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CLINICAL AND EPIDEMIOLOGICAL STUDY

Lack of benefit of preoperative antimicrobial prophylaxis in children with acute appendicitis: a prospective cohort study

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Abstract
Background Preoperative antimicrobial prophylaxis is widely used in pediatric patients undergoing appendectomy, but evidence showing a reduction of postoperative infectious complications is lacking.
Methods A prospective consecutive cohort study on changing from preoperative antimicrobial prophylaxis to no prophylaxis in children undergoing urgent appendectomy was undertaken. The impact of this change in management on postoperative infectious complications was evaluated by comparing the outcome in 100 patients receiving (group A) and a subsequent 100 patients not receiving prophylaxis (group B), which consisted of a preoperative single dose of intravenous metronidazole (10 mg/kg body weight).
Results Histology confirmed acute appendicitis in 92 patients of group A and 95 patients of group B. In patients with histological simple appendicitis, postoperative infectious complications were noted in 2 (3.0 %) of 69 patients from group A and in none of 70 patients from group B, and in patients with histological perforated appendicitis in 5 (22 %) of 23 and 4 (16 %) of 25 patients from groups A and B, respectively. Postoperative infectious complications were more frequent ($p < 0.05$) in perforated than in simple appendicitis. These infectious complications included in simple appendicitis two wound infections in group A, and in perforated appendicitis four intraabdominal abscesses and one wound infection in group A and two intraabdominal abscesses and two wound infections in group B.
Conclusion Postoperative infectious complications were seen more often in patients with perforated appendicitis than in those with simple appendicitis. Preoperative antimicrobial prophylaxis with metronidazole did not reduce the rates of postoperative infectious complications.

Keywords Appendicitis · Appendectomy · Child · Preoperative antimicrobial prophylaxis

Background

Acute appendicitis is the most common cause of acute abdomen and of emergency abdominal surgery in children. The incidence is age-dependent and increases from 15 per 10^5 children and year in the first 4 years of life to 200 per 10^5 children at the age of 15–16 years. Thus, the peak incidence is reached in the second decade of life [1–4]. The outcome is favorable and death from appendicitis today is <1 % [1, 5, 6].

Urgent appendectomy is the treatment of choice of acute appendicitis [1, 7–9]. Nevertheless, alternative approaches such as interval appendectomy are still debated [10]. Simple appendicitis, i.e., not perforated appendicitis, does not require antimicrobial treatment if surgery is done promptly [8, 11]. By contrast, perforated appendicitis is, potentially, a bacterial intraabdominal infection due to bacterial evasion from the gut. Indeed, antimicrobial therapy is a cornerstone of the treatment of perforated appendicitis, as it leads to the most significant reduction of mortality [12]. Accordingly, antibiotic therapy with or without subsequent interval appendectomy has been proposed as a treatment alternative

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for perforated appendicitis, avoiding appendectomy at the acute stage [13–17].

In an attempt to curtail postoperative infectious complications, evidence-based guidelines recommend antimicrobial prophylaxis for surgery entailing entry of the gastrointestinal tract and they include appendectomy [18, 19]. In adults, the advantage of antimicrobial prophylaxis for appendectomy has been confirmed in a review of the literature [20]. However, several studies have questioned the effect of prophylactic antibiotics for simple appendicitis in pediatric patients [21–23], and a recent systematic review of the literature has not found significant differences between antibiotic treatment and placebo groups in children [20]. Notably, the Red book of the American Academy of Pediatrics does not address the issue of preoperative antimicrobial prophylaxis for acute appendicitis in children [24]. Data are needed to support the judicious antimicrobial prescription for this entity.

In our center, pediatric patients with the diagnosis of acute appendicitis traditionally underwent preoperative antimicrobial prophylaxis and urgent appendectomy. Given the questioned advantage or lack of proof of benefit of preoperative antimicrobial prophylaxis in the literature, we decided to prospectively conduct a consecutive cohort study on the changing of management related to preoperative antimicrobial prophylaxis for urgent appendectomy. We chose this approach rather than a randomized trial because of the better practicability. Here, we evaluate the impact of preoperative antimicrobial prophylaxis with metronidazole on postoperative infectious complications [25–28] in pediatric patients undergoing urgent appendectomy before and after a change in the management related to the preoperative administration of antimicrobials.

