

**APPENDICITIS IN CHILDREN: NEW INSIGHTS INTO AN
OLD PROBLEM.**

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PART I: CURRENT PRACTICE

Chapter 2.

Laparoscopic appendectomy: State of the art. Tailored approach to the application of laparoscopic appendectomy

Gorter RR, Heij HA, Eker HH, Kazemier G.

Best Pract Res Clin Gastroenterol 2014;28:211-224

Abstract

Acute appendicitis is the most common surgical emergency in developed countries. The treatment of acute appendicitis is either open or laparoscopic appendectomy. The latter has gained widely acceptance in the past years, although the debate on the true merits of laparoscopic appendectomy is still on going. Some authors prefer this approach as the gold standard for all cases, but in our opinion a tailored approach is warranted for specific patient groups. In addition, a standardised guideline on the technical aspects is still lacking. In the current article, open versus laparoscopic appendectomy and several technical aspects, such as stump closure, appendix extraction and single incision laparoscopic appendectomy are being addressed. In the future perspectives we will briefly discuss the third “newly” introduced antibiotic treatment.

Chapter 3.

The impact of disease severity, age and surgical approach on the outcome of acute appendicitis in children

*Van den Boom AL, Gorter RR, van Haard PM, Doornebosch PG, Heij HA, Dawson I
Pediatr Surg Int 2015;31:339-345*

ABSTRACT

Purpose: Although a national guideline has been implemented, the optimal approach for appendectomy in children remains subject of debate in the Netherlands. Opponents of laparoscopy raise their concerns regarding its use in complex appendicitis as it is reported to be associated with an increased incidence of intra-abdominal abscesses. The aim of this study was to evaluate the outcome of surgical approaches in both simple and complex appendicitis in paediatric patients.

Methods: A 10-year retrospective cohort study was performed (2001-2010) in paediatric patients treated for suspected acute appendicitis. Patients were divided into either simple or complex appendicitis and into different age groups. Primary outcome parameters were complication rate (intra-abdominal abscess (IAA), superficial surgical site infection (SSI) and re-admission) and hospital stay.

Results: In total, 878 patients have been treated (median age 12, range 0-17 years). Two-thirds of the patients younger than 6 years had complex appendicitis, compared to one quarter in the group aged 13-18. In the complex appendicitis group, LA was associated with more IAA and early readmissions. In the simple appendicitis group, the complication rate was comparable between the two approaches. Significantly more IAAs were seen after LA in the youngest age group.

Conclusion: This study demonstrates the unfavourable outcome of LA in the youngest age group and in patients with complex appendicitis. Therefore we advise to treat these patients with an open approach.

Chapter 4

Diagnosis and management of acute appendicitis. EAES consensus development conference 2015

Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, Antoniou SA, Arolfo S, Babic B, Boni L, Bruntink M, van Dam DA, Defoort B, Deijen CL, DeLacy FB, Go PM, Harmsen AM, van den Helder RS, Iordache F, Ket JC, Muysoms FE, Ozmen MM, Papoulas M, Rhodes M, Straatman J, Tenhagen M, Turrado V, Vereczkei A, Vilallonga R, Deelder JD, Bonjer J.

Surg Endosc 2016;30:4668-4690

Abstract

Introduction: Unequivocal international guidelines regarding the diagnosis and management of patients with acute appendicitis are lacking. The aim of the consensus meeting 2015 of the EAES was to generate a European guideline based on best available evidence and expert opinions of a panel of EAES members.

Methods: After a systematic review of the literature by an international group of surgical research fellows, an expert panel with extensive clinical experience in the management of appendicitis discussed statements and recommendations. Statements and recommendations with more than 70% agreement by the experts were selected for a web survey and the consensus meeting of the EAES in Bucharest in June 2015. EAES Members and attendees at the EAES meeting in Bucharest could vote on these statements and recommendations. In the case of more than 70% agreement, the statement or recommendation was defined as supported by the scientific community. Results from both the web survey and the consensus meeting in Bucharest are presented as percentages.

