

General introduction & outline

Acute appendicitis is a common gastro-intestinal disease, affecting approximately 1 in 1000 inhabitants of the Netherlands each year.^{1,2} The lifetime risk of acute appendicitis in the Western world is respectively 7% and 9% for females and males.³ Historically, the treatment of acute appendicitis has varied between surgical removal in all (suspected) cases to a more conservative approach with medical treatment in selected cases.⁴ Nowadays, the standard treatment, both in children and adults, is appendectomy.⁵⁻⁷ This is based upon the entrenched idea that appendicitis is an irreversible progressive disease, beginning with localized inflammation of the (sub)mucosa, eventually leading to necrosis and perforation causing generalised peritonitis and even death in some cases. The result is that approximately 15,000 appendectomies are performed in the Netherlands annually, of which about 5500 appendectomies in patients under 20 years of age.² Although highly effective, an appendectomy is associated with a morbidity rate (i.e. superficial site infection (SSI), intra-abdominal abscess (IAA) and secondary bowel obstructions) of up to 15%.^{8,9} Until recently these potential complications and the risk of removing a non-inflamed appendix did not outweigh the risks associated with missing appendicitis and were therefore considered as unavoidable.

Recently, the invariably irreversible and progressive nature of appendicitis became subject of debate.^{10,11} Rather, two types of appendicitis are envisaged: simple appendicitis (uncomplicated or non-perforated) with no tendency to progress, and complex appendicitis (complicated or perforated).^{10,11} This latter group represents a spectrum of disease severity and consists of perforated appendicitis, gangrenous appendicitis, appendicular mass or appendicular abscess. The exact pathogenesis of each type remains unclear, although it is suggested that invasion of the appendix by intraluminal bacteria may play a central role.¹² Reasons why this results in simple appendicitis in one child while the other child develops complex appendicitis need still to be elucidated.

As appendicitis seems not to be considered a progressive disease, the necessity of an appendectomy can be questioned in case of simple appendicitis. Non-operative treatment strategy, consisting of initial antibiotics and reserving an appendectomy for those not responding or with recurrent disease, is an alternative. This idea is not new.⁴ Prior to the introduction of the appendectomy, around 1890, appendicitis was treated in a non-operative manner; consisting of bed rest, high doses of opiates, no oral intake and no laxatives.⁴ Nowadays the non-operative treatment of acute simple appendicitis has gained new attention. In adults, recent randomised controlled trials (RCT) showed that, with initial non-operative treatment strategy, an appendectomy can be avoided in 48-85% of the patients with simple

appendicitis at one-year follow up, without risk of peritonitis.¹³⁻¹⁷ Meta-analyses of these RCTs showed that this treatment strategy led to a reduction in complications of 31-48%.¹⁸⁻²¹

Considering the recent discussion questioning the progressive nature of appendicitis, the significant morbidity rate of an appendectomy, the availability of antibiotics and accurate preoperative imaging studies, one can debate if appendectomy remains the only treatment option for simple appendicitis in children in this era. Promising results from this treatment strategy have been reported from trials in adults, but data regarding the outcome of this strategy in children are scarce.²²⁻²⁶

The main aim of this thesis is to evaluate the short- and long-term outcome, in terms of complications, recurrent appendicitis and delayed appendectomy, of non-operative treatment strategy for children with simple appendicitis. These results are necessary to compare the advantages and disadvantages of the direct appendectomy strategy with those of the initial non-operative strategy.

To assemble sufficient evidence for a substantiated discussion about both treatment strategies, it is essential to investigate several aspects of appendicitis in children. This thesis is divided in three parts. In part one the general aspects and the outcome of appendectomy are discussed. This is essential to adequately outweigh the advantages and disadvantages of non-operative treatment strategy. Each chapter in this part discusses the current practice from a different perspective. In chapter 2, the current practice of (laparoscopic or open) appendectomy in the general population is discussed. Outcome of laparoscopic and open appendectomy in children is displayed in chapter 3. The last chapter (4) in this part describes the recently published consensus guideline on the diagnosis and management of acute appendicitis on behalf of the European Association of Endoscopic Surgery (EAES). Part two of this thesis focuses on the differences between simple and complex appendicitis in children. This is essential in order to select those patients who will benefit from non-operative treatment, i.e. those with simple appendicitis. In chapter 5 preoperative differences between children with simple appendicitis and children with complex appendicitis are investigated in order to develop an accurate scoring system to distinguish simple from complex appendicitis in children preoperatively. Differences in the composition of the cellular infiltrate to formulate a hypothesis regarding the influence of the immune response on the development of simple and complex appendicitis is shown in chapter 6.

Part three encompasses the outcome of the initial non-operative treatment strategy of acute simple appendicitis in children. Both short-term and long-term outcomes of this strategy from a prospective cohort study are discussed (chapters 7 and 8). A disadvantage of initial non-operative treatment strategy is the fact that harmful underlying diseases such as a carcinoid might be missed. We attempted to quantify this risk in a historical cohort study, which is

presented in chapter 9. Finally, chapter 10 describes a systematic overview of the current available evidence of initial non-operative treatment of acute simple appendicitis in children.

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