Methods

At the University Children's Hospital of Zurich, we conducted a prospective consecutive cohort study on preoperative antimicrobial prophylaxis in patients undergoing urgent appendectomy. This matched cohort study providing data of evidence level II was linked to a change in the management of standard care of these patients. The change consisted in omitting preoperative intravenous administration of intravenous metronidazole (10 mg/kg) as antimicrobial prophylaxis given within 60–30 min before the start of surgery. One hundred patients each were included before and after the change of management, respectively. We prospectively collected the demographic, clinical, histological, and outcome data of the last 100 patients undergoing appendectomy receiving preoperative antimicrobial prophylaxis (group A) and the first 100 patients undergoing appendectomy not receiving preoperative antimicrobial prophylaxis (group B). This study was performed in agreement with the requirements of the Institutional Ethics Committee and in compliance with the Declaration of Helsinki. Written consent was obtained before appendectomy by patients or, according to age, by their parents. Patients were assigned to the respective groups following standard of care.

In general, the presence of acute appendicitis was suspected in patients with a brief history of abdominal pain starting in the umbilical region, shifting to the right lower abdomen, accompanied by nausea and vomiting, and, sometimes, by fever and diarrhea. The clinical findings were tenderness to local pressure and signs of peritoneal irritation localized in the lower right abdomen. Abdominal ultrasound examination was available on request by the consulting physician. Computed abdominal tomography was not performed. If the surgeon in charge judged the patient to have acute appendicitis, appendectomy was carried out the same day, i.e., within 12 h, exceptionally within 24 h from initial presentation to the hospital. Rare individual patients with equivocal signs not qualifying for appendectomy were observed but never treated with antibiotics. Patients were not administered any antimicrobial preoperatively, except a single dose of metronidazole to patients of group A.

Based on the macroscopic aspect during appendectomy, the surgeon classified the episode as no appendicitis, simple appendicitis, or perforated appendicitis. If the surgeon found free purulent peritoneal fluid or abscess formation and, thus, classified the episode as perforated appendicitis, intravenous treatment with amoxicillin (100 mg/kg/day tid), gentamicin (7.5 mg/kg/day qd), and metronidazole (30 mg/kg/day tid) was immediately started for 10 days. No antimicrobial treatment was given when the surgeon classified the episode as no appendicitis or simple appendicitis during surgery. Peritoneal cultures were not done routinely at surgery, since their value has been repeatedly questioned [29, 30], and routine cultures are no longer taken by most surgeons [9]. The peritoneal cavity was rinsed with crystalloids, but without any antibiotics.

All excised appendices were sent for histological examination and review to the Institute of Pathology, University Hospital of Zurich, and were classified as normal appendix (no inflammation), simple appendicitis (subdivided in gangrenous and ulcerophlegmonous appendicitis), or perforated appendicitis.

Postoperative surgical site infections including wound abscesses and intraabdominal abscesses occurring within a warranted follow-up of 30 days after the operation were recorded by physicians of the infectious diseases not involved in the management of these patients. In addition, charts were checked for readmission and visits to the emergency department of our hospital for up to 1 year after

appendectomy. Along with the definitions proposed by the Centers for Disease Control and Prevention (CDC), wound abscess was defined as infection of the skin or subcutaneous tissue of the incision with suppuration confirmed by spontaneous wound rupture, debridement, or incision. Intraabdominal abscesses were defined as surgical organ or space infections within the abdominal cavity diagnosed at surgery, or by rectal examination and/or ultrasound [22, 31].

For the statistical analysis of rates, Fisher's exact test and for the analysis of different groups, the mean, with standard deviation and the Mann–Whitney test, for non-parametric data were used. p-values of <0.05 were considered as statistically significant.

Results

Patient demographics

The targeted total of 200 children undergoing appendectomy was enrolled in a period of 30 months. As per study protocol, the first 100 patients (group A) received a preoperative single intravenous dose of metronidazole (10 mg/kg) and the subsequent 100 patients did not (group B).

