

General discussion and future perspectives

The main aim of this thesis is to investigate the outcome of non-operative treatment strategy for children with simple appendicitis.

Appendectomy as the standard treatment was introduced in the USA around 1890 and was based on the fear of missing complicated appendicitis.¹ This fear led to a treatment strategy, comparable to Odysseus when negotiating the Scylla and Charybdis: it was generally accepted to remove a significant number of healthy appendices in order to prevent leaving one gangrenous or perforated appendix in situ. This evolved before the advent of antibiotics and reliable imaging methods and was transferred from one generation of surgeons to the next without questioning its rationale. In view of the success of appendectomy as an effective and relatively safe procedure, there was little tendency to question or evaluate this approach. Another reason why it received so little attention is its place in the training of future surgeons. It is usually the first intra-abdominal operation performed by trainees, and as such has an important function in surgical training. The interest for non-operative treatment strategy in specific situations (at sea, or in the Antarctic) remained.² Nowadays with the availability of antibiotics, the development of ever improving imaging modalities and refinement of markers to monitor patients' clinical status the role of both strategies needs to be readdressed.

In order to perform a thorough analysis, an outline of the current practice as state of the art is presented in part one of this thesis, focusing on the complications of open and laparoscopic appendectomy. Two major complications of appendectomies are intra-abdominal abscess (IAA) and superficial site infection (SSI). An IAA rate of 2.6% and 1.8% and SSI rate of 3.4% and 1.5%, respectively, were found for an open and laparoscopic appendectomy in children with simple appendicitis in a historical cohort study described in chapter 3. This is comparable to data shown in the literature.^{3,4} Overall complication rates (including, but not limited to SSI, IAA, readmission, reoperations and secondary bowel obstructions), however, are much higher and range up to 15%.^{3,4} Main advantage of non-operative treatment strategy is the fact that it helps to avoid an appendectomy and its potential postappendectomy complications in 62-81% of the children at one year follow-up.⁵⁻⁹

In the second part of this thesis, the differences between simple and complicated appendicitis are studied, both from a clinical (preoperative) and histological (pathology) perspective (chapters 5 and 6, respectively). Preoperative variables appear to differ between children with simple and complex appendicitis. In general, children with complex appendicitis tend to have more systemic signs of inflammation at time of presentation. Our clinical prediction study identified five preoperative variables (more than one day of abdominal pain, body temperature

of more than 37.5 degrees Celsius, CRP level of more than 38 mg/L, variables on ultrasound suggestive for complex appendicitis and diffuse abdominal guarding). Several preoperative variables have been identified in the literature as well to distinguish simple from complex appendicitis, although results of various clinical prediction studies are inconsistent.¹⁰⁻¹³ Our results from the analyses of the cellular infiltrate of the inflamed appendix in children with simple and complex appendicitis reflect the clinical differences. In the appendices of children with complex appendicitis, more MPO+ cells (neutrophils) and significantly less CD20+/CD21+ cells (B-lymphocytes) and CD8+ cells (T-lymphocytes) were found in comparison to those of children with simple appendicitis. This suggests that pathways triggering innate immune responses and reducing potential regulating responses by adaptive immune cells may play an important role in the pathogenesis of complex appendicitis. This is supported by results of increased serum levels of Th17 polarizing cytokine IL-6 and IL-1b and elevated levels of IL-17 in patients with complex appendicitis, reflecting a Th17-immune response in these patients.^{14,15} It confirms the concept that simple and complicated appendicitis are two different disease entities, with a distinctive immune phenotype, and offering the opportunity to apply differentiated treatment strategies.

Based upon the data shown in chapters 7 and 8, we conclude that non-operative treatment strategy has a favourable short-term outcome, avoiding an appendectomy in 92% of the patients (chapter 7). At long-term follow-up (median of 2 years), it has a complication rate comparable to the immediate appendectomy strategy and is still able to avoid an appendectomy in 76% of the children (chapter 8). The argument raised by opponents of this strategy that there is chance of missing potentially harmful underlying pathologies, especially carcinoid, with this strategy seems not to be supported. In our study, we only found a carcinoid in one (0.2%) of the 484 patients that underwent an appendectomy. This patient did not fulfill the criteria for non-operative treatment strategy and in this era we would not offer him this strategy (chapter 9). Evidence about the outcome of initial non-operative treatment for acute simple appendicitis in children in the literature is far from sufficient as shown in chapter 10. It is therefore necessary to confirm these conclusions in future large studies.

