Acute abdominal pain in children
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Chapter 8.

Discussion and future perspective
Scope of the thesis

Acute abdominal pain is the third leading cause of visits to an emergency department by children under 15 years and is associated with high costs and decreased quality of life [1]. There are various causes of acute abdominal pain and it is important to quickly differentiate between life-threatening and non-life-threatening disorders. The aim of this thesis was to broaden our knowledge on the diagnostic process and treatment of acute appendicitis and constipation, two common causes of abdominal pain in children who are admitted to the emergency department.

Acute appendicitis

Factors influencing the diagnostic process

In order to refine the diagnostic process of acute appendicitis in children presenting with acute abdominal pain, it is important to assess the factors that influence this process. One such factor known to negatively influence the diagnostic process of appendicitis is obesity [2-4]. We found that underweight also has a significant negative influence on the diagnostic accuracy of acute appendicitis. As described in Chapter 2, we studied the influence of body mass on the diagnostic process of acute appendicitis by investigating the accuracy and duration of diagnostic process. We found that underweight children had a three times higher chance of a negative appendectomy than children with a normal weight. This meant that they were at a much higher risk of being falsely diagnosed with appendicitis and of undergoing unnecessary surgery. The risk of a negative appendectomy is known to be influenced by age, sex, and the number and types of diagnostic procedure used [5]. However, even after statistical correction for these acknowledged risk factors, underweight still significantly increased the risk of undergoing a negative appendectomy. Moreover, we found no association between children’s body mass index (BMI) and perforation rate, a measure for a possible delay in the diagnostic process. The number of consultations needed for diagnosis was also not influenced by BMI. In conclusion, underweight seems to be an important risk factor for diagnostic accuracy, but it is not a factor that influences the time needed to
diagnose acute appendicitis in children. Therefore, when examining a child who is underweight, one should be aware of the higher risk of a false positive diagnosis of acute appendicitis. In practice, one could consider using additional diagnostic tools such as an ultrasound scan or a diagnostic laparoscopy prior to a (laparoscopic) appendectomy in underweight children.

Factors influencing the treatment outcome
Outcome after appendectomy can be influenced by various factors, such as the occurrence of an appendix perforation or the type of surgical technique. In Chapter 2 we studied the influence of BMI on treatment outcome measured in terms of postoperative complications and length of hospital stay. The influence of BMI on the complication rate after an appendectomy is still subject of debate. Some studies found an increased complication rate in obese patients after appendectomy [6-8], while others found no difference [9,10]. We found a higher complication rate in obese children compared to those with normal weight. This difference, however, was not significant - possibly due to our small sample of obese children. Underweight children did have a three times higher risk of complications compared to children with normal weight. In addition, on average underweight children needed to remain in the hospital one and a half day longer and obese children half a day longer than children with a normal weight. In conclusion, both underweight and obesity are important risk factors for poor outcome after appendectomy. Acute appendicitis is a surgical emergency. It is therefore not possible to correct a patient’s abnormal body weight prior to surgery. Nevertheless, one can take this risk into account by choosing the best type of surgery for underweight or obese patients, a laparoscopic or open approach. As discussed in Chapter 2, obese children benefit from laparoscopic appendectomy in terms of a shorter hospital stay compared to open appendectomy. Several studies support our finding that laparoscopic appendectomy is preferable in obese patients [7,11,12]. They propose that this benefit is related to a lower rate of wound-related complications [13]. In our study we did not find more complications following open appendectomy than following laparoscopic appendectomy in obese children, possibly due to the small sample of obese children. Furthermore, we did not find any differences in treatment outcome between the different surgical approaches for underweight
or overweight children.

**Possibilities for new treatment**

Appendectomy is still the standard treatment for acute appendicitis in most hospitals even though it is associated with complications. Currently, numerous studies are performed on a more conservative treatment with specific antibiotics, and show a high initial success rate of around 90-95% [14-19]. They, however, did find that not all children with acute appendicitis can be treated successfully with antibiotics only, since the success rate does not reach 100% and the readmission rate ranges from 1-32% after one year [12-17]. To gain more insight into why certain conservative treatments are not beneficial to all patients, more knowledge on the etiology and pathophysiology of acute appendicitis is needed. As mentioned earlier, several viral infections are associated with acute appendicitis, albeit mostly in immune compromised patients [20-22]. Nevertheless, it is unclear whether these viruses play a direct role in the pathogenesis of appendicitis or whether they are already present in the appendix and reactivate in case of acute appendicitis [21-22]. In Chapter 3 we studied if two of the most prevalent viruses in children, cytomegalovirus (CMV) and human herpes virus 6 (HHV-6), are associated with acute appendicitis in immunocompetent children. We did not find CMV DNA in blood or appendix samples of patients with or without acute appendicitis. This indicated that in our study population acute appendicitis was not associated with an active CMV infection as reported by other studies [21,23,24]. Possibly CMV is only associated with acute appendicitis in specific patient populations such as immunocompromised patients. However, the sample size of patients with a possible CMV infection was small, due to a low CMV seroprevalence (i.e. a small number of people had a primary CMV infection in the past). Therefore we cannot rule out a possible association between CMV and acute appendicitis. Furthermore, HHV-6 DNA was detected in the appendices of both children with and without appendicitis, indicating that HHV-6 does not seem to play a role in the development of acute appendicitis, or at least not in all cases. In conclusion, we did not find a clear causal relation between CMV or HHV-6 and acute appendicitis in immunocompetent children. More research is needed to better understand the etiology of acute appendicitis.
Recommendations and future research