Results: In total 46 statements and recommendations were selected for the web survey and consensus meeting. More than 232 members and attendees voted on them. In 41 of 46 statements and recommendations more than 70% agreement was reached. All 46 statements and recommendations are presented in this paper. They comprise topics regarding the diagnostic work-up, treatment indications, procedural aspects and postoperative care.

Conclusion: The consensus meeting produced 46 statements and recommendations on the diagnostic work-up and management of appendicitis. The majority of the EAES members supported these statements. These consensus proceedings provide additional guidance to surgeons and surgical residents providing care to patients with appendicitis.

**PART 2: NOVEL INSIGHTS;
SIMPLE VERSUS COMPLEX APPENDICITIS**

Chapter 5.

A scoring system to predict the severity of appendicitis in children

Gorter RR, van den Boom AL, Heij HA, Kneepkens CM, Hulsker CC, Tenhagen M, Dawson I, van der Lee JH.

J Surg Res 2016;200:452-459

Abstract

Background: It appears that two forms of appendicitis exist. Preoperative distinction between the two is essential to optimise treatment outcome. This study aims to develop a scoring system to accurately determine the severity of appendicitis in children.

Materials and Methods: Historical cohort study of paediatric patients (aged 0-17 years old) with appendicitis treated between January 2010 and December 2012. Division into simple, complex appendicitis or another condition based on pre-set criteria. Multiple logistic regression analysis was used to build the prediction model with subsequent validation.

Results: There were 64 patients with simple and 66 with complex appendicitis. Five variables explained 64% of the variation. Independent validation of the derived prediction model in a second cohort (55 simple and 10 complex appendicitis patients) demonstrated 90 [54-99] % sensitivity, 91 [79-97] % specificity, a PPV of 64 [36-86] % and a NPV of 98 [88-100] %. The LR + was 10 [4.19-23.42] and LR- was 0.11 [0.02-0.71]. Diagnostic accuracy was 91 [84-98] %.

Conclusions: Our scoring system consisting of five variables can be used to exclude complex appendicitis in clinical practice if the score is < 4.

Chapter 6

Composition of the cellular infiltrate in patients with simple and complex appendicitis
Gorter RR, Wassenaar E, de Boer OJ, Bakx R, Roelofs JJTH, Bunders MJ, van Heurn LWE, Heij HA.

Revised Version Submitted: Under editorial revision at J Surg Res

Abstract

Background: It is now well established that there are two types of appendicitis: simple (non perforating) and complex (perforating). This study evaluates differences in the composition of the immune cellular infiltrate in children with simple and complex appendicitis.

Materials and Methods: 47 consecutive children undergoing appendectomy for acute appendicitis between January 2011 and December 2012 were included. Intra-operative criteria were used to identify patients with either simple or complex appendicitis and were confirmed histopathologically. Immune histochemical techniques were used to identify immune cell markers in the appendiceal specimens. Digital imaging analysis was performed using Image J.

Results: In the specimens of patients with complex appendicitis significantly more myeloperoxidase (MPO) positive cells (neutrophils) (8.7% vs. 1.2% $p < 0.001$), were detected compared to patients with a simple appendicitis. In contrast, fewer CD8+ T cells (0.4% vs. 1.3% $p = 0.016$), CD20+ cells (2.9% vs. 9.0% $p = 0.027$) and CD21+ cells (0.2% vs. 0.6% $p = 0.028$) were present in tissue from patients with complex compared to simple appendicitis.

Conclusions: The increase in pro-inflammatory innate cells and decrease of adaptive cells in patients with complex appendicitis suggests potential aggravating processes in complex appendicitis. Further research into the underlying mechanisms may identify novel biomarkers to be able to differentiate simple and complex appendicitis.

**PART III: NOVEL INSIGHTS;
TREATMENT OPTIONS**

Chapter 7

Initial antibiotic treatment for acute simple appendicitis in children is safe: Short term results from a multicenter prospective cohort study
*Gorter RR, van der Lee JH, Cense HA, Kneepkens CMF, Wijnen MHW, in 't Hof KH, Offringa M, Heij HA; APAC study group
Surgery 2015;157:916-923*

Abstract

Background: Initial antibiotic treatment for acute appendicitis has been shown to be safe in adults; so far not much is known about the safety and efficacy of this treatment in children. The aims of this study were to investigate the feasibility of an RCT evaluating initial antibiotic treatment for acute appendectomy in children with acute simple appendicitis and to evaluate the safety of this approach.