Definitive conclusions regarding the benefit of non-operative treatment strategy on the long term with respect to avoidance of appendectomy cannot be drawn at this point. In the paediatric population the level of evidence is low due to the lack of prospective randomised trials. In addition, most cohort studies only report the outcome at one year follow-up.⁵⁻⁹ In this thesis, outcomes with a median follow-up of two years show that in 76% of the children an appendectomy was avoided, which is in line with the mentioned 62-81% in the current available literature.⁵⁻⁹ It is essential to investigate this outcome again after 5 and 10 years. It is imaginable that a proportion of the children develops recurrent disease. If this is the case,

the debate regarding the benefit of avoidance of appendectomy with non-operative treatment strategy may change.

When comparing operative and non-operative treatment there is a risk of comparing apples and oranges. Appendectomy is highly effective in that it results in the definitive elimination of the organ that causes the problem. Non-operative treatment alone will therefore always be less effective, even if only a small minority will develop recurrent appendicitis. The comparison therefore has to be on a non-inferiority basis and concentrate on the risk of complications of each treatment strategy. In the adult population, non-operative treatment reduced the risk of complications by 31-48%.¹⁶⁻¹⁹ In the paediatric population, not much is known about this potential benefit. In our systematic review (chapter 10), we found that the occurrence of complications was comparable, ranging from 0-13% and 0-17% for non-operative treatment and immediate appendectomy, respectively.⁵⁻⁹ The fact that in some studies a complication rate of 0% is reported for both treatments raises doubts since larger studies have demonstrated that both are associated with potential complications.³⁻⁹ In this thesis we have not studied secondary outcomes of non-operative treatment strategy like pain, costs and health-related quality of life, because the main aim of our prospective cohort study was to evaluate the safety of the non-operative treatment strategy in terms of complications and delayed appendectomies.⁵⁻⁹ Future studies should focus on investigating the long-term outcome at 5 to 10 year follow-up with incorporation of other secondary outcomes to produce solid evidence regarding the advantages and disadvantages of non-operative treatment strategy.

Opponents of non-operative treatment strategies raise several concerns. First is the relative high rate (19-38%) of appendectomy after initial non-operative treatment,⁵⁻⁹ which leads them to conclude that non-operative treatment is less effective than appendectomy. In our opinion, non-operative treatment strategy consists of initially non-operative treatment (i.e. antibiotics) reserving an appendectomy for those not responding or with recurrent disease. Therefore with both strategies all patients will eventually be cured from their appendicitis. This can either be done with surgery (as all patients will undergo in the appendectomy strategy) or with non-operative treatment initially and surgery only in selected patients, thus avoiding surgery and its potential postappendectomy complications. In this view, a delayed appendectomy should not be considered as a failure. It is part of the treatment strategy for selected patients.

Three main indications to perform a delayed appendectomy are mentioned in the literature: a lack of response to non-operative treatment during clinical phase, recurrent appendicitis, and the so-called interval appendectomy.⁵⁻⁹ The latter consists of an appendectomy either offered by the doctor or on parents' request although there is no suspicion of recurrent appendicitis. It is questionable whether these interval appendectomies are medically indicated. Perhaps

in the future, as more and more evidence becomes available, this number will decrease. Future studies should focus on the characteristics of patients who (a) do not respond to the administered antibiotics and (b) develop recurrent appendicitis. If parameters can be identified for more accurate selection of patients that benefit from non-operative treatment, the number of delayed appendectomies can be further reduced.