Age distribution, gender, co-morbidities, fever, and duration of symptoms on admission were similar in patients of group A and patients of group B (Table 1). The mean ages were 10 and 9.5 years, respectively, and ranged from 3 to 15 years. Boys predominated: 58 (63 %) of 92 group A patients and 58 (61 %) of 95 group B patients. Four children in each group had an underlying disease, including diabetes (one each in groups A and B), thalassemia minor (one each in groups A and B), epilepsy (2 in group A, 1 in group B), and congenital heart disease (one in group B). Thus, based on the demographic data, patients from group A were well balanced with patients of group B.

Nature of acute appendicitis

The macroscopic intraoperative classifications of the episodes were no appendicitis in five patients of group A and four patients of group B, simple appendicitis in 72 patients of group A and 72 patients of group B, and perforated appendicitis in 23 patients of group A and 24 patiets of group B (Fig. 1). Histology confirmed the intraoperative classification in 173 (86.5 %) patients, equally distributed among groups A and B (Fig. 1).

Histology showed no appendicitis in the samples from eight patients of group A and five of group B. These patients were excluded from further analysis. Simple appendicitis was found in the samples from 69 patients of group A and from 70 of group B (Fig. 1), including ulcerophlegmonous (group A: $n = 68$; group B: $n = 66$) and gangrenous (group A: $n = 1$; group B: $n = 4$). A perforated appendicitis was found in samples from 23 patients of group A and from 25 of group B. Thus, the frequencies of simple and perforated appendicitis were similar among patients who received preoperative antimicrobial prophylaxis (group A) and patients who did not (group B).

Patients with perforated appendicitis in group A or group B were, on average, 2 years younger than patients with simple appendicitis ($p < 0.05$) (Table 1). Preoperative abdominal ultrasound examination was requested and performed in 31 patients of group A and 45 patients of group B.

Appendectomy was performed by open surgery in all but four patients, which had laparoscopic surgery (one in group A, three in group B). The mean duration of surgery for histological simple appendicitis in group A patients was shorter than in group B patients ($p < 0.05$). The mean duration of surgery for histological perforated appendicitis was similar for group A and group B patients (Table 1). Taken together, besides the shorter duration of the operation for simple appendicitis in patients from group A

Table 1 Patient characteristics, operation time, and hospital stay in children with simple or perforated appendicitis with or without preoperative antimicrobial prophylaxis

Appendicitis	With prophylaxis		Without prophylaxis	
	Simple ($n = 69$)	Perforated ($n = 23$)	Simple ($n = 70$)	Perforated ($n = 25$)
Mean age in years (range)	10.7 (4–15)	8.2 (3–15)	10 (3–15)	8 (3–15)
Gender (M/F)	47/22	11/12	44/26	14/11
Comorbidity (n)	3	1	4	0
Temperature >38.5 °C rectal (n)	11	13	10	15
Mean duration of symptoms in days (range)	1.26 (1–4)	2.39 (1–7)	1.35 (1–4)	2.56 (1–7)
Mean duration of surgery in minutes (range)	50* (30–100)	65 (30–120)	61* (20–145)	75 (40–115)
Mean hospital stay in days (range)	5.6 (3–16)	12.1 (5–22)	6.1 (4–17)	12 (4–22)

