in 1886. He also suggested surgical treatment for patients with appendicitis.[2] For a long time, the appendectomy was performed by an open procedure through a gridiron incision, as described by Charles McBurney.[3] This diagonal incision lays over over McBurney's point; two-thirds between the umbilicus and the right anterior superior iliac spine. Nowadays, most patients with appendicitis are operated on laparoscopically, a technique introduced by the gynaecologist Kurt Semm in 1983. [4, 5]

It was a longtime belief that acute appendicitis was a progressive disease, starting with mild inflammation, progressing to inflammation with necrosis, eventually leading to perforation. Therefore, it was believed that the appendix should always be removed.

Nowadays, it is thought that there are two different entities of acute appendicitis: uncomplicated (simple) and complicated (complex) appendicitis. [6-9] Uncomplicated appendicitis is the so-called phlegmonous appendicitis with no signs of necrosis or perforation. This type of appendicitis is thought to be reversible and possibly even self-limiting. Besides that, it will not progress to a complicated form of appendicitis. In complicated appendicitis, the appendix is (partially) necrotic and might be perforated. This type of appendicitis is deemed irreversible. This concept has consequences for diagnosis and treatment of uncomplicated as well as complicated appendicitis. In the last two decades, it has been described that patients with suspected uncomplicated appendicitis can be safely treated with non-operative treatment. These patients have been treated with antibiotics, or even without antibiotic treatment, instead of surgery. This non-operative treatment seems to be as effective and safe as surgical treatment. [10] However, patients treated with antibiotics have a chance of recurrent appendicitis up to almost 23% in the first year after treatment. This can increase up to 40% in the five years after non-operative treatment. [11] The current Dutch national guidelines state that the standard treatment for uncomplicated acute appendicitis remains appendectomy, but non-operative treatment can be considered in patients who have an increased risk of surgical complications.

Ruling out complicated appendicitis because of the risk of full thickness necrosis and subsequent perforation is essential before starting non-operative treatment. The difficulty is that there is no gold standard for discriminating complicated appendicitis from uncomplicated appendicitis; the diagnosis is only adequately accurate during surgery. Vice versa, in patients with complicated appendicitis, delay in surgery may lead to a higher risk of perforation, abscess formation, and more postoperative complications. The Dutch national guidelines of acute abdominal pain, emergency procedures and acute appendicitis advise appendectomy within eight hours after diagnosis in patients with suspected complicated appendicitis. [12-14] In patients with suspected uncomplicated appendicitis, surgery can be postponed 24-48 hours after diagnosis. Delaying surgery in patients with suspected uncomplicated appendicitis does not increase the number of perforations or postoperative complications. [15]

In the Netherlands, diagnosis of acute appendicitis includes the use of imaging. It is advised to start with ultrasound (US) as the first imaging modality. If the ultrasound is inconclusive or inconclusive while appendicitis is suspected based on clinical assessment, a Computed Tomography (CT) is performed. With this imaging strategy, still half of the patients with complicated appendicitis are missed.[16] Atema et al. developed a scoring system based on clinical, biochemical and radiological features (from US or CT) which demonstrates to be a more accurate way to discriminate between complicated and uncomplicated appendicitis. Upon development, this scoring system reached a sensitivity of 96.3% and a negative predictive value (NPV) of 94.6% but has not been externally validated yet.

Aim of thesis

This thesis focuses on complicated and uncomplicated appendicitis treatment and diagnostics. Most studies in this thesis were based on data from the Dutch SNAPSHOT Appendicitis database. In a SNAPSHOT study, a cross-sectional study is performed in a high number of participating hospitals to investigate a common condition or treatment. The design rapidly provides data, which gives an excellent insight in the variation of current clinical practices and the data is well suited for hypothesis generating comparative analyses. Many SNAPSHOT studies are resident-led. The SNAPSHOT Appendicitis study was a prospective, observational cohort study, conducted in June and July 2014, including patients who underwent surgery for suspected appendicitis. In the SNAPSHOT study, 1975 patients were included from almost all 62 Dutch hospitals. The database contains preoperative, perioperative variables and a 30-day follow-up. Results have been published earlier.[5]

Chapter 2 contains a summary in English of the updated Dutch guidelines of acute appendicitis. This guideline, published in 2019, provides evidence-based recommendations for acute appendicitis care in the Netherlands. The guideline was written by a working group commissioned by the Dutch Society of Surgery, consisting of four surgeons, two radiologists, a gynaecologist, a paediatrician, two physician-researchers, a resident from the emergency department, a patient representative from the Dutch Patient Federation.

Part one: diagnosing (complicated) appendicitis

In **Chapter 3,** the Dutch SNAPSHOT Appendicitis database is used to describe the diagnostic accuracy of US, CT, Magnetic Resonance Imaging (MRI) or a combination of these imaging modalities for discrimination of uncomplicated and complicated appendicitis. As this is based on Snapshot data, it represents real-world data and reflects the interpretation of radiology reports by treating physicians in daily practice. In **Chapter 4,** a systematic review with a meta-analysis is performed to describe the diagnostic accuracy for US, CT and MRI in discriminating uncomplicated from complicated appendicitis. **Chapter 5** is the study protocol of the Score of Acute appendicitis Severity (SAS) trial.

In this observational, multicenter cohort study, the scoring system developed by Atema et al. will be validated externally. It is hypothesized that SAS can reach a sensitivity and a negative predictive value of both 95% on external validation.[17] If not, SAS will be optimized and validated in a second cohort as part of this study. **Chapter 6** is a narrative review. In this review, our view of diagnosing acute appendicitis is explicated, and the differentiation between uncomplicated and complicated appendicitis is depicted.

Part two: treatment and consequences

In **Chapters 7, 8 and 9,** data is used from the Dutch SNAPSHOT appendicitis database. **Chapter 7** focuses on the delay in surgery. Currently, no direct evidence is available on whether delaying surgery in complicated appendicitis leads to a higher proportion of postoperative complications. In this chapter, primary outcomes are the proportion of patients with complicated appendicitis and the proportion of patients with a postoperative complication in patients who are operated on within eight hours compared to patients who are operated on after eight hours. **Chapter 8** explores the differences in patients with appendicitis who present at the emergency department during day time compared to those presenting at night. It is hypothesized that patients presenting at night have a higher burden to visit the hospital and, therefore, more often might have complicated appendicitis, which eventually may lead to more postoperative complications. In **Chapter 9,** the safety of reassessing patients with acute appendicitis after an emergency department visit is discussed. In some patients, it is unclear whether abdominal pain is because of appendicitis or not. In that case, surgeons can reassess a patient and not admit a patient to the hospital. In this study, postoperative complications between patients with acute appendicitis who are reassessed versus those who are not reassessed.

In the final chapter, **Chapter 10,** 250 Dutch citizens, randomly picked by a Dutch marketing office, are presented with two scenarios; one explaining laparoscopic appendectomy and one about the non-operative treatment. In this chapter, the opinion of the average Dutch population is explored in surgical versus conservative treatment for uncomplicated appendicitis. Knowledge about patient (population) preference is important as up to 40% of all patients with suspected uncomplicated appendicitis treated with antibiotics without surgery may have recurrent appendicitis in the first five years after treatment. On the other hand, these patients are not exposed to the risks and complications of laparoscopic appendectomy, narcosis, and postoperative scars.

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Chapter 2

Updated guideline of diagnostics and treatment for acute appendicitis

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On behalf of the Dutch Society of Surgery

Submitted

Introduction

Appendicitis is one of the most common causes of acute abdominal pain in children and adults, with an incidence of 77 to 89 per 100.000 per year, with a lifetime prevalence of about 9% in Western countries. [1, 2] Despite the high prevalence, variations in care exist between doctors, hospitals, and countries. The previous Dutch guideline for acute appendicitis was published in 2010 and since then diagnostic and treatment strategies for appendicitis have changed. For this reason, the Dutch guidelines recently have been revised. The goals of this guideline are to optimise the following outcomes: perioperative morbidity, length of hospitalisation, recovery to normal functioning, pain, treatment success, and perioperative care. This was done by updating the following subjects: diagnostic work-up, nonoperative treatment of simple appendicitis, treatment of complex appendicitis, and surgical technical aspects. All guideline recommendations are made for three subgroups: children, adults, and pregnant women. This national guideline provides evidence-based recommendations for acute appendicitis care. Its conclusions and recommendations are valuable information for other countries.

Methods

The guideline has been drafted in accordance with the ‘Guidelines 2.0’ report of the Guideline Advisory Committee of the Council on Science, Education, and Quality (WOK). This report is based on the AGREE II instrument ((Appraisal of Guidelines for Research & Evaluation II) (www.agreecollaboration.org)). The guideline was written by a working group commissioned by the Dutch Society of Surgery, consisting of four surgeons, two radiologists, a gynaecologist, a paediatrician, two physician-researchers, a resident from the emergency department, and a patient representative from the Dutch Patient Federation. An external advisory group consisted of a medical microbiologist and another surgeon. The guideline was supported by a consultant, literature specialist and secretary of the Dutch *‘The Knowledge Institute of the Federation of Medical Specialists.’* Possible bottlenecks were explored with help from the Dutch Societies of Emergency Care, Pediatrics, Surgery, Nursery, and Hospitals. All recommendations from the previous (2010) guideline were reviewed. After discussion in the working group, outdated recommendations were converted into clinical queries.

Search Strategy

Medline (OVID) and Embase (Elsevier) were searched for relevant publications for each query. Search terms were drafted, and afterwards conducted together with a literature specialist. Studies were retrieved with the highest level of evidence, preferably with Randomised Controlled Trials (RCTs) and, if absent, observational trials. Articles were screened for relevance by two members of the working group, based on pre-defined selection criteria.

Critical Appraisal

Individual studies were systematically appraised using the validated risk of bias tools recommended by the Cochrane Collaboration: AMSTAR (systematic reviews), Cochrane (Randomized Controlled Trials), ACROBAT-NRS (observational studies) and QUADAS-II (Diagnostic studies). Literature was summarised, and in case sufficient homogenous data were available, they were summarised quantitatively in a meta-analysis with Review Manager 5. The level of evidence was determined using the GRADE-method. Based on these findings, conclusions from the literature were drawn. Then, all outcomes were assessed, and overall conclusions were drawn. After being discussed in the working group, conclusions were then transferred into recommendations.

Commentary and authorisation phase

The draft guideline was submitted to all relevant stakeholders (e.g., several Dutch Societies of medical specialities, Health and Youth Care Inspectorate, Zorgverzekeraars Nederland (The Dutch society of health insurance companies)) for commentary. Comments were collected and discussed within the working group. Afterwards, the draft version was updated and finalised. The Dutch Societies of Emergency Care, Pediatrics, Obstetrics & Gynaecology, Surgery, Nursery, and Hospitals authorised the final version.

Definitions

This guideline uses three definitions of acute appendicitis. [3]

Acute appendicitis:

Acute appendicitis, acute inflammation of the appendix vermiformis. Histologically the acute appendicitis is defined as a transmural infiltration with leukocytes or pus in the lumen. Acute appendicitis has two entities: simple and complex appendicitis.

Simple appendicitis:

Phlegmonous appendicitis without necrosis or perforation, also known as the ‘uncomplicated appendicitis.’ This type is not very progressive and likely reversible. [3]

Complex appendicitis:

A more severe, progressive type of appendicitis with necrosis or perforation of the appendix, also known as the ‘complicated appendicitis’. [3]

The full version of the guideline is available in Dutch at https://richtlijnendatabase.nl/richtlijn/acute_appendicitis/startpagina_-_acute_appendicitis.html

Results

Search strategies can be found in supplement 1. The tables of evidence and risk of bias assessment of the included studies per query are described in supplement 2. The following clinical queries were formulated:

1. “What is the optimal diagnostic strategy for children, adults, and pregnant women with suspected appendicitis?”
2. “Which treatment is preferred in children, adults, and pregnant women with suspected simple appendicitis?”
3. “Which surgical technique is preferred in adults, children, obese, and pregnant women?”
4. “What is the optimal technique for appendix stump closure?”
5. “What is the added value of rinsing combined with suction as compared to suction alone or no suction of the intra-abdominal space during an appendectomy for (complex) appendicitis?”
6. “What is the optimal duration of antibiotic treatment given postoperatively after an appendectomy for complex appendicitis?”
7. “What is the risk of obstetric complications after an appendectomy during pregnancy as compared to pregnant women without appendicitis or appendectomy?”

1. Optimal diagnostic strategy

Conclusions from literature

It is the working group’s opinion that the combined diagnostic accuracy of clinical and biochemical findings for diagnosing acute appendicitis is insufficient, and that imaging is indicated to reliably diagnose acute appendicitis, thereby reducing the negative appendectomy rate. For adults, the diagnostic accuracy of a Computed Tomography scan (CT) appears to be higher compared to ultrasound (US) ([4], GRADE low), with a pooled sensitivity and specificity of 91% and 90% for CT and 78% and 83% for US. However, accuracy of work-up with US and conditional CT (if necessary in case of negative or inconclusive US) is comparable to only CT ([5], GRADE low). Accuracy of US with conditional CT (if necessary) is comparable to a Magnetic Resonance Imaging scan (MRI) with and without US ([6], GRADE low). For children, all available evidence was considered as very low ([7-16], GRADE very low). Therefore, it is unclear whether US, CT, or MRI or a combination performs best in children. Diagnostic accuracy for US seems to be better in children than adults: pooled sensitivity and specificity for US were 89% and 97% for children versus 69% and 81% for adults. [16, 17] In pregnant women, evidence in comparing different imaging modalities was also graded as very low ([8, 18-28], GRADE very low). US was inconclusive more often in pregnancy than in adults and children (up to 97%). [28]

Considerations

The use of imaging in all patients with clinically suspected appendicitis results in lower costs per patient, fewer complications, and fewer negative appendectomies. [29] The usage of US diagnostics in children with suspected appendicitis is associated with lower costs. US is broadly available and avoids radiation. If negative or inconclusive, additional imaging with CT or MRI is needed to prevent unnecessary surgery and anaesthesia. To avoid the radiation dose of CT, MRI should be considered in children and pregnant women.

Recommendations

Perform initially a US in every patient with suspected appendicitis. See flowchart 1, 2, and 3 for the diagnostic work-up in adults, children, and pregnant women.

Adults

Perform a CT or MRI in adult patients with negative or inconclusive US and a high clinical suspicion of acute appendicitis without an alternative diagnosis. MRI is preferred in young adults, especially in female, fertile patients. Perform a diagnostic laparoscopy in patients with an inconclusive MRI or CT but a high clinical suspicion of acute appendicitis. Adult patients with low clinical suspicion of acute appendicitis but without an alternative diagnosis should be reassessed at a later point in time. This reassessment can be done by repeating clinical evaluation and US. A CT is indicated when an adult patient has an abscess or large periappendicular infiltrate on US imaging.

Children

Perform a MRI in children with an inconclusive US and a high clinical suspicion of acute appendicitis without an alternative diagnosis. Consulting a specialised paediatric hospital is advised before performing a diagnostic laparoscopy in case of an inconclusive MRI in children or when MRI is not possible without anaesthesia. Consider reassessing the patient with an inconclusive US and a low clinical suspicion of acute appendicitis. After reassessment of the patient, consider repeating the US, since a CT is not preferable in paediatric patients.

During pregnancy

It is good custom to discuss the diagnostic findings of a pregnant patient also with a gynaecologist. Perform an MRI, if US is inconclusive. If both US and MRI are negative, refer the patient for further evaluation to the Obstetrics and Gynaecology department. Admit pregnant women with clinical symptoms of appendicitis and inconclusive imaging at the Obstetrics and Gynaecology department.

2. Treatment of simple appendicitis

Conclusions from literature

In adults, nonoperative treatment reduces the number of complications compared to appendectomy ([30], GRADE low). However, nonoperative treatment is associated with a considerable number of patients that encounter recurrent appendicitis after initial success, being 21% within one year ([30], GRADE moderate). The number of major complications in the appendectomy group versus the nonoperative treatment group was 8.4% versus 4.9%, respectively. For minor complications this was 13.2% in the appendectomy group versus 2.3% in the nonoperative treatment group.

The results were inconclusive for the efficacy of nonoperative treatment compared to operative treatment in children ([31-33], GRADE very low). No studies were found in pregnant patients.

Considerations

For adults, nonoperative treatment decreases the number of patients with complications, but at a high risk of recurrent appendicitis. Given the current evidence, surgical treatment is still considered to be the preferred treatment. However, the patients' personal preference should be considered, and therefore nonoperative treatment may be offered to patients after shared decision making. An appendicolith is a known risk factor for failure of nonoperative treatment and recurrent appendicitis. [34-36] There is no evidence available for nonoperative treatment in pregnant women and for children; results were inconclusive. Due to the association between systemic infections and obstetric complications such as preterm birth, an appendectomy is indicated.

Recommendations

The standard treatment for patients with simple acute appendicitis remains appendectomy. Nonoperative treatment can be considered in patients who have an increased risk of surgical complications. If nonoperative treatment is considered, a patient must be informed of advantages as well as disadvantages of nonoperative and operative treatment, to come to an informed decision for either treatment option (shared decision making). Do not treat pregnant women, patients with an appendicolith, or patients with suspected malignancy with nonoperative treatment. For children, nonoperative treatment should only be offered as part of clinical research.

3. Open versus laparoscopic appendectomy

Conclusions from literature

For adults, laparoscopic appendectomy decreases the proportion of wound infections compared to open appendectomy ([37-42], GRADE moderate). In addition, laparoscopic surgery lowers the length of hospital stay and leads to lower overall pain scores ([37-39, 41, 42], GRADE low). The evidence comparing laparoscopic to open appendectomy for the risk of an intra-abdominal abscess and the number of re-interventions was graded as very low, also in the subgroup of patients with suspected complex appendicitis ([38, 39, 42, 43], GRADE very low). For children, there is a lower risk of wound infections after laparoscopic appendectomy compared to open appendectomy ([42, 44], GRADE low). However, length of hospital stay is comparable ([42], GRADE low). For pain, outcomes are inconclusive ([42], GRADE, very low). Outcomes are inconclusive concerning obese and pregnant women ([45-47], GRADE very low).

Considerations

Laparoscopy decreases the number of wound infections in both adults (3.3% versus 7.6%, [37-42]) and children (2.4% versus 7.4%, [42, 44]) and may decrease hospitalisation days and Visual Analogue Scale (VAS) pain scores postoperatively. Therefore, laparoscopy is preferred in adults and children. For pregnant women, the gestational age has a significant influence on the choice between the two techniques. In most studies, laparoscopy is used more often in the first and second trimester, while an open approach is used more often in the third trimester. Three studies responsible for the majority of patients included in the guideline's systematic review, are cohort studies and do not provide information about gestational age, which makes it difficult to correct for this variable. This has a direct impact on crucial outcomes such as the miscarriage risk and preterm birth, making it impossible to draw solid conclusions. Although evidence was graded as very low, the working group advises to consider open appendectomy in pregnancies of more than 24 weeks, if the radiologist can mark the location of the appendix. It is the working group's opinion that a laparoscopic introduction could lead to more complications, because the intra-abdominal space is too limited due to the size of the uterus.

In most young children, only a small incision is needed for an open appendectomy. Therefore, one small incision for open appendectomy may be preferred over three small incisions needed for the laparoscopic appendectomy.

Recommendations

Preferably perform a laparoscopic appendectomy. Consider an open appendectomy when experience with laparoscopic surgery is not sufficient or in young children in which only a small incision is needed. Open appendectomy should also be considered in pregnant women with a gestational age of more than 24 weeks after a radiologist has marked the location of the appendix.

4. Staples versus ligature versus endoclips

Conclusions from literature

The working group was unable to draw conclusions from the literature concerning the effect of the different techniques of stump closure - staples versus ligature versus endoclips - on postoperative morbidity, re-hospitalisation, and hospitalisation days ([48-50] GRADE very low).

Considerations

Although no cost-effectiveness evaluations have been performed, there is a significant upfront difference in material costs. Costs for ligature are approximately €50, endoclips €20, and a stapling device €300. [51, 52] Therefore, using a ligature or endoclips is a cheaper alternative as compared to a stapling device. This should be considered when performing an appendectomy. For patients with complex appendicitis, in which the appendix is difficult to mobilise or the base of the appendix too inflamed, the use of a stapling device may be warranted and beneficial.

Conclusion and recommendation

Use ligature or endoclips if the appendix can be mobilized as usual. Consider stapling if the base of the appendix is inflamed, or when mobilising the appendix is difficult.

5. Suction of purulent fluid versus suction combined with rinsing

Conclusions from literature

When comparing suction of purulent fluid and rinsing to suction alone, the working group was unable to draw conclusions from the literature regarding morbidity (defined as intra-abdominal abscesses, wound infections, or re-interventions) and length of hospitalisation ([53], GRADE very low). Combining suction and rinsing may lead to a shortened number of readmissions ([53], GRADE very low). Suction combined with rinsing probably leads to a longer operation time ([53], GRADE moderate). No evidence was found for suction and rinsing compared with no suction and no rinsing.

Considerations

The number of readmissions may be lower when rinsing and suction are combined. However, the evidence is graded low because of the small number of patients and events. Our recommendation was based on consensus in the working group.

Conclusion and recommendation

Use suction without rinsing to remove purulent fluid in case of complex appendicitis with pus. Add rinsing when pus remains in the abdominal cavity despite suction.

6. Postoperative antibiotic treatment duration

Conclusions from literature

The working group was unable to draw conclusions about the effect of antibiotic treatment duration on morbidity after appendectomy for complex appendicitis ([54-56], GRADE very low). It appears that a shorter (3 days) duration of antibiotic administration does not lead to more infectious postoperative complications than a longer duration (> 3 days).

Considerations

A shorter antibiotic course is not associated with a higher risk of infectious complications, e.g., wound infections and intra-abdominal abscesses, after appendectomy for appendicitis. For individual patients, this reduces the length of hospital stay. Shorter antibiotic treatment duration may lead to lower costs, but cost-effectiveness data are lacking.

Conclusion and recommendations

Treat patients with complex appendicitis postoperatively for three days with antibiotics, initially intravenously. If a persistent infection is suspected after three days, diagnostic work-up including imaging should be done to find the cause.

7. Appendicitis and obstetric complications

Conclusions from literature

The working group was unable to draw conclusions about the risk of appendectomy on miscarriage and foetal growth restriction ([57-59], GRADE very low).

Considerations

Although only very low level of evidence is available, there is no evidence of an increased risk of intrauterine foetal death after appendectomy. The risk of preterm birth appears to be higher in pregnant women with appendicitis, especially in pregnancies between 24 and 28 weeks.

Conclusion and recommendations

In pregnant women with appendicitis and a gestational age between 24 and 28 weeks, consult a centre with neonatal intensive care facilities on obstetric policy and possible referral. It is important to take the following into account: signs of preterm birth, the clinical condition of the pregnant patient, and the consequences of delaying appendectomy because of a referral. Instruct patients on the risk of preterm birth in the period after appendectomy and stress the importance of contacting their obstetric caregiver in case of postoperative complaints.

Discussion

Although appendicitis was first described in the 19th century, there are still knowledge gaps. [60] This guideline addresses specific issues of treating appendicitis, specifically the diagnostic work-up, nonoperative treatment, paediatric and pregnant patients, surgical techniques, and postoperative antibiotic treatment.

As compared to other published guidelines, this guideline is based on several new systematic reviews explicitly performed for this guideline. A multidisciplinary working group reached consensus on all topics. Previous guidelines, such as EAES [61] and WSES [62] appendicitis guidelines, are mostly consensuses based and did not perform complete systematic reviews for each primary question separately.

Both EAES and WSES guidelines advise the use of scoring systems. Present guideline working group did not advise the use of a scoring system in our guideline, as the gold standard to diagnose appendicitis is imaging. Many scoring systems have been developed but are not suitable for all patients. For instance, some commonly used diagnostic scoring systems in other countries perform differently between males and females.[63] A recent meta-analysis for published scoring systems found that on initial assessment <3% of patients identified as low risk had appendicitis. However, when these scoring systems were externally validated in other datasets, failure rates increased to up to 32% and therefore seemed unreliable in excluding appendicitis.[63] Besides that, nowadays, low (radiation) dose CT is readily available, which has high accuracy in appendicitis.[64]

Nonoperative treatment for simple appendicitis was not advised in the EAES guideline because of the need for higher quality evidence. The WSES guideline, however, states that nonoperative therapy can be successful in selected patients with uncomplicated appendicitis who wish to avoid surgery and accept the risk for recurrent appendicitis.[62] The WSES recommendation is similar to that of the present guideline, although at a different recurrence rate; a reported recurrence rate of 38% vs a systematic review recurrence rate of 21%). After publication of our guideline, several other RCT's have been published comparing nonoperative therapy versus surgical treatment.[65-67] The results of these studies are comparable with former studies and would not have changed our point of view for patients with uncomplicated appendicitis.

Recommendations on open versus laparoscopic surgery in present guideline are similar to those of the WSES and EAES guidelines. Laparoscopic surgery is advised when equipment and skills are available. However, in present guideline, the working group advises to consider open appendectomy in pregnant patients with a gestational age of > 24 weeks and in small children.

Recommendations in EAES, WSES and present guideline are similar for stump closure and the advice to use suction versus suction and rinsing combined. In a non-inflamed appendix base, ligature or endoclips are advised, based on costs. A stapling device may be warranted in patients with an inflamed base of the appendix. Use suction alone instead of suction and rinsing combined.

For patients who have complicated appendicitis, postoperative antibiotics are advised in all guidelines. The EAES guidelines advise 48 hours of IV antibiotics with subsequent oral administration. However, about the advised total duration of antibiotic treatment remains inconclusive. The WSES guidelines advise 3-5 days of antibiotics for adult patients, and discontinuation of antimicrobial treatment based on clinical and biochemical findings. Both guidelines are comparable to present recommendation, but in the present guideline the recommendation of antibiotic treatment is more specified: For patients with complex appendicitis postoperatively three days of antibiotics, initially intravenously; if a persistent infection is suspected after three days, perform further diagnostic work-up.

Present guideline is the first to recommend consulting a tertiary centre in pregnant patients with a gestational age between 24 and 28 weeks for obstetric policy and possible referral. The EAES guideline advises a multidisciplinary approach to pregnant patients with appendicitis, but no further guidance is provided. The WSES guidelines do not make any recommendations on this topic.

Conclusion

In present guideline preoperative diagnostics, perioperative morbidity, nonoperative treatment of simple appendicitis, treatment of complex appendicitis, and surgical technical aspects have been updated based on new and rigorous systematic reviews on these topics.

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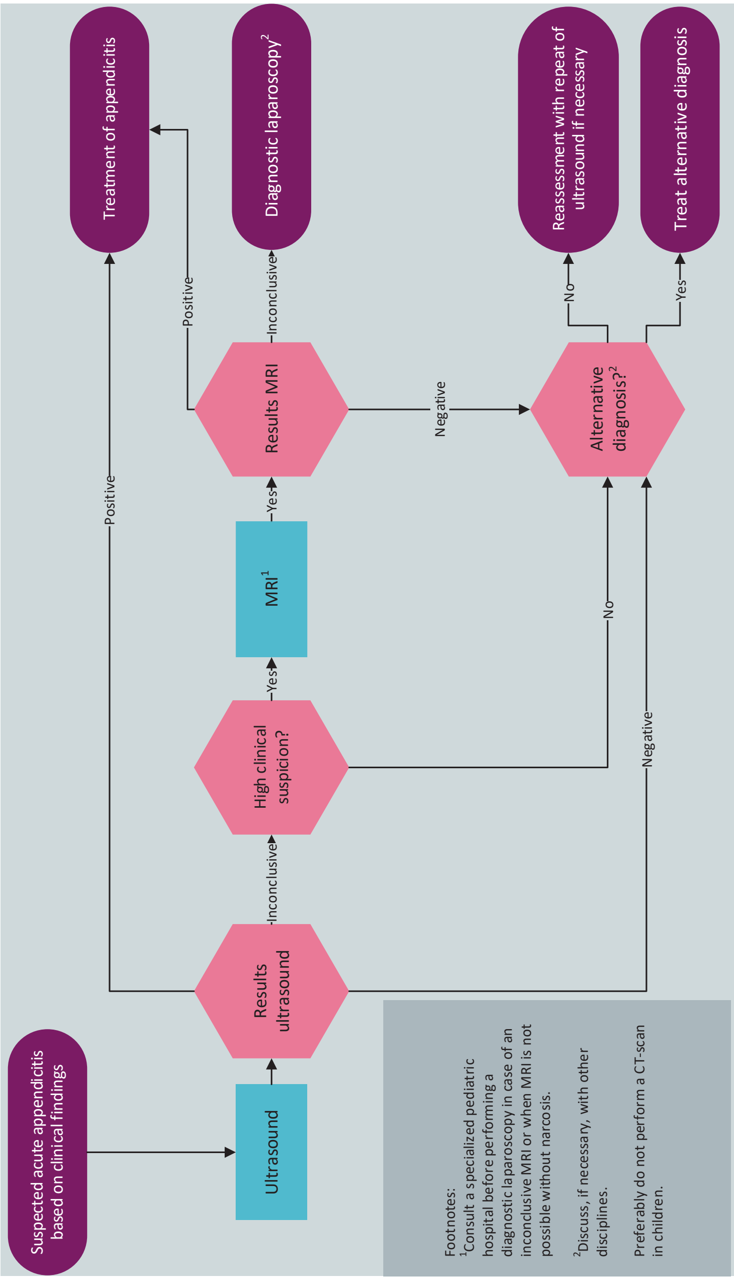

NB1: This flow chart is part of the module "Diagnostic strategy in children" from guideline "Acute appendicitis". Always read the considerations and recommendations of the relevant module for nuances, possible deviating situations and extra background information.

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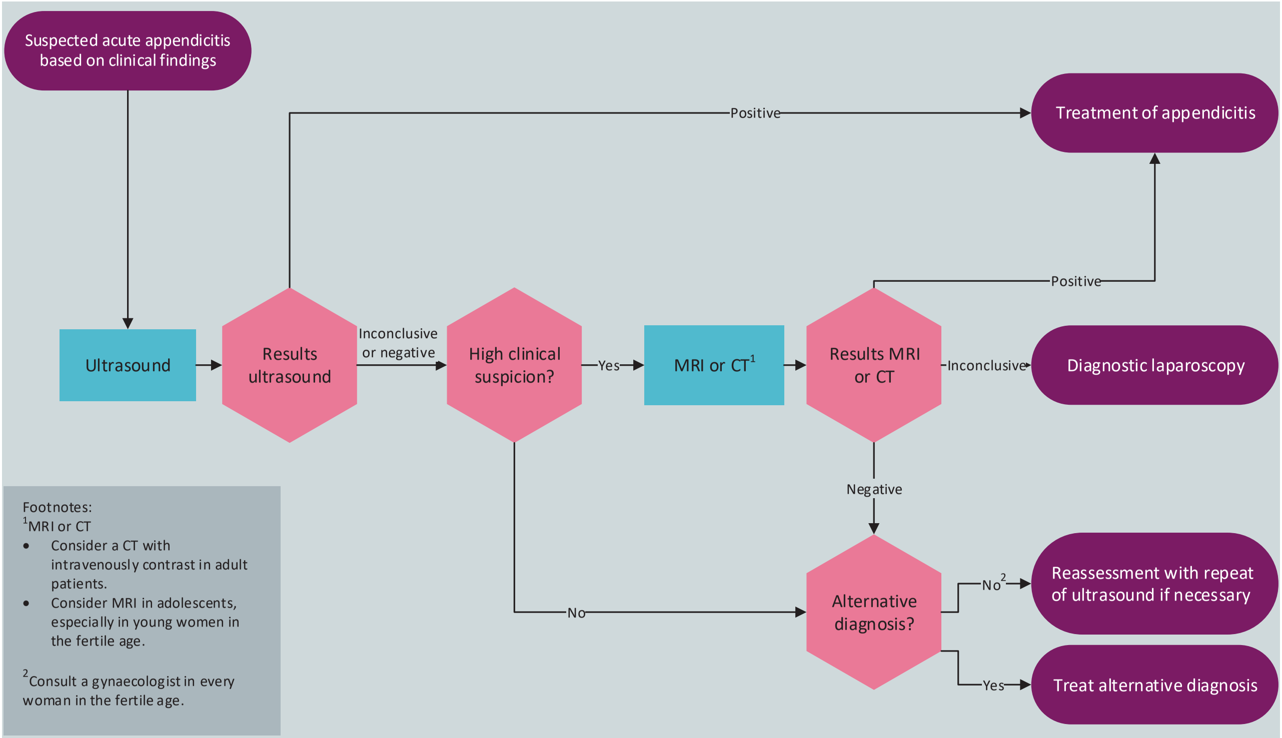
Flowchart 1
Diagnostic strategy in children



Nederlandse Vereniging voor Heelkunde

NB1: This flow chart is part of the module "Diagnostic strategy in adults" from guideline "Acute appendicitis". Always read the considerations and recommendations of the relevant module for nuances, possible deviating situations and extra background information.

Federatie Medisch Specialisten

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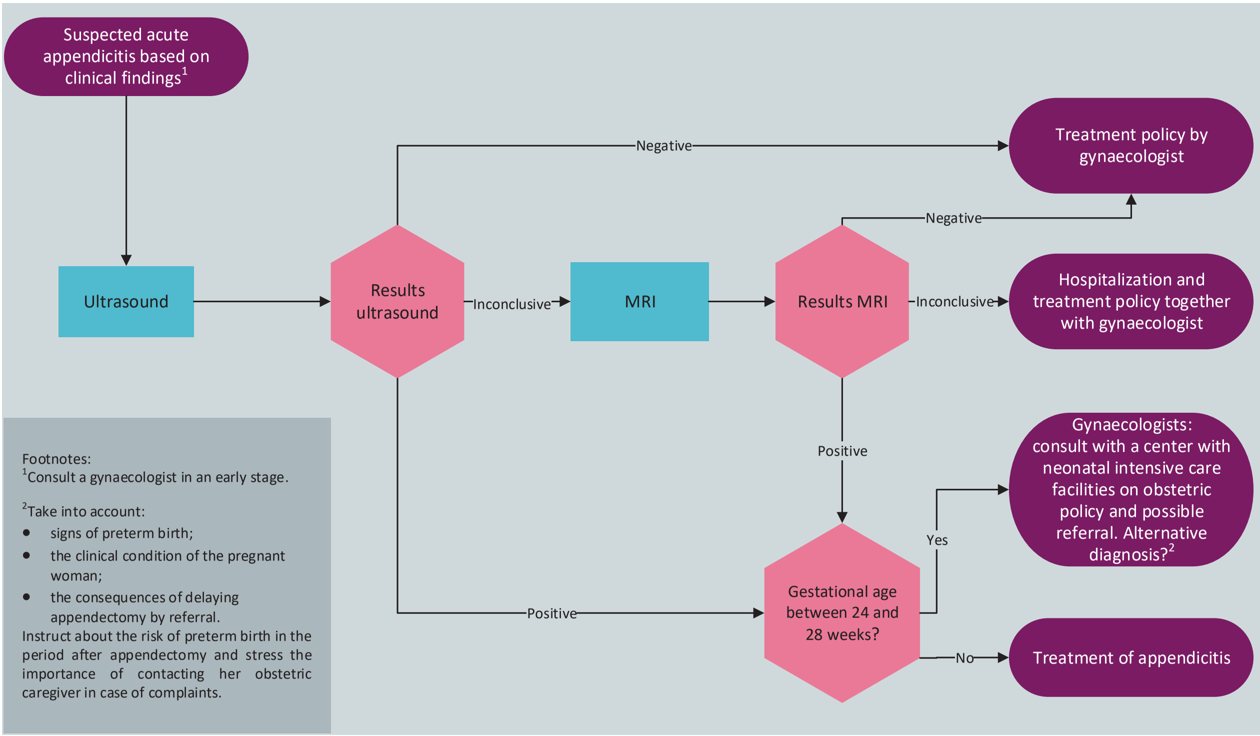
Flowchart 2
Diagnostic strategy in adults



Nederlandse Vereniging voor Heelkunde

NB1: This flow chart is part of the module "Diagnostic strategy in pregnant women" from guideline "Acute appendicitis". Always read the considerations and recommendations of the relevant module for nuances, possible deviating situations and extra background information.

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Flowchart 3
Diagnostic strategy in pregnant women

Supplement 1 and 2

Supplement 1 can be found at:

https://drive.google.com/drive/folders/1A9stRV6J_G5LOEMnsTGGmkxTmZfD2guv?usp=sharing

Or scan:

Supplements S1 and S2

PART I

Diagnosing (complicated) appendicitis

Chapter 3

Accuracy of imaging in discriminating complicated from uncomplicated appendicitis in daily clinical practice

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Abstract

Background

Radiologic imaging can accurately diagnose acute appendicitis, but little is known about its discriminatory capacity between complicated and uncomplicated appendicitis.

Objective

This study aims to investigate the accuracy of imaging in discriminating complicated from uncomplicated appendicitis.

Methods

Data was used from the prospective, nationwide, observational SNAPSHOT appendicitis database, including patients with suspected acute appendicitis who were planned for an appendectomy. Usage of Ultrasound (US), CT, MRI, or a combination was recorded. Radiological reports were used to group for complicated or uncomplicated appendicitis. The reference standard was based on operative and pathological findings. Primary outcomes were sensitivity and specificity in discriminating complicated from uncomplicated appendicitis. Secondary outcomes were diagnostic accuracy results per imaging modality and for the subgroups age, BMI, and sex.