Methods: In a multi-centre prospective cohort study patients aged 7-17 years with a radiologically confirmed simple appendicitis were eligible. Intravenous (IV) antibiotics (amoxicillin/clavulanic acid 250/25 mg/kg 4 times daily; maximum 6000/600mg per day and gentamicin 7 mg/kg once daily) were administered for 48 to 72 hours. Clinical re-evaluation at every six hours, daily blood samples and ultrasound follow up after 48 hours was performed. In case of improvement after 48 hours, oral antibiotics were given for in total 7 days. At anytime in case of clinical deterioration or non-improvement after 72 hours, an appendectomy could be performed. Follow-up until 8 weeks after discharge. Adverse event were defined as major complications of antibiotic treatment, e.g. allergic reactions, perforated appendicitis and recurrent appendicitis.

Results: Of 44 eligible patients, 25 participated (inclusion rate 57%, 95% CI: 42-70%). Delayed appendectomy was performed in two, while the other 23 were without symptoms at the 8 weeks follow-up. Minor complications occurred in three patients. None of the patients suffered from an adverse event, or a recurrent appendicitis.

Conclusion: Our study shows that an RCT comparing initial antibiotic treatment strategy with urgent appendectomy is feasible in children; the intervention appears safe.

Chapter 8

Long-term outcome of initial non-operative treatment strategy and immediate appendectomy for acute simple appendicitis in children

Gorter RR, van der Lee JH, Heijsters FACJ, Cense HA, Bakx R, Kneepkens CMF, Wijnen MHW, van der Steeg AFW, in 't Hof KH, Offringa M, Heij HA; APAC study group

Submitted: Arch Dis Child

Abstract

Background: The long-term outcome of initially non-operative treatment for simple appendicitis in children is unknown. We aimed to compare the long-term outcome of initially non-operative treatment with immediate appendectomy.

Methods: Between September 2012 and June 2014 children aged 7-17 years with a radiologically confirmed simple appendicitis were invited to participate in a multicentre prospective cohort study in which they were treated with an initially non-operative treatment strategy consisting of administration of antibiotics, analgesics and clinical observation for 48 hours; non-participants underwent immediate appendectomy. In October 2015, their rates of complications and subsequent appendectomies, and health-related quality of life (HRQOL) were assessed for all children through a telephone interview, HRQOL questionnaire, and review of the medical charts.

Results: Overall, 44 children were included, of whom 25 were treated with an initially non-operative treatment strategy and 19 with immediate appendectomy; median (range) follow-up was 25 (16-36) and 26 (17-34) months, respectively. The percentage of patients (95%CI) experiencing complications in the initially non-operative group and the immediate appendectomy group was 12 (95% CI 4–30)% and 11 (3–31)%, respectively. At 25 months, appendectomy was shown to be avoided in 19 of the 25 children (76%); none of the 6 patients operated subsequently experienced any post-appendectomy complications after delayed appendectomy. Response rate for the HRQOL in the non-operative treatment group and the appendectomy group was 68% and 21%, respectively. Overall, HRQOL in the non-operative treatment group was similar to that of healthy peers.

Conclusions: Long-term outcome of initially non-operative treatment for acute simple appendicitis in children is favourable and similar to the outcome in those who undergo immediate appendectomy.

Chapter 9

Unexpected findings after surgery for suspected appendicitis rarely change treatment in paediatric patients; results cohort study

Gorter RR, van Amstel P, van der Lee JH, Voorn P, Bakx R, Heij HA

Revised Version Submitted: Under editorial revision at J Pediatr Surg

Abstract

Background: To determine if non-operative treatment is safe in children with acute appendicitis, we evaluated the incidence of unexpected findings after an appendectomy in children, and the influence they have on subsequent treatment.

Methods: A historical cohort study was performed including children, aged 0-17 years, who underwent an appendectomy for the suspicion of acute appendicitis. Patients were divided based upon histopathological examination. Unexpected findings were reviewed, as well as the subsequent treatment plan.

