



Feasibility, acceptance, safety, and effectiveness of antibiotic therapy as alternative treatment approach to appendectomy in uncomplicated acute appendicitis

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Abstract

Purpose Based on results from randomized controlled trials, there is an increasing discussion if antibiotic treatment is an equivalent therapeutic approach to appendectomy in uncomplicated acute appendicitis. This observational prospective study evaluates its feasibility, safety, and effectiveness in clinical practice.

Methods The study included all consecutive adults treated for acute appendicitis over an 18-month period in one hospital. Patients receiving antibiotics were compared to those treated surgically. Follow-up comprised 1 year. The primary endpoint was treatment success, defined as no secondary appendectomy during follow-up (antibiotic group) or successful appendectomy (primary surgical group). Secondary endpoints were complications, duration of hospital stay, pain intensity, and length of absence from work.

Results 54/124 (43.6%) patients were primarily treated with antibiotics and 70/124 (56.4%) surgically. Treatment success at 1 year was 77.1% (95%-CI 62.8–88%) for antibiotic and 100% for surgical treatment. Complications were non-significantly less frequent both among all patients treated with antibiotics and among patients undergoing secondary appendectomy compared to patients undergoing primary appendectomy (20.8% vs. 27.1% and 9.1% vs. 27.1%). The initial hospital stay was significantly shorter in the antibiotic group (mean 3.6 vs. 4.8 days, median 3 days, $p = 0.03$). After 1 year, the cumulative hospital stay was not different between groups.

Conclusions Appendectomy remains the most effective treatment for the definitive cure of acute appendicitis. However, antibiotic therapy can be a safe alternative approach for selected patients with uncomplicated acute appendicitis.

Trial registration DRKS00010401

Keywords Uncomplicated acute appendicitis · Conservative treatment · Antibiotic therapy · Non-operative treatment approach · Effectiveness and safety

Introduction

With a lifetime prevalence of 7% [1, 2], acute appendicitis is one of the most common underlying causes in patients

admitted to emergency departments with acute abdominal pain [3–5]. In industrialized countries, acute appendicitis is the most common indication for abdominal emergency operations [6]. For a long time, every form of appendicitis was an unconditional indication for appendectomy [5, 7]. In 1953 Harrison [8] and in 1959 Coldrey et al. [9] reported on a conservative treatment approach in acute appendicitis [5]. In recent years, based on the results of several randomized controlled trials [10–14], there is an increasing discussion if antibiotic treatment is an equivalent and safe treatment in uncomplicated acute appendicitis, defined as appendicitis without signs of peritonitis, perforation, abscess, or appendicolith [5, 15].

An advantage of antibiotic therapy is that procedure-specific postoperative complications, such as wound infections or incisional hernias, can be avoided. Further presumed

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advantages are a shorter hospitalization, lower costs, and a shorter duration of patients' absence from work [5, 10, 16]. The main risk associated with antibiotic therapy of acute appendicitis is its failure with a potentially complicated course. Furthermore, there is a lifetime risk of recurrent appendicitis. Another critical issue might be the development of antibiotic resistance [5, 10, 17].

In the hitherto largest multicenter randomized controlled trial comparing antibiotic with surgical therapy of uncomplicated acute appendicitis [10], the success rate within the follow-up period of 1 year was 72.7% (186/256) in the antibiotic group and 99.6% (272/273) in the surgical group. The complication rate was significantly lower in the antibiotic group than in the surgical group (2.8% vs. 20.5%, $p < 0.001$) [10]. A recently published meta-analysis showed a success rate of 62.6% for patients primarily treated with antibiotics compared to a success rate of 96.3% for patients primarily treated with appendectomy [5].

The aim of this prospective study was to evaluate the feasibility, acceptance, safety, and effectiveness of antibiotic treatment for acute uncomplicated appendicitis in clinical practice outside of controlled clinical trials.

Methods

Study design

In this prospective observational study, all patients ≥ 18 years treated for acute appendicitis at the Department of Surgery of the University Medical Center Mannheim between January 2016 and June 2017 were included. Patients were enrolled after diagnosis of acute appendicitis and recommendation for surgical or antibiotic therapy by a surgical consultant. Informed consent was obtained from all individual participants included in the study. Diagnostic and treatment procedures were not part of the study protocol and were carried out according to individual physician's choice.

Follow-up

Patients with primary antibiotic treatment were re-evaluated by telephone interviews 1 week, 3 months, and 1 year after the initial hospital stay. They were asked about complications and the need for a subsequent hospital stay with or without secondary appendectomy. Furthermore, duration of absence from work and pain intensity were determined. For patients who could not be reached for follow-up by telephone, a questionnaire with the same questions as in the telephone interview was sent.