Results

Preoperative imaging was performed in 1964 patients. In 1434 patients (73%) only US was used, in 109 (6%) patients only CT was used, and 421 (21%) patients underwent US followed by CT or MRI. Overall, imaging workup as practiced, following the national guideline, had a poor sensitivity for complicated appendicitis of only 35%, although specificity was as high as 93%. For US, accuracy for complicated appendicitis was higher in children than in adults; sensitivity 41.2% vs 26.4% and specificity 94.6% vs 93.4%, respectively, $p=0.003$. For relevant subgroups such as age, sex and BMI, no other differences in the discriminatory performance were found.

Conclusion

A diagnostic workup with stepwise imaging, using a conditional CT or MRI strategy, poorly discriminates between complicated and uncomplicated appendicitis in daily practice.

Introduction

According to the current standard of practice, the use of imaging in the workup for acute appendicitis leads to a decrease in the negative appendectomy rate. [1-3] In the Netherlands, this workup mainly includes an ultrasound (US) followed by a conditional CT-scan (CT) in case of negative or inconclusive US, or in children, young adults and pregnant women an MRI. [2, 4] All imaging modalities are subjected to their availability and accuracy. Besides that, they may have specific disadvantages like radiation.

There is a growing belief that uncomplicated and complicated appendicitis, or simple and complex appendicitis, are two different entities. [5] The presence of necrosis indicates the major difference between uncomplicated and complicated appendicitis. Complicated appendicitis is defined by the presence of necrosis. It is thought that uncomplicated appendicitis does not develop necrosis, and, therefore, will not progress into complicated appendicitis. [6] On the contrary, it could be hypothesised that patients with complicated appendicitis present with complicated appendicitis from the start of the disease.

It is relevant to discriminate complicated from uncomplicated appendicitis. For uncomplicated appendicitis, recent studies suggest that uncomplicated appendicitis may be treated with antibiotics alone. [7-9] Although effective and safe, this conservative treatment has a risk of recurrent appendicitis, increasing to 40% after five years. [10] On the other hand, patients with complicated appendicitis should not be treated with antibiotics alone because of the chance of perforated appendicitis. Guidelines advise to perform surgery for patients with complicated appendicitis as soon as possible, or at least within eight hours after diagnosis. [1, 11]

These differences in the treatment regimen make it essential to recognise and treat complicated appendicitis within eight hours when patients present to the hospital.

Some studies have described the diagnostic accuracy of discriminating between complicated and uncomplicated appendicitis for the imaging workup. [12, 13] Others used a scoring system, including clinical features combined with radiological features. [14, 15] These studies were mostly setup as diagnostic accuracy studies in which operators were aware of study participation. We conducted an audit in which imaging results were collected in all patients operated for acute appendicitis in order to describe the accuracy of different imaging strategies in both uncomplicated and complicated appendicitis. This study aims to investigate the diagnostic accuracy of imaging in discriminating complicated from uncomplicated appendicitis in everyday practice.

Materials and methods

Study design

For this study data, from the SNAPSHOT appendicitis database was used. This database contains data from a prospective, nationwide, observational study, which included 1975 consecutive patients who underwent surgery for suspected appendicitis during two months in 62 Dutch hospitals (3 months in a pilot setting in eight hospitals). Patients who were treated conservatively by antibiotics or radiological drainage for suspected appendicitis, were not included. Complete methods have been described previously. [16]

Data collection

Surgical residents scored clinical variables at the emergency department, and collected findings from imaging, surgical and histological reports. Data about the imaging modality were collected, as were imaging findings as interpreted by this physician. This interpretation was a diagnosis based on the imaging report and could include the following options: uncomplicated appendicitis, complicated/ perforated appendicitis, acute appendicitis with an appendicular infiltrate/abscess or inconclusive. The radiology reports were not standardized and full reports were not collected in the database.

Test methods

The index test was the interpretation of imaging findings and conclusions of the radiologist by the surgical resident. This interpretation is crucial for treatment decisions and is therefore representative for clinical practice. For the index test, complicated/perforated appendicitis or acute appendicitis with an appendicular infiltrate/abscess was classified as complicated appendicitis. The reference standard was a final diagnosis of complicated appendicitis, uncomplicated appendicitis, and no appendicitis based on surgical and histologic findings. Complicated appendicitis was defined as perforated or gangrenous appendicitis, or if antibiotics were required immediately after surgery. The group of patients whose final diagnosis was ‘no appendicitis’ included patients with an uninflamed appendix, a neoplasm of the appendix, or another diagnosis, according to the pathologist or surgeon.

Outcomes

The primary outcome is the diagnostic accuracy in discriminating complicated from uncomplicated appendicitis for the imaging workup as performed in line with the national guideline. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated. Secondly, these values were described for US, primary CT, primary MRI, and a fourth group, including US with conditional CT and US with conditional MRI. In an additional analysis, the reference standard, performed by surgeon only (based on perioperative findings) and pathologist only (based on histopathological findings), was analysed separately. All outcomes were measured for the subgroups of adults vs children and male vs female patients. For patients older than 16, body mass index (BMI) was calculated and divided into subgroups BMI $<$25 vs $\geq$25.

As we only included patients who underwent appendectomy, no true negatives (TN) (patients correctly labelled as having no appendicitis) were available in this dataset. Therefore, no diagnostic accuracy measures for simply the diagnosis of appendicitis could be calculated. The focus of this study was discrimination between complicated and uncomplicated appendicitis.

Uncomplicated versus Complicated appendicitis

To discriminate complicated from uncomplicated appendicitis, 3x3 tables were constructed, comprising the diagnoses complicated appendicitis, uncomplicated appendicitis, and no appendicitis. As it is in our interest to rule out complicated appendicitis, 2x2 contingency tables were constructed out of 3x3 tables. Therefore, patients with inconclusive outcomes were added to the group of expected uncomplicated appendicitis. Patients without primary appendicitis, according to the reference standard, were added to the reference group of uncomplicated appendicitis.

Data analysis

IBM SPSS Statistics version 25.0 was used for analysis. As only descriptive outcomes were calculated, X^2 was used for significant differences for sensitivity and specificity in the subgroups. In this case, only the lowest p-value was reported. A p-value $<$0.05 was considered as statistically significant.

Results

Baseline

Out of the 1975 patients, a total of 1964 patients were used for this study, as in one patient imaging data were missing, and in ten patients, no imaging was performed. Of 1964 patients, 1807 had appendicitis, of which 617 had complicated appendicitis, 1190 had uncomplicated appendicitis, and 157 patients did not have appendicitis according to the surgeon or pathologist. Of these 157 patients without appendicitis, in 99 cases no appendectomy was performed or an uninflamed appendix was found, 36 patients had a neoplasm (both benign or malignant) and 22 patients had another diagnosis (e.g. Crohn's disease or endometriosis). In 1434 patients (73%) US was used without conditional imaging. In 341 (17%) patients US was followed by CT, and in 79 (4%) an US was followed by MRI. In 109 (6%) patients, only CT was used, and one (0.1%) patient had an MRI without an US (see flowchart, figure 1).

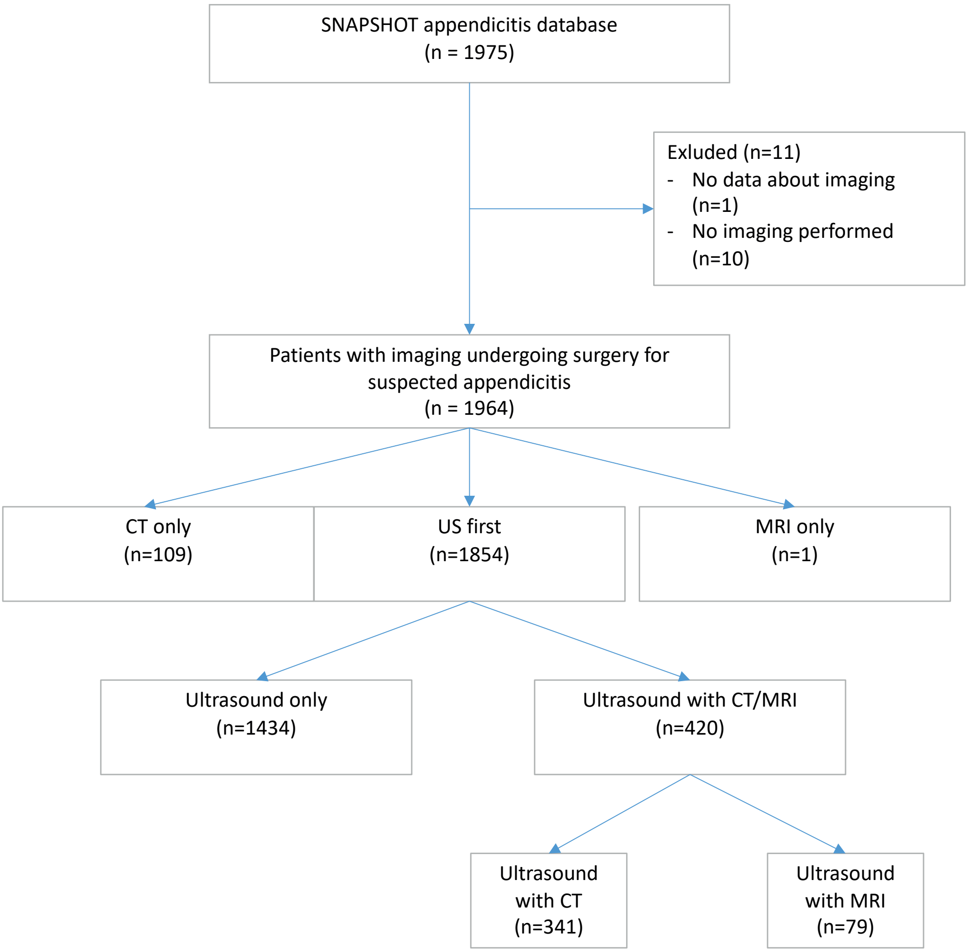

Figure 1, *flowchart*

One thousand fifteen (52%) patients were male, and 535 (27.2%) were aged <18 years. No data were missing for age and sex. For BMI, data was missing in 748 (49%) patients older than 16. For patients with a BMI <25, US as the only modality was performed in 74% compared to 56% of patients with a BMI ≥25, (see table 1). In 91% of children, US was the only imaging modality used versus 66% of adults. According to radiology reports, 314 patients (16%) were labelled as complicated appendicitis and 1526 patients (77%) as uncomplicated appendicitis; imaging was inconclusive in 124 cases (6%).

	US only	CT only	US+CT/MRI*	None
Performed workup	73% (1434/1974)	6% (109/1974)	21% (421/1974)	1% (10/1974)
Age				
- < 18 years	91% (490/541)	0% (0/541)	8% (45/541)	1% (6/541)
- ≥ 18 years	66% (944/1433)	8% (109/1433)	26% (376/1433)	0% (4/1433)
BMI				
- BMI < 25	74% (325/438)	4% (19/438)	21% (94/438)	0% (0/438)
- BMI ≥ 25	56% (187/333)	11% (37/333)	32% (107/333)	1% (2/333)
Sex				
- Male	76% (771/1021)	4% (44/1021)	20% (200/1021)	1% (6/1021)
- Female	70% (663/953)	7% (65/953)	23% (221/953)	0% (4/953)
Final diagnosis				
-Complicated appendicitis	62% (386/620)	9% (58/620)	28% (173/620)	1% (3/620)
-Uncomplicated appendicitis	79% (944/1196)	4% (42/1196)	17% (204/1196)	0% (0/1196)
- No appendicitis	66% (104/158)	6% (9/158)	28% (44/158)	0% (0/158)

***Table 1**, Performed imaging modality per subgroup*
** Conditional CT/MRI (CT only after negative or inconclusive US, as according to national appendicitis guideline)*

Outcomes

Overall workup

Overall, 1840 (94%) of all patients with suspected acute appendicitis had a conclusive result based on imaging. The other 124 (6%) patients were operated with inconclusive imaging. Of 1807 patients with the final diagnosis of acute appendicitis, the radiological diagnosis was appendicitis in 1714 (94.7%) cases.

The sensitivity and specificity of the workup as performed for discriminating complicated from uncomplicated appendicitis were 35% (213/617) and 93% (1246/1347), respectively (see table 2); PPV for complicated appendicitis was only 68% and NPV 76%. Sensitivity and specificity were comparable if the reference standard was defined by the surgeon only or pathologist only (table S1 and S2). For any given imaging workup, sensitivity, specificity, PPV and NPV for complicated appendicitis were not significantly different in age, sex, and BMI (see table 3).

	Sensitivity	Specificity	PPV	NPV
Overall	35% (213/617)	93% (1246/1347)	68% (213/314)	76% (1246/1650)
US	32% (122/386)	94% (926/1048)	65% (122/187)	79% (926/1247)
CT	45% (26/58)	88% (45/51)	81% (26/32)	58% (45/77)
US+CT/MRI*	38% (65/173)	88% (218/248)	68% (65/95)	67% (218/326)

***Table 2,** diagnostic accuracy for complicated appendicitis according to performed imaging workup. PPV, Positive Predictive Value; NPV, Negative Predictive Value*
** Conditional CT/MRI (CT only after negative or inconclusive US, as according to national appendicitis guideline)*

	Sensitivity	Specificity	PPV	NPV	P-value
Age					0.15
- < 18 years	39% (59/150)	94% (362/385)	72% (59/82)	80% (362/453)	
- ≥ 18 years	33% (154/467)	92% (884/962)	66% (154/232)	74% (884/1197)	
BMI					0.45
- BMI < 25	30% (40/133)	94% (286/305)	68% (40/59)	75% (286/379)	
- BMI ≥ 25	30% (35/117)	92% (197/279)	67% (35/52)	73% (197/279)	
Sex					0.09
- Male	32% (103/327)	92% (633/688)	65% (103/158)	74% (633/857)	
- Female	38% (110/290)	93% (613/659)	71% (110/156)	77% (613/793)	

Table 3, *diagnostic accuracy for complicated appendicitis for subgroups after imaging workup.*
PPV, Positive Predictive Value; NPV, Negative Predictive Value
The p-value was calculated by chi-square test for sensitivity and specificity. Only the lowest value was mentioned.

Ultrasound

In 1854 patients, ultrasound was the modality of the first choice, 1706 patients had appendicitis, 148 had an alternative diagnosis. In 420 of 1854 (22.7%) cases US was inconclusive or negative, and an additional CT or MRI was performed. In 1434 patients US was performed without additional imaging. In 84 of 1854 (4.5%) cases US was inconclusive, but patients went for surgery without any further imaging. In 386 of 1434, complicated appendicitis was the final diagnosis, in 944 uncomplicated, and in 104 cases the final diagnosis was other than appendicitis. The sensitivity of US for complicated appendicitis was 34% (122/386), and specificity 94% (983/1048). Diagnostic accuracy was higher in children than adults; sensitivity was 41.2% vs 26.4% and specificity 94.6% vs 93.4%, respectively, p=0.003. For age, sex and BMI, no significant differences in imaging performance were found, see table S1.

CT

In 109 patients, only CT was performed. Of these, 100 patients had a final diagnose of acute appendicitis. Ninety-six per cent (96/100) of patients operated for acute appendicitis, were correctly diagnosed with CT only.

In 58 patients, the final diagnosis was complicated appendicitis, in 42 uncomplicated appendicitis, and in 9 patients no appendicitis. Sensitivity and specificity for complicated appendicitis, in patients who underwent CT only, were 45% (26/58) and 88% (45/51), respectively. No significant differences were found for the subgroups age, BMI, or sex, see table S1.

US with conditional CT or MRI

In 420 cases US was inconclusive, and an additional CT or MRI was performed. Of these, 376 patients did have acute appendicitis. Ninety-four per cent (353/376) of patients operated for acute appendicitis, were correctly diagnosed with US and conditional CT or MRI. In 172 patients, the final diagnosis was complicated appendicitis. Sensitivity and specificity for complicated appendicitis were 37% (64/172) and 88% (218/248), respectively. No significant differences were found in the subgroups age, BMI, and sex, see table S1.

Discussion

Given current imaging workup, on the whole, following the national guideline, 94.7 per cent of patients selected for appendectomy with the final clinical and imaging diagnosis of acute appendicitis had a correct diagnosis of appendicitis. Discriminating complicated appendicitis from uncomplicated appendicitis by imaging workup showed poor results with a sensitivity of 35%, although specificity was 93%. The highest sensitivity (45%) and positive predictive value (81%) for complicated appendicitis were accomplished by a CT scan only approach. For relevant subgroups such as age, sex and BMI, no clinically relevant differences in discriminatory performance of the imaging modalities were found.

A prospective study exploring the diagnostic accuracy of imaging for perforated appendicitis has found a sensitivity and specificity of 55% and 88%, respectively. [17] Another prospective study (OPTIMAP study) describes diagnostic accuracy results for US with conditional CT if necessary and compares these with MRI alone. The results of that study are largely in line with the present study, finding a sensitivity and specificity for complicated appendicitis for US with conditional CT of 48% and 93% and for MRI alone 57% and 86%, respectively. [12] However, we found lower sensitivities in diagnosing complicated appendicitis. This difference may be explained by research bias in former studies. Radiologists in the present study did not know that their reports would be checked and reports were not standardized. Present findings, therefore, represent real-world data of radiological results of patients with suspected appendicitis.

Routine workup with ultrasound combined with MRI or CT, if necessary, is therefore an excellent discriminator between appendicitis and another abdominal disease. In diagnosing acute appendicitis, recent literature shows a pooled sensitivity and specificity for US of 69% (95% CI 59-78%) and 81% (95% CI 73-88%), respectively. [18] For CT, pooled sensitivity and specificity is 91% (95%CI 84-95%) and 90% (95% CI 85-94%)[4] and for MRI 96.6% (95% CI 92-99%) and 96% (95% CI: 89.4%-98.4%). [19] In a conditional CT approach, CT follows US in case of negative or inconclusive US, thereby incorporating the limited sensitivity but high specificity of US for appendicitis in an efficient imaging strategy. For US with conditional CT, a sensitivity for acute appendicitis of 97% and specificity of 91% have been reported previously, and for MRI this is 98% and 88%, respectively. [20]

In discriminating complicated from uncomplicated appendicitis, results of imaging are poor in both the present study and published literature. Scoring systems, including both clinical and imaging features, perform better in ruling out complicated appendicitis. [14, 15] Atema et al. has constructed two scoring systems (Severity of Appendicitis Systems, SAS), one including clinical and US features for complicated appendicitis, one including clinical and CT features. SAS achieves a sensitivity of 97% and 90%, for US-SAS and CT-SAS respectively, and a specificity of 46 and 70%; negative predictive values are 97.1% and 94.7%, respectively. Avanesov et al. also have developed a scoring system, including both clinical and CT features to exclude complicated appendicitis and found a sensitivity of 82% and specificity of 93%.[14] However, both these scoring systems are not externally validated yet, and more research should be conducted.

Limitations

Limitations in the current study include that this dataset does not contain all data on true negative patients i.e. negative imaging results and no appendicitis. Therefore, diagnostic accuracy for the diagnosis of acute appendicitis was not the focus of this study. Importantly, for discriminating complicated from uncomplicated appendicitis, however, contingency tables could be constructed, as all consecutive patients undergoing appendectomy for the imaging diagnosis of appendicitis were included. The availability of BMI data was limited, however, the proportion of overweight patients as found was comparable to the average Dutch population. Therefore it was assumed that these missings were at random.[21]

Another limitation of the present study is that we were not able to evaluate imaging results based on a dichotomised decision of the radiologist assigning either a complicated or uncomplicated appendicitis label to each patient. Radiology reports were not standardized, and in many cases, did not explicitly further define the diagnosis of acute appendicitis in complicated or uncomplicated appendicitis. Therefore, our results might be biased to some extent by retrospective interpretation of radiological reports, or because of under-registration of signs of complicated appendicitis by radiologists in their reports. On the other hand, the present study accurately reflects daily practice at the Emergency Department as surgeons interpret written reports of radiologists and thereby classify patients (subconsciously) in complicated or uncomplicated appendicitis. Radiology reports were interpreted by local researchers, which might lead to interobserver variability. The major strength of this study is that it represents real life data results. In the future, standardised imaging reports might be necessary to investigate the true discriminatory capacity of imaging modalities in differentiating complicated from uncomplicated appendicitis.

Conclusions

A diagnostic workup with stepwise imaging, using a conditional CT or MRI strategy, poorly discriminates between complicated and uncomplicated appendicitis in daily practice. A CT only approach was not associated with better discriminatory performance.

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Supplemental material

	Sensitivity	Specificity	PPV	NPV
Overall	35% (223/638)	93% (1235/1326)	71% (223/314)	75% (1235/1650ss)
US	32% (124/394)	94% (977/1040)	66% (124/187)	78% (977/1247)
CT	44% (27/61)	90% (43/48)	84% (27/32	56% (43/77)
US+CT/MRI*	40% (72/183)	90% (215/238)	76% (72/95)	66% (215/326)

Table S1*, diagnostic accuracy for complicated appendicitis according to performed imaging workup with the peroperative findings by surgeon only as reference standard*
PPV, Positive Predictive Value; NPV, Negative Predictive Value
** Conditional CT/MRI (CT only after negative or inconclusive US, as according to national appendicitis guideline)*

	Sensitivity	Specificity	PPV	NPV
Overall	34% (126/373)	88% (1403/1591)	40% (126/314)	85% (1403/1650)
US	31% (70/228)	90% (1089/1206)	37% (70/187)	87% (1089/1247)
CT	40% (16/40)	77% (53/69)	50% (16/32)	69% (53/77)
US+CT/MRI*	38% (40/104)	83% (261/316)	42% (40/95)	80% (261/326)

Table S2, *diagnostic accuracy for complicated appendicitis according to performed imaging workup with histopathological findings by pathologist only as reference standard*
PPV, Positive Predictive Value; NPV, Negative Predictive Value
** Conditional CT/MRI (CT only after negative or inconclusive US, as according to national appendicitis guideline)*

Chapter 4

Discriminating complicated from uncomplicated appendicitis by Ultrasound, Computed Tomography or Magnetic Resonance Imaging; a diagnostic accuracy systematic review and meta-analysis

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Abstract

Background:

Discriminating complicated from uncomplicated appendicitis is crucial. Patients with suspected complicated appendicitis are best treated by emergency surgery, whereas those with uncomplicated appendicitis may be treated with antibiotics alone. This study aimed to obtain summary estimates of the accuracy of ultrasound imaging, CT and MRI in discriminating complicated from uncomplicated appendicitis

Methods:

A systematic literature review was conducted by an electronic search in PubMed, Embase and the Cochrane Library for studies describing the diagnostic accuracy of complicated versus uncomplicated appendicitis. Studies were included if the population comprised adults, and surgery or pathology was used as a reference standard. Risk of bias and applicability were assessed with QUADAS2. Bivariable logitnormal randomeffect models were used to estimate mean sensitivity and specificity.

Results:

Two studies reporting on ultrasound imaging, 11 studies on CT, one on MRI, and one on ultrasonography with conditional CT were included. Summary estimates for sensitivity and specificity in detecting complicated appendicitis could be calculated only for CT, because of lack of data for the other imaging modalities. For CT, mean sensitivity was 78 (95 per cent c.i. 64 to 88) per cent, and mean specificity was 91 (85 to 99) per cent. At a median prevalence of 25 per cent, the positive predictive value of CT for complicated appendicitis would be 74 per cent and its negative predictive value 93 per cent.

Conclusion:

Ultrasound imaging, CT and MRI have limitations in discriminating between complicated and uncomplicated appendicitis. Although CT has far from perfect sensitivity, its negative predictive value for complicated appendicitis is high.

Introduction

Imaging is part of the standard workup for diagnosing appendicitis. Ultrasound imaging, CT and MRI are used most frequently. A diagnosis of acute appendicitis can be made adequately based on radiological findings. [1-6] The first choice of diagnostic modality differs. In Europe, ultrasonography is often used as the first approach to diagnose acute appendicitis, combined with CT if necessary in patients with inconclusive or negative results [6-8]; in Northern America, CT first is preferred over US.[9]

As well as confirming the diagnosis of appendicitis, imaging may also help in distinguishing between complicated and uncomplicated appendicitis. Nowadays, it is believed that uncomplicated and complicated appendicitis are different entities, and may require different treatment strategies. In patients with complicated appendicitis, early surgical treatment is necessary to avert a complicated postoperative course. [10] In uncomplicated appendicitis, semiurgent surgery and antibiotic treatment may be an option, and even a waitandsee policy is currently being investigated. [11,12]

Several studies[13-15] have evaluated nonoperative treatment of uncomplicated appendicitis. Treatment with antibiotics may be just as safe and effective as surgical treatment, without the risk of surgical complications, similar to management strategies for other inflammatory bowel diseases, such as diverticulitis or colitis.[14-16] Although studies on antibiotic treatment have shown a low initial failure rate (below 10 per cent), 22 per cent of patients need an appendicectomy within 1 year of followup and up to 40 per cent within 5 years. [15, 17] An essential factor in the success of the nonoperative treatment is the selection of patients with truly uncomplicated appendicitis.

Identifying uncomplicated appendicitis is improved by ruling out complicated appendicitis, which indirectly improves the selection of patients in need of urgent surgery. Thus, to employ different treatment strategies, a discriminatory test with high sensitivity and high negative predictive value (NPV) for ruling out complicated appendicitis is of the utmost importance. The two largest published RCTs [18, 19] assessing the effectiveness of antibiotic treatment for uncomplicated appendicitis used CT alone to discriminate between uncomplicated and complicated appendicitis. They reported 18[18] per cent and 1.5[19] per cent complicated appendicitis in the surgery arm. Therefore, diagnosing complicated appendicitis by CT alone may not be good enough. Moreover, if ultrasound imaging or MRI is adequate in discriminating these entities, perforated appendicitis may be detected without the use of radiation or intravenous contrast agent. This systematic review was designed to obtain summary estimates of the accuracy of ultrasonography, CT and MRI in discriminating complicated from uncomplicated appendicitis.

Methods

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020150771. PRISMADTA guidelines[20] for reporting systematic reviews of diagnostic test accuracy studies were used to prepare this manuscript.

Review question

This review aimed to obtain summary estimates of the (comparative) accuracy of ultrasonography, CT and MRI in discriminating complicated from uncomplicated appendicitis. The secondary aim was to explore sources of heterogeneity of the accuracy of these modalities.

Eligibility criteria

Diagnostic accuracy studies were eligible in which ultrasound imaging, CT, MRI or a combination of these imaging modalities were used to discriminate between complicated and uncomplicated appendicitis. The definition of complicated appendicitis could differ among studies but was used as defined in the original publications. In studies comparing 'perforated' and 'nonperforated appendicitis', perforated appendicitis was considered as complicated appendicitis and nonperforated appendicitis as uncomplicated appendicitis. Both histopathological and perioperative findings, or a combination, were valid as a reference standard.

An estimate of sensitivity and specificity for complicated appendicitis was mandatory for inclusion. Both retrospective and prospective studies were eligible. Studies had to mention the radiological diagnosis of complicated appendicitis, and either report or allow the construction of 2x2 tables on accuracy. If the reported data were unclear, the authors were contacted by email. Only studies reporting only or predominantly on adults (at least 75 per cent; at least 15 years of age) were included, as diagnostic accuracy and workup are different in children[21]. If age was not mentioned, or the study did not report the incidence in adults, this was reported and marked as high risk of bias. The electronic search did not use any limitations, but in the fulltext selection only studies reported in English, German or Dutch were selected.

Information sources

An electronic search was performed in PubMed, Embase and the Cochrane Library. Reference lists of included fulltext study reports were searched manually for missing relevant articles. Keywords assigned to the retrieved articles were used for the additional search. The final search date was 12 November 2019.

Literature search

The search strategy is described in Appendix S1.

Study selection:

Two reviewers independently evaluated potentially eligible studies, assessed these for risk of bias, and extracted data. Disagreements were discussed. If no consensus was reached, a consensus meeting with a third reviewer was decisive.

Data extraction and critical appraisal:

Data from the included studies were systematically, independently and blindly extracted by two reviewers using a structured study record form. Disagreements were resolved in consensus meetings.

The following items were extracted: title, year of publication, journal of publication, name of the first author, number of patients, study design, country, inclusion criteria, exclusion criteria, true positives (TP), true negatives (TN), false positives (FP), false negatives (FN), percentage male, median age (with range), radiological features for complicated appendicitis, reference standard, the definition of complicated appendicitis, imaging characteristics and protocols if reported, number of observers and observers experience.

Risk of bias and concerns about applicability to the review questions were assessed with the QUality Assessment of Diagnostic Accuracy Studies tool, version 2[22]QUADAS2). Two reviewers independently assessed the included articles, and disagreements were resolved in consensus meetings including a third reviewer, if necessary. Studies that included patients retrospectively based on an appendicectomy registration code were marked as at high risk of bias in the patient selection domain, as this might have influenced radiologist judgement.

Statistical analysis

For all included studies, true positives, true negatives, false positives and false negatives for patients with complicated appendicitis were extracted. If data were available, the total number of patients was the number of patients with appendicitis according to the reference standard. Patients considered to have appendicitis by the radiologist, but without appendicitis in the reference group, were included for analyses, if the data were available.

When only sensitivity and specificity were mentioned, counts were combined with the prevalence of complicated appendicitis in the study and 2x2 tables for the diagnosis of complicated appendicitis were reconstructed. If possible, 3x3 tables were extracted, adding the diagnosis 'not appendicitis' in both reference and imaging groups. If two imaging observers were used, the mean counts from contingency tables were used and rounded.

Studyspecific estimates of sensitivity and specificity with 95 per cent c.i. are presented in forest plots. Bivariable logitnormal randomeffect models were used to estimate mean sensitivity and specificity with 95 per cent confidence intervals. A hierarchical summary receiver operating characteristic (HSROC) curve was plotted. Projected posttest probabilities were calculated based on the median prevalence of complicated appendicitis in the eligible studies, and the summary estimates of sensitivity and specificity. As complicated appendicitis needs to be ruled out, a sensitivity of at least 90 per cent and a specificity of at least 50 per cent were deemed necessary. Data were analysed with Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and R (The R Foundation for Statistical Computing, Vienna, Austria) using the mada package.

Potentials sources of heterogeneity were explored, related to imaging characteristics, reader experience, use of intravenous contrast medium, slice thickness, and CT with a standard *versus* low radiation dose. Bivariable metaregression was planned if sufficient studies were available.

Results

The search identified 5285 studies, of which 147 potentially eligible studies were selected for fulltext evaluation. After evaluation of eligibility, 13 studies[23-35] were included in the review (Fig. 1). Eleven studies reported on CT[23, 25-33, 35], one study[24] on ultrasound imaging alone and one study[34] described ultrasound imaging, ultrasonography with conditional CT (CT after negative or inconclusive ultrasound imaging) and MRI. Thus data on ultra sound imaging could be obtained from two studies, CT from 11 studies, and MRI from one study. The combination of ultrasonography with conditional CT was reported in one study[34].

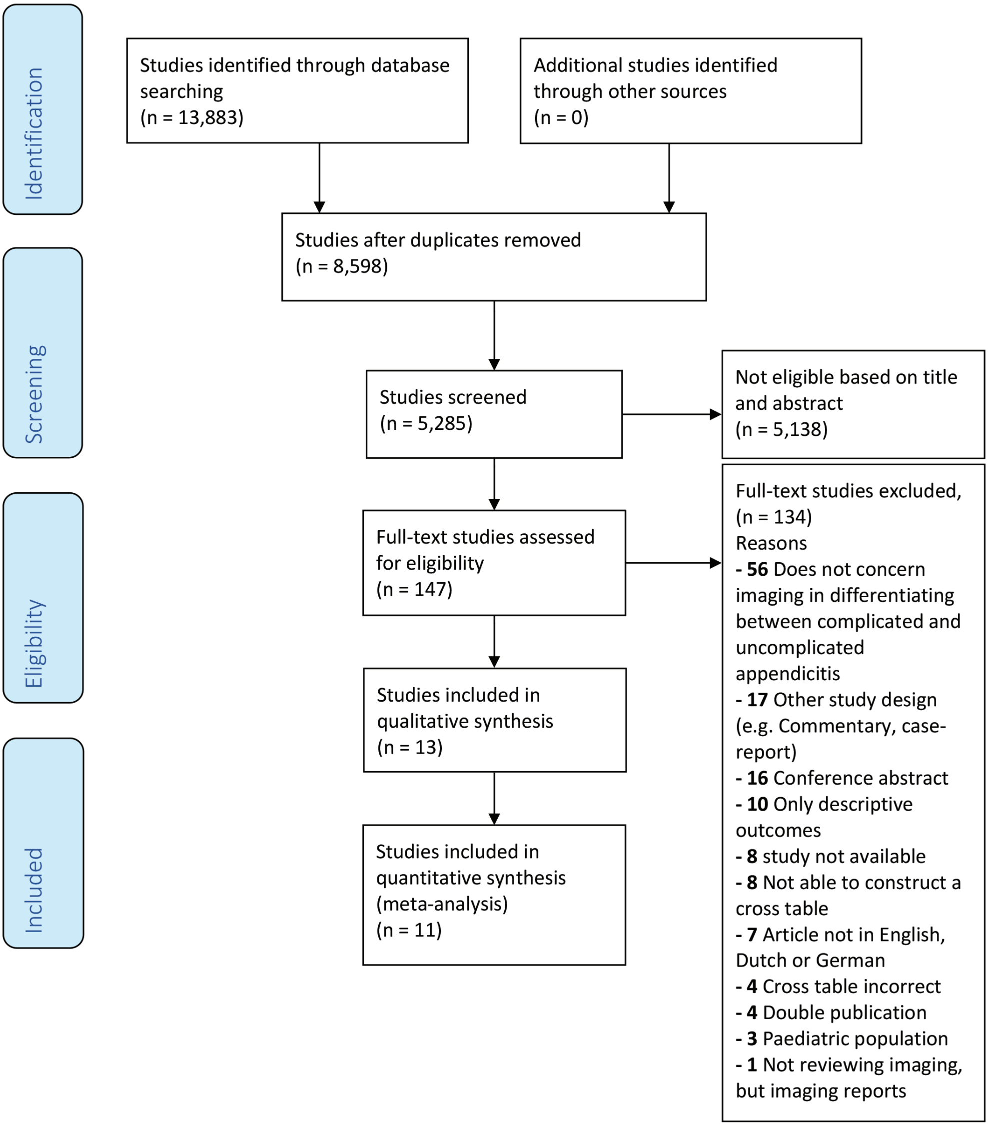

Figure 1, *Prisma flowchart*

Study and patients characteristics

Study characteristics are shown in *Table 1*. Nine studies were retrospective, and two studies were prospective (1 study[33] reported on CT and the other[34] on ultrasonography alone or with conditional CT and MRI). In two studies[23, 25], it was unclear whether the study was performed prospectively or retrospectively. Three studies described the role of low *versus* highdose radiation CT, of which two[29, 31] were performed retrospectively and one[30] prospectively. Ten studies[23, 24, 26, 28-33, 35] used perforated appendicitis (rather than complicated appendicitis) as the outcome. Only 3[25, 27, 34] of 13 studies evaluated complicated appendicitis (rather than of perforated appendicitis). One study[23] only used histopathology as the reference standard. One study[34] used an expert panel for final diagnosis.

In total, data on 1892 patients were reported, of which 620 had complicated appendicitis (*Table 2*). The median prevalence of complicated appendicitis was 25 per cent. For ultrasound imaging data were available on 218 patients, for CT 1667, for MRI 120, and the combination of US and CT 125. In four studies, the proportion of adults was unclear[24-26, 28]. Two[27, 32] of the studies included approximately 75 per cent adults (based on mean(s.d.) age) and were therefore included. The remaining seven studies[23, 29-31, 33-35] included only adult patients (above 15 years of age). For further details, see *Tables S1* and *S2*.

Study	Year	Country	P/R/U	Modality	Reference standard by	Definition target condition
Borushok et al	1990	USA	R	US	S+PA	Perforated
Choi et al	1998	USA	U	CT	S+PA	Necrotizing and perforated appendicitis
Foley et al	2005	USA	R	CT	S+PA	Perforated
Miki et al	2005	Japan	R	CT	S+PA	Gangreneous and perforated appendicitis
Tsuboi et al	2008	Japan	R	CT	S+PA	Perforated
Seo et al	2009	South Korea	R	CT H/L	S+PA	Perforated
Suthikeeree et al	2010	Thailand	R	CT	S+PA	Perforated
Kim et al	2011	South Korea	R	CT H/L	S+PA	Perforated
Suh et al	2011	South Korea	R	CT	S+PA	Perforated
Kim et al	2012	South Korea	P	CT H/L	S+PA	Perforated
Leeuwenburgh et al	2014	The Netherlands	P	US; US+CT; MRI	S+PA	Perforated appendicitis or pus in abdomen
Liu et al	2015	China	R	CT	S+PA	Perforated
Ali et al	2018	Pakistan	U	CT	PA	Perforated

Table 1, *Study characteristics*
P=prospective; R=retrospective; U=Uncertain; H/L = High and low radiation dose; S= Surgery; PA= histopathology

Study	# pts appendicitis	complicated	Age (average)	Age (range)	% adult
Ali et al	236	42 (18%)	40	15-NA	100%
Borushok et al	100	22 (22%)	29	1-71	NR
Choi et al	105	69 (66%)	NR	NR	NR
Foley et al	86	21 (24%)	34	8-87	NR
Kim et al 2011	52	7 (13%)	28	15-40	100%
Kim et al 2012	180	42 (23%)	30	22-37	100%
Leeuwenburgh et al (US)	118	31 (26%)	35*	24-49*	100%
Leeuwenburgh et al (US+CT)	125	31 (25%)	35*	24-49*	100%
Leeuwenburgh et al (MRI)	120	30 (25%)	35*	24-49*	100%
Liu et al	187	41 (22%)	48	19-87	100%
Miki et al	64	28 (44%)	32	4-78	~75%
Seo et al	79	24 (30%)	39	15-80	100%
Suh et al	528	226 (43%)	29|28	15|20	~75%
Suthikeeree et al	48	27 (56%)	56	15-96	100%
Tsuboi et al	102	40 (39%)	37	4-82	NR

Table 2, *Patient characteristics*
**Median with Interquartile range; NR: not reported*

4

Risk of bias

The risk of bias was high in 9 of 13 studies in the following domains: patient selection, index test and reference standard. Applicability concerns were considered high in 9 studies for the domains patient selection, index test and reference standard, and low in three studies. The QUADAS2 characteristics and summary are depicted in *Fig. 2* and *Table 3*.