Results: In total 484 patients, treated between January 2004 and December 2014, were included in this study. In the overall group, unexpected findings were noted in 10 (2.1%) patients in the overall group of which two patients intra-operatively with a non-inflamed appendix (Ileitis terminalis N=1 and Ovarian torsion N=1) and in 8 patients on histopathological examination. They consisted of 4 patients with concomitant simple appendicitis (Parasitic infection N=3 and Walthard cell rest N=1), two with concomitant complex appendicitis (Carcinoid N=1 and Parasitic infection N=1) and two patients with a non-inflamed appendix (Endometriosis N=1 and Parasitic infection N=1). Treatment was changed in 4 patients (<1%).

Conclusions: Results from this study corroborate the safety of non-operative strategy for acute simple appendicitis, as the occurrence of unexpected findings was low, with extremely few necessary changes of the treatment plan due to serious findings.

Chapter 10

Systematic review of initial non-operative versus operative treatment for acute uncomplicated (simple) appendicitis in children.

Gorter RR, The SML, Gorter-Stam MAW, Eker HH, Bakx R, van der Lee JH, Heij HA

Submitted: J Pediatr Surg

Abstract

Background: To compare the risk of complications between initial non-operative treatment and appendectomy of uncomplicated (simple) appendicitis in children.

Methods: Systematic literature search. Eligible for inclusion were (non-) randomized controlled trials and cohort studies including children in which the outcome of non-operative treatment of uncomplicated appendicitis was reported with a minimum follow-up period of one year. Two authors extracted data independently and assessed quality. Primary outcome parameter was the percentage of children experiencing complications. Secondary outcomes were early failures, recurrent appendicitis and appendectomies, for all indications and on request.

Results: Five of the 1907 articles screened were eligible for inclusion, including 147 children (non-operative treatment) and 173 children (appendectomy) with one year follow-up. Percentage of children experiencing complications ranged from 0–13% versus 0- 17% for non-operative and appendectomy, respectively. Non-operative treatment avoided an appendectomy in 62-81% of the children after one year follow-up.

Conclusion: The evidence base for initial non-operative treatment of acute uncomplicated appendicitis in children is by far insufficient. It suggests that the percentage of patients experiencing complications in the initial non-operative treatment group is comparable to the appendectomy group, and it may avoid an appendectomy in the large majority of children after one year follow-up.

SUMMARY

The main aim of this thesis is to evaluate the short – and long-term outcome of non-operative treatment strategy for children with simple appendicitis.

Part 1: Current practice

Till date, appendectomy is the gold standard of choice for treating patients (both adults and children) with acute appendicitis. In chapter two, a comprehensive systematic review discusses some key elements regarding appendectomy. Specific attention is made for the role of laparoscopic appendectomy in managing children with acute simple appendicitis. It was concluded that based upon the available literature definitive conclusions regarding the preferred approach are hard to make. To investigate the outcome of appendectomy in children with simple and complex appendicitis, a retrospective analysis was performed in 878 consecutive children over a ten-year time period. (CHAPTER 3) Children were divided according to disease severity (simple and complex appendicitis). In this study, we noted an intra-abdominal abscess rate (IAA) of 2.6% (7/265), superficial site infection (SSI) rate of 3.4% (9/265) and early readmission rate of 3.4% (9/265) for children with simple appendicitis that underwent an open approach. In those who underwent the laparoscopic approach, an IAA rate of 1.8% (6/333), SSI rate of 1.5%(5/333) and early readmission rate of 2.4% was noted. There were no statistical differences regarding these outcomes in the children with simple appendicitis. Lastly, the newly published consensus guideline on the diagnosis and management of acute appendicitis of the European Association of Endoscopic Surgery (EAES) is discussed (CHAPTER 4). Statements and recommendation were formulated based upon a systematic review of the current literature by a team of experts and research fellows, following the Delphi method for reaching consensus. These 46 statements and recommendations were then discussed during the EAES conference in Bucharest in June 2015 and during a web survey. Laparoscopic appendectomy as the treatment of choice for acute simple appendicitis in children reached the benchmark of 70% agreement. Non-operative treatment of simple appendicitis in adults is not suggested due to lacking of high quality evidence at that time.