* $p < 0.05$; all other comparisons were not significantly different

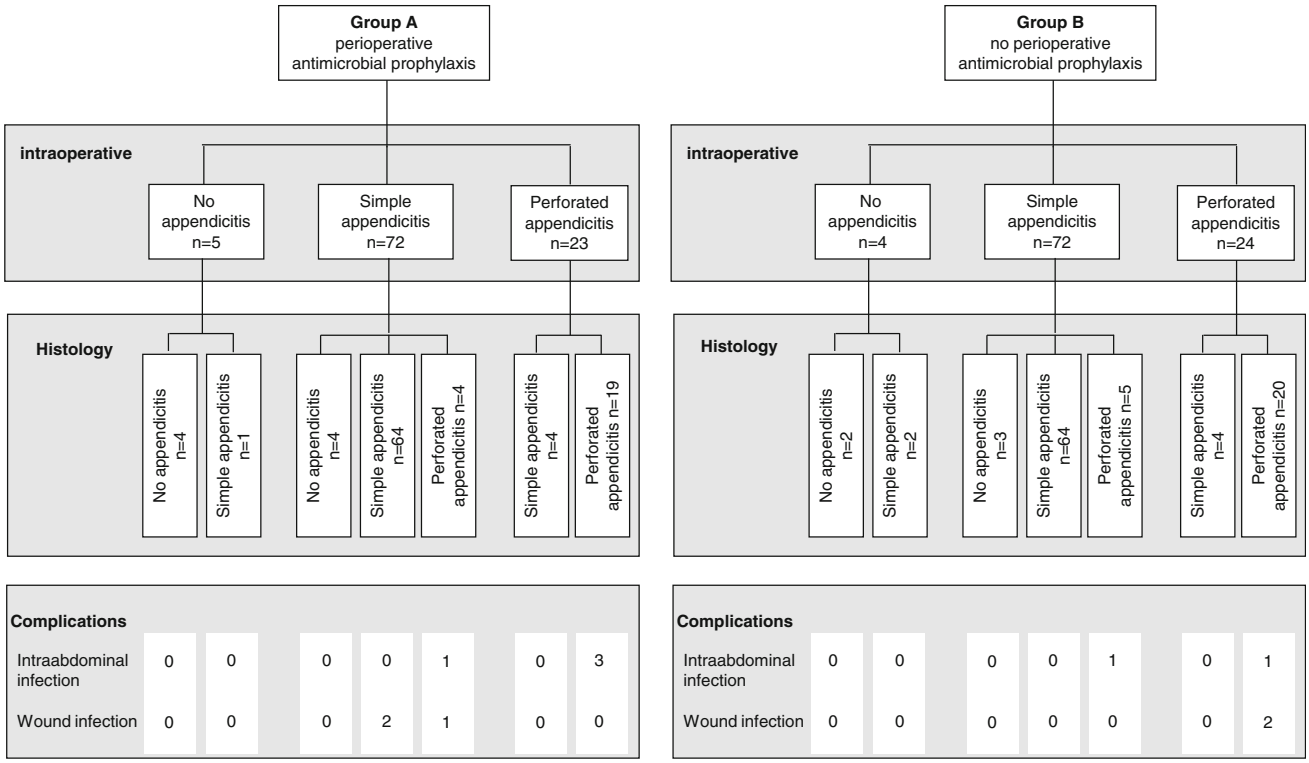

Fig. 1 Children with acute appendicitis undergoing appendectomy with (group A) or without (group B) preoperative antimicrobial prophylaxis

compared to patients of group B, all clinical, histological, and duration of surgery data were well balanced between both patient groups, similar to the demographic data.

Postoperative infectious complications

Among the samples from five patients of group A and among those from four patients of group B which were classified by the surgeon as not having acute appendicitis at appendectomy, the samples of one patient and of two patients, respectively, showed simple appendicitis in the histological analysis. No postoperative infectious complication was observed in any of the patients with no histological appendicitis.

Postoperative infectious complications among patients with histological simple appendicitis were noted in 2 (3.0 %) of 69 patients from group A and in none from group B. The complications were wound infections (Fig. 1), occurring 7 and 8 days after surgery, respectively. Cultures from one wound grew *Streptococcus milleri* and *Escherichia coli*, and from the other *S. milleri*. Treatment of both patients consisted of drainage and parenteral amoxicillin, gentamicin, and metronidazole for 5 and 10 days, respectively.

In four patients of group A and five of group B, perforation was macroscopically not evident at appendectomy but evident in the histological examination (Fig. 1). These patients, classified during surgery as having simple appendicitis, were not started on triple antimicrobial treatment intraoperatively, except one patient of group A and two patients of group B. In these three patients, the surgeon had judged the appendix to be close to perforation and, therefore, decided to commence antimicrobial treatment for 10 days. Despite this antimicrobial treatment, one patient of group B developed a Douglas abscess, which afforded drainage. Among the six patients with histological perforated appendicitis and who did not receive antimicrobial triple combination because they were clinically classified as having simple appendicitis, one patient of group A had an intraabdominal abscess and another patient of group A had a wound infection. The abscess was diagnosed 10 days after appendectomy and was treated with parenteral amoxicillin, gentamicin, and metronidazole for 10 days. The wound infection occurred 4 days postoperatively. Wound cultures grew *S. milleri* and *E. coli*. Treatment consisted of local incision. Taken together, perforation was macroscopically not evident in a similar proportion of patients in group A and group B. The rates of postoperative complications in these patients were similar, irrespective of the distinct preoperative antimicrobial prophylaxis management.