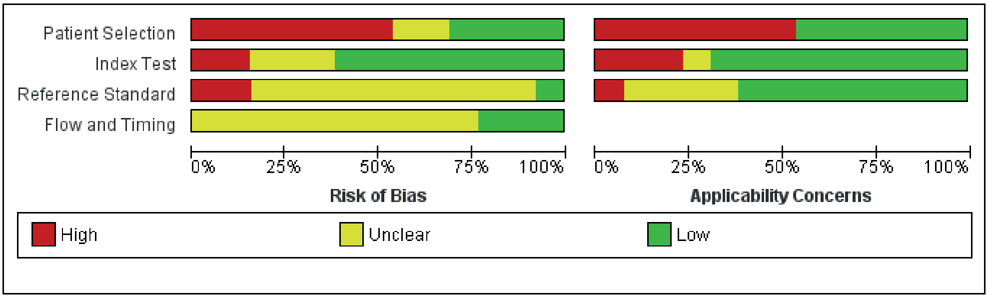

Figure 2, *Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies*

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ali 2018	?	?	–	?	+	?	–
Borushok 1990	–	–	+	+	–	–	+
Choi 1998	–	?	?	?	–	+	+
Foley 2005	–	+	?	?	–	+	+
Kim 2011	+	–	?	?	+	–	+
Kim 2011 Low dose							
Kim 2012	+	+	?	?	+	+	+
Kim 2012 Low dose							
Leeuwenburgh 2014	+	+	?	?	+	+	+
Liu 2015	?	+	?	?	+	+	?
Miki 2005	–	+	?	?	–	+	?
Seo 2009	+	+	?	+	+	+	+
Seo 2009 Low dose							
Suh 2011	–	?	?	?	–	–	?
Suthikeeree 2010	–	+	–	?	–	+	?
Tsuboi 2008	–	+	?	+	–	+	+

– **High** ? **Unclear** + **Low**

Table 3, *Summary of risk of bias and applicability concerns: review authors' judgements about each domain for each study*

Diagnostic accuracy

Ultrasound imaging

One retrospective cohort[24], based on patients with surgically and histopathology proven appendicitis, reported on the diagnostic accuracy of ultrasound imaging for complicated appendicitis, with a sensitivity of 86 per cent (19 of /22) and a specificity of 60 per cent (47 of 78). Based on a prevalence of 25 per cent, the positive predictive value (PPV) was calculated to be 42 per cent and the NPV as 93 per cent.

Another study, of a prospective cohort, included all patients with clinically suspected appendicitis. If ultrasonography was in conclusive, conditional CT was performed. Outcomes for ultra sound imaging alone were not reported separately, but could be calculated from the data. For ultrasound imaging, the sensitivity was 32 per cent (10 of 31) and specificity was 93 per cent (81 of 87). Based on a prevalence of 25 per cent, PPV and NPV were 60 and 80 per cent respectively. Patients with a diagnosis other than appendicitis were excluded in these calculations.

Because of high heterogeneity, caused by differences in study design (retrospective *versus* prospective studies) and patient se lection (proven *versus* suspected appendicitis), no meta-analysis was performed. For both studies[24, 34], it was not possible to construct a 3x3 table that included the diagnosis 'no appendicitis'.

CT

Eleven studies evaluated the diagnostic accuracy of CT for detect ing complicated appendicitis: eight retrospective studies[26-32, 35], one prospective study[33], and two studies[23, 25] with unclear design. Reported estimates ranged from 28 to 95 per cent for sensitivity and 71 to 100 per cent for specificity. The forest plot is depicted in *Fig. 3*. The summary estimates were 78 (95 per cent c.i. 64 to 88) per cent for sensitivity, with a specificity of 91 (85 to 99) per cent. See *Fig. 4* for the HSROC curve. At a median prevalence of complicated appendicitis of 25 per cent, the PPV of CT would be 74 per cent and the NPV 93 per cent.

The only prospective study[33] on the diagnostic accuracy of CT for complicated appendicitis reported a sensitivity of 55 per cent and a specificity of 88 per cent. For the eight retrospective studies[26-32, 35], the summary estimate of sensitivity was 81 (95 per cent c.i. 62 to 91) per cent with a specificity of 93 (95 per cent c.i. 84 to 97) per cent. The two studies[23, 25] with unclear design were not analysed separately.

Three studies[29, 31, 33] compared accuracy for low *versus* standard radiation dose CT. The estimates for sensitivity and specificity were not significantly different ($P = 0.286$). For regular-dose CT, the sensitivity was 68 (95 per cent c.i. 45 to 85) per cent at a specificity of 88 (80 to 93) per cent; for low-dose CT, these estimates were 58 (32 to 80) per cent and 75 (40 to 94) per cent respectively. There were insufficient data to test for differences related to radiologist experience, intravenous contrast or slice thickness (*Table S3*). It was not possible to construct a 3x3 table that included the diagnosis no appendicitis for any of these studies.

Reference	TP	FP	FN	TN	Sensitivity	Specificity
Choi *et al.*[25]	61	7	8	29	0.88 (0.78, 0.95)	0.81 (0.64, 0.92)
Miki *et al.*[27]	25	2	3	34	0.89 (0.72, 0.98)	0.94 (0.81, 0.99)
Foley *et al.*[26]	13	6	8	59	0.62 (0.38, 0.82)	0.91 (0.81, 0.97)
Tsuboi *et al.*[28]	38	2	2	60	0.95 (0.83, 0.99)	0.97 (0.89, 1.00)
Seo *et al.*[29]	20	4	4	51	0.83 (0.63, 0.95)	0.93 (0.82, 0.98)
Sulhikeeree *et al.*[30]	25	6	2	15	0.93 (0.76, 0.99)	0.71 (0.48, 0.89)
Suh *et al.*[31]	63	1	163	301	0.28 (0.22, 0.34)	1.00 (0.98, 1.00)
Kim *et al.*[31]	5	9	2	36	0.71 (0.29, 0.96)	0.80 (0.65, 0.90)
Kim *et al.*[33]	23	17	19	121	0.55 (0.39, 0.70)	0.88 (0.81, 0.93)
Liu *et al.*[35]	37	7	4	139	0.90 (0.77, 0.97)	0.95 (0.90, 0.98)
Ali *et al.*[23]	30	18	12	176	0.71 (0.55, 0.84)	0.91 (0.86, 0.94)

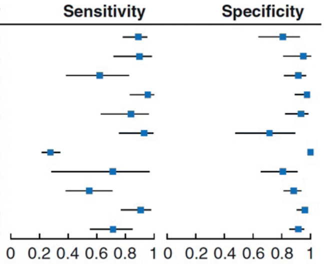

Figure 3, *Forest plots of sensitivity and specificity for the diagnostic accuracy of CT in detecting complicated appendicitis*

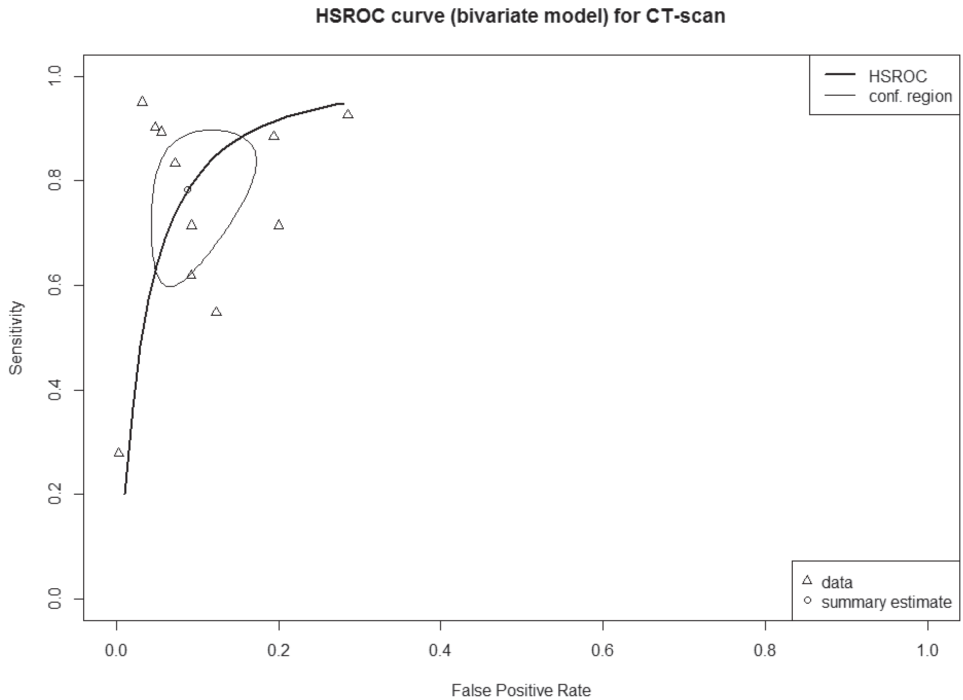

Figure 4, *Hierarchical summary receiver operating characteristic curve for CT*
HSROC, hierarchical summary receiver operating characteristic.

MRI

One study[34] reported on the diagnostic accuracy of MRI in detecting complicated appendicitis: sensitivity was 57 (95 per cent c.i. 37 to 75) per cent and specificity was 86 (77 to 92) per cent. At a prevalence of 25 per cent, this would indicate a PPV of 58 per cent and NPV of 86 per cent. The 3x3 table, including the diagnosis of no appendicitis, is shown in *Table S4*.

Ultrasonography with conditional CT

One study[34] reported accuracy estimates for ultrasound imaging followed by CT in patients with an inconclusive or negative ultra sound scan. The sensitivity was 48 (95 per cent c.i. 30 to 67) per cent at a specificity of 93 (85 to 97) per cent. At a prevalence of 25 per cent, a PPV of 70 per cent and NPV of 84 per cent was calcu lated. The 3x3 table, including the diagnosis of no appendicitis, is seen in *Table S4*.[36]

Discussion

Based on currently available evidence, ultrasonography, CT, MRI alone, or a combination ultrasound imaging and CT (conditional CT) have limitations in discriminating between complicated and uncomplicated appendicitis. Imaging cannot reliably rule out a complicated presentation of acute appendicitis in need of urgent surgery, as a sensitivity of 90 per cent does not appear to be reached and there is high heterogeneity between studies. With respect to ruling in complicated appendicitis, CT seems to reach a specificity above 90 per cent but still is not perfect, and ruling in is considered less important. In the absence of comparative studies, no headtohead comparisons could be made between imaging techniques or strategies. In a meta-regression comparing low-dose with normal-dose radiation CT, no significant difference that caused the heterogeneity in CT studies was found. Diagnostic accuracy was worse in prospective studies, which is important as these are the closest to daily clinical practice.

A recent meta-analysis[37] described 10 CT features to discriminate between complicated and uncomplicated appendicitis, nine of which showed high individual specificity but low sensitivity. Periappendicular fat infiltration had a sensitivity of 94 per cent, but a specificity of 40 per cent[37]. Another study[38] built a regression model based on radiological features. Although the authors of that study did not report results for diagnostic accuracy, only 12 of 21 patients with a gangrenous appendicitis were identified as such, leading to a sensitivity of 57 per cent. However, in clinical practice, radiological features are not interpreted separately. The radiologist's decision will be based on a combination of specific features, together with the severity of the feature.

Ultrasound imaging has limitations as a single technique in detecting acute appendicitis (sensitivity 69-83 per cent and specificity 81-93 per cent)[16,19]. Thus it is intrinsically limited in distinguishing between complicated and uncomplicated appendicitis. This was also shown in the one prospective study[34], which reported a sensitivity of 32 per cent and a specificity of 93 per cent. CT and MRI were better at detecting acute appendicitis. CT had a sensitivity for acute appendicitis of 91-94 per cent and a specificity of 90-94 per cent[3, 21], whereas MRI has a sensitivity of 96 per cent and a specificity of 96per cent[39]. The 3x3 tables, including the diagnosis no appendicitis, were performed in only one study[34], describing both ultrasonography with CT if necessary and MRI. The 3x3 tables, including the diagnosis no appendicitis, were performed in one study only, describing both US with conditional CT if necessary and MRI. [34] Merely reporting the discriminatory capacity of imaging, in which the radiologist is confident of the final diagnosis of appendicitis, might lead to bias. Incorrect classification of appendicitis type may be associated with the wrong treatment choice. In addition, patients without acute appendicitis, but falsely diagnosed as having simple appendicitis, are overtreated.

Studies not included in this review have reported data on the performance of the Alvarado and Appendicitis Inflammatory Response (AIR) scores, with respect to discrimination between complicated and uncomplicated appendicitis. [35, 40-42] The authors concluded there might be an association between score level and complexity of appendicitis, but no data on diagnostic accuracy measures were presented. Others authors[43, 44] created a prediction model for complicated appendicitis using clinical features but also failed to report diagnostic accuracy statistics. Two further studies reported on a combination of clinical and radiological features. [45, 46] Atema and collegues[45] developed two scoring systems, combining clinical and radiological features: one with ultrasonographic features and one with CT features. The ultrasonographic system reached a sensitivity of 96.6 per cent and a specificity of 45.7 per cent, for CT sensitivity and specificity were 90.2 and 70.3 per cent respectively. Avanesov and coworkers[46] developed a scoring system with CT features; the sensitivity was 82 per cent and the specificity of 93 per cent. However, these scoring models have not yet been validated externally. Current studies on surgery *versus* antibiotics in uncomplicated appendicitis have shown that on average, 18 per cent of patients considered before surgery to have uncomplicated appendicitis, were found to have complicated appendicitis at operation. [14] Most studies used imaging to rule out complicated appendicitis but misclassified about one in six patients. The only study[19] with a low proportion of false negative patients with complicated appendicitis in the surgery arm used CT alone and was probably biased by the preselection of patients eligible for nonoperative treatment.

Limitations of the studies included in this review involve the predominantly retrospective designs, which may have resulted in an overestimation of accuracy. Another limitation is the variation in the diagnostic accuracy of the radiologists reading the examinations. For two studies in the meta-analysis, the outcomes of two readers were reported; both reported differences in diagnostic accuracy. [26, 29] Kim et al. reported on the performance of CT in differentiating between complicated and uncomplicated appendicitis. [47] Their study was not included in the present review, as they used CT scans from an RCT that already had been included.[33] However, in that more recent report[47] the sensitivity of the radiologists' assessment for complicated appendicitis ranged from 31 to 81 per cent, and the specificity ranged from 60 to 93 per cent, indicating that that the performance of radiologists in detecting complicated appendicitis is likely to vary.

The debate regarding the best strategy to discriminate complicated from uncomplicated appendicitis will probably continue. Scoring systems seem to perform better in ruling out complicated appendicitis, but there are no adequately validated scoring systems yet. Most studies reporting on the effect of nonoperative treatment for uncomplicated appendicitis have included patients based on CT alone. Although CT has a far from perfect, and highly varying, sensitivity, its NPV for complicated appendicitis is high. Ultrasound imaging, CT and MRI all have limitations in discriminating between complicated and uncomplicated appendicitis.

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Supplemental materials

Basics	Inclusion/exclusion criteria	Definition of golden standard
Borushok 1990 Ultrasound Retrospective, monocenter n=100 Mean age: 29, range(1-71)	Included patients: Appendicitis on ultrasound confirmed by surgery Excluded patients: Not mentioned	Perforated appendicitis based on surgery and histopathology
Leeuwenburgh 2014 MRI Prospective, multicenter N=120 age 35, IQR 24-49	Included patients: Adult patients with clinically suspected appendicitis presenting to the emergency department Excluded patients: Pregnant women, patients with any contraindication to MRI, critically ill patients	Perforated appendicitis or pus in abdomen based on judgement by an expert panel
Leeuwenburgh 2014 US+conditional CT when in doubt Prospective, multicenter N=125 age 35, IQR 24-49	Included patients: Adult patients with clinically suspected appendicitis presenting to the emergency department Excluded patients: Pregnant women, patients with any contraindication to MRI, critically ill patients	Perforated appendicitis or pus in abdomen based on judgement by an expert panel
Choi 1998 CT Not clear whether pro/retrospective Monocenter N=105	Included patients: Patients with clinically suspected appendicitis presenting to the emergency department Excluded patients: Thin patients, premenopausal or pregnant women and pediatric patients were referred initially for US, and came to CT only if US was non diagnostic or if further definition of extent of disease was desired.	necrotizing (transmural inflammation leading to gross or microscopic perforation) appendicitis based on surgery and histopathology
Foley 2005 CT Retrospective monocenter N = 86 Age: 33.7 range (8.2-87.1)	Included patients: Patients with acute abdominal pain presenting at the emergency department, who underwent CT and who underwent appendectomy within 24 hours Included patients: Not fulfilling inclusion criteria	Perforated appendicitis based on surgery and histopathology

Basics	Inclusion/exclusion criteria	Definition of golden standard
Tsuboi 2008 CT Retrospective Monocenter n=102 Age: 37.3 (range 4-82)	Included patients: Patients with surgically and pathologically proved appendicitis Included patients: Surgery 24 hours after CT and iatrogenic perforation	Perforated appendicitis based on surgery and histopathology
Seo 2009 CT Retrospective Monocenter Age: 38.7 range (15-80)	Included patients: Patients with acute lower or right-lowerqudrant abdominal pain for which a CT-scan had been performed Included patients: No surgical exlploration or loss to follow-up	Perforated appendicitis based on surgery and histopathology
Suthikeeree 2010 CT Retrospective Monocenter N=48 Age range 15-96	Included patients: Patients of 15 year and older with surgery and pathology confirmed appendicitis, with a CT in advance. Included patients: Malignancy	Perforated appendicitis based on surgery and histopathology
Kim 2011 CT (+Low dose) Retrospective Monocenter N=52 Age 27.6 range 15-40	Included patients: Patients from 15 to 40 years with acute abdominal pain presenting at the emergency department, who underwent CT Excluded patients: Loss to follow-up	Perforated appendicitis based on surgery and histopathology
Suh 2011 CT Retrospective Monocenter N=528 28.63 (±15.00) 27.43 (±19.98) npa vs pa	Included patients: All patients who underwent laparoscopic appendectomy Excluded patients: Not mentioned	Perforated appendicitis based on surgery and histopathology
Kim 2012 CT (+Low dose) Prospective Monocenter N=180 29.5 (range 22-37)	Included patients: Patients undergoing CT for suspected appendicitis Excluded patients: Not mentioned	Perforated appendicitis based on surgery and histopathology

Basics	Inclusion/exclusion criteria	Definition of golden standard
Liu 2015 CT Retrospective Monocenter N=187 Age: 47.9 SD 17.6	Included patients: Patients with complete medical records to calculate RIPASA and Alvarado scores and with CT-scan Excluded patients: Children, pregnant females, patients with allergies to iodinated contrast material and appendectomy performed >24 hours following CT	Perforated appendicitis based on surgery and histopathology

Table S1, *Baseline Characteristics*

Basics	Imaging features for complicated appendicitis	Radiological diagnosis	Reference standard
Borushok 1990 Ultrasound Retrospective, monocenter	Loss of submucosal layer of appendix Loculated pericecal fluid Prominent pericecal fat	1 or more signs	Perforated appendicitis Based on pathology and surgery reports
Xu 2017 Ultrasound Retrospective, monocenter	Loss of echogenic submucosal layer Periapendiceal fluid periappendiceal hyperechoic fat Presence of appendealmurl hyperemia Appendicoliths Appendiceal maximum outside diameter	Loss of echogenic submucosal layer	Complicated appendicitis Based on pathology and surgery reports
Leeuwenburgh 2014 MRI Prospective, multicenter	Extraluminal free air Periappendiceal presence of abscess Appendicolith Restricted diffusion of appendiceal wall, lumen and focal fluid collections Complete visualization of appendix Appendix diameter Peri-appendiceal fat infiltration	Discretion of the radiologist	Perforated appendicitis/pus in the abdomen Judgement by a panel of experts based on peroperative observations, histopthological findings and outcome at 3-month follow-up
Leeuwenburgh 2014 US+conditional CT when in doubt Prospective, multicenter	Extraluminal free air Periappendiceal presence of abscess Appendicolith periappendiceal fluid absence of intraluminal air destruction of the appendiceal wall Complete visualization of appendix Appendix diameter Peri-appendiceal fat infiltration	Discretion of the radiologist	Perforated appendicitis/pus in the abdomen Judgement by a panel of experts based on peroperative observations, histopthological findings and outcome at 3-month follow-up
Choi 1998 CT Not clear whether pro/retrospective Monocenter	extraluminal free air extraluminal abcess focal absence of wall enhancement or continuity	"mostly on focal absence of wall enhancement or coninuity and on the presence of extraluminal abscess or air"	Perforation peroperative and transmural acute inflammatory infiltrate with necrosis leading to microperforation perforation Based on pathology and surgery reports

Basics	Imaging features for complicated appendicitis	Radiological diagnosis	Reference standard
Foley 2005 CT Retrospective monocenter	visualization of the appendix appendiceal location appendiceal diameter relative appendiceal enhancement compared with adjacent bowel enhancement (ie, enhancement less than, equal to, or greater than that of the adjacent bowel or no enhancement) focal defect in the enhancing appendiceal wall the presence and degree of periappendiceal inflammatory stranding the presence of discrete periappendiceal fluid and other abdominal fluid collections the presence of an abscess the presence of appendicolith(s), extraluminal air, cecal inflammation, and mesenteric lymphadenopathy, subjective assessment of bowel dilatation.	Radiologists discretion	Perforated appendicitis Based on pathology and surgery reports
Tsuboi 2008 CT Retrospective Monocenter	defect in enhancing appendiceal wall abscess phlegmon extraluminal air extraluminal appendicolith	1 or more signs	Perforated appendicitis Based on pathology and surgery reports
Seo 2009 CT Retrospective Monocenter	extraluminal gas periappendiceal fluid extraluminal appendicolith small-bowel ileus severe periappendiceal fat stranding phlegmon defect in the appendiceal wall	Radiologists discretion	Perforated appendicitis Based on pathology and surgery reports
Suthikeeree 2010 CT Retrospective Monocenter	appendiceal perforation extraluminal air extraluminal appendicolith defect in enhancing wall of appendix	One or more of the following classic findings: abscess, extraluminal air or extraluminal appendicolith OR defect in enhancig wall for appendix	Perforated appendicitis Based on pathology and surgery reports
Kim 2011 CT (+Low dose) Retrospective Monocenter	periappendiceal abscess phlegmon, extraluminal air, extraluminal appendicolith, defect in the enhancing appendiceal wall.	Radiologist discretion	Perforated appendicitis Based on pathology and surgery reports

Basics	Imaging features for complicated appendicitis	Radiological diagnosis	Reference standard
Suh 2011 CT Retrospective Monocenter	Defects in enhancing the appendiceal walls abscesses phlegmon extraluminal air extraluminal appendicoliths	Radiologist discretion	Perforated appendicitis Based on pathology and surgery reports
Kim 2012 CT (+Low dose) Prospective Monocenter	extraluminal gas appendicolith periappendiceal fluid phlegmon severe periappendiceal fat stranding defect in the appendiceal wall.	Radiologist discretion	Perforated appendicitis Based on pathology and surgery reports
Liu 2015 CT Retrospective Monocenter	diameter was >6mm with at least one of five specific CT signs: defect in enhancing appendiceal wall phlegmon abscess extraluminal air extraluminal appendicolith.	1 or more signs	Perforated appendicitis Based on pathology and surgery reports

Table S2, *Imaging features*

Author	Year	IV Contrast given	Slice thickness	Radiation given	Radiologists experience
Borushok	1990	NA	NA	NA	Unknown
Choi	1998	yes	5mm	unknown	Two radiologists, experience unknown
Foley	2005	In 78 of 86 patients	5mm	unknown	Two experienced abdominal radiologists (6 and 10 years experience)
Kim, K	2012	Yes	5 mm thick, images with a thickness of 2 mm were reviewed as needed with the use of the multiplanar sliding-slab averaging technique	2msv vs 8msv	radiologists, fellows, and residents
Kim, S.Y.	2011	Contrast	thick (5-mm) and thin (2-mm) sections	2msv vs 8-10msv	2 two radiologists,(8 and 4 years experience in abdominal CT)
Leeuwenburgh	2014	No	6mm	NA	Two radiologists with over 500 MRI's experience
Leeuwenburgh	2014	Yes	unknown	unknown	radiologists, fellows, and residents
Liu	2015	both	1mm	unknown	two radiologists with>8 years' experience
Seo	2009	Low dose unenhanced, highdose enhenced	5mm	4.2mSv vs 8mSv	Two radiologists (8 and 6 years experience)
Suh	2011	unknown	3mm	unknown	A single radiologist
Suthikeeree	2010	yes	1.25 or 1.5mm	unknown	unknown
Tsuboi	2008	yes	Original transverse sections at 3- or 2-mm collimation and 1.5- or 1.0-mm intervals	unknown	Images were evaluated by two radiologists (12 years experience; 17 years experience)
Xu	2017	NA	NA	NA	abdominal radiologist with more than 25 years experience
Leeuwenburgh	2014	NA	NA	NA	radiologists, fellows, and residents
Miki	2005	Yes	2mm	unknown	Two radiologists

***Table S3**, Imaging protocols*

Complicated Appendicitis		Reference standard		
		Uncomplicated appendicitis	No appendicitis	
Diagnosis by Conditional CT (CT only after negative or inconclusive US)	Complicated appendicitis	15	6	1
	Uncomplicated appendicitis	16	78	9
	No appendicitis	0	3	102
Diagnosis by Magnetic Resonance Imaging	Complicated appendicitis	17	12	1
	Uncomplicated appendicitis	13	71	6
	No appendicitis	0	4	99

Table S4, *3x3 tables*
3x3 Table, reported by Leeuwenburgh et al.
No other 3x3 tables could be constructed as other included studies do not report enough details
Conditional CT: concordant classification 195 / 230 = 84.8%; discordant classification 35 / 230 = 15.2%
MRI: concordant classification 187 / 223 = 83.9%; discordant classification 36 / 223 = 16.1%

APPENDIX S1

Search Strategy PubMed:

(appendicitis[mesh] OR appendic*) AND (complex OR simple OR perforat* OR ruptu* OR complicated OR uncomplicated OR phlegmon* OR gangren*)

AND (MRI OR CT-scan OR US OR Radiology OR CT OR ultrasound OR sonoograph*)

Search Strategy Embase:

1	exp appendicitis/ or exp acute appendicitis/	26160
2	appendicitis.ti,ab,kw.	21728
3	1 or 2	29153
4	exp nuclear magnetic resonance imaging/	748229
5	ct.mp. or exp CT-SPECT scanner/ or exp whole body CT/	1016669
6	ultrasound.mp. or exp ultrasound/	385994
7	(MRI or CT or 'computed tomography' or echosonograph* or ultraso*).ti,ab,kw.	1215434
8	(complex or simple or perfor* or ruptu* or complicated or uncomplicated or phlegmon* or gangren*).ti,ab,kw.	5473171
9	4 or 5 or 6 or 7	2200716

Search strategy Cochrane:

Appendicitis

Chapter 5

Optimizing diagnostics to discriminate complicated from uncomplicated appendicitis – a prospective cohort study protocol

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Abstract

Introduction

Growing evidence is showing that complicated and uncomplicated appendicitis are two different entities that may be treated differently. A correct diagnosis of the type of appendicitis is therefore essential. The Scoring system of Appendicitis Severity (SAS) combines clinical, laboratory and imaging findings. The SAS rules out complicated appendicitis in 95% (negative predictive value, NPV) and detects 95% (sensitivity) of patients with complicated appendicitis in adults suspected of acute appendicitis. However, this scoring system has not yet been validated externally. In this present study, we aim to provide a prospective external validation of the SAS in a new cohort of patients with clinical suspicion of appendicitis. We will optimise the score when necessary.

Methods and analysis

The SAS will be validated in 795 consecutive adult patients diagnosed with acute appendicitis confirmed by imaging. Data will be collected prospectively in multiple centres. The predicted diagnosis based on the SAS score will be compared with the combined surgical and histological diagnosis. Diagnostic accuracy for ruling out complicated appendicitis will be calculated. If the SAS does not reach a sensitivity and NPV of 95% in its present form, the score will be optimised. After optimisation, a second external validation will be performed in a new group of 328 patients. Furthermore, the diagnostic accuracy of the clinical perspective of the treating physician for differentiation between uncomplicated and complicated appendicitis and the patient's preferences for different treatment options will be assessed.

Ethics and dissemination

Ethical approval was granted by the Amsterdam UMC Medical Ethics Committee (reference W19_416 # 19.483). Because of the observational nature of this study, the study does not fall under the scope of the Medical Research Involving Human Subjects Act. Results will be presented in peer-reviewed journals. This protocol is submitted for publication before analysis of the results.

Introduction

Background

Acute appendicitis is one of the most common abdominal infectious diseases.[1,2] It was a long-held belief that every uncomplicated appendicitis would ultimately progress into a complicated (gangrenous or perforated) appendicitis, with an associated increase in morbidity. For this reason, appendectomy has been the standard treatment of acute appendicitis since it was invented in 1886.[3-5] However, growing evidence shows that complicated and uncomplicated appendicitis are two different entities.[6-9]

The two different entities of appendicitis may be treated differently. Patients with complicated appendicitis could benefit from timely surgery. The unpublished secondary analysis of a Dutch prospective cohort study [10], consisting of 1975 patients who had been operated on for suspected acute appendicitis, showed that patients with complicated appendicitis who are operated within 8 hours after presentation have fewer postoperative complications than patients with an in-hospital delay of more than 8 hours. In contrast to patients with complicated appendicitis, surgery for uncomplicated appendicitis can be delayed safely up to 24 hours without increasing the risk of morbidity or postoperative complications.[11] Moreover, an increasing number of studies showed that treating uncomplicated appendicitis with antibiotics might be a safe, effective and cost-saving alternative for appendectomy.[12-15] Some studies even suggest that uncomplicated appendicitis can be treated by supportive treatment without antibiotics.[16,17] For these different treatment options, a correct diagnosis is essential.

Current diagnostic strategies have insufficient discriminatory accuracy to correctly differentiate complicated from uncomplicated appendicitis.[18,19] Although imaging modalities are good to excellent for the diagnosis of acute appendicitis in general, the ability to distinguish between complicated and uncomplicated appendicitis is inadequate.[18,19] This shortcoming is highlighted by a meta-analysis of RCTs on the antibiotic treatment of uncomplicated appendicitis.[20] Although all trials intended to include only patients with uncomplicated appendicitis, 16.9% of patients randomised to surgery were found to have complicated appendicitis.[20] Better identification of patients with complicated appendicitis is needed to discover the actual merits of antibiotic treatment.[20]

The Scoring system of Appendicitis Severity (SAS) has been developed for this differentiation.[21] The SAS combines clinical parameters and imaging features.[21] Two variants of the SAS were developed: SAS-US and SAS-CT, see Table 1. Using a cut-off score of five points or less for the SAS-US and six points or less for the SAS-CT, the scores reach sensitivities of 96.6% and 90.2% and negative predictive values (NPVs) of 97.1% and 94.7% for complicated appendicitis, respectively.[21] Average sensitivity and NPV are around 95% when the ratio of patients diagnosed by ultrasound (US) and CT is considered.

This ratio was 68.2/31.8, according to national SNAPSHOT data from the Netherlands.[10] Based on this accuracy, the SAS would be sufficient in ruling out complicated appendicitis. However, the SAS has not yet been validated externally in a well-designed prospective study. This is one of the main reasons why the SAS is not currently used in clinical practice. When non-surgical treatment of appendicitis will become a more frequently used treatment option and not all patients undergo appendectomy, a reliable tool to distinguish between uncomplicated and complicated appendicitis becomes crucial.

	SAS-US	**SAS-CT**
Age >45 years	2	2
Temperature		
≤37.0	0	0
37.1-37.9	2	2
≥38.0	4	4
Duration of symptoms ≥48 hours	2	2
WBC >13*10^9/L	2	2
CRP (mg/L)		
≤50	0	0
51-100	4	2
>100	5	3
Presence on imaging:		
Free air	-	5
Peri-appendiculair fluid	2	2
Appendicolith	2	2

Table 1, *Scores and features from SAS-US and SAS-CT*

If patients with complicated appendicitis can be identified reliably, for example using the SAS, antibiotic treatment may become a standard alternative for surgery. In selecting the right treatment option, it is important to acknowledge the patient's preferences for non-operative or operative treatment. Few studies have described the patient's choice for treatment of uncomplicated appendicitis, and a wide range of patients preferring non-operative treatment has been reported, varying from 9.4% to 57%.[22-24] This wide range may be explained by the different ways of informing the participants and by the type of the included patients. To facilitate shared decision making for uncomplicated appendicitis, the correct group of participants should be surveyed, and accurate information must be provided about the risks and advantages of both antibiotic and surgical treatment.

Study objectives

This study aims to validate the SAS in adults suspected of acute appendicitis externally. Validation will be completed if the target 95% sensitivity and 95% NPV are reached (scenario A). If the validation of the SAS does not match these targets, optimisation of the SAS will be performed (scenario B). In this scenario, inclusions will continue to create a new validation cohort. Optimisation and validation of the modified score will be secondary objectives. A secondary aim of this study is to evaluate the preference for antibiotic or surgical treatment of uncomplicated appendicitis in adult patients who had undergone an appendectomy.

Methods

Overall study design

A multicentre, prospective, observational study will be conducted in Dutch teaching and non-teaching hospitals. Diagnostic work-up will be performed according to the current standards (Dutch guidelines). The Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 guidelines are used.[25]

Study population

Consecutive adult patients will be included at the emergency department (ED). Inclusion started at the first hospital on 26 January, 2020, was subsequently hampered by the COVID-19 pandemic and was then expanded to multiple hospitals. Inclusion will continue until the minimum number of required participants is reached. Inclusion takes place when the patient is diagnosed with acute appendicitis based on clinical, laboratory, and imaging findings (see Figure 1).

Inclusion criteria:

To be included, patients must fulfil all of the following criteria:

- ≥18 years of age
- Imaging-confirmed or –highly suspected diagnosis of acute appendicitis
- Treatment by surgery with the intention to perform an appendectomy

Exclusion criteria:

Patients fulfilling one or more of the following criteria will be excluded:

- No surgery with the intention of appendectomy has been executed because a surgical specimen is needed as a reference standard
- The surgery took place >48 hours after diagnosis based on the last performed imaging. It was considered that after 48 hours, the preoperative diagnostic results, and thereby the associated SAS score, are not representative of the intraoperative diagnosis
- The patient is pregnant, as the SAS has been developed based on data in which pregnancy was an exclusion criterion
- Patients who undergo surgery for suspected neoplasm as a cause of their appendicitis

Data collection

All parameters will be collected prospectively. Data will be collected using standard reports as saved in the electronic health record (EHR). Data will be stored in an online database, namely CASTOR EDC (Electronic Data Capture). In addition to all prospectively scored variables, the final radiology, operation and histology reports will be collected for additional information.

Emergency department

The treating physician at the emergency department (ED) will complete a standardised report (see online supplemental, case report from (CRF) ED) that is saved in the EHR. The report consists of all parameters included in the SAS-score and other potentially predictive factors for complicated appendicitis, that is smoking status, complaints of vomiting, and the numeric pain rating scale (NPRS).[26] We do not hand a scoring card to the treating physicians, nor will the final SAS score be shown in the acute setting.

Radiology report

Imaging results will be collected according to a standardised radiology report, including the following parameters: visualisation of the entire appendix, appendiceal diameter, presence of peri-appendiceal fat infiltration, presence of periappendiceal and/or intra-abdominal free fluid, presence of an appendicolith, presence of abscesses, including its diameter if present and destruction of the appendiceal wall (perforation). Destruction of the appendix wall is a discontinuity of the wall; a well-known finding and a sign used for diagnosing perforation.[27-29] For CT and MRI, the presence of extraluminal air outside the appendix will be scored as well. Intra-abdominal free air cannot be reliably ruled out by US and is therefore not scored for this modality. For MRI, the presence of restricted diffusion will also be scored.[30, 31] This is an MRI-specific parameter that cannot be described using US or CT.

Clinical perspective

After diagnosing acute appendicitis, both the treating physician at the ED and the radiologist will be asked to differentiate between complicated or uncomplicated appendicitis. All available information can be used for this decision, including clinical, laboratory and imaging findings, augmented by their clinical experience. Information will be collected about the physician's years of experience, their working department and the level of certainty for this differentiation, based on an 11-point Likert scale.