Endpoints

The primary endpoint was treatment success, defined as no secondary appendectomy during follow-up and no recurrent appendicitis treated conservatively (primary antibiotic group), or successful appendectomy, defined as performed appendectomy (primary appendectomy group). Secondary endpoints were duration of hospitalization, pain intensity (measured on a numeric rating scale, NRS), incidence and type of complications (according to the Clavien-Dindo classification [18]), and duration of absence from work (only in the primary antibiotic group).

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Endpoints were compared between patients receiving antibiotics and those treated surgically. In addition, endpoints were analyzed separately for patients undergoing secondary appendectomy.

Continuous variables were presented using mean, standard deviation, median, percentiles, and 95% confidence intervals (95% CI). Categorical variables were presented using frequency and percentage. Differences between groups regarding categorical variables were tested using the chi-square test, or Fisher's exact test if a category contained five or less observations. Continuous variables were compared with the t test if they were normally distributed and the Mann-Whitney U test if they were not normally distributed. A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using "IBM SPSS Statistics version 25.0".

Ethical considerations and trial registration

This study was approved by the ethical committee II of the Medical Faculty Mannheim of the University of Heidelberg (2015-906W-MA) and followed the principles of the declaration of Helsinki. Informed consent was obtained from all participants included in the study. Trial registration: DRKS00010401 (German Clinical Trials Register, http://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00010401).

Diagnostic and therapeutic algorithm

The clinical algorithms used during the study period are explained below, even if diagnostic and treatment procedures were not part of the study protocol. For the diagnosis of acute appendicitis, history, physical examination, laboratory results (leukocytes, C-reactive protein), and imaging such as ultrasound or computed tomography when ultrasound was inconclusive or the appendix was

not visible, were used. Complicated appendicitis was assumed when the presence of an appendicolith, perforation, peritonitis, or abscess was suspected [14]. In all patients with complicated appendicitis, appendectomy was recommended. In the case of uncomplicated appendicitis and age ≥ 18 years, the possibility of antibiotic treatment, including expected treatment success according to the available evidence and the possible associated risks, was discussed with the patient. The decision between surgical and antibiotic treatment was then taken by the patient.

Surgical treatment was performed as open or laparoscopic appendectomy. Patients treated with antibiotics received intravenous ceftriaxone 2 g 1-0-0 plus metronidazole 500 mg 1-0-1 during the intended hospital stay of 3 days. After discharge, intravenous antibiotic treatment was followed by 7 days of oral ciprofloxacin 500 mg 1-0-1 plus metronidazole 400 mg 1-0-1. The total duration of antibiotic treatment was 10 days. The clinical status was re-evaluated within the first 24 h every 8 h and then every 12 h until discharge. If a patient in the antibiotic group deteriorated clinically (increasing level of pain, persisting or rising fever, signs of peritonitis), a sonographic re-evaluation followed and appendectomy was recommended. Patients were discharged when their clinical status was stable and after oral food intake was well tolerated, but at the earliest 72 h after initial contact in the emergency department.

Results

Patient characteristics and distribution among treatments

Between January 2016 and June 2017, 138 patients with acute appendicitis were treated at the Department of Surgery of the University Medical Center Mannheim. Figure 1 shows the distribution of severity of appendicitis and the number of patients treated with the respective approach. Sixty-seven (48.6%) patients had uncomplicated acute appendicitis and 71 (51.4%) patients had complicated acute appendicitis. Antibiotic therapy was not offered to seven patients with uncomplicated appendicitis because of age < 18 years (five patients) or doubts regarding compliance (two patients). Of the remaining 60 patients with whom the possibility of antibiotic treatment was discussed, 55 (91.7%, 82.1% of all patients with uncomplicated acute appendicitis) decided for antibiotic therapy and five patients for primary surgical treatment. Overall, 124 patients (54 patients with antibiotic treatment and 70 patients with primary appendectomy) were included in the analysis (Fig. 1). Table 1 shows baseline characteristics of patients in both treatment groups.

Primary endpoint

50/54 (92.6%; 95%-CI 82.1–98%) patients primarily treated with antibiotics were discharged from the hospital without requiring secondary appendectomy. Four patients deteriorated clinically and underwent secondary appendectomy during the initial hospital stay. Two of these four patients underwent appendectomy on admission day and two on the following day. 48/54 (88.9%) patients treated with antibiotics completed the 1-year follow-up with information on the primary endpoint available. Primary endpoint information was missing for six patients who were lost to follow-up (Fig. 1). 7/48 (14.6%) patients underwent secondary appendectomy within 1 year after the initial hospital stay. Therefore, a total of 11/48 (22.9%) patients underwent secondary appendectomy during the 1-year follow-up. Treatment success at one year was 77.1% (95%-CI 62.8–88%) for antibiotic and 100% for surgical treatment. Secondary appendectomy took place at a median of 65 days after the onset of treatment. Primary appendectomy was performed laparoscopically in 52, open in 14, and converted from laparoscopy to open in three cases. In the secondary appendectomy group, all patients were operated laparoscopically (Table 2).