All 47 patients classified as having perforated appendicitis at appendectomy were started on antimicrobial therapy with amoxicillin, gentamicin, and metronidazole from

operation for 10 days, as per protocol. Histology did not confirm perforation in four patients of group A and four patients of group B. Antimicrobial triple therapy was given in these patients as planned for 10 days, since the histological results became available only thereafter.

Postoperative infectious complications among patients with histological perforated appendicitis were noted in 5 (22 %) group A patients and in 4 (16 %) group B patients (Fig. 1). The complications included intraabdominal abscesses in four patients of group A and in two patients of group B, and wound infections in one patient of group A and in two patients of group B. Three of the four intraabdominal abscesses in patients of group A were diagnosed by ultrasound examination 10 days after appendectomy and treated with parenteral amoxicillin, gentamicin, and metronidazole for 10 days. No samples for microbiological cultures were collected from these patients. The fourth intraabdominal abscess required surgical drainage. Cultures from the abscess grew *S. milleri* and *E. coli*. Treatment consisted of intravenous amoxicillin, gentamicin, and metronidazole for 14 days. One intraabdominal abscess in a patient of group B was diagnosed 2 days after appendectomy and was managed by relaparotomy, drainage, and intravenous amoxicillin, gentamicin, and metronidazole for 10 days. The other intraabdominal abscess was treated by drainage and intravenous amoxicillin, gentamicin, and metronidazole for 10 days. In both intraabdominal abscesses, no samples for microbiological cultures were collected. The wound infection in group A was treated by local incision only. No additional antibiotic therapy was given besides the preoperative prophylaxis with metronidazole. One of the two wound abscesses in the patients from group B was diagnosed 10 days after appendectomy and treated by drainage only, and the other was diagnosed 7 days after appendectomy and was drained and treated with intravenous amoxicillin, gentamicin, and metronidazole for 12 days. Cultures from both wound abscesses grew *S. milleri* and *E. coli*.

Overall, the number of infectious complications was higher in patients with histological perforated appendicitis than in those with histological simple appendicitis ($p < 0.05$). The mean duration of hospitalization for patients with histological simple appendicitis was similar for patients of group A compared to patients of group B and for patients with histological perforated appendicitis for patients of group A compared to patients of group B.

Discussion

The aim of this prospective consecutive cohort study was to assess if omitting preoperative antimicrobial prophylaxis in pediatric patients undergoing urgent appendectomy resulted in an increase in postoperative infectious complications. We found no differences in the number of postoperative infectious complications between patients receiving a single preoperative dose of metronidazole and those not receiving such a dose. Our results suggest that preoperative antimicrobial prophylaxis with metronidazole is of no benefit in pediatric patients undergoing appendectomy because of suspected acute appendicitis.

Preoperative antimicrobial prophylaxis has been widely recommended to minimize postoperative complications, and this approach is commonly used for operations entailing the entry of the gastrointestinal tract, including appendectomy [9, 18, 19]. However, there are several inconsistencies with this general tenet. First, the evidence has not been comparatively evaluated and defined with respect to antimicrobial agents [7, 20, 22, 32–34], dose [7], duration [7, 22], and route of administration [33]. Here, we applied metronidazole alone as antibacterial prophylaxis. Although metronidazole does not cover both aerobic and anaerobic bacteria, such a regimen is shown to be effective and currently used [22, 25–28]. Second, a recent systematic review of studies comparing the use of antibiotics versus placebo did not show a significant difference for preventing postoperative infection after appendectomy in children [20]. In this comprehensive meta-analysis, preoperative prophylaxis with aerobic and anaerobic coverage decreases postoperative infections in adults. Due to the lack of such a significance in similar studies available among children, Andersen et al. [20] conclude that, "it is only reasonable to assume that the overall antibiotic efficacy also is representative for children". This, however, has not been shown so far. Possible factors explaining such a difference between adults and children are the different pathogenesis of appendicitis in children, the more difficult diagnosis of appendicitis in children, and the higher incidence of complicated appendicitis in childhood. Third, the pathogenic model applied for many years that simple appendicitis, if not treated, will necessarily proceed to perforation may not be appropriate. A distinct pathophysiology between simple and perforated appendicitis has been repeatedly suggested in the last 20 years, with good epidemiological reasons [4, 12, 35]. This, indeed, will eventually question the appropriateness, first, of emergency operations in children with simple appendicitis and, second, the need for antimicrobial prophylaxis to prevent infectious complications of perforation. Considering these facts, we felt that studying the effects of omitting preoperative antimicrobial prophylaxis in pediatric patients undergoing appendectomy was justified.