Surgery report

Intraoperative findings will be collected using standardised paper forms or similar standardised electronic reports (See online supplemental file 1, CRF Surgeon). Parameters that will be collected are the presence and aspect of intra-abdominal fluid, the need for postoperative antibiotic treatment, the occurrence of iatrogenic perforation and the intraoperative diagnosis. The surgeon chooses one of the following diagnoses: (1) normal appendix, (2) uncomplicated appendicitis, (3) gangrenous appendicitis, (4) perforated appendicitis, (5) acute appendicitis with a large infiltrate, or (6) other, specify: ... . Furthermore, the surgeon will take a picture of the appendix intra-abdominally before removing it and one of the specimen on a white background after removal. These pictures can be used for consensus in case of doubt of the final diagnosis.

Pathological report

Histological findings will be collected using a standardised report in the EHR, including inflammation, necrosis, a perforation and presence of a neoplasm.[6] Transmural inflammation is defined by inflammation localised from mucosa up to and including the muscularis propria. Necrosis is present if any form of necrosis is seen, ranging from localised to transmural necrosis. If one of the above cannot be answered for some reason, an explanation can be given. In addition, complete histology reports will be collected. Other signs of uncomplicated appendicitis, such as ulceration of the mucosa, will be actively sought in cases without transmural inflammation.

Questionnaires

A standardised patient-reported outcome measure questionnaire will be disseminated after 3-months of follow-up to explore the patients' thoughts about the surgical and antibiotic treatment of uncomplicated appendicitis. Based on a scenario of a patient with uncomplicated appendicitis, participants will be asked about their preferred treatment after outlining the advantages and risks of both options. For instance, in the patient preference questionnaire we mention a 1-year recurrence rate of acute appendicitis of 23%, as is described in a recent meta-analysis by Sallinen et al.[32] Additionally, we ask them to substantiate their choice by checking a list of prespecified arguments. As a final question, patients will be asked which risk percentage of recurrence of appendicitis after 1 year they would accept in case of antibiotic treatment. The preferred treatment is not asked before start of treatment as all appendicitis patients still undergo surgery and non-surgical treatment of appendicitis is not a true preference option in our clinical setting. We have chosen to send the patient preference questionnaire only after treatment to avoid ambiguity about the upcoming treatment. All patients undergo surgery. Questionnaires will be distributed by email via CASTOR EDC in a web survey. These answers will be digitalised and stored within CASTOR EDC.

Data processing

Data will be collected from the EHR, paper CRF's and, in case of the questionnaires, directly in CASTOR ECD. A local researcher will collect the data. The researcher will collect the data without calculating the final scores of the SAS. All data will be pseudonymised and stored in CASTOR EDC.

Outcomes

Index test: SAS score

Depending on the last performed imaging modality, the SAS-US or SAS-CT score will be calculated. Patients who undergo CT after negative or inconclusive ultrasound results will be scored using the SAS-CT. Table 1 describes the points given for both SAS variants. Patients will be classified as *uncomplicated appendicitis* (SAS-US ≤ 5 points or SAS-CT ≤ 6 points) or as *complicated appendicitis* (SAS-US > 5 points or SAS-CT > 6 points). This predicted diagnosis will be compared with the reference standard. The predicted SAS-US and SAS-CT diagnoses will be merged into the overall SAS score of the total cohort.

Reference standard

The reference standard will be the final diagnosis based on the combination of surgical and histological findings. *Uncomplicated appendicitis* is defined as transmural inflammation or ulceration of the appendix or periappendix without evident signs of necrosis or perforation both microscopically and macroscopically. *Complicated appendicitis* is defined as transmural inflammation of the appendix with either clear signs of necrosis or gangrene as described by the pathologist, a perforation as described by the surgeon, or the presence of an intraperitoneal abscess or large periappendicular infiltrate as described by the surgeon. Since histological assessment is standard after appendectomy in the Netherlands, it is expected that both surgical and histological reports will be present in all patients. If there are cases without histological assessment, the surgical diagnosis will be used as the reference standard. In mismatches between the final diagnoses of the surgeon and pathologist, the reference standard will be established by the consensus of an expert panel. This panel consists of two surgeons, two radiologists, one pathologist and one ED physician / surgical resident who will review a structured summary of clinical information during admission, operative notes, the pathology report, imaging findings and CRFs from the surgeon and pathologist. In case of disagreement among expert panel members, a final diagnosis will be assigned during a consensus meeting of the expert panel concerning the disagreement cases. Patients with a final diagnosis other than uncomplicated or complicated appendicitis will be assigned to one of both groups for the primary analysis. Patients with a normal appendix and no other diagnosis in need of surgery are referred to as non-urgent patients. These patients will be assigned to the group of patients with uncomplicated appendicitis for the primary analysis. Patients with a diagnosis other than appendicitis but where surgery was needed are referred to as urgent patients. These patients will be assigned to the group of patients with complicated appendicitis for the primary analysis.

Primary outcomes

The primary endpoints are the *sensitivity* and *NPV* of the SAS for complicated appendicitis.

Secondary outcomes

The secondary outcomes are defined as:

- Specificity and PPV of complicated appendicitis.
- Sensitivity analysis of patients with genuinely acute appendicitis. Sensitivity, specificity, NPV and PPV will be calculated for the SAS score in this subgroup.
- Sensitivity, specificity, NPV, PPV for excluding complicated appendicitis for the SAS-US and SAS-CT separately.
- The discriminatory capacity of the SAS, SAS-US, and SAS-CT by calculating the area under the curve.
- The patient-reported preferred treatment (antibiotics vs appendectomy) in a case of uncomplicated appendicitis, according to the online questionnaire.
- Sensitivity, specificity, NPV, and PPV of the physician at ED and the radiologist in distinguishing complicated from uncomplicated appendicitis compared to SAS.

Data analysis

Primary outcomes

Contingency tables will be constructed, including the SAS score and the reference standard. The sensitivity and NPV of SAS for complicated appendicitis will be calculated. The 95% CIs and 97.5% one-sided CI for the lower limit will be calculated using the Wald statistic.

Secondary outcomes

Specificity and PPV will be calculated using the SAS score. Furthermore, contingency tables will be constructed for both the SAS-US and SAS-CT separately. Sensitivity, specificity, PPV, and NPV will be calculated. The area under the curve of the SAS will be plotted and calculated in a receiver operating characteristic (ROC) curve. A similar analysis will be performed for the SAS-US and SAS-CT separately.

Sensitivity analysis will be performed, including only patients with truly acute appendicitis. Initially, included patients with a final diagnosis other than acute appendicitis will be excluded for this analysis. Sensitivity, specificity, NPV and PPV will be calculated for the SAS score in this subgroup.

Questionnaires will be analysed. The proportion of patients choosing antibiotic treatment, surgery or patients without a preference will be reported. The most important arguments for this choice and the 1-year recurrence risk of appendicitis patients are willing to accept if treated by antibiotics will be presented.

The diagnostic accuracy of the physician at the ED and the radiologist in distinguishing complicated from uncomplicated appendicitis will be calculated in terms of sensitivity, specificity, NPV and PPV for both ‘tests’. This objective estimation will be compared to the results of the SAS. Stratification will be made using the level of certainty of the specific diagnosis. On an 11-point Likert scale (score 0-10), a score of 7 points or higher will be defined as ‘certain’, while a score of 6 points or less will be interpreted as ‘uncertain’. Patients with a ‘certain’ clinical diagnosis of uncomplicated appendicitis will be highlighted because in these patients’ antibiotic treatment may be an option in the future. The significance of the differences will be calculated by the chi-square test. All binomial 95% CI will be calculated by the Wilson score interval. [33]

Optimisation

It is hypothesised that the SAS reaches an NPV of at least 95% and a sensitivity of 95% for complicated appendicitis. A lower limit of 3 per cent as the only limit of the corresponding one-sided 97.5% CI will be considered the bare minimum. If the sensitivity or NPV point estimates are below 92%, the scoring system will be optimised. We will perform the optimisation of the SAS using data from the first cohort. For the optimisation, possible variables collected from the CRF’s and medical reports will be used. These variables are identified as known predictors of complicated appendicitis from the literature. The variables that are included in the SAS will be re-evaluated or rescaled. Additionally, all extra collected data (see data collection) will be added to a multivariable model to optimise the SAS.

Continuous variables will be categorised. An optimal cut-off score will be chosen by visually exploring the possible associations between the variables and the final diagnosis of complicated appendicitis using restricted cubic spline functions. ‘Knots’ in these smooth spline functions are tested as possible cut-offs for the categorisation. This way, new variables will be categorised, and continuous SAS variables may be rescaled.

A multivariable logistic regression model with the categorical predictors, including the parameters used in the SAS, will be constructed and reduced with supervised backward selection. In general, parameters with a p-value above 0.15 will be excluded stepwise. However, supervised backward selection allows that parameters expected to be of diagnostic value based on literature data and etiology remain included to facilitate future studies. The model will be transformed into a clinically applicable scoring system, multiplying the adjusted coefficient of each parameter and rounding it to the nearest integer. Total scores for every patient will be calculated. A cut-off analysis will be performed using the ROC curve to select patients with predicted complicated appendicitis, not exceeding 5% of false negatives. In addition to this rounded score model, options for a computer-based algorithm will be explored. In this model, continuous data will be used without cut-offs only if this increases the diagnostic accuracy of the model.

Optimisation of the model will be performed for both US and CT. Diagnostic accuracy measures will be calculated, and the score will be validated. The second cohort of patients will be included for this validation of the modified SAS score (see the sample size calculation section). Data from these patients will be collected in the same manner as in the initial validation period.

Missing data

Missing data analysis will be performed for missing parameters needed for the primary outcome, that is SAS criteria, using the missing value analysis module in SPSS. Patients in whom more than 30% of these data points are missing will be excluded from the study. In the other cases of missing less than 30% of the data, the data will be imputed. Multiple imputations by chained equations will be performed. The number of imputed datasets will be based on the percentage of missing data for each parameter required for the primary outcome with a minimum of 5 up to a maximum of 50 imputation sets.[34] Missing data analysis will show which parameters to include in the imputation model. Sensitivity analysis will be performed to show any differences between the initial data and the data including imputations.

In the case of optimisation, eligible parameters will be examined. Only parameters present in at least 60% of all patients will be included in the analysis. If necessary, these variables will be imputed as described above. The percentage of missing data and imputed parameters will be described.

Sample size calculation

Validation period

The targeted sensitivity and NPV for complicated appendicitis are both 95%. A lower margin of 3 per cent will be considered as the only limit of the corresponding one-sided 97.5% CI the bare minimum. When the number of complicated appendicitis equals 228, the one-sided 97.5% adjusted Wald CI will extend 3% from the observed percentage for an expected percentage of at least 95% for sensitivity. Given a prevalence of 28.7% complicated cases in the target population [10], about 795 patients need to be included initially to reach a minimum of 228 patients with complicated appendicitis among all included appendicitis.

With the same extent of 3% from the observed percentage for an expected percentage of at least 95% for NPV, a total of 228 patients of which the SAS score predicts uncomplicated appendicitis is needed. The SAS-US predicted uncomplicated appendicitis in 33.7% within the original cohort; for the SAS-CT, this was 52.8%. [21] Within the target population, 66.1% is expected to be diagnosed based on US and 30.6% based on CT, initially or secondary to US. [10] Patients with a diagnosis based on MRI or without imaging will be excluded for the validation. This results in predicted uncomplicated appendicitis for the combined SAS of 38.4% in all patients. Based on the previous SAS results, 594 patients need to be included.

To report both reliable sensitivity and reliable NPV, we need to include the highest number of those two. After including at least 228 patients with complicated appendicitis to achieve the target sensitivity and at least 228 patients with a SAS score predicting uncomplicated appendicitis to accomplish the target NPV, we will test our hypothesis and validate the SAS. The expected required number of patients is 795 for this validation cohort. The sample size has been adjusted to achieve a better precision of estimating p and achieve that the interval includes p close to 1-alpha of the time. Also, the adjusted Wald CI will not be symmetrical, and thus its upper limit will not cross 1, contrary to the unadjusted Wald CI, based on the normal distribution. [35]

Optimisation period

If the validation does exceed the margin of 3% of the adjusted Wald statistics of the sensitivity or NPV, optimisation of the SAS will be executed. Optimisation will be performed by using the data of the 795 patients. To externally validate the optimised SAS, we need a new cohort of patients. We will include these patients after having the primary 795 patients. We again intend to achieve a sensitivity of 95%, now with a lower limit of 5% as the only limit of the corresponding one-sided 97.5% CI as the bare minimum. Because of the large cohort in which the SAS will be optimised, we consider a lower limit of 5% instead of 3% will suffice. We calculated that 328 patients are needed for this second validation cohort in case of the need for optimisation of SAS.

A maximum expected 1123 patients would be included. This total consists of the primary validation/optimisation cohort of 795 patients and, if needed, a second external validation cohort of 328 patients.

Patient and public Involvement

No patients were involved in the development of the research question or the study design. As mentioned above, questionnaires will be sent to all participants to inquire about their treatment preferences. Patient input will be solicited in this way. All participants will be asked if they wish to be informed about the results of the study. Results will be communicated to these patients via email.

Ethics and dissemination

Patient recruitment

Patients will be recruited 24 hours a day. Informed consent will be obtained at the ED or the ward, both preoperatively and postoperatively. Information about the study will be given, and a medical doctor will answer questions before signing the informed consent. If a patient leaves the hospital before informed consent is obtained, informed consent will be accepted by letter or email. In consultation with our juridical department, this is in line with the design of this study. The study was declared to be not subject to the Medical Research Involving Human Subjects Act (WMO), as judged by the Medical Ethical Committee of the Amsterdam UMC, location AMC.

Intervention and risk

The SAS can be applied without adding diagnostics other than standard diagnostic workup protocols. It is a purely diagnostic study without direct management consequences for the included patients. Participants will receive diagnostics and treatment according to current standards, and there is no additional burden except for a single time point patient-reported outcome and preferences questionnaire. Participation will not result in any risks for the patients.

Compensation

No financial compensation will be provided. There is no indication of a travel allowance.

Patient privacy

Only relevant data will be collected from the electronic patient file, such as patient characteristics and primary and secondary outcomes specified as above. These data will be encrypted. The encrypted data will be stored in private storage, only available for involved researchers. The encryption code will be secured by a password and is only accessible for the (local)head researcher. The patient questionnaires will be anonymous and will only be marked by the study number. Pictures of the appendices intraoperatively will be collected too. The filing of these pictures with a unique study number will not be traceable to the patient. After pseudonymisation, all data will be collected in multiple centres and shared after encryption via the data collection programme CASTOR EDC. The data will be stored for 15 years. After this period, the data will be destroyed. When patients give their permission, the data can be used in other subject related studies for a more extended period. The collection of patient data will be reported to the local privacy officer. Collected data are open for reuse for research on the topic of appendicitis.

Publication and implementation

The results will be published in an international peer-reviewed journal. They will also be disseminated through international conferences, (inter)national guidelines and will be the base for further research and a change in practice. Data will be open for reuse after the publication of our results according to the FAIR principles.

After completion of the study, the national guideline can be adjusted according to the findings of this study. If the SAS shows to be accurate enough to rule out complicated appendicitis, non-surgical treatment is likely more effective than published results have shown to date. A new RCT comparing appendectomy to antibiotic treatment using this more accurate way to select uncomplicated appendicitis may be needed to see the real potential of non-surgical treatment of truly uncomplicated appendicitis.

If the SAS is implemented in the guidelines, it will be easier to stimulate its use. Pocket maps can be produced to disseminate the use of the SAS. Moreover, a web-based application or app could aid any doctor involved in diagnosing and treating patients with acute abdominal pain and the suspicion of acute appendicitis.

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Authors' contributions

Initial study design and grant proposal was conducted by WBo, AvG, SG, KT, CvR, JSt, WBe, MD and MB. WBo, JSc, SU, AvG, SG, KT, CvR, LK, JSt, WBe, MD and MB contributed to the design of the study protocol and all authors approved the study protocol for publication in its present form.

Competing interests

The authors declare that they have no competing interests. MB reported receiving institutional grants from J&J/Ethicon, KCI/3M, Bard and New Compliance; and being an advisory board member and/or speaker and/or instructor for KCI/3M, J&J/Ethicon, Allergan, Bard, Gore, Smith & Nephew.

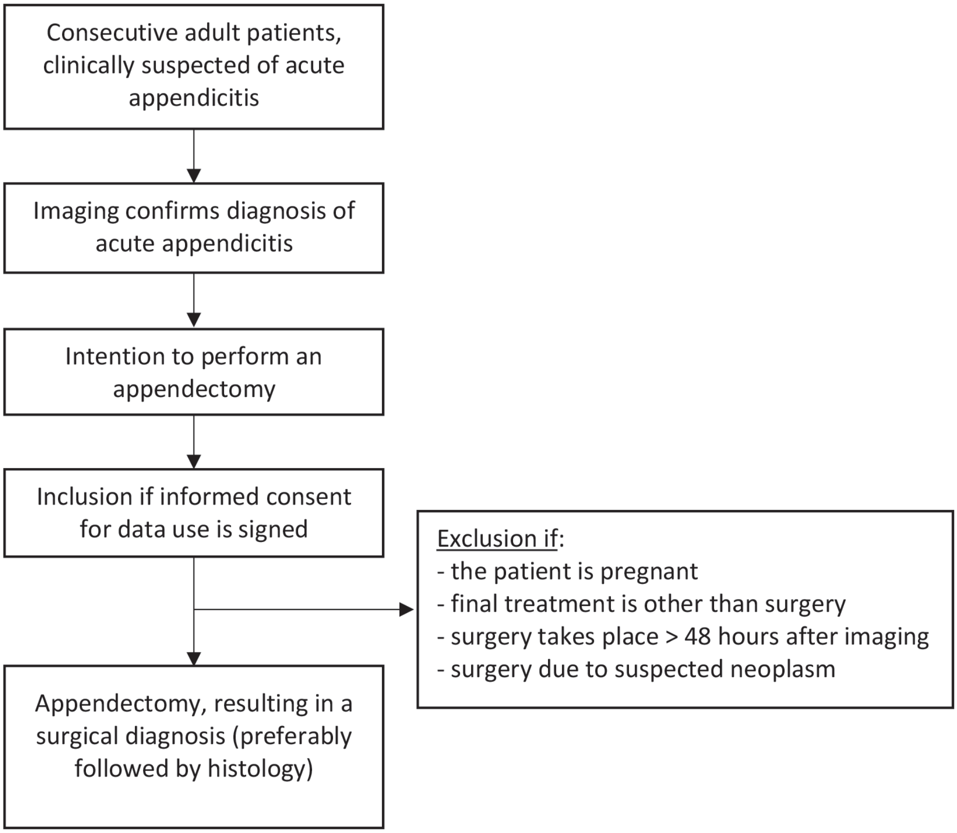

Figure 1, *Flowchart of inclusion and exclusion*

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Chapter 6

Diagnosis of uncomplicated and complicated appendicitis in adults

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Abstract

Background

Diagnostic work-up of acute appendicitis remains challenging. While some guidelines advise to use a risk stratification based on clinical parameters, others use standard imaging in all patients. As non-operative management of uncomplicated appendicitis has been identified as feasible and safe, differentiation between uncomplicated and complicated appendicitis is of paramount importance. We reviewed the literature to describe the optimal strategy for diagnosis of acute appendicitis.

Methods

A narrative review about the diagnosis of acute appendicitis in adult patients was conducted. Both diagnostic strategies and goals were analyzed.

Results

For diagnosing acute appendicitis, both ruling in and ruling out the disease are important. Clinical and laboratory findings individually do not suffice, but when combined in a diagnostic score, a better risk prediction can be made for having acute appendicitis. However, for accurate diagnosis imaging seems obligatory in patients suspected for acute appendicitis. Scoring systems combining clinical and imaging features may differentiate between uncomplicated and complicated appendicitis and may enable ruling out complicated appendicitis. Within conservatively treated patients with uncomplicated appendicitis, predictive factors for non-responsiveness to antibiotics and recurrence of appendicitis need to be defined in order to optimize treatment outcomes.

Conclusion

Standard imaging increases the diagnostic power for both ruling in and ruling out acute appendicitis. Incorporating imaging features in clinical scoring models may provide better differentiation between uncomplicated and complicated appendicitis. Optimizing patient selection for antibiotic treatment of appendicitis may minimize recurrence rates, resulting in better treatment outcomes.

Acute appendicitis

Appendicitis is the most common infectious disease in the abdomen. With a lifetime risk of almost 1 in 11 persons, appendicitis has been diagnosed in innumerable patients worldwide [1]. Still, there is a lot to learn about the diagnostic approach. Guidelines vary in their advice for standard diagnostics [2, 3]. Multiple clinical prediction rules have been described during the past decades [4]. Most scores provide some evidence for a risk stratification without including imaging features. For practicing such clinical scores, selective imaging has been proposed; a score result in the low-risk category may end further investigation for the diagnosis of acute appendicitis, an intermediate risk score may lead to imaging, and a high-risk score may result in direct surgical exploration [3]. While some guidelines advise the use of clinical scoring systems, others recommend standard imaging in all patients with suspected appendicitis [5].

Besides reliable diagnosis of acute appendicitis instead of alternative explanations of abdominal pain, discriminating uncomplicated from complicated appendicitis becomes more and more relevant as evidence is growing for the feasibility of treatment with antibiotics compared to surgery in uncomplicated appendicitis [6, 7]. This discrimination is based on the principle that uncomplicated and complicated appendicitis are two different entities [8-10]. Simple or uncomplicated appendicitis is defined as a phlegmonous inflamed appendix without signs of necrosis or perforation, whereas complex or complicated appendicitis has focal or transmural necrosis, which eventually may lead to perforation. Differentiation between both entities is important, as uncomplicated appendicitis may be treated conservatively with antibiotics without the need for surgery [6, 7], or may even resolve spontaneously without the need for antibiotic treatment [9-12]. In contrast, patients with complicated appendicitis require emergency appendectomy with the exception of patients presenting with a periappendicular abscess [3, 13].

In this narrative review, we will focus on the different ways of diagnosing acute appendicitis, discuss the considerations, and zoom in on the differentiation between uncomplicated and complicated appendicitis. We will base our view on available literature, preferring the use of randomized controlled trials or well-designed meta-analyses over single cohort studies.

Diagnostic Accuracy: To Rule In or to Rule Out?

When diagnosing acute appendicitis in a patient with abdominal pain, the diagnostic accuracy is, in a simplified way, based on the classical contingency or 2x2 table, see figure 1.

	Disease*	No disease*		
Test positive	True positive	False positive	←	Row entries for determining **positive predictive value**
Test negative	False negative	True negative	←	Row entries for determining **negative predictive value**
	↑	↑		
	Column entries for determining **sensitivity**	Column entries for determining **specificity**		

Figure 1, *Standard contingecny table*
**Status of person according to 'gold standard'*

However, the actual diagnostic situation is more complex. Patients with abdominal pain and suspicion of appendicitis present with a spectrum of diseases, including the two levels of appendicitis severity. The difficult diagnostic task is to differentiate between at least four different categories:

I. Patients with abdominal pain without appendicitis and with no other condition needing treatment (traditionally called non-specific abdominal pain (NSAP)) and therefore do not need to be diagnosed or treated.
II. Patients with acute appendicitis
    a. Patients with uncomplicated appendicitis who do not need urgent surgical treatment or surgical treatment at all
    b. Patients with complicated appendicitis in need of urgent surgical treatment
III. Patients with other conditions that need further diagnostic work-up or treatment

To diagnose acute appendicitis correctly, a 'two-stage' approach is suggested, see Fig. 2. In the first stage, the diagnosis acute appendicitis needs to be made. For patients without acute appendicitis, a correct other cause of their complaints needs to be found, as some abdominal pathologies require urgent treatment. After confirming the diagnosis of acute appendicitis, a distinction will be made between uncomplicated and complicated appendicitis in the second stage, as different treatment options can be considered for these different diseases.

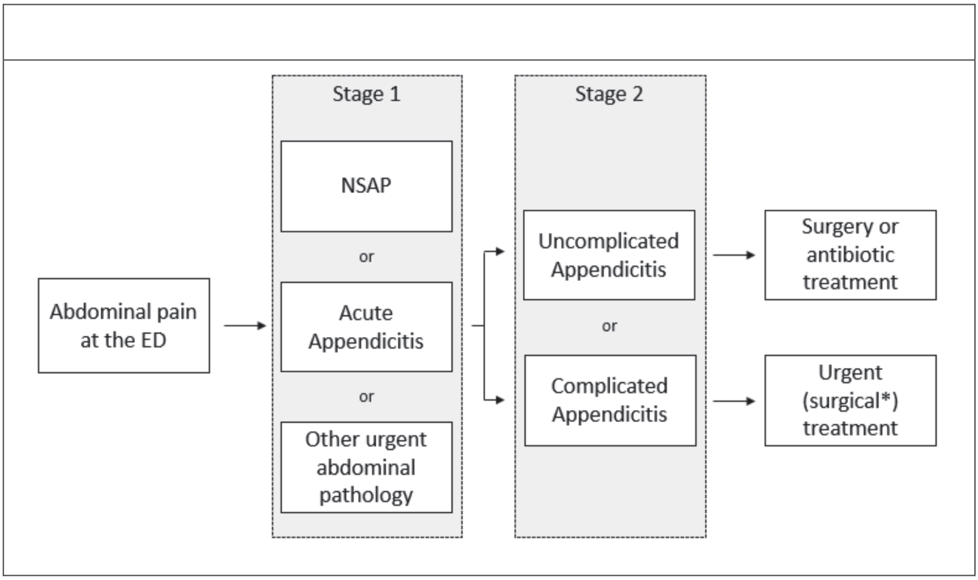

Figure 2, *'Two-stage' diagnostic approach*
Abbreviations: ED, emergency department; NSAP, non-specific abdominal pain
**except for patients with an intra-abdominal abscess*

There are several strategies to diagnose the different categories of abdominal pathology in stage 1. For selecting the right diagnostic approach, it is important to clarify the diagnostic goal: ruling in or ruling out a disease. To rule in a disease, both specificity and positive predictive value (PPV) need to be high, while for ruling out, sensitivity and negative predictive value (NPV) should both be high. At higher sensitivity, specificity may be lower, and vice versa. Diagnostic characteristics need to be considered when selecting a diagnostic test.

In case of diagnosing acute appendicitis in the first diagnostic stage, low sensitivity or low NPV may lead to discharge from the emergency room (ER) of patients who actually have appendicitis. Missed diagnoses lead to treatment delay. In patients with uncomplicated appendicitis, a delay for up to at least 24h does not appear to increase the postoperative complication rate [13]. However, in complicated appendicitis, delaying appendectomy leads to more complications [13]. In contrast, low specificity or low PPV may lead to overdiagnosis, causing high negative appendectomy rates (NARs). Therefore, both ruling in and ruling out acute appendicitis are important.

For discrimination between uncomplicated and complicated appendicitis in the second diagnostic stage, ruling out complicated appendicitis seems more important than ruling in. If antibiotic treatment is considered, complicated appendicitis should be ruled out. Therefore, sensitivity and NPV for complicated appendicitis must be high. Ruling in complicated appendicitis is less important, as patients with a false positive test for complicated appendicitis – actually having uncomplicated appendicitis - will undergo surgery, which is at the moment the standard therapy for any acute appendicitis.

Diagnostic Work-Up for Acute Appendicitis

Several guidelines, international and national, give advice about the diagnostic work-up for suspected acute appendicitis [2, 3]. The diagnostic work-up differs per country, which leads explicitly to differences in NARs [14]. Some guidelines use scoring systems, some only use clinical assessment of the treating physicians, and some guidelines use standardized imaging to diagnose acute appendicitis in all patients or in a selected group of patients [2, 3, 5, 15].

Clinical View

The traditional way of setting a diagnosis is based on clinical assessment. History taking and physical examination combined with laboratory findings are still seen as the cornerstone of diagnosing acute appendicitis, but have a high intra-observer variability and a far from perfect accuracy. The correct clinical diagnosis of both surgical trainees and surgeons failed in 44% and 43% of patients with acute abdominal pain, respectively, when based on medical history, physical examination findings, and routine laboratory tests, but no imaging [16]. For the diagnosis of acute appendicitis, diagnostic accuracy of trainees and surgeons is comparable; sensitivity and specificity vary from 76% to 85% and 82% to 87%, respectively [16]. These data mean that if only the clinical assessment of the surgeon or surgical trainee is used to set a diagnosis in patients with suspected appendicitis, 15-24% of patients with acute appendicitis are missed and an NAR of 13-18% will be seen, which is much higher than the ideal upper limit of 5%. Therefore, patients cannot be accurately ruled in or ruled out based on clinical assessment only.

Laboratory Tests

In addition to clinical examination, laboratory tests such as white blood cell (WBC) count or C-reactive protein (CRP) are widely used as a next step in diagnosing acute appendicitis [3]. Individually, these inflammatory markers are weak discriminators, but when combined they achieve a higher discriminatory power in diagnosing acute appendicitis versus no appendicitis [17]. Nevertheless, according to a study of prospective data, including 1024 patients presenting with clinical suspicion of acute appendicitis, this combination is not able to sufficiently rule in or rule out appendicitis [18]. By exploration of different cut-off values for WBCs and CRP a maximal NPV of 88% can be reached for ruling out appendicitis [18]. Although this maximal NPV seems high, it is found only in a small subgroup (9.9% of the total cohort) consisting of typical patients having WBC $<10 \times 10^9$/L or CRP <10 mg/L. Since the NPV is less optimal in other patient categories, ruling out appendicitis based only on laboratory tests is not a good strategy. For ruling in appendicitis based on inflammatory markers only, a PPV up to 74.2% is found; this maximum is seen in patients with WBC $> 20 \times 10^9$/L who comprise only 6.1% of the

1024 patients in the cohort [18]. Therefore, ruling in appendicitis based only on laboratory tests is even more troublesome than ruling out. This is not surprising as CRP and WBC are general and non-specific inflammatory markers, and thereby less helpful for a specific diagnosis. Structured models, such as clinical scoring systems including laboratory tests, may be helpful.

Clinical Scoring Systems

To overcome subjective interpretation of clinical signs and lab tests, standardized clinical risk scores have been composed. Originally, the Alvarado score is the best-known scoring system based on clinical parameters for the diagnosis of acute appendicitis. However, standards have changed to more recent scoring models. The 2020 update of WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis recommend the use of the Appendicitis Inflammatory Response Score (AIRS) and Adult Appendicitis Score (AAS) as diagnostic scores of acute appendicitis [3], see Table 1.

		Alvarado	AIRS	AAS
Migration/relocation of pain		1	-	2
Anorexia		1	-	-
Nausea/Vomiting		1	-	-
Vomiting		-	1	-
Pain in RIF/RLQ		2	1	2
Rebound pain/tenderness:	Mild Moderate Severe	1 1 1	1 2 3	- - -
Guarding:	Mild Moderate/Severe	- -	- -	2 4
RLQ tenderness:	Women (16-49 y) All other patients	-	-	1 3
Elevated temperature		1 (>37.5°C)	1 (>38.5°C)	-
WBC (x10^9)	7.2 – 10 10 – 10.9 10.9 – 14 14 – 15 ≥ 15	- 2 2 2 2	- 1 1 1 2	1 1 2 3 3
Shift of WBC to the left (>75% neutrophils)		1	-	-
Polymorphonuclear leukocytes		-	0 (< 70%) 1 (70-84%) 2 (≥ 85%)	2 (62-75%) 3 (75-83%) 4 (≥ 83%)
CRP level, mg/L for symptoms < 24 h		-	0 (< 10) 1 (10-49) 2 (≥ 50)	2 (4-11) 3 (11-25) 5 (25-83) 1 (≥ 83)
CRP level, mg/L for symptoms > 24 h		-	0 (< 10) 1 (10-49) 2 (≥ 50)	0 (< 12) 2 (12-152) 1 (≥ 152)

Table 1*, Clinical Diagnostic Scores: Alvarado, AIRS and AAS*
Abbreviations: AAS, adult appendicitis score; AIRS, appendicitis inflammatory response score; CRP, C-reactive protein; RIF, right iliac fossa; RLQ, right lower abdominal quadrant; WBC, white blood cell count; y, years of age.

Low-risk for appendicitis (rule out)

A diagnostic score may be able to classify a subgroup of patients as 'low-risk for acute appendicitis', which is used to rule out acute appendicitis. A recent study has validated 15 scoring systems for the identification of these low-risk patients in a cohort of patients presenting with acute right iliac fossa (RIF) pain in the United Kingdom[19]. According to their standards, the ideal scoring system has a high specificity, while maintaining a failure rate (1-NPV) of less than five per cent [19]. In other words: an ideal appendicitis score should be able to (1) correctly classify patients without appendicitis as 'no appendicitis' or rule out acute appendicitis accurately (in terms of a maximum acceptable failure rate of 5%) and (2) correctly classify patients with appendicitis as 'appendicitis' in terms of the best achievable specificity. After finding the best model, the scoring systems have been externally validated in data sets from other European countries [19]. In the British cohort of 3613 women, the AAS performs best. Using a cut-off score of 8 or less, a specificity of 63.1% is found, associated with a failure rate of only 3.7%. This means that based on the AAS, only 69 out of 1856 patients who score a low-risk of acute appendicitis do have an appendicitis. However, external validation in other countries has resulted in a failure rate up to 17.5%. In 1732 male British patients, not the AAS but the AIRS has performed best; the failure rate was 2.4% with a specificity of 24.7% at a cut-off score of 2 or less. This failure rate, however, increases during validation in cohorts from other countries, and is as high as 32%. The RIFT study group states that their study results 'should be extrapolated cautiously to settings outside the UK' [19]. Indeed, although the results of the RIFT study group seem promising in a cohort of UK patients, ruling out appendicitis based on a mere clinical scoring system does not perform well in other cohorts and will also not enable differentiation between complicated and uncomplicated appendicitis [19].-

High-risk for appendicitis (rule in)

Ruling in appendicitis is a different story; these patients are classified as 'high-risk for acute appendicitis'. The WSES guideline suggests that cross-sectional imaging may be avoided in patients younger than 40 years with a high-risk for appendicitis score result and one can proceed to (diagnostic) laparoscopy. High-risk patients are defined as patients with an AIR or Alvarado score of 9 and higher, or an AAS of 16 and higher. However, meta-analysis data on ruling in acute appendicitis based on clinical risk scores are lacking. Several studies have validated scoring models for the identification of patients at high-risk for appendicitis. Four studies have validated the Alvarado score[20-23], five the AIRS[20, 21, 23-25] and two the AAS[23, 26], but results are very heterogeneous. We used a bivariate logitnormal random-effect model to pool results of the included studies for present review; the reported sensitivity and specificity for the Alvarado score were 24% and 97%, for the AIRS 22% and 97%, and for the AAS 53% and 93%, respectively. With a median prevalence of acute appendicitis of 37%, this would lead to a PPV of 82% for the Alvarado score, 81% for AIRS, and 82% for AAS. Although a high specificity is reached, these PPVs will lead to high NARs (18% - 19%) when the final diagnosis of acute appendicitis is made only based on one of these clinical diagnostic rules. Standard use of imaging leads to less negative appendectomies[14] and therefore lower avoidable risks for the patient.

The three test zone concept (low-, intermediate-, and high-risk scores)

The concept of three test zones with two cut-off points for appendicitis scores to determine the need for imaging to diagnose appendicitis seems promising [27]. However, we need more reproducible data in different cohorts, showing a stable performance of such test zones, before such a clinical decision rule can be used to bypass imaging. Even if patients can be pointed out being at 'high risk' of having acute appendicitis based on a three-zone clinical score, a low-dose computed tomography (CT) scan (or step-wise conditional CT after initial ultrasound (US)) seems less harmful than standard 'diagnostic' surgery, Surgery without imaging is accompanied by higher NARs compared to the known rates after a standard imaging approach [14, 28]. This argument is illustrated by comparing two prospective national SNAPSHOT audits [14]. Standard imaging, by means of the step-up approach of US with additional CT or magnetic resonance imaging (MRI) if needed, in 1934 Dutch patients of whom 99.5% underwent preoperative imaging, resulted in an NAR of 3.2% [14]. Within a population of 3326 British patients, only 32.8% underwent preoperative imaging, which resulted in an NAR of 20.6% [14].

Imaging

To diagnose acute appendicitis with high accuracy, standardized imaging plays an important role. US, CT scanning and MRI can all be used to diagnose acute appendicitis. With standard US equipment the appendix can be visualized using a graded compression technique. Contrast-enhanced abdominal CT can be performed in the portal-venous phase [15]. Studies show that intravenous contrast enhanced low-dose CT has comparable accuracy to normal-dose CT and should therefore be preferred [28, 29]. CT protocols are mainly based on helical scanners with a single detector or multidetector and slice thickness of 3 to 5 mm with an interval of 3 to 10 mm [30, 31]. Alternatively, MRI can be performed. Standard is the use of a 1.5T MRI with half-Fourier-acquisition single-shot turbo spin-echo (HASTE) sequences and a combination of T1, T2 and T2 fat suppression [15, 32]. Intravenous contrast can be used in MRI, but is not standard [15, 32].