Part 2 Novel insights: Simple versus Complex appendicitis

As two types of appendicitis exist, it is key to differentiate these two types of appendicitis based upon clinical symptoms, laboratory and radiological findings in order to select those patients that might benefit from non-operative treatment (i.e. those with simple appendicitis). In CHAPTER 5, a multiple logistic regression analysis was performed on 64 children with simple appendicitis and 66 children with complex appendicitis. Five variables explained 64% of the variance and were put into our scoring system. An optimal cut-off value was established at < 4 . This scoring system was subsequently validated in a second cohort. Positive and negative likelihood ratio of 10 (4.19-23.42) and 0.11 (0.02-0.71) respectively were demonstrated. Based upon these results, it was concluded that this scoring system could be used to exclude complex appendicitis in clinical practice if the score is < 4 . Differences between simple and complex appendicitis not only exist in clinical presentation, but also in the composition of the cellular infiltrate in the inflamed appendix. Histopathological samples from 24 children with complex appendicitis and 23 children with simple appendicitis were analyzed, after immune histochemical staining, using Image J software. We found that the cellular infiltrate in children with complex appendicitis contains significantly more MPO+ cells (neutrophils) and significantly fewer CD20+/CD21+ cells (B-lymphocytes) and CD8+ T cells in comparison to children with simple appendicitis. These findings suggest that simple and complex appendicitis are characterized by a unique immune mononuclear cellular infiltrate in the appendix and might reflect a difference in immune response.

Part 3 Novel insights: Treatment options

Short- and long-term results from initial non-operative treatment strategy for acute simple appendicitis in children is discussed. (CHAPTER 7 & 8) Between September 2012 and June 2014, a prospective non-randomized, multicenter cohort study was performed; including children aged 7-17 years old with a radiological confirmed simple appendicitis. Of 44 eligible patients, 25 participated and were treated with non-operative treatment strategy (inclusion rate 57%, 95% CI: 42-70%). Delayed appendectomy was performed in two, while the other 23 were without symptoms at the 8 weeks follow-up. (CHAPTER 7) In October 2015, these 25 children were compared to the 19 patients who did not want to participate and thus underwent an immediate appendectomy. Follow-up period in both cohorts was 25 (16-36) and 26 (17-34) months, respectively. The percentage of patients (95%CI) experiencing complications in the non-operative group and the immediate appendectomy group was 12 (95% CI 4–30)% and 11 (3–31)%, respectively. At 25 months, appendectomy was avoided in 19 of the 25 children (76%). (CHAPTER 8) A

potential disadvantage of non-operative treatment is the fact that other types of pathology such as a malignancy when no operation and subsequent histological examination can be missed. A retrospective study in 484 children (241 with simple appendicitis, 222 with complex appendicitis and 21 with a non-inflamed appendix) showed that the overall occurrence of unexpected finding was 1.7% in the overall group. (CHAPTER 9) In more detail, unexpected findings during histopathological examination were noted in 4 (1.6%) patients with simple appendicitis, 2 (1.0%) patients with complex appendicitis and 2 (9.6%) patients with a non-inflamed appendix. Unexpected findings during surgery were noted in two patients with a non-inflamed appendix (ovarian torsion and extensive inflammation of the terminal ileum). Of the ten patients with unexpected findings, only 4 required alteration in treatment.

Lastly, the current available evidence regarding the outcome of initial non-operative treatment strategy is discussed in CHAPTER 10. A systematic review of the literature, identified 5 studies performed in children, including 147 children (non-operative treatment) and 173 children (appendectomy) with one-year follow-up. Percentage of children experiencing complications ranged from 0–13% versus 0–17% for non-operative and appendectomy, respectively. Non-operative treatment avoided an appendectomy in 62–81% of the children after one-year follow-up. Although the evidence base for initial non-operative treatment of acute uncomplicated appendicitis in children is by far insufficient, it suggests that the percentage of patients experiencing complications in the initial non-operative treatment group is comparable to the appendectomy group. In addition, it may avoid an appendectomy in the large majority of children after one-year follow-up.