Another concern raised by the opponents is the old fear of missing a complex appendicitis (with its consequent morbidity if appendectomy is delayed). In our cohort study (chapter 7 & 8), none of the 25 patients in the non-operative treatment group suffered from complex appendicitis. Also in the group of 6 patients who underwent a delayed appendectomy none had complex appendicitis. In the immediate appendectomy group, surprisingly, in 4 of the 19 patients complex appendicitis was noted during surgery, despite the fact that they fulfilled the criteria for non-operative treatment strategy. It is not standard policy to treat patients with a perforated appendicitis with non-operative treatment strategy. Moreover, in case of perforated appendicitis, the general idea is that the patient will not improve with antibiotics, but his clinical condition might deteriorate if appendectomy is delayed. It is therefore essential to accurately distinguish simple from complex appendicitis. To facilitate this, prediction models have been developed, but they have limited applicability in the Netherlands.¹¹⁻¹³ This is due to the fact that most prediction models do not include results from imaging studies, which are performed routinely in the Netherlands since the implementation of our national guideline in 2010.²⁰ The imaging study of choice in the Netherlands is an ultrasound.²⁰ CT, which has been incorporated in one clinical prediction model¹¹, is not performed routinely in the Netherlands due to the potential harmful effect of radiation exposure in children.²¹ Ultrasound has been shown to be of value to differentiate simple from complex appendicitis.²² For this reason, findings from ultrasound have been included as a variable in our prediction model (chapter 5). Our prediction model adequately excludes complex appendicitis (as reflected by its negative predictive value of 98%), but it is still not 100% accurate. Nor are the prediction models available in the literature.¹¹⁻¹³ It is therefore essential to identify new biomarkers that are able to distinguish them. As shown by our study (chapter 6), it appears that the cellular infiltrate in the inflamed appendix is different in children with simple and complex appendicitis. Future studies should focus on elucidating the pathogenesis including aetiological factors and immunological responses of simple and complex appendicitis. This might result in identifying new biomarkers that are able to accurately discriminate simple from complex appendicitis in children.

The third concern of opponents of the non-operative strategy is the fact that potential unexpected underlying pathologies, such as a malignancy, might be missed, as the appendix will not be removed and subsequently no histopathological examination is performed. Carcinoid has a reported prevalence below 0.5% in the pediatric population.^{23,24} In our

study, only one of the 484 patients was diagnosed with an unexpected carcinoid (chapter 9). Preoperatively, complex appendicitis was suspected, although preoperative imaging was not performed. This would exclude this patient from non-operative treatment strategy. In the patients eligible for non-operative treatment strategy, relatively benign unexpected findings were noted that required no or minimal alteration in treatment. In our opinion, as the use of preoperative imaging studies will increase, we expect the number of unexpected findings to decrease overtime. Furthermore, in cases of recurrent appendicitis, we would recommend to perform an appendectomy as in rare cases an underlying carcinoid might be causing the (recurrent) appendicitis.

The increasing problem of antibiotic resistance might be the cause why some medical professionals are reluctant to apply this new strategy. We acknowledge the fact that it is important to critically review the indications for antibiotic therapy. We do however want to point out that several factors contribute to the development of appendicitis, but all lead to the common pathway of invasion of the appendix by intraluminal bacteria.²⁵ Antibiotic therapy is therefore indicated. It would be of interest to investigate the exact type of bacteria in simple and complex appendicitis in order to narrow the antibiotics administered. Furthermore, strategies to reduce the risk of antibiotic resistance should be followed.²⁶

The successful surgical treatment of all patients with suspected acute appendicitis has on one hand led to the virtual elimination of mortality due to appendicitis, which is one of the great achievements of modern surgery. On the other hand it has led to unnecessary operations, certainly in patients without appendicitis and, probably, in patients with acute simple appendicitis. Moreover, it has made appendicitis a minor problem from a scientific point of view. Many questions remain regarding the aetiology, the pathophysiology and genetics of appendicitis. In addition to prospective clinical studies, basic research is also needed to elucidate the true nature of appendicitis.

In conclusion, high-level evidence regarding the effectiveness of non-operative treatment strategy for acute simple appendicitis in children is lacking in current literature. Data from this thesis support its safety. Large, well-designed randomised controlled trials are necessary to evaluate the effectiveness compared to the immediate appendectomy strategy in this category of patients. To improve the selection of patients that might benefit from this strategy, additional studies should focus on elucidating the exact pathogenesis of simple and complex appendicitis in children.

References

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