While US usually is low-priced, quick and has no burden on ionizing radiation, CT and MRI reach better diagnostic results. According to a meta-analysis by Giljaca et al., US alone has a sensitivity and specificity for acute appendicitis of 69% and 81%, respectively[33]. Meta-analyses of Van Randen et al. and Duke et al. demonstrate that CT and MRI are better in detecting acute appendicitis than US with a summary sensitivity and specificity for acute appendicitis of 91% and 90% for CT [30], and 97% and 96% for MRI [32]. The median prevalence of US, CT and MRI, as reported in the reviews, is 76%, 50% and 58%, respectively. Since a pre-selection probably resulted in higher prevalence of acute appendicitis, results of these imaging studies cannot directly be compared to those of the clinical diagnostic scores. For practicable test characteristics as PPV and NPV, this prevalence is essential. For instance, suppose that a highly specific test is applied in an unselected population with low prevalence of appendicitis. This results in low PPV, but high NPV. Conversely, within a selected high-risk group of patients, a low NPV and a high PPV could be found. When incorporating the mentioned prevalences into the calculations, PPV and NPV for US were 92% and 45%, respectively, for CT 90% and 91%, and for MRI 97% and 96%. If the before mentioned clinical scores would be applied to a population of patients suspected for appendicitis with an appendicitis prevalence of 50%, similar to the prevalence in the CT study population, this would result in a PPV and NPV of 89% and 56% for the Alvarado score, 88% and 55% for the AIRS, and 88% and 66% for the AAS. The diagnostic characteristics of CT and MRI are therefore much better than achieved by the three clinical diagnostic scores.

A more pragmatic approach instead of using only one imaging modality, may be using a diagnostic work-up in which an initial US is performed, followed by a conditional CT or MRI in case of an inconclusive or negative US [34]. Leeuwenburgh et al. have demonstrated that the combination of US and CT leads to a sensitivity and specificity of 97% and 91% for the diagnosis of appendicitis. At the published study prevalence of 51%, a PPV of 92% and an NPV of 97% were found for conditional CT strategy. For US with conditional MRI, sensitivity, specificity, PPV and NPV are 98%, 88%, 88%, and 98%, respectively [34]. However, there are some limitations. US has high inter-observer variability, which leads to a diagnostic accuracy that varies between different radiologists. For CT, radiation and intravenous contrast are used. Especially in fertile females, children and young adults, this should be avoided if possible. However, low-dose CT has comparable accuracy [28, 29, 35], markedly reducing the possibility of radiation-induced cancer. Contrast allergy and contrast-induced nephropathy are infrequent. Experience in reading an MRI is less common among radiologists and some may need additional training [36]. However, training with direct feedback improves the accuracy of both radiologists and residents even after evaluating only 100 cases, with sensitivity and specificity reaching 92% and 88%, respectively, for the diagnosis of appendicitis [36]. In addition, MRI has a longer in-room time, is logistically challenging, and may not be available 24/7. Costs of diagnostics are also important.

Although imaging has higher initial costs, standard imaging has shown to be cost-effective [37] as well as reducing the NAR [14].

Discriminating Complicated from Uncomplicated Appendicitis

Guidelines do not clearly advise how to differentiate between uncomplicated and complicated appendicitis [2, 3]. Nevertheless, the same guidelines state that complicated appendicitis should be treated within higher urgency, and that uncomplicated appendicitis may be treated with antibiotics only [2, 3]. Due to these different strategies, differentiation between uncomplicated and complicated appendicitis has become more relevant. In order to differentiate treatment according to severity of appendicitis, we need to establish uniform criteria for findings suggestive of complicated appendicitis and determine factors that are predictive for failure of conservative treatment in patients who were initially diagnosed with uncomplicated appendicitis. As mentioned in a previous section, the main purpose is ruling out complicated appendicitis.

While many studies have analyzed the diagnosis of acute appendicitis itself, only a few have tried to distinguish between uncomplicated and complicated appendicitis. Several studies have described the capability of the AIRS and Alvarado score to discriminate uncomplicated from complicated appendicitis [38-41]. None of these studies mentioned diagnostic accuracy measures, and therefore sensitivity and specificity cannot be calculated. Two other studies reported the design of a scoring system including clinical and biochemical features; neither reported diagnostic accuracy measures [42, 43]. Imaging seems to be an essential step in differentiating uncomplicated from complicated appendicitis. A recent meta-analysis identifies CT features such as abscess, extraluminal air, intra- and extraluminal appendicolith, and periappendicular fluid to be associated with complicated acute appendicitis [44]. Although high specificity is reached, all parameters fall short in sensitivity [44], and are therefore not able to reliably rule out complicated appendicitis. Appendicolith on imaging as risk factor for complicated appendicitis is discussed below.

		SAS-US[45]	**SAS-CT[45]**	**APSI[46]**
Age	< 45 years ≥45 years ≥ 52 years	0 2 2	0 2 2	0 0 1
Body temperature in degree Celsius	≤ 37.0 37.1 – 37.4 37.5 – 37.9 ≥ 38.0	0 2 2 4	0 2 2 4	0 0 1 1
Duration of symptoms ≥ 48 hours		2	2	1
WBC count > 13 x 10^9/L		2	2	-
C-reactive protein (mg/l)	≤ 50 50 – 100 > 100	0 4 5	0 2 3	-
Imaging parameters, based on US (SAS-US) or CT (SAS-CT and APSI)				
Appendiceal diameter	≥ 14 mm	-	-	1
Periappendiceal fluid		2	2	2
Extraluminal air present		-	5	1
Appendicolith		2	2	-
Abscess		-	-	3

Table 2, *Appendicitis Severity Scores*
Abbreviations: APSI, appendicitis severity index; CT, computed tomography; US, ultrasound; WBC, white blood cell count.

Only two studies have described a scoring system combining clinical and imaging features to distinguish between uncomplicated and complicated appendicitis, see Table 2 [45, 46]. Atema et al. have developed two Scoring systems for Appendicitis Severity (SAS) that combine imaging with clinical and biochemical features; one using US features (SAS-US) and the other using CT features (SAS-CT) [45]. Sensitivity, specificity, PPV and NPV for US-SAS are 97%, 46%, 42% and 97%, respectively [45]. For the scoring system with CT features, SAS-CT, these test features are 90% sensitivity, 70% specificity, 55% PPV and 95% NPV [45]. The SAS scoring systems provide excellent diagnostic characteristics (high sensitivity and NPV) to rule out complicated appendicitis, but do not perform well in ruling in complicated appendicitis. Avanesov et al. have also developed a scoring system, the APpendicitis Severity Index (APSI), that combines with clinical and biochemical features with CT features [46]. Sensitivity, specificity, PPV and NPV were 82%, 93%, 92% and 83% [46]. That scoring system provides diagnostic characteristics (high specificity and PPV) needed for accurate ruling in of complicated appendicitis. The major drawback of these three scoring systems is that none have been validated externally in prospective studies yet.

A recent systematic review and meta-analysis from our group compared all available studies on imaging modalities differentiating between uncomplicated and complicated appendicitis [47]. Eleven studies using CT were found. Summary estimates were 78% for sensitivity and 91% for specificity, resulting in a PPV of 74% and an NPV of 93% for diagnosis of complicated appendicitis [47]. Results were highly heterogeneous, with sensitivities ranging from 28-95% [47]. One study has described the discriminatory capability when an initial US is performed followed by a conditional CT or MRI in case of an inconclusive or negative US. A sensitivity of 48%, specificity of 93%, PPV of 68% and NPV of 84% are found for the diagnosis of complicated appendicitis [48].

Randomized trials comparing conservative and surgical treatment of uncomplicated appendicitis have found remarkable differences in number of erroneously included patients with complicated appendicitis. Two large randomized control trials (RCTs) have used standardized CT in their diagnostic approach to select only patients with uncomplicated appendicitis for study inclusion [49, 50]. While both trials used a CT protocol with standard intravenous contrast, Vons et al. found complicated appendicitis in 18% of patients randomized for surgery versus only 1.5% in the surgery group of Salminen et al. [50]. This difference may be explained by the fact that Salminen et al. exclude patients presenting with an appendicolith before randomization. Post-hoc analyses of Vons et al. show a significant association between the presence of an appendicolith and the diagnosis of complicated appendicitis [50]. In fact, when excluding the subgroup of patients without the presence of an appendicolith, there is no difference in 30-day post-intervention peritonitis between operated and conservatively treated patients [50]. The Appendicitis acuta (APPAC) trial has excluded patients with an appendicolith before randomization, which may have led to the substantial lower percentage of unintentional included complicated appendicitis patients. The presence of an appendicolith has previously been described as a significant predictor of the need for surgery after failed conservative treatment in acute appendicitis [51], and this may be because of an association with complicated appendicitis. The most recent RCT on this subject, the (Comparison of Outcomes of antibiotic Drugs and Appendectomy (CODA) trial, also demonstrates this association between the presence of an appendicolith and higher risk of complicated appendicitis in the included patients with an assumed uncomplicated appendicitis[7]. In addition, a significant higher risk for appendectomy after initial antibiotic treatment is seen in patients with an appendicolith[7]. Atema et al. incorporated the presence of an appendicolith in their SAS scoring system to differentiate between uncomplicated and complicated appendicitis [45].

The previously mentioned meta-analysis by Kim et al. found a pooled sensitivity and specificity of 43% and 74% of the presence of an intraluminal appendicolith for complicated appendicitis [44], and presence of an appendicolith results in 2 points in both the SAS-CT and the SAS-US [45]. Considering these numbers, an appendicolith does not seem to be decisive for differentiation between uncomplicated and complicated appendicitis. Nonetheless, the effect of excluding patients with an appendicolith in selection for antibiotic treatment appears to be significant on outcomes and appendicitis recurrence rates in large RCTs[7, 49, 50], and therefore it does have clinical impact and in further studies, better defining the role of appendicoliths is needed.

Conclusion

Although the subject of appendicitis diagnostics is not new, a watertight work-up to accurately diagnose acute appendicitis remains challenging. A two-stage diagnostic work-up with adequate accuracy in both steps is needed. In the first diagnostic stage, acute appendicitis must be distinguished from other urgent or non-urgent abdominal disease diagnoses. In the second diagnostic stage of patients diagnosed with acute appendicitis, a differentiation between complicated and uncomplicated appendicitis is needed.

As no clinical or laboratory test has both high sensitivity and high specificity, relying only on such parameters means balancing the tradeoffs between the risk of delaying treatment of complicated appendicitis (inadequate sensitivity for complicated appendicitis) and the risk of negative surgical explorations (inadequate specificity for complicated appendicitis). Standard imaging increases the diagnostic power for both ruling in and ruling out appendicitis. Imaging can be combined with or even incorporated in scoring systems. Moreover, imaging plays an important role in differentiating between appendicitis and other abdominal pathology, for those patients with abdominal pain suspected of a cause in need of treatment. Even if a clinical scoring model would be able to rule out acute appendicitis, imaging is still needed in most cases to correctly diagnose the cause of the abdominal pain for that particular patient. And in case of appendicitis, imaging is still needed for a differentiation between complicated and uncomplicated appendicitis.

Today, probably the most sensible way to use clinical scoring systems for suspected appendicitis is to select patients for immediate imaging (intermediate and high-risk scores) or reassessment the next day (low-risk scores). If a clinical diagnostic model stratifies a patient at low-risk of having acute appendicitis, reassessment the next day in outpatient setting or discharge to family physician care seems preferable over inpatient observation for adequate use of resources. Importantly, if all patients with a high-risk score for appendicitis based on clinical scoring systems undergo imaging, the NAR will be minimized to an acceptable level.

As non-operative management of uncomplicated appendicitis has been identified as a feasible and safe treatment option, cross-sectional imaging is obligatory to distinguish between uncomplicated and complicated appendicitis in the second stage of diagnosing acute appendicitis. Cross-sectional imaging can rule out complicated appendicitis to a certain extent, but when CT features are combined with clinical and laboratory features in the SAS scoring system, specifically designed to differentiate between uncomplicated and complicated disease among patients with acute appendicitis, NPV for complicated disease can be as high as 95%. Implementing standardized low-dose CT protocols for appendicitis diagnosis is of paramount importance to avoid unnecessary radiation in patients with suspected acute appendicitis. In addition, determination of uniform diagnostic predictors for complicated acute appendicitis or recurrent appendicitis after conservative treatment is essential in order to both adequately rule out complicated appendicitis and optimize patient selection for antibiotic treatment of uncomplicated appendicitis.

Identifying predictive factors for both non-responsiveness to antibiotic treatment after accurate diagnosis and recurrence after antibiotic treatment would lead to less appendicitis recurrences optimizing treatment outcomes. As the number of patients with uncomplicated acute appendicitis either not responding to antibiotic treatment or encountering appendicitis recurrence is quite low, we need international scientific collaboration combining large prospective patient databases to be able to identify these factors. Future trials need to investigate the potential further improvement of antibiotic treatment results with achieving optimal selection of patients with uncomplicated appendicitis.

Standardized and low threshold imaging plays an important role for accurate diagnosis of acute appendicitis. It reduces the risk that another diagnosis is missed as cause of abdominal pain in need of (urgent) treatment. It minimizes NARs and it may help to differentiate between uncomplicated and complicated appendicitis, which is important because this may lead to different management strategies. In addition, with innovations in diagnostic imaging modalities and CT equipment, the as-low-as-possible radiation principle without compromising diagnostic accuracy is improving rapidly. With the current and ever increasing improvements in CT techniques, especially so for the low-dose CT modalities, it is hard to imagine a diagnostic paradigm in acute appendicitis not taking advantage of modern imaging. In this respect, leaving out imaging features in scoring systems may have no promising future. A surgeon's clinical assessment is and will always be needed as interpretation of results and act upon it remains a skill, but a surgeon needs to have the benefit from modern imaging, at least in middle- and high-income countries. Cross-sectional imaging is not needed in patients with abdominal pain at low-risk of appendicitis or any other disease requiring treatment.

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PART II

Treatment and its consequences

Chapter 7

In hospital delay of appendectomy in acute, complicated appendicitis

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Abstract

Background

Present theory is that uncomplicated and complicated appendicitis are different entities. Recent studies suggest, it is safe to delay surgery in patients with uncomplicated appendicitis. We hypothesize that patients with complicated appendicitis are at higher risk for postoperative complications when surgery is delayed.

Methods

Data was used from the multicenter, prospective SNAPSHOT appendicitis study of 1975 patients undergoing surgery for suspected appendicitis. Adult patients (≥18 years) who underwent appendectomy for appendicitis were included in this study. The primary outcome was the difference in postoperative complications between patients with complicated appendicitis who were operated within and after 8 h after hospital presentation. Secondary outcomes were the incidence of both uncomplicated and complicated appendicitis in relationship to delay of appendectomy. Follow-up was 30 days. A multivariable analysis was performed.

Results

Of 1341 adult patients with appendicitis, 34.3% had complicated appendicitis. In patients with complicated appendicitis, 22.8% developed a postoperative complication compared to 8.2% for uncomplicated appendicitis ($P < 0.001$). Delay in surgery (>8 h) increased the complication rate in patients with complicated appendicitis (28.1%) compared to surgery within 8 hours (18.3%; $P = 0.01$). Multivariate analysis showed a delay in surgery as an independent predictor for a postoperative complication in patients with complicated appendicitis (OR 1.71; 95%CI 1.01-2.68, $P = 0.02$).

Conclusion

In-hospital delay of surgery (>8 h) in patients with complicated appendicitis is associated with a higher risk of a postoperative complication. It is important that we recognize and treat these patients early.

Introduction

Acute appendicitis is traditionally considered an ongoing disease, eventually resulting in perforation[1] and immediate surgery is necessary to decrease the risk of morbidity and mortality. The current theory is that complicated appendicitis and uncomplicated appendicitis are two different disease entities with each a different course of disease[2-4]. Based on this theory, different treatment options (non-operative treatment vs. surgery) and the timing of an emergency appendectomy are frequently analyzed and debated in literature. In recent years, several authors have challenged the acute appendectomy by demonstrating that administration of antibiotics alone is a safe treatment of appendicitis in patients with uncomplicated appendicitis[5-8]. Guidelines therefore advise to consider a non-operative approach in this group and discuss advantages and disadvantages of both treatment options with the patient[9]. Nonetheless, in most hospitals, surgery is still the gold standard of treatment, but controversy remains about the timing of appendectomy. Recent meta-analysis shows that delaying surgery in patients with uncomplicated appendicitis (up to 24 h) is not associated with more postoperative complications and is therefore safe in this group[10]. In patients with suspected complicated appendicitis, surgery should be performed within 8 h according to Dutch Guidelines[11]. This is partly based on the earlier mentioned review. Evidence for this recommendation is scarce; however, it is mainly a expert based opinion.

This study aims to compare postoperative complications in patients with complicated appendicitis in whom surgery was performed within 8 h versus after 8 h after hospital presentation. The hypothesis is that patients with a complicated appendicitis with delayed surgery have a higher risk of developing a postoperative complication.

Methods

Study Design

For this study, data was used from the multicenter, prospective SNAPSHOT study appendicitis of all patients undergoing surgery for suspected appendicitis, conducted in a 2-month period (June and July 2014). Data from 62 Dutch academic and general community hospitals was entered in an online Snapshot database. The initial cohort has already been described[12], which was designed and led by surgical residents, who collected the data together with house officers. Patients with non-operatively treated acute appendicitis, an appendectomy following initially non-operatively treated acute appendicitis or a planned resection of the appendix were not included in this original database.

Adult patients (≥ 18 years) were included in current analysis when the diagnosis of acute appendicitis was confirmed during intraoperative evaluation and an appendectomy was performed. Patients with appendiceal malignancy and patients in whom an appendectomy was performed > 48 h after hospital admission were not included.

Definitions

Duration of Symptoms and Timing of Surgery

Time from symptom onset to surgery was divided into two-time intervals; time from symptom onset to presentation on the emergency department in days (prehospital symptom time) and time from presentation on the emergency department to appendectomy in hours (time to surgery). Delayed surgery was defined when performed 8 h after presentation to the emergency department.

Uncomplicated and Complicated Appendicitis

Uncomplicated appendicitis was defined as phlegmonous appendicitis, without signs of necrosis or perforation during intraoperative evaluation. Complicated appendicitis was defined as gangrenous or perforated appendicitis[13]. All patients with complicated appendicitis were postoperatively treated with antibiotics. Results were based on surgical reports, as reported by the local collaborators. When the surgical reports were unclear, patients with continued antibiotics postoperatively, were also defined as complicated appendicitis

Postoperative Complications

Postoperative complications were defined as any adverse event within 30 days following surgery, causing a longer duration of hospitalization. Surgical site infection, intraabdominal abscess, other abdominal infections, bowel obstruction longer than 5 days and readmission were scored specifically.

Interventions were defined as reoperations or percutaneous drainage procedures.

The total length of hospital duration was evaluated in days.

Data Extraction and Outcome Parameters

Patient characteristics, surgical details, postoperative complications and histological results were collected by local collaborators. The primary outcome was the difference in proportion of patients with postoperative complications between patients who were operated within and after 8 h, in patients with complicated appendicitis. Secondary outcomes were the incidence of complicated appendicitis in the groups operated within and after 8 h. For both complicated and uncomplicated appendicitis analyses were performed separately. Follow-up was 30 days following surgery.

Statistical Analysis

Normally distributed data was presented as mean with standard deviation (SD) and non-normally distributed data as median with interquartile range (IQR). To determine whether differences in these continuous variables were significant, the t-test and Mann-Whitney-U test were used, respectively. Categorical data were analyzed using the chi-square test and the Fisher's exact test was used when the expected count for one of the cells was below 5. $P < 0.05$ was considered statistically significant. We performed a multivariate binary logistic regression to see whether patients with complicated appendicitis were significantly more at risk for postoperative complications when surgery was delayed >8 h and when possible confounders were implemented. Possible confounders selected were age, previous visit of emergency department, prehospital symptom time, temperature, leukocyte count, CRP, ASA-classification, possible complicated appendicitis on imaging and time to surgery. Variables with $P < 0.2$ in univariate analysis were selected for multivariate analysis. Backward selection was performed by removing variables with the highest p-value from the regression, until all variables had $P < 0.05$. All data was analyzed using IBM SPSS statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

In total, 1975 patients underwent surgery for suspected acute appendicitis. Of these patients, 1390 adults (≥ 18 years of age) had acute appendicitis. Of these, 29 were excluded, eventually leaving 1341 patients eligible for analysis (*Fig. 1*). The median age of all patients was 39 years (IQR 27-54) and 50% (671/1341) were men. The prehospital symptom time was longer than 2 days in 19.0% and median time to surgery was 7 h.

In total, 56.2% (753/1341) of all patients were operated within 8 h and 34.4% of the patients had complicated appendicitis (461/1341). The proportion of patients with a postoperative complication was lower in patients operated within 8 h (11% (83/753) versus 16% (94/588); p=0.008). All baseline demographics are described in Table 1.

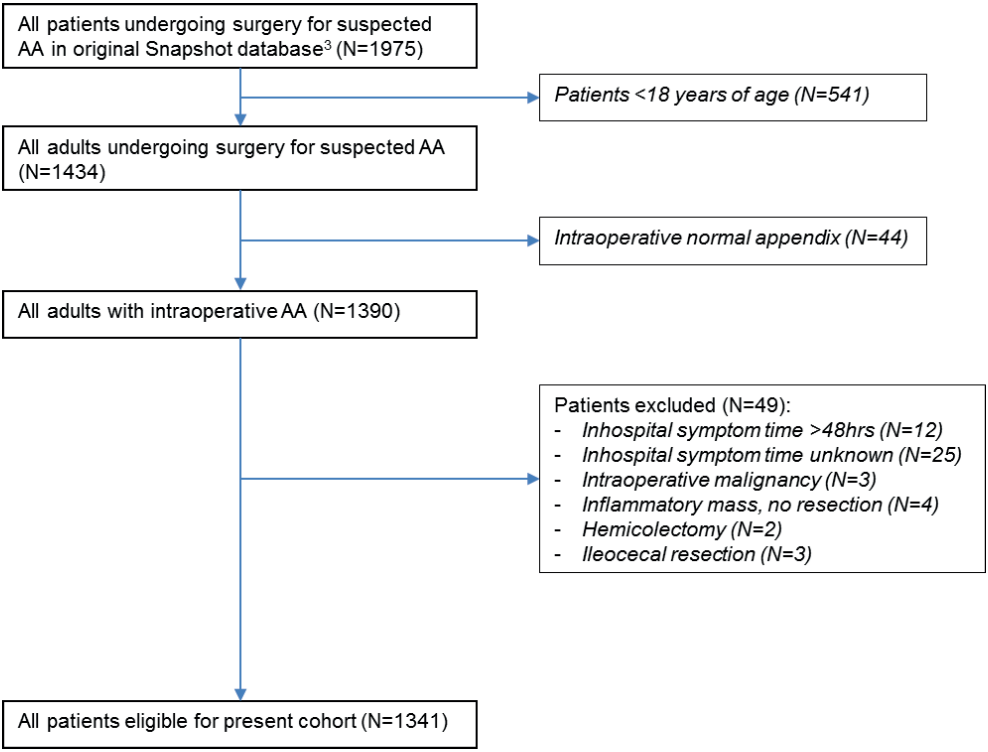

Figure 1*, Patients eligible for present cohort (N=1341). AA= acute appendicitis.*

		Total (N=1341) n (%)	CA (N=461) n (%)	<8h (N = 753) (%)	>8h (N = 588) (%)	p-value
Age, yrs (med, IQR) Missing n=0		39 (27;54)	50 (34;62.5)	39 (28;54)	37.5 (26;53)	0.258
Sex, male Missing n=0		671 (50)	236 (51.2)	382 (50.7)	289 (49.1	0.30
Previous visit emergency department Missing n=46 (CA n=21)		161 (12)	39 (8.5)	73 (10.1)	88 (15.4)	<0.01
ASA (n, %)	I-II	1292 (96.3)	437 (94.8)	728 (96.7)	564 (95.9)	0.28
Missing n=0	III-IV	49 (3.7)	24 (5.2)	25 (3.3)	24 (4,1)	
Pre-hosp symptom time (n, %)	<2 days	1062 (79.2)	314 (68.1)	589 (80.4)	473 (81.8)	0.27
Missing n=30 (CA n=16)	>2 days	249 (18.6)	131 (28.4)	144 (19.6)	105 (18.2)	
Migration of pain (n, %) Missing n=39 (CA n=17)		572 (42.7)	184 (39.9)	312 (43.1)	260 (45)	0.26
Nausea (n, %) Missing n=31 (CA n=10)		908 (67.7)	343 (74.4)	500 (68.3)	408 (70.6)	0.20
Vomiting (n, %) Missing n=28 (CA n=9)		456 (34)	203 (44)	248 (33.9)	208 (35.8)	0.25
Temperature, ˚C Missing n=76 (CA=32)	(mean, SD)	37.3 (0.8)	37.7 (0.8)	37.4 (0.79)	37.4 (0.77)	0.60
Peritonitis (n,%)	Localized	122 (9.1)	71 (15.4)	658 (90.8)	511 (90.3)	0.42
Missing n=50 (CA= 19)	Diffuse	1169 (87.2)	371 (80.5)	67 (9.2)	55 (9.7)	
Biochemics	WBC, 10^9/L (mean, SD) Missing n=2	13.8 (4.5)	14.7 (4.5)	13.75 (4.4)	13.83 (4.5)	0.87
	CRP, mg/L (med, IQR) Missing n=5 (CA=1)	38 (13;84)	80.5 (34;165)	41 (17;90)	33.5 (10;76)	<0.01
Time to surgery, hrs (med, IQR) Missing n=0		7.1 (4.5;13.3)	7.1 (4.6;12.8)	4.8 (3.5;6.0)	14.6 (10.7;19.8)	<0.01
Type of surgery (n, %)	Lap.	1030 (76.8)	339 (73.5)	562 (74.6)	468 (79.6)	0.09
Missing n=0	Open	274 (20.4)	95 (20.6)	170 (22.6)	104 (17.7)	
	Conversion	37 (2.8)	27 (5.9)	21 (2.8)	16 (2.7)	
Complicated appendicitis on imaging (n, %) Missing n=0		213 (15.9)	155 (33.6)	122 (16.2)	91 (15.2)	0.39

Table 1, *Baseline characteristics*
Tests: *a. Mann-whitney U, b. chi-square, c. T-test.*
CA: Complicated Appendicitis; ASA: American Society of Anesthesiologist

Primary Outcome

The overall proportion of patients with a complication within 30 days postoperatively was 22.8% (105/461) in patients with complicated appendicitis, compared to 8.2% (72/880) for patients with uncomplicated appendicitis (P < 0.01). In patients with complicated appendicitis, surgery was performed within 8 h in 54.4% (251/461). As compared to 57.0% (502/880) for uncomplicated appendicitis. In patients with complicated appendicitis, patients with a time to surgery of less than 8 h had fewer postoperative complications (18.3% (46/251) versus 28.1% (59/210);P < 0.01) and less reinterventions (3.2% (8/251) versus 8.1% (17;210);P = 0.02), when compared to patients operated after 8 h (Table 2).

	Uncomplicated (N=880)			**Complicated (N=461)**		
	<8hrs (N=502)	**>8hrs (N=378)**	**p-value**	**<8hrs (N=251)**	**>8hrs (N=210)**	**p-value**
Complication < 30days (n, %)	37 (7.4)	35 (9.3)	0.31	46 (18.3)	59 (28.1)	<0.01
WI (n, %)	18 (3.6)	8 (2.1)	0.20	12 (4.8)	12 (5.7)	0.65
IAA (n, %)	11 (2.2)	6 (1.6)	0.52	17 (6.8)	23 (11)	0.11
BO >5dys (n, %)	3 (0.6)	2 (0.5)	1.0a	9 (3.6)	10 (4.8)	0.53
Pneumonia (n, %)	1 (0.2)	-	1.0a	1 (0.4)	2 (1)	0.59a
UTI (n, %)	1 (0.2)	1 (0.3)	1.0a	1 (0.4)	1 (0.5)	1.0a
Readmission (n, %)	17 (3.4)	26 (6.9)	0.02	17 (6.8)	20 (9.5)	0.28
Reoperation (n, %)	5 (1)	3 (0.8)	1.0a	6 (2.4)	10 (4.8)	0.17
Reintervention (n, %)	7 (1.4)	7 (1.9)	0.59	8 (3.2)	17 (8.1)	0.02
Mortality (n, %)	1 (0.2)	-	1.0a	1 (0.4)	-	1.0a
Hosp stay, dys (med, IQR)	2 (1;2)	2 (1;2)	<0.01	4 (3;6)	5 (3;7)	<0.01

Table 2. *In hospital delay and postoperative complications of patients with UA and CA time to surgery < or >8hrs (N=1341)*
Tests: *a. fishers exact*
(WI: Wound Infection; IAA: Intra Abdominal Abcess; BO: Bowel Obstruction; UTI: Urinary Tract Infection)

Early versus late surgery

Baseline characteristics between patients with surgery within 8 hours or after 8 hours were similar, except for a higher C-reactive protein count in patients operated in the within group (41 vs 33.5; P < 0.01) Patients with an earlier emergency department visit were more frequently operated in the after group. (73 vs 88; P < 0.01). (Table 1)

The proportion of patients with complicated appendicitis was comparable when surgery was performed within 8 h (33.3% (251/753), or after 8 h (35.7% (210/588); P = 0.20. (Table 3)

The overall proportion of patients with a complication within 30 days postoperatively was 16.0% (94/588) in the after group, compared to 11.0% (83/753) in the within group(p=0.01) (Table 2).

	<8hrs (N=753)	>8hrs (N=588)	P-value
Complication < 30days (n, %)	83 (11)	94 (16)	<0.01
WI (n, %)	30 (4)	20 (3.4)	0.58
IAA (n, %)	28 (3.7)	29 (4.9)	0.27
BO >(n, %)	12 (1.6)	12 (2)	0.54
Pneumonia (n, %)	2 (0.3)	2 (0.3)	1.0[a]
Urinary tract infection (n,%)	2 (0.3)	2 (0.3)	1.0[a]
Hosp stay, dys (med, IQR)	2(1;3)	2(2;4)	<0.01
Readmission (n, %)	34 (4.5)	46 (7.8)	<0.01
Reoperation (n, %)	11 (1.5)	13 (2.2)	0.30
Reintervent (n, %)	15 (2)	24 (4.1)	0.02
Mortality (n, %)	2 (0.3)	-	0.51

Table 3. *In hospital delay and postoperative complications of total cohort time to surgery < or >8hrs (N= 1341)*
Tests: *a. fishers exact*
(WI: Wound Infection; IAA: Intra Abdominal Abcess; BO: Bowel Obstruction)

Multivariable analysis

For all patients with appendicitis, multivariable regression analysis showed that a time to surgery of more than 8 h, C reactive protein, age and complicated appendicitis on imaging were independently associated with a postoperative complication (*Table 4*).

In patients with complicated appendicitis, time to surgery longer than 8 h (OR 1.71; 95% CI 1.10-2.68) and age (OR 1.02; 95% CI 1.01-1.04) were associated with a postoperative complicated course. In uncomplicated appendicitis multivariable logistic regression analysis showed no risk factors, including time to surgery, for a postoperative complication. (Table 5).

	Univariable odd's			Multivariable adjusted odd's		
	OR	95%CI	p-value	OR	95%CI	p-value
Age (years)	1.02	1.01-1.03	<0.01	1.02	1.01-1.03	<0.01
ASA III-IV (versus I-II)	1.72	0.81-3.62	0.16	-	-	-
Pre-hosp symptom time (days)	1.1	1.00-1.20	0.04	-	-	-
Previous visit Emergency department	1.23	0.78-1.96	0.37			
Temperature	1.11	0.90-1.40	0.33	-	-	-
Leucocytes	1.04	1.00-1.08	0.07	-	-	-
CRP	1.00	1.00-1.00	0.06	1.00	1.0-1.0	<0.01
Complicated appendicitis on imaging	1.55	1.01-2.38	0.05	1.70	1.14-2.52	<0.01
Time to surgery >8hrs (versus <8hrs)	1.64	1.16-2.32	<0.01	1.62	1.17-2.50	<0.01

Table 4, *Multivariable analysis for postoperative complications (N=1341)*

	Uncomplicated (N=880)						Complicated (N=461)					
	Univariable odd's			Multivariable adjusted odd's			Univariable odd's			Multivariable adjusted odd's		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Age (years)	1.01	1.00-1.03	0.17	-	-	-	1.02	1.01-1.04	<0.01	1.02	1.01-1.04	<0.01
ASA III-IV (versus I-II)	2.20	0.74-6.60	0.16	-	-	-	2.57	1.11-5.97	0.03	-	-	-
Pre-hosp symptom time (days)	1.09	0.96-1.24	0.19	-	-	-	1.10	0.99-1.23	0.09	-	-	-
Previous visit ED	1.00	0.50-2.01	1.0	-	-	-	2.27	1.13-4.49	0.02	-	-	-
Temperature	1.40	0.98-1.90	0.08	-	-	-	0.96	0.73-1.27	0.78	-	-	-
Leucocytes	1.01	0.96-1.07	0.70	-	-	-	1.01	0.96-1.06	0.70	-	-	-
CRP	1.00	1.00-1.00	0.25	-	-	-	1.00	1.00-1.00	0.07	-	-	-
Complicated appendicitis on imaging	1.60	0.70-3.67	0.27	-	-	-	1.36	0.87-2.14	0.18	-	-	-
Time to surgery >8hrs (versus <8hrs)	1.28	0.80-2.08	0.31	-	-	-	1.74	1.12-2.70	0.01	1.71	1.10-2.68	0.02

Table 5, *Multivariable analysis for postoperative complications in uncomplicated and complicated appendicitis*

Discussion

This prospective cohort study demonstrates that patients with a complicated appendicitis treated surgically more than 8 h after presentation at the emergency department have an increased risk of a postoperative complication, compared to patients who undergo surgery within 8 h. In patients with uncomplicated appendicitis no increased risk of surgical delay was demonstrated.

Only surgery performed after more than 8 hours and increasing age were identified as risk factors in multivariable analysis for a postoperative complicated course in patients with complicated appendicitis. These patients had more postoperative complications with consequently more readmissions and reinterventions and a longer hospital stay.

A recent review demonstrated that patients with uncomplicated appendicitis, delayed appendectomy does not increase the risk of postoperative complications[10]. This review, however, did not focus on patients with complicated appendicitis. Our results support the conclusion that it is safe to delay patients with uncomplicated appendicitis for more than 8 h, but shows that surgery after 8 h is associated with more postoperative complications in patients with complicated appendicitis. Hospital admission was longer and more frequently a reintervention was performed. The proportion of patients with a complicated appendicitis was comparable when surgery was performed within or beyond 8 h after presentation. This suggests that surgery was not postponed or accelerated based on the preoperative differentiation of complicated and uncomplicated appendicitis. It also shows that patients with appendicitis are not at higher risk of developing complicated appendicitis when surgery is delayed. These results in our multicenter study confirm what other studies showed in smaller retrospective cohort studies[14].

Prehospital delay (more than two days), however, seems to increase the proportion of patients with complicated appendicitis. Our results emphasize the necessity of recognizing patients with complicated appendicitis in an early stage to provide direct and accurate treatment.

Our study might be biased because of inter-observer variability, as 62 local collaborators judged the surgical reports for the definition of complicated and uncomplicated appendicitis, but to this date, no clinical evaluation tool is available to differentiate between uncomplicated and complicated appendicitis in adults. Preoperative administration of antibiotics was registered in our cohort. Therefore, the association between a delayed appendectomy and postoperative complications in patients with complicated appendicitis could be over or under estimated. It should be mentioned that patients with non-operatively treated appendicitis are not included, and some baseline data are missing.

We conclude that patients with complicated appendicitis undergoing surgery within 8 h after emergency department presentation have less postoperative complications, as compared to those who undergo surgery after 8 h. Differentiating complicated from uncomplicated appendicitis by imaging alone is difficult and new scoring systems are being developed[15]. Early recognition and treatment of patients with complicated appendicitis is imminent in the prevention of a postoperative complication.

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Chapter 8

Daytime versus nighttime in acute appendicitis

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Abstract:

Background

Little is known about patients with appendicitis presenting at nighttime. It is hypothesized that patients presented at night more frequently have a complicated (gangrenous or perforated) appendicitis and therefore develop more postoperative complications.

Methods

In this study data were used from the nationwide, prospective SNAPSHOT study appendicitis, including 1975 patients undergoing surgery for suspected appendicitis. This study included only adults. Two primary outcomes were defined: (A) The proportion of patients with complicated appendicitis and (B) the proportion of patients with a complication postoperatively presenting during daytime versus nighttime period. Analysis for both complicated and uncomplicated appendicitis was performed, and a multivariate model was used to correct for baseline characteristics and time to surgery.

Results

In total, 1361 adult patients with appendicitis were analyzed. Both at nighttime and at daytime, 34% had complicated appendicitis. In patients presenting in the daytime, 12.1% developed a postoperative complication versus 18.6% for presentation at night ($p = 0.008$). In a multivariate analysis, the risk for a postoperative complication when presenting at night was significantly increased (adjusted OR 1.74; 95% CI 1.14–2.66, $p = 0.01$). Surgery within eight hours after presentation does not lower this risk (adjusted OR 1.37; 95% CI 0.97–1.95, $p = 0.078$).

Conclusion

Complicated appendicitis is seen as frequently during the day as at nighttime. For patients who present at nighttime with acute appendicitis, the risk of a postoperative complication is higher compared with a presentation at daytime. In multivariate analysis, nighttime presentation but not surgery within 8 h after presentation is independently associated with postoperative complication risk.