In the first part of this thesis, which focuses on acute appendicitis, we showed that underweight was a risk factor for the misdiagnosis of acute appendicitis in children. Therefore, in case of underweight children one should always consider using additional diagnostic tools such as an ultrasound. Moreover, in underweight children, when appendectomy is considered on account of a high suspicion of appendicitis, it is advisable to perform a diagnostic laparoscopy prior to a (laparoscopic) appendectomy. Furthermore, we demonstrated that underweight and obesity were risk factors for poor treatment outcomes after appendectomy, because they were associated with higher complication rates and prolonged hospital stays. Even though it is not possible to correct the body mass index of a child during the brief period before surgery, one should be aware of this risk. In addition, we recommend using laparoscopic appendectomy instead of open appendectomy in obese children, because this technique was associated with better treatment outcomes in these children. Finally, we showed that CMV and HHV-6 did not seem to be associated with acute appendicitis in immunocompetent children. More knowledge on the exact etiology of acute appendicitis is needed to find new treatment options, for example by studying the relation between other viruses or bacteria and acute appendicitis in different patient populations.

Constipation

Current problems regarding diagnostic process of constipation

Constipation is a collective term that describes a certain set of symptoms, such as painful or hard bowel movements, episodes of fecal incontinence, and sometimes abdominal pain, without making a distinction as to the underlying cause. The current diagnostic process for constipation in children with abdominal pain consists of asking various questions, performing a relatively invasive digital examination, or performing imaging studies that lack sensitivity and/or specificity [25-29]. In Chapter 5 we studied current problems at different stages of the diagnostic process of constipation. We found that approximately half of the children with a defecation disorder rated the quality of their bowel
Chapter 8 habits as good or very good, regardless. This confirms that many children do not recognize abnormal bowel habits and are therefore unlikely to seek medical help [30,31]. In addition, the ever-present taboo on discussing bowel habits and defecation disorders amplifies the problem of not seeking medical help for constipation [32]. This large group of constipated children who do not seek help are consequently left untreated for their disorder. Even if children seek medical help, constipation may still be difficult to diagnose due to the variety in symptoms. Merely questioning children about their stool frequency and consistency is insufficient to diagnose or exclude constipation, as we demonstrated that the bowel habits of the majority of constipated children were considered normal. It is therefore important to extend the range of diagnostic questions for constipation, for example by asking about straining, incomplete evacuation, and anorectal blockage [25,28]. Due to the problems with diagnosing constipation, many constipated children are left untreated, which may result in chronic pain. Moreover, if the diagnosis of constipation is missed in children with acute abdominal pain, they may be falsely diagnosed with acute appendicitis, which in turn results in unnecessary surgery [33].

New diagnostic methods for constipation

As explained in Chapter 7, we developed a questionnaire to diagnose defecation disorders such as constipation. The Groningen (Pediatric) Defecation and Fecal Continence questionnaire contains a broad range of questions on constipation, fecal incontinence, and anorectal functioning. Because of its extensive range, the Groningen DeFeC questionnaire is a feasible screening tool for defecation disorders as well as to determine causative factors. Importantly, the questionnaire consists of a pediatric and adult version comprising the same questions and scores. This provides medical specialists and/or general practitioners the possibility to follow-up patients during their transition from childhood to adult life. Some cross-cultural adaptations will be necessary to extend the use of the questionnaire to other countries and further use of the questionnaire is necessary to extend its validation in specific patient populations. In addition, in its current form the questionnaire is too long to be used in emergency departments. Future studies are needed to investigate which questions in the questionnaire are most relevant to diagnose or exclude con-
Discussion and future perspective