The overall rate of postoperative infectious complications in this series comparing two groups of patients with well-balanced characteristics was as low as 5 %. This figure is well within the range of 3–9 % reported in other

pediatric series [6–8, 23, 36–41]. In patients with simple appendicitis, postoperative wound infections were observed but there were no intraabdominal infections, neither in this nor in other series [8, 21–23]. Notably, patients with histological perforated appendicitis showed an up to 17-fold higher rate of postoperative complications compared with patients with histological simple appendicitis. This is in agreement with the literature as well [6, 8, 42]. Importantly, here, the rates of infectious complications did not differ between patients receiving preoperative antimicrobial prophylaxis and patients not receiving such prophylaxis, neither in those with histological perforated appendicitis nor in those with histological simple appendicitis.

Patients clinically classified at appendectomy as having a perforated appendicitis were immediately started on intravenous triple combination of amoxicillin, gentamicin, and metronidazole. Thus, preoperative antimicrobial prophylaxis in this subgroup of patients was unlikely to provide an additional benefit. Indeed, among patients macroscopically classified as having perforated appendicitis, we found almost identical complication rates in patients receiving prophylaxis and in patients not receiving prophylaxis. This holds true even after exclusion of the patients shown to have simple appendicitis by histology and, thus, to have been wrongly classified at appendectomy. By contrast, a potential benefit of preoperative antimicrobial prophylaxis would rather have been expected in patients classified as having simple appendicitis at appendectomy but shown to have perforated appendicitis by histology, since these patients did not receive immediate triple antimicrobial treatment and, thus, were potentially exposed to bacteria from the gut. Nevertheless, the rate of postoperative infectious complications was slightly higher in patients receiving prophylaxis compared to those not receiving prophylaxis. Admittedly, the number of patients in this category was small, but the rate of complications ranged between 20 and 50 %.

The rates of postoperative infectious complications in patients with clinical and histological classification as simple appendicitis were 3 % or lower. Considering this low complication rate, our study was statistically underpowered. According to a power calculation before the study, one would need to have included several hundred patients. This would not have been feasible in a reasonable time frame and, thus, not in a comparable way. However, if we assume that prophylaxis could prevent 50 % of postoperative infectious complications in this patient group, the calculated number needed to treat to prevent one postoperative infectious complication would be at least 66. This number is similar to the number of patients with histological simple appendicitis in this series who did not receive preoperative antimicrobial prophylaxis and who also did not show any postoperative infectious complication. Thus, the size of the investigated groups would have allowed detecting any benefit of preoperative antimicrobial prophylaxis in urgent appendectomy if the number needed to treat would be lower. Theoretically, a randomized controlled trial would be preferred; as such, an intervention study may be biased. Nevertheless, we chose the observational approach because of the better practicability. As shown in the results, there was no difference in the patient characteristics, diagnostic approach, operative technique, surgeons, and postoperative management. Thus, we have no indication for the presence of a bias.

Conclusions

Our consecutive cohort study on the management of appendectomy in children focusing on postoperative infections did not show any advantage of preoperative antimicrobial prophylaxis. This holds true also for patients with perforated appendicitis who undergo prompt appendectomy and are started antimicrobial treatment during surgery. Our results suggest that, in pediatric patients undergoing appendectomy, preoperative antimicrobial prophylaxis can be omitted.

Conflict of interest The authors declare that they have no competing interests.

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