Introduction

Appendicitis is a common cause of abdominal infections and has been extensively studied. Currently, it is thought that there are two types of appendicitis: complicated (gangrenous or perforated appendicitis) and uncomplicated (phlegmonous) appendicitis. Nevertheless, there is still controversy about the timing of appendectomy. A recent meta-analysis has demonstrated that delaying appendectomy for presumed uncomplicated appendicitis is not a risk factor of developing complicated appendicitis [1]. Moreover, it is safe to delay surgery for uncomplicated appendicitis up to 24 h without an increase of postoperative complications. These results suggest that surgeons can postpone appendectomy overnight in patients with suspected uncomplicated appendicitis [1]. On the other hand, guidelines advise that patients presenting with complicated appendicitis should be operated on within 8 h after diagnosis [2,3]. Interestingly, a study analyzing the prevalence of perforated appendicitis related to the time of presentation demonstrated that patients presenting between 09:00 and 15:00 have an increased risk of having perforated appendicitis up to 30% compared to early morning/late night presenters [4]. In the Netherlands, 50% of patients present during the day (between 08:00 and 18:00) and the other half presents in the evening or at night [5]. Therefore, it is essential to know if patients who present at night are the same type as patients presenting during the daytime, as patients who present later in the evening and at night are more likely to have their surgery postponed to the next day.

Until now, no studies have described the characteristics and postoperative outcome of patients with acute appendicitis who present during daytime as compared to those at nighttime. Studies reporting on delayed appendectomy, only correct for time to surgery, unrelated to time of day [1]. The burden or threshold for a patient to go to the hospital is higher at night as compared to during the day. Therefore, patients with appendicitis who present at night may be more severely sick and thereby more likely to have a complicated disease type. In that case, delay of surgery may be less preferred during nighttime, at the very time that resources are diminished.

The aim of this study is to assess differences in characteristics and postoperative outcomes between patients with appendicitis who present during daytime versus those who present late in the evening or at nighttime. It is hypothesized that at nighttime, the proportion of patients with complicated appendicitis is higher and therefore have a higher risk of postoperative complications. Prospectively collected data from the Dutch SNAPSHOT appendicitis will be used to evaluate this hypothesis [5].

Materials and Methods

Study Design

Data was used from the SNAPSHOT appendicitis study, of which the full protocol has been published before [5]. This snapshot study is a prospective, observational, nationwide audit performed in The

Netherlands in 62 Dutch hospitals, which included 1975 consecutive patients undergoing surgery for suspected appendicitis during a 2-month study interval (3 months in eight pilot centers; 219 inclusions in May, 887 in June and 869 in July 2014). The medical ethics committee of the Academic Medical Centre in Amsterdam approved the study design and judged that informed consent from patients was not necessary.

For the current study, a retrospective analysis was performed of the previously conducted prospective study. Only patients 18 years and older were included. Patients found to have a diagnosis other than appendicitis during surgery or who underwent surgery other than appendectomy were excluded. In addition, patients with unknown times of presentation at the emergency department were excluded.

Baseline Characteristics

The following baseline characteristics were reported: age, sex, days of complaints, presence of vomiting, signs of peritonitis during physical examination, ASA-classification, body temperature, C reactive protein (CRP), Leucocyte counts, suspicion of complicated appendicitis on imaging, time of presentation at the ED, and the time in hours between presentation at the ED and surgery. It was also reported whether surgery was performed by a resident without supervision, or by (or under supervision of) a consultant surgeon, surgical approach (laparoscopic or open) and what the operating time was.

Primary Outcomes

Two primary outcomes were defined:

a. The proportion of patients with complicated appendicitis presenting during daytime period versus nighttime period;
b. The proportion of patients with a postoperative complication for patients with acute appendicitis who present during daytime versus those at nighttime.

Secondary Outcomes

Baseline characteristics for complicated and uncomplicated appendicitis were reported. Other secondary outcomes were the following variables: proportion of patients with perforated appendicitis, a wound infection, another infectious complication, a re-intervention, a re-hospitalization, number of hospitalization days, time to surgery (hours), and mortality. These were compared for all patients with acute appendicitis who present at nighttime vs. those during daytime. This was analyzed separately for the subgroups of patients with complicated and uncomplicated appendicitis. The proportion of patients with any complications was also analysed separately for patients with complicated and uncomplicated appendicitis.

A comparison of postoperative complications was made in daytime versus nighttime among the strata ‘surgery performed within 8 h after presentation’ versus ‘surgery performed more than 8 h after presentation’. This was also performed for subgroups of patients with complicated or uncomplicated appendicitis.

Definitions and Outcome Characteristics

Nighttime was defined as the time between 22:00 and 07:00 the subsequent morning; this definition of nighttime was used for time of presentation at ED and time of surgery. In contrast, ‘daytime’ was defined as the time between 07:00 and 22:00. Complicated appendicitis was defined as having perforated or gangrenous appendicitis, as described in the surgical report. Immediate postoperative start of antibiotic therapy was also viewed as indicative of a complicated form of appendicitis and therefore ranked as complicated appendicitis. This is according to the Dutch national guideline ‘Acute Appendicitis’ [3]. Complications were described as any adverse events during 30-days after surgery. Surgical site infections were classified as wound infections or abscesses. Re-interventions were defined as any surgical and/or radiological intervention. Time to surgery was the time between arrival time at the emergency department and the start of surgery.

Data Analysis

Parametrical data were expressed in means with standard deviations, and unpaired T-tests were used to determine whether differences were significant. Non-parametrical data were expressed in medians with interquartile ranges, and a Mann–Whitney U test was used to determine significance. Chi-square was used for comparison of proportions, and if the expected count for one of the cells was below five, Fisher’s exact test was used. To analyze the proportion of complicated appendicitis per hour, chi-square was used. Significance was defined with a p-value of <0.05. A multivariate analysis was performed to determine whether the potential difference between patients who present at day and night remains significantly different or not. Variables added to the model were variables that predict complicated appendicitis (age, days of complaints, temperature, CRP, leucocyte count, and suspected complicated appendicitis on imaging) and baseline characteristics which might be considered as confounders.

After selection variables with a $p < 0.2$, a multivariate binary logistic regression was performed. With a backward selection, variables with the highest p-value were removed from the regression until all variables had a $p < 0.05$. As patients presenting at nighttime as well as patients receiving surgery <8 h were in our interest, these variables were fixed and would not be removed from the analyses. If data for multiple variables in the final model were missed in 10% of cases, data were imputed for the binary logistic regression.

Results

Baseline Characteristics

From the database comprising 1975 patients with the clinical suspicion of acute appendicitis and with the intention of appendectomy, 541 children were excluded (Flowchart, Figure 1). Of 1434 adult patients, 1378 indeed received an appendectomy for appendicitis. From 56 patients who were operated but did not receive an appendectomy, the appendix was not inflamed in 47 patients. In the remaining nine patients, the appendix was not removed in four patients, because of a periappendicular inflammatory mass; in five patients, an ileocecal resection or right hemicolectomy was performed. In 17 patients, no time of presentation at the ED was administered. Therefore, 1361 patients were included in the present study.

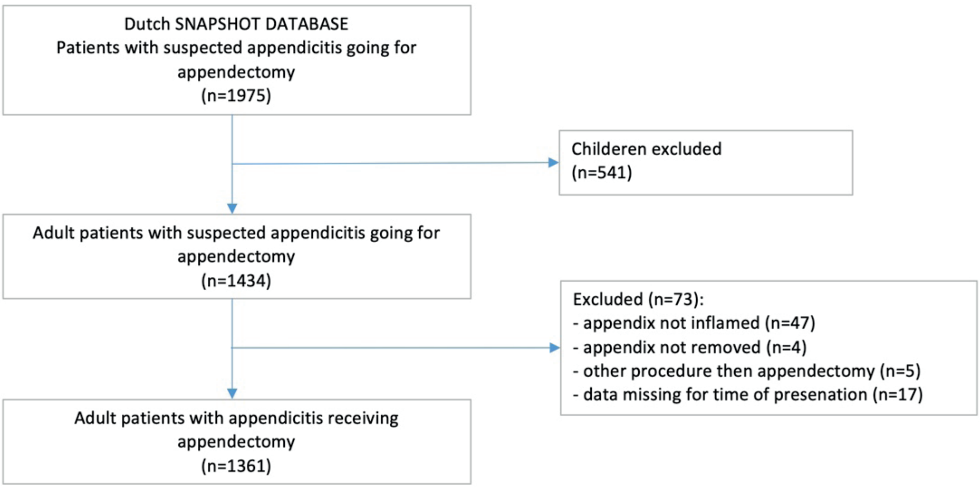

***Figure 1**, Flowchart of included patients.*

Patterns for the time of presentation were comparable for complicated and uncomplicated appendicitis (Figure 2). Of 1361 patients with appendicitis who underwent appendectomy, 469 (34.5%) had complicated appendicitis and 892 (65.5%) uncomplicated appendicitis. Two hundred thirty-one patients (17%) presented at nighttime, 1130 (83%) at daytime. Patients who presented at nighttime were younger (33 years vs. 40 years, $p < 0.001$), more often experienced vomiting (43% vs. 33%, $p = 0.005$), had higher leukocyte counts (14.6 vs. 13.6, $p = 0.004$), lower CRP levels (20 vs. 41 mmol/L, $p < 0.001$) compared to patients who presented at daytime. Importantly, the nighttime patients were operated on less often within 8 h compared to daytime patients (15% vs. 64%, $p < 0.001$). Similar trends were seen for uncomplicated and complicated appendicitis (Table 1). Patients who presented at night were not operated on within eight hours more often when they had complicated appendicitis compared with patients with uncomplicated appendicitis (17.7% vs. 13.2%, $p = 0.35$).

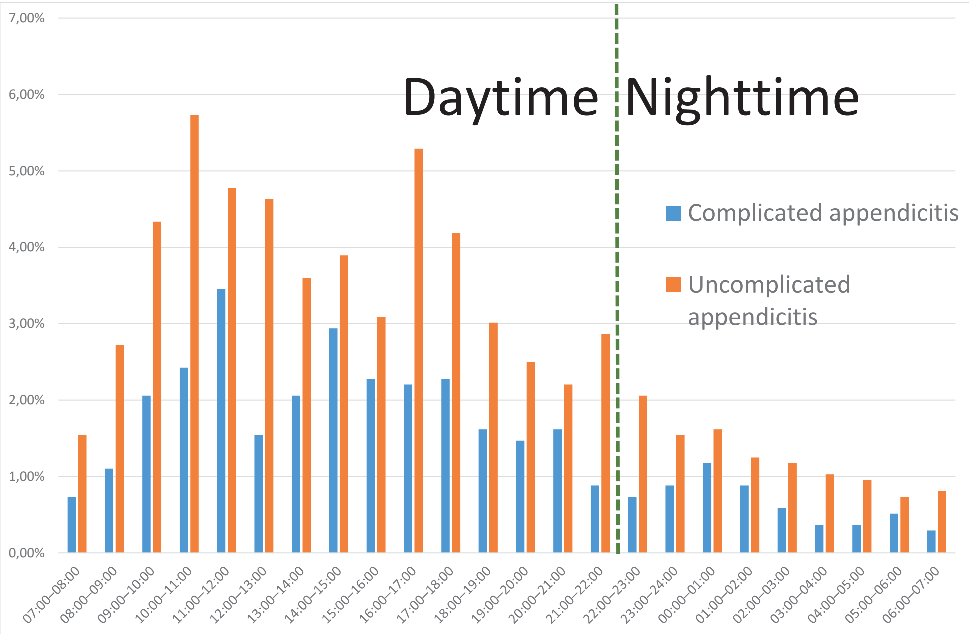

Figure 2, *Hourly proportion (from total over 24 h) of patients with appendicitis presenting at the emergency department, for uncomplicated and complicated appendicitis.*

8

	% missing	All Appendicitis (n = 1361)			Uncomplicated Appendicitis (n = 892)			Complicated Appendicitis (n = 469)		
		Day (n = 1130)	Night (n = 231)	p-Value	Day (n = 740)	Night (n = 152)	p-Value	Day (n = 390)	Night (n = 79)	p-Value
Age (years)	0%	40 (28–55)	33 (25–48)	<0.001	36 (25–50)	29 (22–42)	<0.001	50 (35–62)	49 (32–63)	0.68
% male	0%	50.2%	58.1%	0.55	49.7%	46.1%	0.41	51.0%	51.9%	0.89
Days of complaints	2.2%	1 (1–2)	1 (1–2)	<0.001	1 (1–2)	1 (1–1)	<0.001	2 (1–3)	1 (1–1)	0.15
Absence of diffuse peritonitis	3.7%	90.1%	91.0%	0.69	93.6%	95.9%	0.28	83.5%	81.3%	0.65
Migrating pain	2.9%	44.0%	40.4%	0.32	44.7%	45.0%	0.95	42.8%	31.6%	0.069
Vomiting	2.2%	33.1%	42.7%	0.005	27.6%	37.3%	0.017	43.5%	53.2%	0.12
ASA 1 or 2	0%	95.8%	98.3%	0.077	96.5%	100%	0.014 #	94.6%	94.9%	1.0 #
Temperature (°C) *	5.6%	37.4 (0.8)	37.4 (0.7)	0.57	37.3 (0.7)	37.4 (0.7)	0.034	37.7 (0.8)	37.5 (0.7)	0.108 *
Leucocytes (10^9/L) *	0.1%	13.6 (4.5)	14.6 (4.5)	0.004	13.1 (4.4)	14.2 (4.2)	0.007	14.5 (4.4)	15.3 (5.0)	0.194 *
Complicated appendicitis on imaging	0%	15.9%	16.0%	0.97	6.6%	7.2%	0.78	33.6%	32.9%	0.91
CRP (mmol/L)	0.4%	41 (16–88)	20 (6–66)	<0.001	30 (11–60)	13 (4–38)	<0.001	86 (36–173)	68 (17–141)	0.049
Time to surgery (h)	0.6%	6.3 (4.3–10.8)	13.9 (10–17)	<0.001	6 (4–11)	14 (11–17)	<0.001	6 (4–11)	14 (10–18)	<0.001
Surgery < 8 h	0.6%	64.1%	14.7%	<0.001	66%	13.2%	<0.001	61.1%	17.7%	<0.001
Surgery by resident without supervision	0%	18.4%	23.4%	0.081	19.7%	28.3%	0.019	15.9%	13.9%	0.66
Surgical time (min)	4.5%	42 (32–55)	45 (35–57)	0.11	40(30–50)	42 (32–54)	0.06	48 (36–64)	51 (37–60)	0.91
Laparoscopic surgery	0%	79.2%	81.8%	0.37	79.1%	82.9%	0.28	79.5%	79.7%	0.96

Table1,*BaselineCharacteristics.*

*Numbers are reported in median (interquartile range) or percentages * Normally distributed, reported as average (standard deviation), unpaired t-test was performed.*
 # Expected count in one of the cells <5, therefore Fisher's exact test was performed.

Primary Outcome

1. At daytime, 390 of 1130 patients (34.5%) had a complicated appendicitis compared with 79 of 231 (34.2%) at nighttime ($p = 0.93$). No statistically significant difference in the proportion of patients with complicated appendicitis per daily hour was found ($p = 0.44$). (Figure 3).

2. Forty-three of 231 (18.6%) nighttime patients developed a postoperative complication versus 137 of 1130 (12.1%) daytime patients ($p = 0.008$) (Table 2).

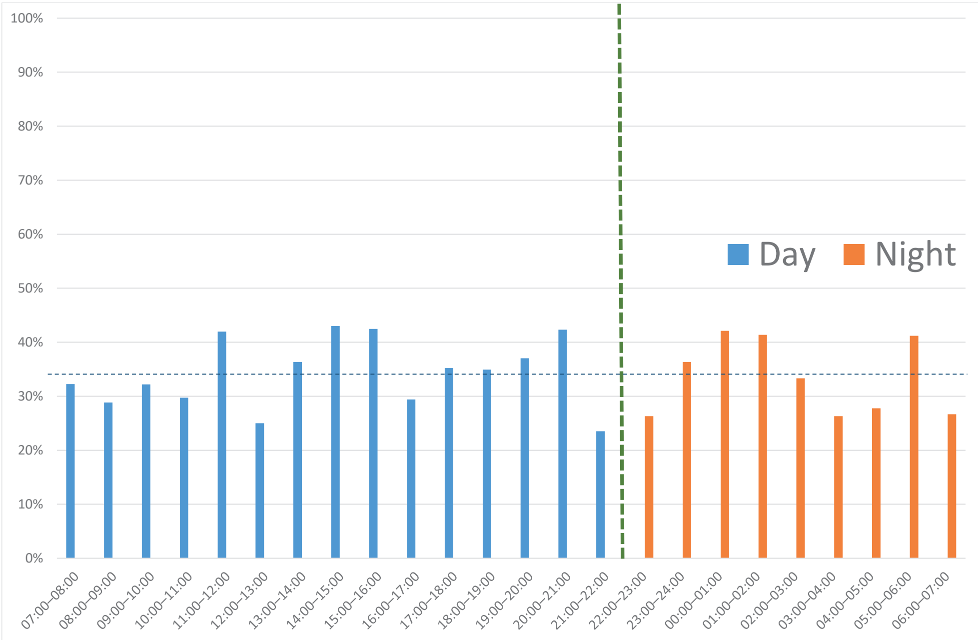

Figure 3, *Proportion of patients with a complicated appendicitis relative to all patients with appendicitis per hour. Average difference day vs. night is 34.5% vs. 34.2% (p = 0.93), per hour p = 0.44.*

	All Appendicitis (n = 1361)			Uncomplicated Appendicitis (n = 892)			Complicated Appendicitis (n = 469)		
	Day (n = 1130)	Night (n = 231)	p-Value	Day (n = 740)	Night (n = 152)	p-Value	Day (n = 390)	Night (n = 79)	p-Value
Perforated appendicitis [1]	19.1%	22.1%	0.30	-	-	-	55.4%	64.6%	0.13
Complications (overall)	12.1%	18.6%	0.008	7.7%	11.8%	0.09	20.5%	31.6%	0.03
Infectious complications	6.8%	10.8%	0.04	4.2%	5.9%	0.35	11.8%	20.3%	0.04
Mortality	0.2%	0%	1.0 #	0.1	0	1.0 #	0.3%	0%	1.0 #
Reinterventions	2.4%	6.1%	0.003	1.4%	3.9%	0.04 #	4.4%	10.1%	0.05 #
Hospitalization days	2 (1–4)	2 (1–4)	0.89	2 (1–2)	2 (1–2)	0.46	5 (3–6)	4 (3–7)	0.70
Re-admission	5.5%	8.7%	0.07	4.5%	7.9%	0.08	7.4%	10.1%	0.42

***Table 2,** Postoperative outcomes.*
1 Diagnosed intraoperatively # Fisher exact test.

All Appendicitis

For both complicated and uncomplicated appendicitis, most complications were caused by wound infections (Supplementary Table S1). Significantly more re-interventions were seen in patients who presented at nighttime versus those during daytime (6.1% vs. 2.4%, $p = 0.003$).

In daytime patients, surgery within eight hours after presentation at the ED led to fewer complications compared to surgery after eight hours (10.4% vs. 15.1%, $p = 0.02$). For nighttime patients, the trend was in the opposite direction, but no significant difference was found comparing surgery within 8 h versus after 8 h (23.5% vs. 17.8%, $p = 0.43$). Postoperative complications were comparable for surgery during daytime versus surgery at nighttime (13.4% vs. 12.4%, respectively; $p = 0.65$). For patients operated by a consultant surgeon (or a resident under the direct supervision of one), 144 (13.1%) of 1099 patients developed a postoperative complication versus 36 (13.7%) of 262 patients, who were operated by a resident without supervising consultant ($p = 0.78$). Surgery by a resident without supervision did not increase the number of infections in the strata presentation at night versus day.

Uncomplicated Appendicitis

For patients with uncomplicated appendicitis, 57 of 740 daytime patients (7.7%) developed a complication versus 18 of 152 (11.8%) nighttime patients ($p = 0.09$). Surgery within 8 h led to comparable results compared to surgery after 8 h in daytime as well as nighttime (7.1% vs. 8.7%, $p = 0.42$; 15.0% vs. 11.4%, $p = 0.71$, respectively).

Complicated Appendicitis

For patients with complicated appendicitis, significantly fewer daytime patients (80 of 290, 20.5%) developed a postoperative complication compared to nighttime patients (25 of 79, 31.6%; $p = 0.03$). During the daytime, surgery within 8 h led to significantly fewer complications compared to surgery after 8 h (17.3% vs. 25.8%, $p = 0.043$). At nighttime, there was no significant difference (35.5% vs. 30.8%, $p = 0.76$).

Multivariate Analysis

The results from the multivariate analysis for all patients are shown in Table 3. Overall, 9.6% of cases were missing for this analysis, and, therefore, non-imputed data was used. Variables in the model after multivariate analysis were age, CRP, complicated appendicitis on imaging, surgery more than 8 h after presentation, and presenting at nighttime. The adjusted odds ratio for a postoperative complication of patients presenting at nighttime was 1.74 (95% CI 1.14–2.66, $p = 0.010$). For undergoing surgery more than 8 h after presentation at the emergency department, an adjusted OR of 1.37 (95% CI 0.97–1.95, $p = 0.078$) was found.

	Univariable Odds Ratio			Multivariate Adjusted Odds Ratio		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age (per year)	1.03	1.02–1.04	<0.001	1.02	1.01–1.03	<0.001
Days of complaints	1.14	1.05–1.24	0.001	-	-	-
Diffuse peritonitis	1.71	1.07–2.73	0.025	-	-	-
Vomiting	1.08	0.77–1.50	0.66	-	-	-
ASA 3 or 4	2.89	1.55–5.40	0.001	-	-	-
Temperature (per °C)	1.31	1.06–1.60	0.01	-	-	-
Leucocytes (per 10^9/L)	1.03	0.99–1.06	0.11	-	-	-
CRP (per mmol/L)	1.004	1.003–1.006	<0.001	1.003	1.001–1.005	0.002
Complicated appendicitis on imaging	2.26	1.56–3.25	<0.001	1.67	1.13–2.48	0.01
Surgery > 8 h	1.54	1.12–2.11	0.008	1.37	0.97–1.95	0.078
Presenting at nighttime	1.66	1.14–2.42	0.008	1.74	1.14–2.66	0.010
Surgery by resident without supervision	1.06	0.71–1.57	0.78	-	-	-

Table 3, *Multivariate analysis for a postoperative complication.*

Similarly, multivariate analyses were performed in the subgroups of complicated appendicitis and uncomplicated appendicitis. For complicated appendicitis, the only significant variable remaining in the model was age per year (adjusted OR 1.02, 95% CI 1.01–1.04, $p < 0.001$). Surgery after 8 h and presentation at nighttime both were not significantly associated with postoperative complications (adjusted OR 1.47 (95% CI 0.92–2.36, $p = 0.11$) and 1.58(95% CI 0.89–2.80, $p = 0.12$), respectively). For uncomplicated appendicitis, age (adjusted OR 1.02, 95% CI 1.003–1.032, $p = 0.02$) and surgery by a resident without supervision (adjusted OR1.93, 95% CI 1.14–3.26) were the only significant variables associated with postoperative complication remaining in the model after multivariate analysis. Again, adjusted odds ratios for surgery after eight hours and for presentation at nighttime were not significantly associated (adjusted OR 1.12 (95% CI 0.66–1.93, $p = 0.66$) and 1.65 (95% CI 0.87–3.14, $p = 0.13$), respectively).

Discussion

Based on the SNAPSHOT appendicitis data, patients presenting at night were younger, vomited more often, had lower CRP levels, higher leucocytes and were often not operated on within eight hours after presentation. The percentage of adults with complicated appendicitis presenting at the ER during nighttime was comparable to that of patients who present in the daytime. Nevertheless, patients who presented at night developed a complication postoperatively more frequently than patients who presented during daytime (18.1% vs. 12.1%, $p = 0.008$). This difference in complication rate was predominantly observed for the complicated appendicitis subgroup but was not associated with a delay in surgery beyond 8 h after ED presentation.

In a multivariable model adjusted for possible confounders, surgery within eight hours did not decrease the proportion of complications significantly. Patients who presented at nighttime still had a significantly higher chance of a complication than those who presented during daytime.

A possible explanation may be that nighttime operations were performed predominantly in the more severely ill patients presenting at nighttime, having an inherently higher risk of a postoperative complication. However, this was not confirmed in our data. Another explanation is that patients who present at night are diagnosed later, as their imaging may be delayed until early morning. Moreover, these patients probably did not get any antibiotics while waiting for diagnosis until subsequent surgery. This may have increased the chance of a complication. Unfortunately, our data lack sufficient detail to explore underlying explanatory mechanisms.

As no other studies have correlated the clinical outcome after appendectomy with the time of presentation, our data could not be compared to other results. Drake et al. [4] described that patients who present midday had a higher risk of perforated appendicitis. Looking at their data shows that differences are minor, with percentages fluctuating between 11 and 25% per daily hour. They found a significant, minor difference in groups per 4 h, which seems to disappear if groups are compared per hour. By eyeballing, no clear pattern is seen in their data. Differences in postoperative complications are not reported in that study.

The strengths of the present study include the definition of complicated appendicitis. Using the intraoperative diagnosis as the reference standard for complicated appendicitis results are closer to an intention to treat analysis rather than defining the reference standard according to pathology results. Furthermore, intraoperative outcomes are a better predictor of postoperative complications [6]. Secondly, the prospective and nationwide character of collecting data makes sure that no patients were missed in the given time period. It represents the daily clinical practice in the Netherlands.

Possible limitations include the fact that children were excluded. This was done as the decision to go to the ER is influenced by parents and not only by the patient. A second limitation is that the data was collected by many residents, leading to possible inter-observer variability; this is due to the SNAPSHOT design. On the other hand, it represents the best data reporting about daily clinical practice. A third limitation is the missing data for possible antibiotic treatment given at the ED or ward before surgery.

Complicated appendicitis is not seen more frequently at nighttime than during the day. Patients presenting with acute appendicitis at the emergency department at nighttime have more postoperative complications. Exploring various subgroups and variables, no clear explanation was found for this increased postoperative complication rate at nighttime presentation. Surprisingly, surgery within eight hours after presentation at nighttime was not independently associated with a lower risk of postoperative complications.

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Supplementary materials

	All appendicitis (n=1361)			**Uncomplicated appendicitis (n=892)**			**Complicated appendicitis (n=469)**		
	Day (n=1130)	**Night (n=231)**	**P-value**	**Day (n=740)**	**Night (n=152)**	**P-value**	**Day (n=390)**	**Night (n=79)**	**P-value**
Complications (overall)	12.1%	18.6%	0.008	7.7%	11.8%	0.09	20.5%	31.6%	0.03
Infectious complications (grouped)	6.8%	10.8%	0.04	4.2%	5.9%	0.35	11.8%	20.3%	0.04
Woundinfection	3.5%	4.8%	0.34	2.7%	3.9%	0.43#	4.9%	6.3%	0.58#
Intra-abdominal abcess	3.6%	7.4%	0.01	1.8%	3.3%	0.21#	7.2%	15.2%	0.02
Ileus	1.7%	2.6%	0.42#	0.7%	0.7%	1.0#	3.6%	6.3%	0.34#
Pneumonia	0.4%	0.4%	1.0#	0.3%	0%	1.0#	0.5%	1.3%	0.43#
Urinary tract infection	0.4%	0%	1.0#	0.3%	0%	1.0#	0.5%	0%	1.0#
Bleeding complication	0.5%	0%	0.60#	0.3%	0%	1.0#	0.4%	0%	1.0#
Cardiopulmonal failure	0.7%	0%	0.37#	0%	0%	1.0#	2.1%	0%	0.36#
Death	0.2%	0%	1.0#	0.1%	0%	1.0#	0.3%	0%	1.0#
Other	0.4%	2.2%	0.02#	0.3%	1.3%	0.14#	0.8%	3.8%	0.06#

Table S1, All complications
Numbers are reported in percentages; #Expected count in one of the cells<5, therefore fisherman exact test was performed

Chapter 9

Re-assessment in patients with suspected acute appendicitis

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Abstract

Background

The effect of diagnosing appendicitis at re-assessment on post-operative outcomes is not clear. This study aims to compare patients diagnosed with appendicitis at initial presentation versus patients who were diagnosed at re-assessment.

Patients and Methods

Data from the Dutch SNAPSHOT appendicitis collaborative was used. Patients with appendicitis who underwent appendectomy were included. Effects of diagnosis at re-assessment were compared with diagnosis at initial presentation. Primary outcomes were the proportion of patients with complicated appendicitis and the post-operative complication rate.

Results

Of 1,832 patients, 245 (13.4%) were diagnosed at re-assessment. Re-assessed patients had a post-operative complication rate comparable to those diagnosed with appendicitis at initial presentation (15.1% vs. 12.7%; p=0.29) and no substantial difference was found in the proportion of patients with complicated appendicitis (27.9% vs. 33.5%; p=0.07). For patients with complicated appendicitis, more post-operative complications were seen if diagnosed at re-assessment than if diagnosed initially (38.2% vs. 22.9%; p=0.006).

Conclusions

For patients in whom appendicitis was not diagnosed at first presentation, but at re-assessment, both the proportion of complicated appendicitis and the post-operative complication rate were comparable to those who were diagnosed with appendicitis at initial presentation. However, re-assessed patients with complicated appendicitis encountered more post-operative complications.

Introduction

Although appendicitis is the most common cause of abdominal infections, diagnosing acute appendicitis has its difficulties. Whereas ruling in appendicitis seems quite accurate, ruling out appendicitis remains difficult. More and more scoring models are available to diagnose appendicitis or to predict the risk of having appendicitis.[1] These scoring models can identify patients as having a low risk for appendicitis.[1, 2] Still, a substantial number of patients will have an unclear presentation of appendicitis. Imaging should be performed for all patients with suspected appendicitis, but even then, it remains difficult to rule out acute appendicitis combining clinical and or radiological findings.[3]

If appendicitis is not diagnosed at initial presentation, nor any other diagnosis was found in patients presenting at the emergency department with acute abdominal pain, it is difficult to choose the next step. The workup is based mostly on the clinical view of the treating physician. Depending on the level of suspicion, imaging is performed. A patient can be hospitalized and observed or hospitalized for a diagnostic laparoscopy. However, a low suspicion patient can also be discharged from the emergency department with an appointment for re-assessment the next day. Re-assessing patients with acute abdominal pain, not admitted to the hospital, seems to be safe, even if they are diagnosed with appendicitis at re-assessment.[4-6] These results have been adapted and implemented in national and international guidelines.[7-9]Re-assessing patients with non-specific abdominal pain is routine care. However, downsides of a re-assessment strategy may be that patients with acute appendicitis, diagnosed at re-assessment rather than at first presentation, run the risk of developing a more complicated appendicitis or more often develop post-operative complications.

In this study, baseline and peri-operative characteristics and clinical outcomes of patients diagnosed with appendicitis at initial presentation were compared with patients who were diagnosed with appendicitis only at re-assessment after an initial visit at the emergency department.

Patients and Methods

Study design

For this study, data from the Dutch SNAPSHOT collaboration group were used. In this prospective, nationwide, observational cohort study, patients with suspected appendicitis, planned for appendectomy, were included. Between May and July 2014, all consecutive patients suspected of appendicitis in 62 Dutch hospitals were included. Both children and adults were included. Patients who were treated non-operatively were not included. The complete methods of the study have been published previously. [10] The study design was judged by the medical ethics committee of the Academic Medical Centre in Amsterdam. They considered informed consent from patients unnecessary because, of the observational study design without an additional burden for the patient.

Study population

Of the SNAPSHOT cohort, only patients who underwent appendectomy for appendicitis were included in the present study. If another diagnosis than appendicitis was found or a treatment other than appendectomy was performed, patients were excluded. Only patients with appendectomy and explicit registration whether the diagnosis was made at first presentation or at re-assessment were included. Of the re-assessed patients, no data were available of a preceding emergency department presentation, because they were registered in the SNAPSHOT study at the time of their appendicitis diagnosis.

Baseline and peri-operative characteristics

The following baseline and operative characteristics were collected: age, gender, days of complaints, presence of vomiting, signs of peritonitis during physical examination, presence of migrating pain, American Society of Anesthesiologists (ASA-) classification, body temperature, C reactive protein (CRP), leucocyte counts, and the time in hours between presentation at the emergency department and surgery. Also, the duration of surgery was reported.

Primary outcome

Primary outcomes were defined as the proportion of patients with complicated appendicitis and the proportion of patients with a post-operative complication in patients with appendicitis who were diagnosed at re-assessment after initial presentation with acute abdominal pain compared with those who were diagnosed with appendicitis at first presentation. These results were analyzed for both complicated and uncomplicated appendicitis.

Secondary outcomes

Analyses of the proportion of patients with uncomplicated or complicated appendicitis between the initially diagnosed versus re-assessed groups was performed. Post-operative complications were divided into the following subgroups: wound infections, intra-abdominal abscesses, re-hospitalizations, and re-interventions (surgical and or radiologic). Furthermore, differences in the baseline and peri-operative characteristics were described. All secondary outcomes were analyzed separately for both complicated and uncomplicated appendicitis and also for the subgroups of adult versus pediatric patients.

Definitions

Patients were defined as re-assessed if they had recently visited the emergency department with similar complaints. In re-assessed patients, only data from the last visit at which point the final appendicitis diagnosis was made, were available. Therefore, data from patients who were re-assessed could not be compared with data from their initial emergency department visit.

Complicated or complex appendicitis was defined as gangrenous or perforated appendicitis, as determined by the surgeon. Patients who continued antibiotic agents direct post-operatively, based on intra-operative findings, were also defined as complicated appendicitis. A post-operative complication was defined as any adverse event in the post-operative course.

Data analysis

Parametric data were expressed by means and standard deviations, and when compared, statistical significance was calculated by t-tests. Non-parametric data were expressed with medians and interquartile ranges, and significance was calculated with Mann-Whitney U tests. For proportions, counts were given and were compared for statistical significance with χ^2 tests, or with Fisher exact test, when the expected count was less than five in one of the cells. Statistical significance was defined as $p<0.05$. A multivariable analysis was not performed because of the risk of bias, because data of the initial presentation of patients who were re-assessed were not present.

Results

In 1,901 patients, appendectomy was performed for acute appendicitis. Within this group, data regarding whether a patient was re-assessed or not were available in 1,832 patients. Therefore, these 1,832 with acute appendicitis who underwent an appendectomy were included in the present study. The median age of this cohort was 30 years, 72.6% were adults (≥18 years), and 52.5% were male (Table 1). In 245 patients, appendectomy was performed only after appendicitis was diagnosed during re-assessment, whereas 1,587 patients were operated after the diagnosis was made at their initial presentation. In 600 (32.8%) patients overall, complicated appendicitis was diagnosed intra-operatively, and 238 (13.0%) patients developed one or more post-operative complications.

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Baseline and operative characteristics

For most variables of baseline and operative characteristics, results were comparable between the re-assessed group and the group operated on at the initial presentation (Table 1). Re-assessed patients were younger (26 years vs. 31 years; $p < 0.001$), had a longer duration of complaints (2 days vs. 1 day; $p < 0.001$), lower leucocyte counts (12.6 vs. 14.3; $p < 0.001$) and a lower temperature (37.2^{o}C vs. 37.5^{o}C; $p < 0.001$). The time to surgery after presentation at the emergency department was longer in patients diagnosed during re-assessment (8 hours vs. 7 hours; $p = 0.002$; (Table 1).

	Acute appendicitis, all (n=1832)	Non-reassessed patients (n=1587)	Reassessed patients (n=245)	p-value
Age, years	30 (16-48)	31 (17-50)	26 (15-39)	0.001
Adult (≥ 18 years)	72.6% (1330)	73.2% (1162)	68.6% (168)	0.13
Male sex, no./total no. (%)	52.5% (961)	52.3% (830)	53.5% (131)	0.73
Days of complaint	1 (1-2)	1 (1-2)	2 (1-2)	<0.001
Diffuse peritonitis, no./total no. (%)	175/1780 (9.8)	158/1549 (10.2)	17/231 (7.4)	0.18
Migrating pain, no./total no. (%)	766/1797 (42.6)	648/1557 (41.6)	118/240(49.2)	0.03
Vomiting, no./total no. (%)	730/1812 (39.8)	636/1569(40.5)	94/243 (38.7)	0.58
ASA 1 or 2, no./total no. (%)	1780/1832 (97.2)	1540/1587 (97.0)	240/245 (98.0)	0.42
BMI (kg/m^2)*	24.5 (22.0-27.9)	24.5 (22.0-27.9)	24.1 (21.6-27.3)	0.41
Temperature (^{o}C)**	37.4 (0.8)	37.5 (0.8)	37.2 (0.8)	<0.001
Leucocytes ($10^9/L$)**	14.1 (4.7)	14.3 (4.7)	12.6 (4.8)	<0.001
CRP (mmol/L)	35 (12-83)	35 (11-84)	36 (16-75)	0.67
Imaging performed, no./total no. (%)	1348/1831 (73.6)	1170/1586 (73.8)	178/245 (72.7)	0.71
- Ultrasound only	412/1831 (22.5)	357/1586 (22.5)	55/245 (22.4)	0.98
- CT as final modality	65/1766 (3.5)	53/1586 (3.3)	12/245 (4.9)	0.22
- MRI as final modality	6/1831 (0.3)	6/1586 (0.4)	0/245 (0)	1.0
- No imaging				
Time to surgery after presentation (hours)	7 (4-13)	7 (4-12)	8 (5-15)	0.002

***Table 3**, baseline and operative characteristics*
*Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CRP, C-reactive protein. Numbers are reported in median (Inter Quartile Range) or percentages. For non-parametrical data, Mann-Whitney-U tests were used. For dichotomous data Chi-square or Fisher-exact test. *Only calculated for patients >16 years **Normally distributed, reported as average (Standard deviation), unpaired T-Test was performed*

Post-operative complications

Of all re-assessed patients, 37 of 245 (15.1%) developed a post-operative complication versus 201 of 1,587 (12.7%) of patients who were operated on after being diagnosed at initial presentation ($p = 0.29$; Table 2). No significant differences were seen between both groups in specific post-operative complications, such as wound infections, intra-abdominal abscesses, or ileus. A somewhat higher proportion of re-assessed patients were re-admitted to the hospital after appendectomy (8.6% vs. 5.6%; $p = 0.07$).