In addition, we have developed a different diagnostic approach to constipation in children with acute abdominal pain, by first treating these children as if they suffered constipation (Chapter 4). Because they are both efficient and safe laxatives and/or enemas are the standard treatment for fecal disimpaction in children with constipation [28,34,35]. We hypothesize that a relatively high percentage of children with acute abdominal pain, who have not been diagnosed during the first consultation, are simply constipated, and therefore using laxatives and enemas would lead to rapid reduction of pain. In addition, such pain reduction would provide more certainty about constipation indeed being the cause of the abdominal pain (with the exception of therapy-resistant constipation). It appeared problematic, however, to evaluate our hypothesis on account of the negative attitude of Dutch parents regarding medicine use by their children and resulted in a high rate of refusals (23%) and low medication adherence (37%). Poor medication adherence is a well-known issue, also in the case of chronic constipation, where the rate is approximately 38% during the first month [36]. To increase the power of the study, it would be necessary to set up a larger multicenter investigation, possibly even abroad in a country where parents have a more positive attitude towards the use of medication by their children. Nevertheless, we hope that our diagnostic method will contribute toward improving the diagnostic process of constipation in children with acute abdominal pain. Hopefully, in the future, constipation will be recognized more efficiently in children with acute abdominal pain, resulting in fewer children developing chronic abdominal pain due to chronic constipation [37,38].

Current problems with treatment of constipation

On account of the problems with the diagnostic process of constipation in children efficient treatment is equally problematic. Only a small number of children who suffer from a defecation disorder are actually treated for their symptoms, as is demonstrated in Chapter 6. Laxatives were mostly used in case of constipation. Nevertheless, a significant proportion of people with constipation used their fingers or hand to help pass stool, probably because they did not receive adequate treatment or the treatment was insufficient. Such under-treatment is, among others, due to the low percentage of children...
and their parents who recognize their problem and consequently seek medical help. Besides, not all children may receive complete and adequate treatment for their constipation problems, because it is often assumed that children will outgrow their defecation disorders in adulthood [39,40]. In Chapter 6, however, we demonstrated that the prevalence rate of constipation and occurrence of associated symptoms were not lower in young adults compared to children. In addition, 43% of the constipated children had symptoms for more than five years and 20% of the young adults had suffered from constipation since childhood. Thus, because not all children outgrow their defecation disorders, constipation should be treated as early as possible, as is proposed by other studies [41,42]. Then it might be possible to prevent episodes with abdominal pain in constipated children for which they need to visit the emergency department.

**Recommendations and future research**

In the second part of this thesis, which focuses on constipation, we showed that there are several problems with the diagnostic process of constipation. Firstly, many constipated children and their parents did not recognize the child’s defecation disorder as a problem. In combination with a taboo on discussing defecation, this led to a small percentage of constipated children who sought help for their problems. It is therefore important to provide better education for children and parents on correct toilet postures, bowel habits, and defecation disorders in order to improve recognition and remedy existing taboos. In addition, more attention should be paid to the school environment. In our opinion, fixed times when children are allowed to go to the toilet in combination with unclean toilets may contribute to problems with defecation. Moreover, merely questioning children about defecation patterns is not sufficient to diagnose or exclude constipation, considering that the majority of constipated children had stool frequencies and consistencies that are considered normal. Thus, medical specialists should interview children suspected of constipation more extensively. In future after it has been shortened, the Groningen Pediatric DeFeC may be used for this purpose in emergency departments. Moreover, the diagnostic method of supporting fecal production with laxatives and enemas in children with acute abdominal pain may hopefully contribute to the future diagnostic process of constipation. Finally, we believe that many children are not com-
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cpletely and adequately treated for constipation, because it is often assumed that children outgrow their defecation disorders. We have, however, demonstrated that the prevalence rates and occurrence of associated symptoms of constipation and fecal incontinence were not lower in young adults than in children. Therefore, we recommend treating every child with constipation and/or fecal incontinence as early as possible.

Conclusion

With this thesis we aimed to broaden our knowledge on the diagnostic process and treatment of acute appendicitis and constipation, the two common causes of abdominal pain in children who are admitted to the emergency department. In the first part we demonstrated new risk factors for the diagnosis and treatment of acute appendicitis and offered recommendations on how to adjust these factors in clinical practice. In addition, we explored the etiology of acute appendicitis in more detail to see if we could find new treatment targets. In the second part of this thesis we explored several factors that influence the diagnosis of constipation. In addition, we presented two methods that may in future contribute to optimizing the diagnostic process of constipation in emergency departments. Finally, we recommend treating constipation as early as possible, because prevalence rates of constipation are no lower, nor are associated symptoms fewer, in young adults.

References