Complicated versus uncomplicated appendicitis

Complicated appendicitis was diagnosed in 532 of 1,587 (33.5%) patients during surgery in patients diagnosed at initial presentation versus 68 of 245 (27.9%) patients operated on after appendicitis diagnosis only at re-assessment ($p = 0.07$; Table 2). In patients with complicated appendicitis, more post-operative complications were seen when diagnosed at re-assessment compared with patients who were diagnosed at initial presentation (38.2% vs. 22.9%; $p = 0.006$). In patients with uncomplicated appendicitis, the proportions of patients with a post-operative complication were comparable; 6.2% (11/177) of re-assessed patients versus 7.5% (79/1055) of patients operated on at initial presentation ($p = 0.55$).

	Acute appendicitis, all (n=1832)			Uncomplicated appendicitis (n=1232)			Complicated appendicitis (n=600)		
	Non-reassessed (n=1587)	Reassessed (n=245)	p-value	Non-reassessed (n=1055)	Reassessed (n=177)	p-value	Non-reassessed (n=532)	Reassessed (n=68)	p-value
Complicated appendicitis - Perforated appendicitis, no./total no. (%)	532/1587 (33.5) - 305/1587 (19.2)	68/245 (27.9) - 36/245 (14.8)	0.07	-	-	-	-	-	-
Overall postop complications, no./total no. (%)	201/1587 (12.7)	37/245 (15.1)	0.29	79/1055 (7.5)	11/177 (6.2)	0.55	122/532 (22.9)	26/68 (38.2)	0.006
Wound infections, no./total no. (%)	50/1587 (3.2)	9/245 (3.7)	0.67	25/1055 (2.4)	5/177 (2.8)	0.72	25/532 (4.7)	4/68 (5.9)	0.67
Intra-abdominal abscess, no./total no. (%)	74/1587 (4.7)	13/245 (5.3)	0.66	19/1055 (1.8)	0/177 (0.0)	0.10	55/532 (10.3)	13/68 (19.1)	0.03
Ileus (>5 days) , no./total no. (%)	28/1587 (1.8)	8/245 (3.3)	0.13	5/1055 (0.5)	1/177 (0.6)	1.0	23/532 (4.3)	7/68 (10.3)	0.07
Readmission, no./total no. (%)	89/1587 (5.6)	21/245 (8.6)	0.07	45/1055 (4.3)	7/177 (4.0)	0.85	44/532 (8.3)	14/68 (20.6)	0.001
Reinterventions, no./total no. (%)	57/1587 (7)	8/245 (3.3)	0.80	16/1055 (1.5)	1/177 (0.6)	0.49	41/532 (7.7)	7/68 (10.3)	0.46
Hospital stay, median (IQR), days	2 (1-3)	2 (1-3)	0.04	2 (1-2)	2 (1-2)	0.03	4 (3-6)	5 (3-6)	0.56

Table 2, *Outcomes*
No data was missing for the outcomes

Pediatric patients versus adults

Five hundred two pediatric patients (<18 years) and 1,330 adult patients (≥18 years) were included (Table 3). Of the 502 pediatric patients, 77 (15.3%) were re-assessed versus 168 (12.6%) of 1,330 ($p = 0.13$) of the adult patients. In adult patients who were re-assessed, the proportion of patients with complicated appendicitis was substantially lower compared with adult patients operated on at initial presentation (35.6% vs. 25.0%; $p = 0.007$). In pediatric patients, these proportions were 27.8% versus 33.8%, respectively ($p = 0.28$). Re-assessed pediatric patients were more often re-admitted (13.0% vs. 4.2%) compared with patients operated on at initial presentation.

	Acute appendicitis (n=1832)			Pediatric patients (n=502)			Adult patients (n=1330)		
	Non-reassessed (n=1587)	**Reassessed (n=245)**	**p-value**	**Non-reassessed (n=425)**	**Reassessed (n=77)**	**p-value**	**Non-reassessed (n=1162)**	**Reassessed (n=168)**	**p-value**
Complicated appendicitis, - Perforated appendicitis, no./total no. (%)	532/1587 (33.5) - 305/1587 (19.2)	68/245 (27.8) - 36/245 (14.7)	0.07	118/425 (27.8) -71/425 (16.7	26/77 (33.8) - 14/77 (18.2)	0.28	414/1162 (35.6) - 234/1162 (20.1)	42/168 (25.0) - 22/168 (13.1)	0.007
Overall postop complications, no./total no. (%)	201/1587 (12.7)	37/245 (15.1)	0.29	48/425 (11.3)	12/77 (15.6)	0.29	153/1162 (13.2)	25/168 (14.9)	0.54
Wound infections, no./total no. (%)	50/1587 (3.2)	9/245 (3.7)	0.67	6/425 (1.4)	3/77 (3.9)	0.15	44/1162 (3.8)	6/168 (3.6)	0.89
Intra-abdominal abscess, no./total no. (%)	74/1587 (4.7)	13/245 (5.3)	0.66	22/425 (5.2)	8/77 (10.4)	0.11	52/1162 (4.5)	5/168 (3.0)	0.37
Ileus (>5 days) , no./total no. (%)	28/1587 (1.8)	8/245 (3.3)	0.13	10/425 (2.4)	2/77 (2.6)	1.0	18/1162 (1.5)	6/168 (3.6)	0.11
Readmission, no./total no. (%)	89/1587 (5.6)	21/245 (8.6)	0.07	18/425 (4.2)	10/77 (13.0)	0.005	71/1162 (6.1)	11/168 (11.)	0.86
Reinterventions, no./total no. (%)	57/1587 (3.6)	8/245 (3.3)	0.80	18/425 (4.2)	6/77 (7.8)	0.24	39/1162 (3.4)	2/168 (2)	0.13
Hospital stay, median (IQR), days	2 (1-3)	2 (1-3)	0.04	2 (1-3)	2 (1-3)	0.37	2 (1-4)	2 (1-3)	0.003

Table 3, *Pediatric versus adult patients*
No data was missing for the outcomes.

Discussion

Overall, the proportion of patients with a post-operative complication was comparable between patients who underwent an appendectomy after being diagnosed with appendicitis only after re-assessment and those diagnosed and operated on at their initial presentation. However, patients with complicated appendicitis had worse outcomes if operated on after re-assessment rather than at initial presentation. Adult patients appear to have a substantially lower proportion of complicated appendicitis when diagnosed during re-assessment compared with patients operated on at first presentation.

No previous studies have described re-assessment solely in patients with acute appendicitis, but several studies explored re-assessment in patients with acute abdominal pain in general. Most of patients with acute abdominal pain who present at emergency department, have a self-limiting disease that does not require surgical intervention or admission for observation. [6] Onur et al.[4] randomly assigned patients with non-specific abdominal pain after evaluation at the emergency department for either admission for active clinical observation or for discharge and outpatient evaluation during three days with intervals of eight to 12 hours. No substantial difference in complications or morbidity were seen between both groups, consisting of 105 patients in total. Toorenvliet et al. [6] prospectively re-assessed all patients who presented at the emergency department for acute abdominal pain, but were not admitted to the hospital. In 500 patients who presented up for re-assessment, a change in final diagnosis was described in 30%. Twenty of these patients (4%) were admitted to the hospital for surgery, of whom 16 underwent appendectomy because of appendicitis. Toorenvliet et al. [6] reported that in only six patients (1.2%) was a diagnosis seen during re-assessment that should have led to immediate surgery, including three patients with perforated appendicitis, but no post-operative complications were seen in those six patients. According to these results, Toorenvliet et al. [6] stated that re-assessment could safely be used as a tool to distinguish between surgical abdominal pathology presenting in an early stage from mild, self-limiting disease in patients with equivocal abdominal pain at the emergency department. This corresponds with the primary outcome of our study, as no increase in post-operative complications were seen in patients who were operated on after re-assessment. However, these results contradict our subgroup of patients with complicated appendicitis, who developed more post-operative complications when operated on after re-assessment. This might be caused by the small group of patients with perforated appendicitis that were present in the study by Toorenvliet et al.[6]

Appendicitis prediction models might be useful in selecting patients who can safely be re-assessed. International guidelines state that motivated, adult patients with a low risk for appendicitis based on Alvarado[9, 11], or a combination of Alvarado, Adult Appendicitis Score (AAS) [12] and/or Appendicitis

Inflammatory Response Score (AIRS) [13] could be discharged for outpatient follow-up if no warning symptoms are present.[8] A recent study compared all available risk prediction models for diagnosing acute appendicitis of patients presenting with acute right iliac fossa (RIF) pain. [1] The aim was to determine the proportion of true negatives in patients with a low-risk for appendicitis based on the prediction scores. Initial validation was performed using a large RIF cohort from the United Kingdom (n=5,345), separately analyzing prediction in women and men. In women (n=3,613), the AAS was able to triage 63.1% of patients with RIF, but without appendicitis, within the low-risk group. A failure rate of 3.7% was seen, meaning 69 patients with true appendicitis were scored as a low-risk based on the AAS. Of these 69 patients, nine turned out having a gangrenous or perforated appendicitis (0.5%). In men (n=1,732), the AIRS stratified 24.7% of patients without appendicitis correctly as low-risk with a failure rate of 2.4%, of whom none had complicated appendicitis. The study also verified the scoring models in cohorts from other countries (Ireland, Italy, Portugal and Spain), leading to failure rates for the AAS in women and the AIRS in men of 17.5% and 32%, respectively. Although these failure rates are much higher than the initial validation, clinical prediction scores might still be useful, for example if combined to imaging results. Patients with an equivocal diagnosis, but low suspicion for appendicitis could be eligible for re-assessment.

The course of patients suspected of having but without concrete diagnosis of appendicitis after combined clinical work-up and imaging was described by Ramarajan et al.[14] In a retrospective study of 620 children suspected of having appendicitis, they analyzed the work-up and findings after equivocal ultrasound result. In this workup, selection for either computed tomography (CT) scanning, surgery or discharge for observation at home was done by the emergency department physicians. Appendicitis was found in 62 of 280 (22.1%) children in the CT cohort, in 16 of 17 (94.1%) in the surgery group, but in none of the 323 (0%) children who were discharged after equivocal ultrasound. Higher age (>10 years old), secondary signs toward acute appendicitis during ultrasound (e.g., free fluid, thickened bowel wall) and leukocytosis were variables associated with the decision to order a CT scan. This suggests that a combined clinical and imaging prediction model could point out true low-risk children. Until such a prediction model has been designed, re-assessment could provide a safety net in doubtful cases.

The current study shows a relation between diagnosis during re-assessment and post-operative complications in patients with complicated appendicitis.

Although no data regarding the initial presentation are available, progression from uncomplicated to complicated appendicitis during the re-assessment period could not be analyzed. According to the traditional idea that uncomplicated appendicitis eventually will perforate over time, the delay because of re-assessment the next day should possibly cause a higher perforation rate. However, previous studies contradict this theory and describe two different entities of uncomplicated *and* complicated appendicitis.[15, 16] In line with these studies, a meta-analysis of 45 studies shows no substantially higher risk for complicated appendicitis when appendectomy was delayed for up to 24 hours in cases of presumed uncomplicated appendicitis.[17] Our results are in line with this statement; in re-assessed patients no higher proportion of complicated appendicitis was seen. In fact, a decrease of the proportion of complicated appendicitis was seen in the subgroup of adults when diagnosed at re-assessment. An explanation for this decrease could be that the complicated appendicitis cases were more likely to be diagnosed during initial presentation. Although differentiation between uncomplicated and complicated appendicitis is difficult, even while using imaging[18], it could be hypothesized that differentiation between patients stratified as low-risk of appendicitis and patients with complicated appendicitis may be more reliable than differentiation between uncomplicated from complicated appendicitis.

The most important limitation of this study is the fact that no data regarding initial presentation were available for patients who were diagnosed during re-assessment. It is not clear in which patients imaging was performed initially. We do not know if a suspicion for appendicitis was already present and therefore no analysis can be done regarding progression of uncomplicated to complicated appendicitis. Because no variables from initial presentation for prediction of appendicitis can be determined, no advice can be given regarding in which patients re-assessment can be performed and which patients should be admitted or operated on immediately. Only a description was provided of the (post)-operative results of patients who were re-assessed according to the usual Dutch care system.

Re-assessment in general does not increase the risk of complicated appendicitis nor the risk of post-operative complications. However, missing the diagnosis of complicated appendicitis at the initial presentation is associated with a higher post-operative complication rate. Re-assessment may be a good alternative for diagnostic laparoscopy in most cases, although complicated appendicitis still is missed one of four patients after first presentation.

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Chapter 10

Population preference for treatment of uncomplicated appendicitis

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Abstract

Background

Non-operative treatment of uncomplicated appendicitis is safe and increasing in popularity but has other risks and benefits compared with appendicectomy. This study aimed to explore the preference of the general population regarding operative or antibiotic treatment of uncomplicated appendicitis.

Methods

In this prospective study, a clinical scenario and questionnaire were submitted to a panel comprising a sample of an average adult population. The survey was distributed by an independent, external research bureau, and included a comprehensive explanation of the risks and benefits of both treatment options. The primary outcome was the proportion of participants who would prefer antibiotics over surgery. Secondary outcomes were reasons for this preference and the accepted recurrence rate within 1 year when treated with antibiotics only. All outcomes were weighted for the average Dutch population.

Results

Of 254 participants, 49.2 per cent preferred antibiotic treatment for uncomplicated appendicitis, 44.5 per cent preferred surgery, and 6.3 per cent could not make a decision. About half of the participants preferring antibiotics would accept a recurrence risk of more than 50 per cent within 1 year. Avoiding surgery was their main reason. In participants preferring surgery, many tolerated a recurrence risk of no more than 10 per cent when treated with antibiotics. Removal of the cause of appendicitis was their main reason.

Conclusion

Around half of the average population sample preferred antibiotics over surgical treatment of uncomplicated appendicitis and were willing to accept a high recurrence risk to avoid surgery initially. Participants who preferred surgery tolerated only a very low recurrence risk with antibiotic treatment.

Introduction

Non-operative treatment for suspected uncomplicated appendicitis has been a hot topic in the past decade. Studies[1,2] have shown that initial antibiotic treatment without surgery can be just as safe and effective as surgical treatment by appendicectomy. Appendicectomy brings an 8 per cent risk of postoperative complications in patients with uncomplicated appendicitis.[3] Complication risks are lower for antibiotic treatment, but there is a 1-year recurrence risk of about 23 per cent, increasing to almost 40 per cent in the first 5 years.[4,5] Guidelines[6-10] recommend laparoscopic operative treatment as standard, although latest versions[7-10] also consider antibiotic treatment as an alternative to surgery if there is low suspicion of gangrenous or perforated appendicitis and the patient is aware of the recurrence risk. In fact, the Royal College of Surgeons stated in 2017 that "antibiotic treatment is already offered by many British surgeons".[11] To be able to discuss both therapies with a patient, an understanding of their perspectives about treatment options and their view of the risks and benefits, is essential.

Few studies have evaluated patients' preferences in the treatment of uncomplicated appendicitis. A wide range from 9.4 to 57 per cent of patients preferring antibiotic over surgical treatment has been reported.[12-14] However, these studies appear to be biased owing to the type of participants included. The populations questioned vary from visitors and patients (without appendicitis) presenting at the emergency department[14] to medical students[12] or a randomly-assigned cohort recruited through social media or at public venues[13], making it hard to translate these results to the general population. Survey design or interview structure can also influence the study results. Ideally, information is needed about appendicitis treatment preferences of the average population; that is, those who may experience appendicitis in future.

This study aimed to explore the preference for surgical or antibiotic management of uncomplicated appendicitis in a sample of the average Dutch population.

Methods

A web-based survey was developed, with a scenario of a patient presenting with uncomplicated appendicitis. Information on treatment options with associated risks and benefits was provided in a stepwise manner, alternating with questions about treatment preference. After being fully informed, the participant had to choose between 'antibiotic treatment', 'surgery' or 'I could not make a decision'. Participants were then asked to substantiate their choice based on 10 listed arguments using a seven-point Likert scale (1, very unimportant; 7, very important) and to rank their top-three reasons for treatment preference from the listed arguments. Finally, participants were asked what recurrence risk of appendicitis after 1 year they would accept if treated with antibiotics. All background information provided was extracted from systematic reviews, RCTs, and national data. The full questionnaire and list of arguments is available in Appendix S1.

Baseline characteristics

The following baseline characteristics of each participant were collected: age, sex, socioeconomic status (education, profession, income), history of abdominal surgery, general anaesthesia, appendicitis, intravenous antibiotics or a medical complication in the hospital. Participants were asked whether they were a nurse or doctor.

Participant recruitment

The recruitment of participants was done by No Ties (Zekeringstraat, Amsterdam), an independent external research bureau. Participants were members of the inVotes panel of No Ties. This panel consists of approximately 50 000 members, recruited on a diversity of websites. Of these, 25 000–30 000 are considered active panel members. Members of the inVotes panel have to update their profile data annually, or are excluded from further participation. Participants are rewarded by points, collected for each study in which they participate. These points can be cashed in several online shops, or online gift cards. The panel is certificated by the International Organization of Standardization. No Ties follows the rules of the Centre for Marketing Intelligence and Research.

Sample size

Based on the literature, the expected range of the population preferring antibiotics could vary from 9 to 57 per cent. The broadest confidence interval is expected for an expected proportion of 50 per cent. For a proportion of 50 per cent preferring antibiotics with an absolute precision of 10 per cent and a 95 per cent confidence interval, 97 participants would be needed. For an absolute precision of 5 per cent, 385 patients would be needed. A study population of 250 participants would give an absolute precision of 6.2 per cent, which was chosen for pragmatic reasons and provided an acceptable error margin for the study goal.

Outcomes and analysis

The primary outcome was the proportion of participants who would prefer antibiotic treatment. Secondary outcomes were the most important reasons for their preference. The rankings of these arguments were presented as bar plots and percentages. The answers from the Likert-scale matrix questions were expressed as means and depicted in a bar plots for each subgroup. The proportion of accepted recurrence within 1 year was expressed as the first percentage crossing the median. In addition, the proportion of participants accepting a recurrence risk of appendicitis comparable to the actual risk of 22.6 per cent in the literature was calculated.

All outcomes and results were weighted to mimic the average Dutch population, according to the standard of the national Centre for Marketing Intelligence and Research. Weighting features included sex, age group, social class, and residential area. Differences between groups were calculated as odds ratios with 95 per cent confidence intervals. The mean difference with 95 per cent confidence interval was calculated for normally distributed continuous data.

Results

In total, 808 members of the inVotes panel were approached between 17 April 2020 and 23 April 2020. Of these, 254 (31.4 per cent) completed the survey. All results are reported after weighting. In total, 50.0 per cent of participants were men and the mean (s.d.) age was 49 (17) years (*Table 1*). Of the 254 participants, 113 (44.5 per cent) preferred surgical treatment, 125 (49.2 per cent) preferred antibiotic treatment, and 16 (6.3 per cent) were undecided.

When asked for an acceptable recurrence risk after initial antibiotic treatment, the majority (55.5 per cent) of all participants would accept a risk of 31 per cent or higher for recurrent appendicitis (*Table 2*). Moreover, 63.4 per cent of all participants would accept a recurrence risk higher than 21 per cent, resembling the recurrence risk described in the literature.

	All participants (n=254)	**Preferring surgical treatment (n=113)***	**Preferring antibiotic treatment (n=125)***	**OR (95% CI)**
Age, mean (SD), years	49 (17)	47(17)	50 (17)	3.19 (-1.21-7.60)**
Male sex (%)	127 (50%)	60 (53%)	63 (50%)	1.11 (0.67-1.85)
History of abdominal surgery (%)	69 (27%)	36 (32%)	29 (23%)	1.57 (0.88-2.78)
History of anesthesia (%)	180 (71%)	84 (74%)	85 (68%)	1.36 (0.78-2.40)
History of appendicitis (%)	27 (11%)	17 (15%)	9 (7%)	2.31 (0.98-5.41)
History of IV antibiotics (%)	76 (30%)	38 (34%)	31 (25%)	1.54 (0.88-2.70)
History of a medical complication (%)	29 (11%)	15 (13%)	13 (10%)	1.32 (0.60-2.91)
Works or has worked as nurse or doctor (%)	13 (5%)	3 (3%)	6 (5%)	0.54 (0.13-2.22)

Tabel 1. *Baseline Characteristics*
Abbreviations: CI, confidence interval; IV, intravenous; OR, odds ratio; SD, standard deviation.
**This table excluded patients who were unsure for surgical or antibiotic treatment in the subgroups and numbers and percentages are shown after weighting to mimic the average Dutch population.*
***For age the mean difference with 95% CI was calculated.*

Acceptable risk of recurrent appendicitis (%)	All participants (n=254)	Preferring surgical treatment (n=113)*	Preferring antibiotic treatment (n=125)*
0% (I would always prefer surgery)	54 (22%)	51 (46%)	1 (1%)
1-10%	14 (6%)	11 (10%)	3 (3%)
11-20%	24 (9%)	16 (14%)	7 (6%)
21-30%	20 (8%)	11 (10%)	6 (5%)
31-40%	27 (11%)	5 (5%)	19 (15%)
41-50%	24 (9%)	4 (4%)	17 (14%)
51-60%	29 (11%)	6 (5%)	21 (17%)
61-70%	15 (6%)	1 (1%)	14 (11%)
71-80%	18 (7%)	3 (2%)	14 (11%)
81-90%	7 (3%)	3 (3%)	4 (3%)
91-99%	5 (2%)	1 (1%)	4 (3%)
100% (I would always prefer antibiotics)	16 (6%)	0 (0%)	14 (11%)

Table 2*. Treatment preference in relation to risk of recurrent appendicitis*
**This table excluded patients who were unsure for surgical or antibiotic treatment in the subgroups and numbers and percentages are shown after weighting to mimic the average Dutch population.*

Participants preferring surgical treatment

Among participants preferring surgical treatment, 'removal of the cause of appendicitis by surgery' was ranked among the top three reasons by 70.7 per cent and in 46.7 per cent it was ranked as the most important argument (*Fig. 1*). 'The chance of recurrent appendicitis' was ranked in the top three reasons by 62.9 per cent. 'The fact that surgery is usual care' was the third most important argument and ranked among the top three reasons by 38.1 per cent. The majority (55.2 per cent) of participants preferring surgical treatment would only accept antibiotic treatment without surgery at a risk of recurrent appendicitis of 10 per cent or less (*Table 2*). About one-third of participants preferring surgical treatment nevertheless would accept antibiotic treatment at a recurrence risk of at least 21 per cent.

Participants preferring antibiotic treatment

Among participants preferring antibiotic treatment, 'avoiding surgery', was ranked among the top three reasons by 83.1 per cent, and 60.1 per cent ranked it as most important (*Fig. 2*). 'The chance of a complication after surgery' and 'avoiding anaesthesia' were ranked in the top three reasons by 72.1 per cent and 58.8 per cent respectively. The majority (56.8 per cent) of participants preferring antibiotic treatment would accept a risk of more than 50 per cent for recurrent appendicitis if antibiotic treatment was given (*Table 2*). Finally, 90.9 per cent of participants preferring antibiotic treatment would accept an appendicitis recurrence risk of 21 per cent or more.

Mean reason for preference scores

The mean scores for each reason for preferring antibiotic treatment or surgical treatment are shown in *Fig. 3*. The only reason that scored under 4 (neutral) in both preference groups, was 'avoiding a scar'

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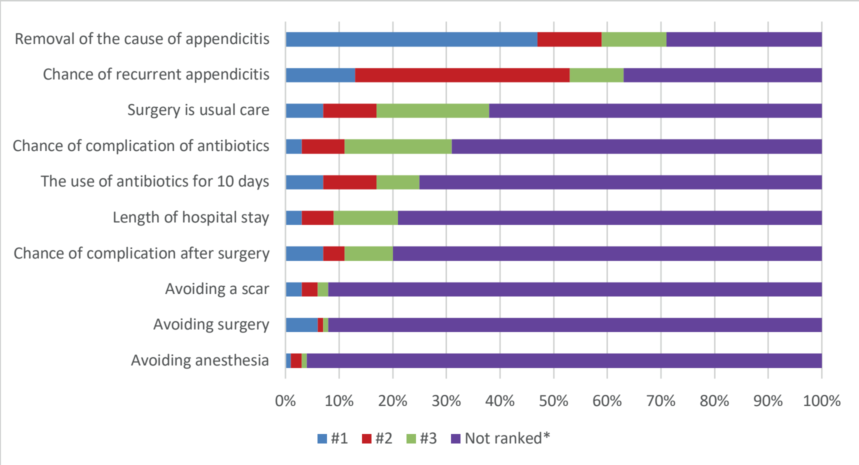

Figure 1, *Ranking reasons for treatment choice of participants who overall prefer surgery*
**Participants were asked to rank a top 3 of most important reasons for their treatment choice out of these 10 provided reasons. 'Not ranked' means that the presented percentage of participants did not rank the statement in their top 3.*

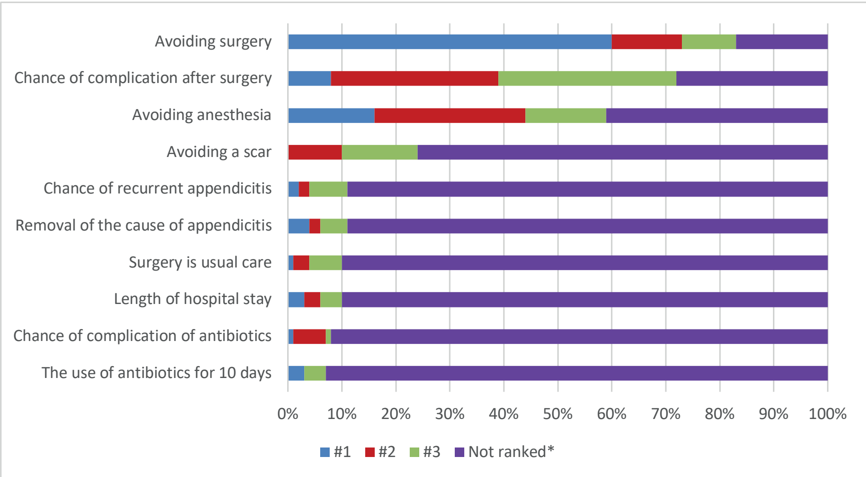

Figure 2*. Ranking reasons for treatment choice of participants who overall prefer antibiotic treatment*
**Participants were asked to rank a top 3 of most important reasons for their treatment choice out of these 10 provided reasons. 'Not ranked' means that the presented percentage of participants did not rank the statement in their top 3.*

10

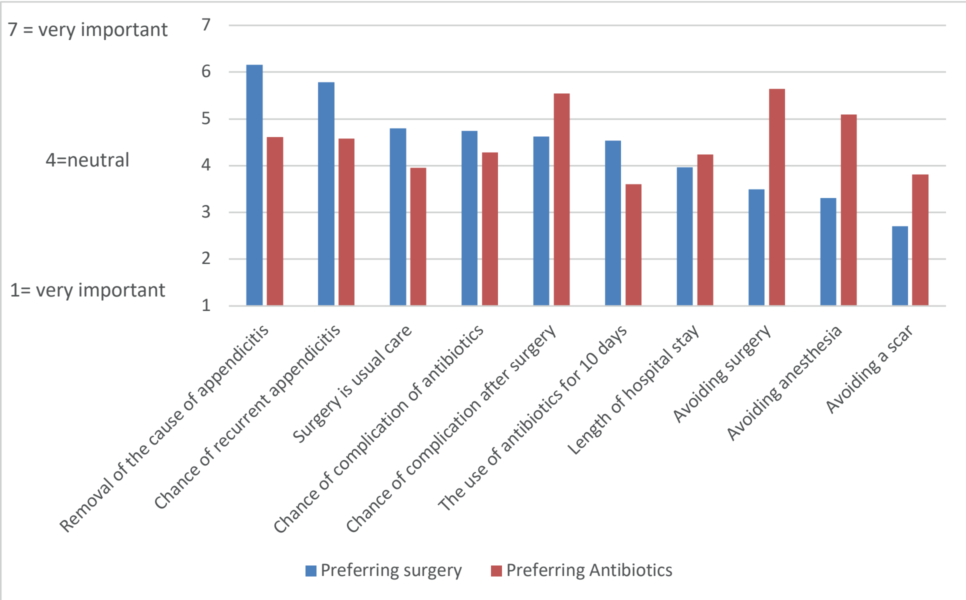

Figure 3, *Mean scores of preference reasons for participants preferring surgery or antibiotics*

Discussion

The present study has shown that, when choosing surgical or antibiotic treatment for uncomplicated appendicitis, there are two distinct preference groups that accept divergent risks of recurrence of appendicitis after antibiotic treatment without surgery. Approximately half of participants reflecting the average Dutch population preferred antibiotic over surgical treatment. The majority of these participants accepted a risk of recurrent appendicitis of 50 per cent or more within 1 year. Avoiding surgery was the most essential reason for participants to prefer antibiotic treatment. On the other hand, the majority of participants preferring surgical treatment accepted a recurrence risk of no more than 10 per cent for treatment with antibiotics. The most prominent reason was that surgery removes the cause of appendicitis.

Three studies[12-14], all undertaken in the USA, have previously explored patient preference in the treatment of uncomplicated appendicitis. Kadera and colleagues[14] included 129 patients without suspicion of appendicitis in the emergency department, using interviews to test patients' knowledge of appendicitis and informing them about antibiotic treatment. In 57 per cent of these patients without appendicitis, antibiotic treatment was preferred over surgery. In patients with a history of appendicitis, this increased to 74 per cent. However, treatment options were presented as comparable options, without explanation of (recurrence) risks and advantages. The other two studies did inform about the risks and advantages of both treatments. Althans and co-workers[12] used a questionnaire on 255 medical students, and reported that 66 per cent preferred surgery, 24 per cent antibiotics, and 9 per cent were undecided. Hanson *et al.*[13] also included participants from the medical community: 1728 participants for an online survey, distributed by the University of North Dakota (UND) and UND School of medicine and Health Sciences Newsletter, posters on the UND campus, social media, the American College of Surgeons discussion board and the Association of VA Surgeons 2016 annual meeting. Only 9 per cent preferred treatment with antibiotics. Afterwards, in interviews of 220 participants recruited at public venues, antibiotic treatment was viewed as more appealing when short-term failure and long-term recurrence rates were lower.

Two of the previous studies informed about risks and benefits, although presented information conflicts with data from published systematic reviews.[1,5] This may well have led to less favourable scenarios for antibiotic treatment.[15] Furthermore, both scenario survey studies[12,13] focused on medical participants, which may have influenced the results. In the present study, the data provided were extracted from recent systematic reviews, RCTs, and national data, and up-to-date clinical data on surgical and antibiotic treatments. Moreover, the participants were a sample of the average Dutch population and the results are therefore more generalizable.

In the present study, the scenario provided describes a patient with uncomplicated appendicitis, without including diagnostic dilemmas. Risk assessment by the participant is based on this uncomplicated diagnosis. In practice, differentiation between uncomplicated and complicated appendicitis remains challenging. The CODA collaborative[2] included 1552 patients with assumed uncomplicated appendicitis based on imaging and compared antibiotic and surgical treatment. An appendiceal perforation was found in 15 per cent of initially operated patients. An association was described between the presence of an appendicolith and having complicated appendicitis[2]. The Appendicits Acuta (APPAC) trial[16] only included patients without an appendicolith and the rate of complicated cases in the initial surgery arm was only 1.5 per cent. Patients with an appendicolith are potential non-responders to antibiotic treatment and perhaps should not be offered non-operative treatment. Moreover, the chance of having complicated appendicitis has to be taken into account and should be explained to patients.

A recent study[17] has evaluated quality of life and patient satisfaction after intervention in an observational follow-up of an RCT comparing appendicectomy with antibiotic treatment. Quality of life was similar in both groups. However, more patients were satisfied with appendicectomy than antibiotic treatment (68 per cent very satisfied, 21 per cent satisfied, 6 per cent indifferent, 4 per cent unsatisfied, and 1 per cent very unsatisfied in appendicectomy group; 53 per cent very satisfied, 21 per cent satisfied, 13 per cent indifferent, 7 per cent unsatisfied, and 6 per cent very unsatisfied in antibiotic group; $P < 0.001$). This difference is explained by the subgroup of patients initially randomized to antibiotics but eventually needing surgery. Of this subgroup, however, 33 per cent still chose antibiotic treatment as their first choice. The recurrence rate after antibiotics in the APPAC trial (27.3 per cent had an appendicectomy within 1 year) lies below the recurrence risk that present study participants who preferred antibiotics were willing to take. Because patients were randomized to either antibiotics or surgery in the APPAC trial, satisfaction may have been greater when patients were assigned to a treatment group of their own preference. This patient preference model was used by Minneci and colleagues[18], who compared antibiotic treatment with surgical management in children (7-17 years old), and treatment was assigned based on the preference of patients and their families. Of all 102 patients, 37 chose non-operative treatment of whom 24 per cent underwent appendicectomy within 1 year. Compared with the initial surgery group, patients in the antibiotic group had a shorter period of disability days (8 *versus* 21 days) and lower appendicitis-related healthcare costs. The incidence of complicated appendicitis was lower in the antibiotic group, but the difference was not statistically significant (2.7 *versus* 12.3 per cent, $P = 0.15$).[18] This type of study could increase validity compared with RCTs, without compromising internal validity.[19] Moreover, such studies reflect a situation more comparable to daily clinical practice.

Limitations of this study are the involvement of participants who did not have acute appendicitis at the time of the surgery; only 10.6 per cent had experienced appendicitis once. The web-based survey did not offer an opportunity to validate understanding of all risks and benefits by the participants. Moreover, in real life, the decision about either treatment would often be discussed with family, which was not part of the study. Furthermore, in the light of the latest results from the CODA collaborative[2,] and the APPAC II[20] trial, this narrative may have undersold antibiotics. Conservative treatment may need hospital admission for only 1 day or possibly no hospital stay at all[2,20,21] instead of the 2 days outlined in the questionnaire, which was common at the time of designing this study. Finally, the narrative did not include information about the rare possibility and unanswered consequence of missed appendiceal neoplasms. As the questionnaire was composed before the results from the CODA collaborative and the APPAC II trial were published, these data were not included in the survey.

The use of antibiotics as first-choice treatment in uncomplicated appendicitis is still under discussion. Guidelines are cautious in advising antibiotics only as standard treatment.[6,7] The present study contributes to the available evidence that one in two average people may prefer (initial) antibiotic treatment. This group is willing to accept a high risk of recurrent appendicitis when receiving antibiotic treatment instead of surgery, even higher than the actual recurrence risk after antibiotic treatment. In contrast, the surgery preference group would tolerate only a low recurrence risk. Patients with uncomplicated appendicitis should be counselled about both treatment options.

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Supplementary information

The questionnaire was published in a web-survey in Dutch. This is a translation. We provided references in this appendix. In the original survey, references were not added.

1. Answer the following questions with Yes or No

The answers were randomly presented.

a. Have you ever had abdominal surgery?
b. Have you ever been under general anesthesia (during anesthesia you are put to sleep before surgery)?
c. Have you ever had an appendicitis?
d. Have you ever received antibiotics through an intravenous drip while being admitted?
e. Have you ever had a complication while being admitted to a hospital?
f. Are, or have you been, a nurse or a doctor?

The answers to question two are randomly presented. In questions 3-7, they are presented in the same order as question 2.

2. Imagine that you come to the emergency department with complaints of acute abdominal pain. The doctors think, after blood results and imaging tests, that you have a simple (uncomplicated, not dangerous) appendicitis. In this type, the appendix is not perforated and will not perforate 1. Two treatment options are presented to you. Which of the following treatment methods do you prefer, at first sight without further explanation?

a. You will have an operation
b. You are not operated but treated with medications (antibiotics). If this does not work as expected, you will still need to have an operation

3. We now explain the options in more detail. First of all, the treatment itself. Which of the options below do you prefer, based on the treatment?

a. **Treatment by surgery.** The treatment is as follows: After admission to the hospital, it takes an average of 8 hours, but sometimes up to 24 hours, until you undergo surgery [2]. You will be anesthetized before surgery. Usually the surgeon operates through keyhole surgery (in 80% of cases) [2]. In such keyhole surgery, three cuts are made in the abdomen, each about 1-2 cm in size; one at the navel, one above the pubic bone and one at the bottom left in the abdomen. If everything goes well, you can go home the day after the operation.

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b. **Treatment with antibiotics.** You will be hospitalized from the emergency department. You will be given antibiotics through an IV drip. You will stay in the hospital for 2 nights. The nurses and doctors will monitor you closely. Normally, you can go home after these two days [3]. The abdominal pain is then reduced or absent, and you do not feel sick [3].

4. After treatment, a recovery period will follow for both options. Which of the options do you prefer? In addition to the treatment itself, you also weigh the expected recovery after treatment.

a. **Treatment by surgery.** At home, you don't need to take any medication, except for a mild analgesic. You can resume your daily work and activities based on how you feel. After ten days, you will be called to ask how you are doing.

b. **Treatment with antibiotics.** At home, you will use antibiotics for another eight days. You can resume your daily work and activities based on how you feel. After ten days, you will be called to ask how you are doing.

5. Every treatment has possible complications. Which of the options do you prefer? In addition to treatment and recovery, you also weigh possible complications.

a. **Treatment by surgery.** In 20 out of 100 people, surgery cannot be performed through keyhole surgery, and the scar is larger when open surgery is needed [2]. This scar is located at the bottom right of the abdomen and is about 8 cm. A complication occurs in 8 out of 100 people [2]. The most common complications of this operation are wound infection or an infection deeper in the abdomen. You may need extended hospitalization. You may be given antibiotics, and you may even undergo additional surgery. The risk of the anesthesia is negligible.

b. **Treatment with antibiotics.** Less than 1 in 100 people experience a side effect from antibiotics for appendicitis (for example diarrhea and nausea or an allergic reaction but this is very rare) [4]. Since the appendix is not removed, there is a chance that an appendicitis will return. This happens to 8 out of 100 people within the first month [4]. This occurs in 23 out of 100 people within the first year [4]. You will then have to be readmitted to have your appendix removed this time. This does not increase the chance of complications from the operation, compared to if you would have had an operation immediately [5].

6. Thus, each treatment has advantages and disadvantages. Which of the options do you prefer if we again list the pros and cons for you?

a. **Treatment by surgery.** An advantage is that recurrent appendicitis will not happen, after all, the appendix is removed. A disadvantage is that you have a scar after the operation. A possible disadvantage is that you go under anesthesia. The anesthetic drugs have no major disadvantages, but some people find this stressful. Another disadvantage is that in 8 out of 100 people there is a complication from the operation, such as a wound infection or an infection deeper in the abdomen [2].

b. **Treatment with antibiotics.** If you are successfully treated with antibiotics, you will not be operated on, so you will not have the disadvantages of an operation (see the disadvantages of the operation). You will then not have a scar and will not be anesthetized. There is a chance that you will still need surgery for the appendix (this happens in 23 out of 100 people within the first year [4]), which is a possible disadvantage (two treatments). Another disadvantage is that there is a chance of a complication from the antibiotics, such as diarrhea and nausea or an allergic reaction, however this is less than 1% [4].

7. Here again, a summary of all information. After reading this information, which option would you choose?

The table was shown small but was mandatory to click to magnify it. This makes it more likely that people read it closely.

	Treatment with antibiotics, without surgery	Surgery
What does it mean?	• 2 days admission to the hospital • 2 days of antibiotics through an IV drip, then you take antibiotics tablets at home for 8 days	• You will have an operation ○ 80% keyhole surgery (3 small cuts of about 2-3 cm) ○ 20% open surgery (1 larger cut, about 8 cm) • You have to wait an average of 8 hours after admission before taken to surgery • You will stay in the hospital for an average of 1 night after the operation
Recovery	• When you go home, the abdominal pain is gone and you don't feel sick • When you are at home, you can resume your daily activities	• When you go home, the abdominal pain is gone and you don't feel sick • When you are at home, you can resume your daily activities and activities
In how many people does it help?	• 92 out of 100 people do not need surgery within a month • 77 out of 100 people do not need surgery within a year	• 100 out of 100 people are relieved of their appendicitis
What are the advantages?	• You will have no scar • You do not need surgery	• Recurrent appendicitis is not an issue
What are the disadvantages?	• There is a chance that appendicitis will return and you still need to have surgery • This does not lead to greater risks of complications than if you were operated on immediately • There is a very small chance (<1%) of a side effect of the antibiotics	• You will have a scar and will be anesthetized • A complication occurs in 8 out of 100 people. This will extend your time in hospital, and you may need antibiotics or reoperation.

Options:

a. Treatment by surgery (removal of the appendix).

b. Treatment by use of medication (antibiotics).

c. I cannot make that decision

8. Indicate to what extent the listed statements play a role in your choice. 1 stands for "totally unimportant" and 7 for "very important".

Matrix of: very unimportant, quite unimportant, somewhat unimportant, neutral, somewhat important, quite important, very important; items are presented randomly

a. Avoiding surgery
b. Avoiding anesthesia (being put to sleep before surgery)
c. Avoiding a scar
d. The chance of a complication after surgery
e. That the cause of appendicitis is removed by surgery so that appendicitis cannot come back
f. Having to take antibiotics (for ten days)
g. The risk of a complication from the use of antibiotics
h. The chance that appendicitis can come back with antibiotics and you still need surgery
i. The length of hospital stay
j. The fact that surgery is usually performed for appendicitis

9. Which of the following matters most in your choice? Please choose the three most important aspects. First, click on the most important aspect. This aspect gets a 1. Then select the second most important aspect, this gets a 2, and so on.

a. Avoiding surgery
b. Avoiding anesthesia (being put to sleep before surgery)
c. Avoiding a scar
d. The chance of a complication after surgery
e. That the cause of appendicitis is removed by surgery, so that appendicitis cannot come back
f. Having to take antibiotics (for ten days)
g. The risk of a complication from the use of antibiotics
h. The chance that appendicitis can come back with antibiotics and you still need surgery
i. The length of hospital stay
j. The fact that surgery is usually performed for appendicitis
k. None of the above

10. Are there other factors that play a role in your decision?

a. No
b. Yes, being .....

11. After treatment with antibiotics, the appendicitis can become infected again. In that case, the patient must still be operated on. In many people, the choice between immediate surgery and antibiotic treatment is expected to depend on the chance that appendicitis may return with antibiotic treatment. In that case, surgery is required.

At what percentage of "again appendicitis after antibiotic treatment" would you choose to operate immediately instead of antibiotic treatment?

By percentage, we mean the percentage of patients in which appendicitis returns within a year after antibiotic treatment.

a. 0% (I would always choose for direct surgery)
b. 1% t/m 10%
c. 11% t/m 20%
d. 21% t/m 30%
e. 31% t/m 40%
f. 41% t/m 50%
g. 51% t/m 60%
h. 61% t/m 70%
i. 71% t/m 80%
j. 81% t/m 90%
k. 91% t/m 99%
l. 100% (I would never choose for direct surgery)

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Appendices

Summary of thesis

Nederlandse samenvatting

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Dankwoord

About the author

Summary of thesis

Appendicitis is one of the most common causes of abdominal pain. Knowledge about appendicitis is already extensive. However, not too long ago a new theory emerged; two entities of appendicitis can be distinguished (complicated and uncomplicated). This provides new opportunities and challenges in the diagnosis and treatment of appendicitis.

Many studies in this thesis were based on data from the Dutch SNAPSHOT database. This study was a prospective, observational cohort study, including patients who underwent surgery for expected appendicitis. Almost all Dutch hospitals participated (62) and a total of 1975 patients were included. The database contains preoperative and perioperative variables and a 30-day follow-up was performed. Study protocol and primary results have been published earlier.

In **Chapter 2**, the Dutch guideline for acute appendicitis was summarised. The guideline was published in 2019 and is an updated version of the guideline from 2010. In a working group, seven queries were formulated, and a search was performed for each query. The guideline addresses specific issues of treating appendicitis, being the diagnostic work-up, non-operative treatment, surgical techniques and post-operative antibiotic treatment. The guideline also provides published data analysis for paediatric, adult and pregnant patients. Conclusions and recommendations were drafted for each query.

In **Chapter 3,** data from the SNAPSHOT study was used to investigate the discriminatory capacity of imaging to distinguish complicated appendicitis from uncomplicated appendicitis. A SNAPSHOT collaborator grouped patients for complicated or uncomplicated appendicitis based on the radiological reports. The reference standard was based on operative and pathological findings. Overall, imaging work-up as practiced, following the national guideline, had a poor sensitivity for complicated appendicitis of only 35% but with a high specificity of 93%. The study represents daily practice at the Emergency Department and represents real-life data. However, data may have been biased by retrospective interpretation of radiological reports or because of under-registration of imaging features of complicated appendicitis by the radiologist.

The discriminatory accuracy of imaging for complicated and uncomplicated appendicitis was described in **Chapter 4.** This chapter presents a systematic literature review for studies describing the diagnostic accuracy of complicated appendicitis versus uncomplicated appendicitis. Thirteen studies were included, and summary estimates were calculated if possible. Summary estimates for sensitivity and specificity of US, MRI and US with conditional CT in detecting complicated appendicitis could not be calculated because of lack of data. For CT, mean sensitivity was 78% (95% confidence interval (CI) 64%-88%) and mean specificity 91% (95%CI 85%-99%). At a median prevalence of 25%, the positive predictive value of CT for complicated appendicitis would be 74%, and its negative predictive value

93%. Although CT has a far from perfect and highly varying sensitivity, its negative predictive value for complicated appendicitis is high. US, CT and MRI all have limitations in discriminating between complicated and uncomplicated appendicitis.

Chapter 5 is the study protocol of the Score of Acute appendicitis Severity (SAS) trial. In this observational, multicenter cohort study, the scoring system, previously developed by our research group, will be validated externally. It is hypothesised that SAS can reach a sensitivity and a negative predictive value of 95% to detect complicated appendicitis in an external cohort. If this hypothesis proves to be incorrect, SAS will be optimised and validated in a second external cohort.

Chapter 6 is a narrative review. In this review, our view of diagnosing acute appendicitis is explained, and the differentiation between complicated and uncomplicated appendicitis further enlightened. We believe that standardised and low threshold imaging plays an essential role in accurately diagnosing acute appendicitis. It reduces the risk that another diagnosis is missed as a cause of abdominal pain in need of (urgent) treatment. It minimises negative appendectomy rates and may help differentiate between uncomplicated and complicated appendicitis, which is essential because this may lead to different management strategies and timing of intervention. In this respect, scoring systems without imaging features may not be accurate enough.

Chapters 7, 8 and 9 also used data from the Dutch SNAPSHOT appendicitis database. **Chapter 7** focused on the delay in surgery. Currently, no direct evidence is available on whether delaying surgery in complicated appendicitis leads to a higher proportion of post-operative complications. In this study, adult patients who underwent appendectomy for appendicitis were included, and the difference in complications between patients who were operated on within and after eight hours after hospital presentation was reported. In patients with complicated appendicitis, a higher proportion of complications was found in patients operated after eight hours than patients operated within eight hours (28.1% vs 18.3%, p=0.01). Multivariate analysis showed a delay in surgery as an independent predictor for post-operative complications in patients with complicated appendicitis. This emphasizes the importance of adequate recognition and early surgery, in particular in this subgroup of appendicitis patients.

Chapter 8 describes the difference in adult patients with appendicitis who presented at the emergency department during the day versus those who presented at night. No difference was found in the proportion of patients with complicated appendicitis among patients who presented at day versus those at night time (both 34%). However, in patients presented during daytime, 12.1% developed a post-operative complication versus 18.6% for presentation presented during the night (p=0.008). In a multivariate analysis, the risk of a postoperative complication when presenting at night was significantly increased (adjusted OR 1.74; 95%CI 1.14-2.66, p=0.01). Surgery within eight hours after presentation did not lower this risk (adjusted OR 1.37; 95%CI 0.97-1.95, p=0.078). After exploring in several subgroups and variables, no clear explanation was found for this increased post-operative complication rate at nighttime presentation.

Chapter 9 depicted the number of complications in patients with appendicitis. All patients with appendicitis who underwent appendectomy for appendicitis were included. The effects of appendicitis diagnosis at reassessment was compared to appendicitis diagnosis at initial presentation. Reassessed patients had a comparable post-operative complication rate as those diagnosed with appendicitis at initial presentation (15.1% vs 12.7% p-0.29). In addition, the proportion of patients with complicated appendicitis was not significantly different (27.9% vs 33.5%, p=0.07). Nevertheless, in patients with complicated appendicitis, more post-operative complications were reported in patients diagnosed at reassessment compared to those diagnosed initially (38.2% vs 22.9%, p=0.006). This is in line with the results described in **chapter 7**.

In the final chapter, **Chapter 10**, 250 Dutch citizens, randomly picked by a Dutch marketing office, were presented with two scenarios; one explaining laparoscopic appendectomy and one about the non-operative treatment with antibiotics. In this chapter, the opinion of the average Dutch population was explored in surgical versus conservative treatment for uncomplicated appendicitis. Of 254 participants, 49.2% preferred antibiotic treatment for uncomplicated appendicitis, 44.5% preferred surgery, and 6.3% could not make a decision. About half of the participants preferring antibiotics would accept a recurrence risk of more than 50% within one year. Avoiding surgery was their main reason. In participants preferring surgery, most tolerated a recurrence risk of no more than 10% when treated by antibiotics. Removal of the cause of appendicitis was their main reason. The results in this chapter contribute to the available evidence that one in two average persons may prefer (initial) antibiotic treatment. This group is willing to accept a high risk of recurrent appendicitis when having antibiotic treatment instead of surgery, even higher than the actual recurrence risk after antibiotic treatment. In contrast, the surgery preference group only tolerates a low recurrence risk. Patients with uncomplicated appendicitis should be counselled about both treatment options.

Nederlandse samenvatting

Appendicitis is een van de meest voorkomende oorzaken van buikpijn. Over appendicitis is al veel bekend. Nog niet zo lang geleden ontstond er echter een nieuwe theorie; twee entiteiten van appendicitis kunnen worden onderscheiden (gecompliceerde en ongecompliceerde appendicitis). Dit biedt nieuwe kansen en uitdagingen bij de diagnose en behandeling van appendicitis.

Veel studies in dit proefschrift zijn gebaseerd op gegevens uit de Nederlandse SNAPSHOT database. Deze studie was een prospectieve, observationele cohortstudie, waar patiënten die een operatie ondergingen bij de verdenking op appendicitis. Vrijwel alle Nederlandse ziekenhuizen deden mee (62) en in totaal werden 1975 patiënten geïncludeerd. De database bevat preoperatieve en perioperatieve variabelen en er was een follow-up van 30 dagen. Het onderzoeksprotocol en primaire resultaten zijn eerder gepubliceerd.

In **Hoofdstuk 2 is** de Nederlandse richtlijn voor acute appendicitis samengevat. De richtlijn is in 2019 gepubliceerd en is een geactualiseerde versie van de richtlijn uit 2010. In een werkgroep zijn zeven zoekopdrachten opgesteld en is per zoekopdracht een zoekopdracht uitgevoerd. De richtlijn behandelt specifieke onderwerpen van de behandeling van appendicitis, zoals de diagnostische opwerking, niet-operatieve behandeling, chirurgische technieken, postoperatieve antibioticabehandeling. De richtlijn biedt ook een analyse van gepubliceerde data specifiek voor pediatrische, volwassen en zwangere patiënten. Per zoekvraag zijn conclusies en aanbevelingen opgesteld.

In **Hoofdstuk 3** zijn gegevens uit de SNAPSHOT studie gebruikt om het onderscheidend vermogen van beeldvorming te onderzoeken om gecompliceerde appendicitis te onderscheiden van ongecompliceerde appendicitis. Een SNAPSHOT-medewerker groepeerde patiënten voor gecompliceerde of ongecompliceerde blindedarmontsteking op basis van de beschikbare radiologie verslagen. De referentiestandaard was gebaseerd op operatieve en pathologische bevindingen. Over het algemeen had het beeldvormend onderzoek zoals toegepast volgens de nationale richtlijn een hele beperkte sensitiviteit voor gecompliceerde appendicitis (slechts 35%), maar een hoge specificiteit van 93%. Het onderzoek geeft de dagelijkse praktijk op de Spoedeisende Hulp weer en real-life data weer. Gegevens kunnen echter vertekend zijn door retrospectieve interpretatie van radiologie verslagen of door onderregistratie van kenmerken op beeldvorming van gecompliceerde appendicitis door de radioloog.

De diagnostische accuratesse van beeldvorming voor gecompliceerde en ongecompliceerde appendicitis werd beschreven in **Hoofdstuk 4**. Dit hoofdstuk presenteert een systematische review voor studies die de diagnostische accuratesse van gecompliceerde appendicitis versus ongecompliceerde appendicitis beschrijven. Dertien studies werden geïncludeerd en indien mogelijk werden gepoolde waarden berekend. Gepoolde waarden voor sensitiviteit en specificiteit bij het opsporen van gecompliceerde appendicitis konden niet worden berekend vanwege een gebrek aan gegevens voor echo, MRI en echo eventueel gevolgd door CT. Voor CT alleen was de gepoolde sensitiviteit 78% (95% betrouwbaarheidsinterval (BI) 64%-88%) en de gemiddelde specificiteit 91% (95%BI 85%-99%). Bij een mediane prevalentie van 25% zou de positief voorspellende waarde van CT voor gecompliceerde appendicitis 74% zijn, en de negatief voorspellende waarde 93%. Hoewel CT een verre van perfecte en sterk variërende sensitiviteit heeft, is de negatief voorspellende waarde voor gecompliceerde appendicitis hoog. Echo, CT en MRI hebben allemaal beperkingen bij het onderscheiden van gecompliceerde en ongecompliceerde appendicitis.

Hoofdstuk 5 is het onderzoeksprotocol van de Score of Acute appendicitis Severity (SAS) trial. In deze observationele, multicenter cohortstudie zal het eerder door onze onderzoeksgroep ontwikkelde scoresysteem extern gevalideerd worden. De hypothese is dat SAS een sensitiviteit en een negatief voorspellende waarde van 95% kan bereiken om gecompliceerde appendicitis uit te sluiten. Als deze hypothese onjuist blijkt te zijn, zal SAS worden geoptimaliseerd en gevalideerd in een tweede cohort.

Hoofdstuk 6 is een 'narrative review'. In deze review wordt onze kijk op het diagnosticeren van acute appendicitis toegelicht en wordt het onderscheid tussen gecompliceerde en ongecompliceerde appendicitis verder toegelicht. Wij zijn van mening dat gestandaardiseerde en laagdrempelige beeldvorming een essentiële rol speelt bij het nauwkeurig diagnosticeren van acute appendicitis. Het verkleint de kans dat een andere diagnose wordt gemist als oorzaak van buikpijn die (dringend) moet worden behandeld. Het minimaliseert het aantal negatieve blindedarmoperaties en kan helpen onderscheid te maken tussen ongecompliceerde en gecompliceerde appendicitis, wat essentieel is omdat dit kan leiden tot verschillende managementstrategieën en verschillen in timing van interventie. In dit opzicht zijn scoresystemen zonder beeldvormende functies mogelijk niet nauwkeurig genoeg.

Hoofdstukken 7, 8 en 9 gebruikten ook gegevens uit de Nederlandse SNAPSHOT appendicitis database. **Hoofdstuk 7** richtte zich op de vertraging van operatie. Momenteel is er geen direct bewijs beschikbaar over de vraag of het uitstellen van een operatie bij gecompliceerde appendicitis leidt tot een hoger percentage postoperatieve complicaties. In deze studie werden volwassen patiënten geïncludeerd die een appendectomie ondergingen voor appendicitis, en het verschil in complicaties tussen patiënten die binnen, en acht uur na ziekenhuisopname werden geopereerd, werd gerapporteerd. Bij patiënten met gecompliceerde appendicitis werd een groter aandeel complicaties gevonden bij patiënten die na acht uur werden geopereerd dan bij patiënten die binnen acht uur werden geopereerd (28,1% vs. 18,3%, p=0,01). Multivariate analyse toonde een vertraging in chirurgie aan als een onafhankelijke voorspeller voor postoperatieve complicaties bij patiënten met gecompliceerde appendicitis. Dit benadrukt het belang van adequate herkenning en vroege chirurgie, in het bijzonder bij deze subgroep van appendicitis patiënten.

Hoofdstuk 8 beschrijft het verschil tussen volwassen patiënten met appendicitis die zich overdag op de Spoedeisende Hulp meldden en degenen die zich 's nachts meldden. Er werd geen verschil gevonden in het aandeel patiënten met gecompliceerde appendicitis tussen patiënten die zich overdag presenteerden versus die 's nachts (beide 34%). Bij patiënten die overdag gepresenteerd werden, ontwikkelde 12,1% echter een postoperatieve complicatie versus 18,6% voor presentatie gepresenteerd tijdens de nacht (p=0,008). In een multivariate analyse was het risico op een postoperatieve complicatie bij nachtelijke presentatie significant verhoogd (gecorrigeerde OR 1.74; 95%CI 1.14-2.66, p=0.01). Een operatie binnen acht uur na presentatie verlaagde dit risico niet (gecorrigeerde OR 1.37; 95%CI 0.97-1.95, p=0.078). Na onderzoek in verschillende subgroepen en variabelen werd geen duidelijke verklaring gevonden voor deze verhoogde postoperatieve complicaties bij nachtelijke presentatie.

Hoofdstuk 9 beschrijft het aantal complicaties bij patiënten met appendicitis. Alle patiënten met appendicitis die een appendectomie ondergingen werden geïncludeerd. De effecten van diagnose appendicitis bij herbeoordeling werden vergeleken met de diagnose appendicitis bij de eerste presentatie. Herbeoordeelde patiënten hadden een vergelijkbaar postoperatief complicatiepercentage als patiënten met de diagnose appendicitis bij de eerste presentatie (15,1% versus 12,7% p=0,29). Bovendien was het aandeel patiënten met gecompliceerde appendicitis niet significant verschillend (27,9% versus 33,5%, p=0,07). Toch werden bij patiënten met gecompliceerde appendicitis meer postoperatieve complicaties gemeld bij patiënten die bij herbeoordeling werden gediagnosticeerd vergeleken met patiënten die bij eerste presentatie werden gediagnosticeerd (38,2% versus 22,9%, p=0,006). Dit is in lijn met de resultaten beschreven in **Hoofdstuk 7**.

In het laatste hoofdstuk, **Hoofdstuk 10**, kregen 250 Nederlanders, willekeurig gekozen door een Nederlands marketingbureau, twee scenario's voorgeschoteld; een uitleg over laparoscopische appendectomie en een over de niet-operatieve behandeling met antibiotica. In dit hoofdstuk is de mening van de gemiddelde Nederlandse bevolking onderzocht in chirurgische versus conservatieve behandeling van ongecompliceerde appendicitis. Van de 254 deelnemers gaf 49,2% de voorkeur aan een antibioticabehandeling voor ongecompliceerde blindedarmontsteking, 44,5% gaf de voorkeur aan een operatie en 6,3% kon geen beslissing nemen. Ongeveer de helft van de deelnemers die antibiotica prefereren, accepteert binnen een jaar een herhalingsrisico van meer dan 50%. Het vermijden van een operatie was hun belangrijkste reden. Bij deelnemers die de voorkeur gaven aan een operatie, tolereerden de meesten een herhalingsrisico van niet meer dan 10% bij behandeling met antibiotica. Het wegnemen van de oorzaak van appendicitis was hun belangrijkste reden. De resultaten in dit hoofdstuk dragen bij aan het beschikbare bewijs dat gemiddeld één op de twee personen een (initiële) behandeling met antibiotica prefereert. Deze groep is bereid een hoog risico op recidiverende blindedarmontsteking te accepteren bij een antibioticabehandeling in plaats van een operatie, zelfs hoger dan het daadwerkelijke recidief risico na antibioticabehandeling. Daarentegen tolereert de voorkeursgroep voor chirurgie slechts een laag recidief risico. Patiënten met ongecompliceerde appendicitis moeten over beide behandelingsopties worden voorgelicht.

Future perspectives

The treatment of acute appendicitis is entering a new era; the era of conservative treatment. In 1886, Reginal Fitz was the first to describe the inflamed appendix. He suggested surgical treatment for patients with appendicitis.[1] It is remarkable that more than a hundred years later, surgery does not seem to be the only treatment for all patients with acute appendicitis. Several RCTs and meta-analyses have been conducted in which conservative treatment by antibiotics were compared to surgical treatment.[2-7] These trials have proven that conservative treatment with antibiotics may be just as safe and effective as surgical treatment without the risk of surgical complications, just like management strategies changed for other colonic diseases such as diverticulitis or colitis. Major complications are seen in 8.4% of patients after appendectomy for uncomplicated appendicitis versus 4.9% after antibiotic treatment without appendectomy.[8] For minor complications these percentages are 12.5% versus 2.2% in favor of antibiotic treatment. On the other hand, these studies also have revealed that approximately 25% of patients have recurrent appendicitis within the first year, and after five years this proportion increases up to 40%. To decrease the number of recurrent or persistent appendicitis, patient selection is crucial. The Dutch guideline for acute appendicitis (2019) already advises to consider treatment with antibiotics alone for adults, but does not specify clearly in which patient group[9]. For successful conservative treatment, it is mandatory that patients with uncomplicated appendicitis are accurately identified, as patients with complicated appendicitis need surgical treatment.

Etiology

Little is known about the etiology of acute appendicitis. Obstruction of the appendiceal lumen may cause obstruction, for example by lymphoid hyperplasia or faecoliths, but appendicitis due to luminal obstruction tends to be less common than other causes.[10] Infectious agents may trigger acute appendicitis, but still the full range of specific causes remains unknown. A new trend in medicine is the microbiome. It is thought that the appendix might serve as a microbiome reserve in case of bacterial overgrowth in gastro-intestinal infections. In Finland, currently a trial is conducted to evaluate microbiological en immunological responses in appendicitis to explore its etiology, and to assess differences in uncomplicated and complicated appendicitis.[11] Understanding the etiology may contribute to optimisation of effective treatment for both complicated and uncomplicated appendicitis.

Patient selection

Complicated vs uncomplicated appendicitis

Imaging is an essential step to differentiate between complicated and uncomplicated appendicitis. Kim et al. has described several features associated with complicated appendicitis, such as abscess, extraluminal air, intra- and extraluminal appendicolith, and periappendicular fluid. In their systematic review with meta-analysis, a high specificity is seen for most parameters but with a poor sensitivity. For this reason, these features are not suitable to rule out complicated appendicitis.[12] Our systematic review and meta-analysis as conducted in **Chapter 4,** revealed summary estimates for CT of 78% for sensitivity and 91% for specificity, resulting in a PPV of 74% and an NPV of 93% in diagnosing complicated appendicitis by trained radiologists.[13] Results were highly heterogeneous, with sensitivities ranging from 28% to 95%. In the Netherlands, workup to diagnose appendicitis is performed with US with conditional CT if necessary. Using this strategy revealed a sensitivity of 48%, specificity of 93%, PPV of 68%, and NPV of 84% for the diagnosis of complicated appendicitis. This means that over 50% of all patients with complicated appendicitis are missed, and falsely classified as uncomplicated appendicitis.

Another way to discriminate complicated from uncomplicated appendicitis, is by the use of a scoring system, which ideally includes parameters that also systematically score for imaging features. Only two studies have described a scoring system combining clinical and imaging features to distinguish between uncomplicated and complicated appendicitis.[14, 15] Atema et al. have developed the Scoring systems for Appendicitis Severity (SAS) that combines imaging with clinical and biochemical features. SAS consists of two models, one for imaging performed by US and one for CT.[14] Sensitivity, specificity, PPV, and NPV for SAS if US was performed are 97%, 46%, 42%, and 97%, respectively. For the scoring system with CT features, SAS-CT, these test features are 90% sensitivity, 70% specificity, 55% PPV, and 95% NPV. With these high sensitivities and NPVs, SAS provides excellent diagnostic accuracy parameters to rule out complicated appendicitis. Avanesov et al. have also developed a scoring system, the APpendicitis Severity Index (APSI), that combines clinical and biochemical features with CT features.[15] Sensitivity, specificity, PPV, and NPV were 82%, 93%, 92%, and 83%. This scoring system provides excellent diagnostic accuracy to rule in complicated appendicitis, but ruling in complicated appendicitis is less interesting when selecting for antibiotic treatment of uncomplicated appendicitis. The major limitation of these scoring systems is they have not been validated externally yet. However, as described in **Chapter 5**, currently the external validation of the SAS trial is performed, which will provide information on the usefulness of this scoring system in daily practice.

In two large randomized controlled trials (RCTs) comparing antibiotic treatment for uncomplicated appendicitis with surgery, too many patients with complicated appendicitis have been included by mistake. Both RCTs have used standardized CT in their diagnostic approach to select only patients with uncomplicated appendicitis for study inclusion.[3, 4] Vons et al.[4] has found 18% complicated appendicitis in their patients randomized for surgery versus only 1.5% in the surgery group of Salminen et al.[3] It remains unclear what causes this difference.

Responsive appendicitis vs non-responsive appendicitis

The previously mentioned meta-analysis by Kim et al. has found that the presence of an intraluminal appendicolith has a pooled sensitivity of 43% and a pooled specificity of 74% for the presence of complicated appendicitis.[12] Furthermore, the presence of an appendicolith seems predictive for complicated appendicitis in both the SAS-CT and the SAS-US.[14] All and all, the mere presence of an appendicolith is not able to differentiate between uncomplicated and complicated appendicitis but it is a risk factor for complicated appendicitis and a predictor of unsuccessful antibiotic treatment. Post hoc analyses of Vons et al. indeed show a significant association between the presence of an appendicolith and the diagnosis of complicated appendicitis.[4] The presence of an appendicolith has previously been described as a significant predictor of failure of antibiotic treatment in patients with suspected uncomplicated appendicitis.[16] The most recent RCT on this subject, the Comparison of Outcomes of antibiotic Drugs and Appendectomy (CODA) trial, also demonstrates this association between the presence of an appendicolith and a higher risk of complicated appendicitis in the included patients with an assumed uncomplicated appendicitis.[7] In addition, in patients with an appendicolith, a significantly higher risk for appendectomy after initial antibiotic treatment is seen.[7]

In an extra analysis of the CODA trial[17], it is found that female sex and radiographic finding of wider appendiceal diameter were associated with increased odds of undergoing appendectomy within 30 days. Another study has found that an appendix diameter of 15mm or more on CT and a temperature of 38 ^{o}C or higher are associated with non-responsiveness of antibiotic treatment.[18]

Other factors leading to the failure of antibiotic treatment may co-exist, but these factors have yet to be explored in combined data from RCTs.

Patient preference

In The Netherlands, conservative treatment for uncomplicated appendicitis is sometimes considered but not standard care yet. Most surgeons learn in their training that appendicitis is a possible lethal condition for which surgery is needed. Most patients are not familiar with antibiotic treatment for uncomplicated appendicitis. But as described in **Chapter 10**, about half of the Dutch population is willing to accept a high risk of recurrent appendicitis. Half of these people would even accept a risk of 50% or higher to avoid surgery. Therefore, patients suspected of uncomplicated appendicitis should at least be involved in the decision whether or not to perform surgery.

Antibiotics vs placebo

Yet, antibiotic treatment for uncomplicated appendicitis may not be the end of the line. Two RCTs thus far have compared treatment with antibiotics versus placebo in patients with suspected uncomplicated appendicitis.[19, 20] Both studies have found no statistically significant differences in treatment failure.

However, both studies included only a small number of patients. More data are needed to reveal the true efficacy of conservative treatment without antibiotics for uncomplicated appendicitis.

Optimalisation of conservative treatment

In antibiotic treatment for suspected uncomplicated appendicitis, many questions are still unanswered. The type of antibiotics, the duration and way of administration are different in all RCTs. In the APPAC II study, treatment with oral versus intravenous antibiotics is compared. The study goal was to demonstrate non-inferiority for treatment success with oral antibiotics, however, this was not achieved. Both treatments did reach treatment success rates greater than 65%.

Disadvantages

Although maybe minor, the antibiotic treatment also has disadvantages. Antibiotics may lead to allergic reactions, and in the long term to antimicrobial resistance. Besides that, patients may experience discomfort complaints because of side effects such as diarrhoea, nausea and vomiting. Another disadvantage of not operating is the chance of missing appendicular neoplasms. A study including 21,069 appendicular specimens of patients under 50 years old with uncomplicated appendicitis, detected cancer in 0.9%.[21] In the APPAC study, an RCT comparing antibiotics treatment with surgery, cancer was diagnosed in 4 out of 272 (0.1%) participants undergoing surgery. In the five year follow-up, no patients in the antibiotic arm were detected to have cancer. However, the chance of missing cancer in patients with suspected uncomplicated appendicitis does raise questions about the follow-up after non-surgical treatment and how to treat elderly patients with uncomplicated appendicitis who may have a higher risk of appendiceal cancer.[21]

Where do we go from here?

In the next few years, research on acute appendicitis should focus on the following topics. First of all, RCTs exploring conservative treatment versus appendectomy for suspected uncomplicated appendicitis have answer the question which patients respond well to conservative treatment and which patients do not. Combing data from existing RCTs in an Individual Patient Data Meta-Analysis (IPDMA) is a good start. These data may reveal the true efficacy and safety of conservative treatment and criteria about which patient should receive which treatment. Next, the conservative treatment itself should be optimised, for example duration of antibiotic treatment and route of administration (oral or intravenous). Finally, the need for follow-up of patients treated conservatively should be clarified; it is not clear whether follow-up is needed for a small risk of missing appendiceal cancer which may become symptomatic later on. Long term data on RCTs investigating conservative versus antibiotic treatment can assist in this respect, and would be presented best in an IPDMA.

Furthermore, we can learn much from a patient preference study in uncomplicated appendicitis. In such a study, patients can choose the treatment of their preference and are treated accordingly in their respective study arm. When the patient has no preference for a specific treatment, they will be randomised in an extra non-surgical study arm and an extra surgical arm. This type of study increases the validity and generalisability compared with RCTs without a patient preference design. The next step would be to implement the optimal treatment or equivalent treatment options into clinical practice. The guidelines already state that conservative treatment may be considered in patients with suspected uncomplicated appendicitis. However, this is not common practice in The Netherlands. There should be more education for surgeons about conservative treatment for surgeons. In addition, a proper way of presenting data for shared decision making needs to be developed to enable patients to make a well-informed choice.

Next to clinical research, research about the etiology of appendicitis should be performed. The appendix as a safe house for microbiome of the intestine and the role of the microbiome in both complicated and uncomplicated is to be explored. Furthermore, a search for new biomarkers or new imaging settings (such as specific additional CT or MRI protocols) capable of discriminating complicated and uncomplicated appendicitis is an important step forward. Currently, there is no biomarker with both high sensitivity and specificity.

Conclusions

Nonoperative treatment for suspected uncomplicated appendicitis will most likely become more common. However, many questions remain about its etiology, how to optimise accurate patient selection, details of the treatment itself, and the need for follow-up relative to age.

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- Surgical Infectious Society, 06-2018, Athene
  Timing for appendectomy; is longer time to surgery associated with more complications in patients with complicated appendicitis?
- Wetenschapssymposium Tergooi, 01-2019, Hilversum
  Circadian rhythm in both complicated and uncomplicated appendicitis; is delay for surgery really that safe?
- Surgical Infectious Society, 06-2019, Dublin
  Circadian rhythm in both complicated and uncomplicated appendicitis; is delay for surgery really that safe?
- Chirurgendagen, 05-2019, Veldhoven
  Update richtlijn acute appendicitis
- Symposium Werkgroep Coloproctologie Midden Nederland, 07-2019, Bosch en Duin
  Complexiteit van simpele en complexe appendicitis
- Refereeravond Regio II, Tergooi, 11-2019, Hilversum
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List of publications related to this thesis

Bom, W. J., M. D. Bolmers, S. L. Gans, C. C. van Rossem, A. A. W. van Geloven, P. M. M. Bossuyt, J. Stoker, and M. A. Boermeester. "Discriminating Complicated from Uncomplicated Appendicitis by Ultrasound Imaging, Computed Tomography or Magnetic Resonance Imaging: Systematic Review and Meta-Analysis of Diagnostic Accuracy." *BJS Open* 5, no. 2 (Mar 5 2021). https://dx.doi.org/10.1093/bjsopen/zraa030.

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About the author

Wouter Jaap Bom was born on 15 September 1990 in Eindhoven, the Netherlands. After six years of living in Eindhoven, Leusden and Wezep, he moved to Hattem. Hattem is a Hanzestad and its inhabitants are known to be proud to live there. After finishing high school at the Gymnasium Celeanum in Zwolle in 2008, he moved to Amsterdam to study medicine at the 'Vrije Universiteit'. He graduated in 2015 and started working at Tergooi MC as a non-training resident in surgery. In 2016, he transferred to the Academic Medical Centre in Amsterdam as a non-training resident in surgery and in 2017 he commenced his research at the Department of Surgery. His thesis was under the supervision of promotor prof. dr. M.A. Boermeester and co-supervisors dr. A.A.W. van Geloven and dr. S.L. Gans. Firstly, he coordinated the EPOCH trial for two years. In this period, he applied for the MLDS grant 'slimme en snelle diagnostiek' with the SAS trial. With this grant, Jochem Scheijmans was hired to become the study coordinator of the SAS trial. In the last, and third, year of Bom's period as a full-time researcher, he was paid by the scientific institute of Tergooi MC to focus on appendicitis mainly. In the final stage of his research in 2020, he worked for 6 months as a non-training resident in surgery at the Flevoziekenhuis, in Almere. He started as a surgical trainee at the University of Amsterdam in 2021 and has returned at Tergooi MC under the supervision of dr. A.A.W. van Geloven, where he has worked with great enthusiasm until now.

Besides his PhD thesis, he conducted research concerning radio frequency ablation in benign thyroid nodules under the guidance of the endocrinologist dr. H. de Boer, which has resulted in two scientific publications.

In his spare time, he enjoys spending time on his skies, ice skates, kitesurf board or racing bike. In addition, he enjoys experiencing adventures with his friends; during the weekend in Amsterdam, and during a holiday abroad.