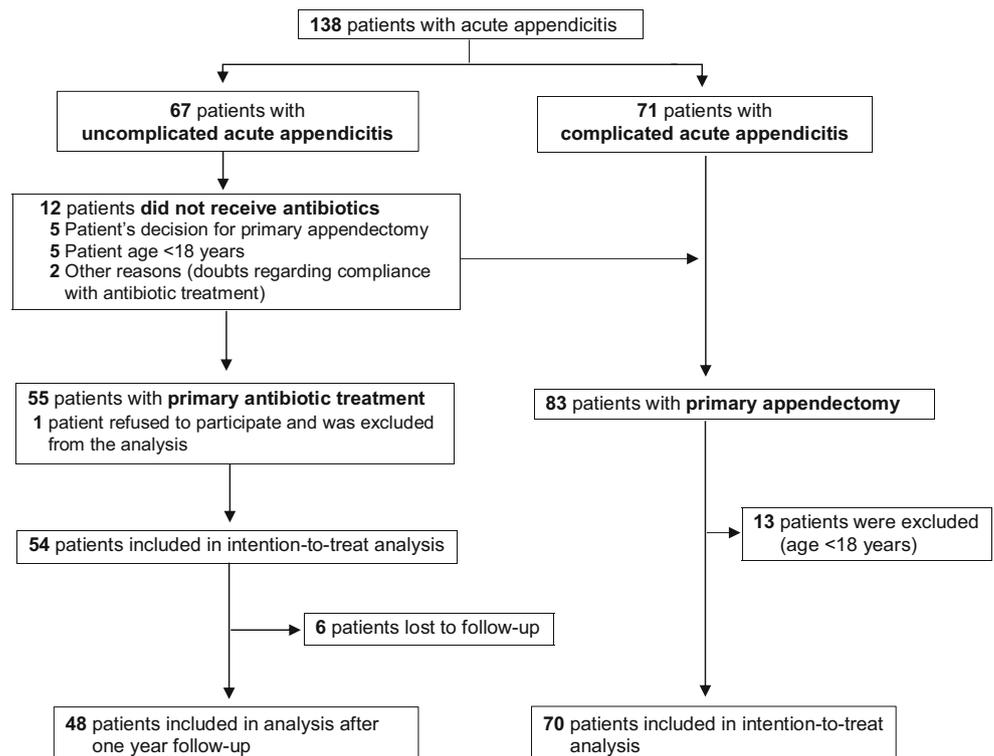
Based on intraoperative findings and histopathological examination (signs of perforation, peritonitis, abscess, and appendicolith), 21/70 (30%) patients in the primary surgery group and 2/9 (22.2%) patients in the secondary appendectomy group had complicated acute appendicitis (Table 2). The rate of negative appendectomies, defined as appendectomy without intraoperative macroscopic or histopathological signs of appendicitis, was 2.9% (2/70) in the primary appendectomy group and 11.1% (1/9) in the secondary appendectomy group. In the primary appendectomy group, one patient had appendiceal neoplasia and underwent right hemicolectomy and one patient had a macroscopically and microscopically normal appendix. In the secondary appendectomy group, one patient had endometriosis without signs of appendicitis.

Secondary endpoints

During the initial hospital stay, the complication rate was significantly ($p < 0.001$) lower in the antibiotic group than in the surgical group: 1/54 (1.9%, 95%-CI 0.1–9.9%) vs. 19/70 (27.1%, 95%-CI 17.2–39.1%). Table 3 shows the results for secondary endpoints in both treatment groups.

In the surgical group, most complications were grade I–IIIb according to the Clavien-Dindo classification. Complications of grade IIIb (requiring intervention under general anesthesia) or higher occurred in five patients. After 1-year follow-up, complications were non-significantly less frequent both among all patients treated with antibiotics and among patients undergoing secondary appendectomy compared to patients undergoing primary appendectomy (20.8% vs. 27.1%, $p =$

Fig. 1 Flow chart-distribution of severity of appendicitis and number of patients treated with the respective approach



0.43, and 9.1% vs. 27.1%, $p = 0.28$; Tables 2 and 3). Patients treated with antibiotics had a 6.3% (95%-CI -0.1–22%) lower overall complication rate, and patients with secondary appendectomy had an 18% (95%-CI -2–38%) lower overall complication rate than patients with primary appendectomy (27.1%). 9/10 complications in the antibiotic group were grades I–II (requiring no or only pharmacological treatment). In the secondary appendectomy group, one patient with

phenprocoumon long-term therapy had postoperative hemorrhage from a trocar wound.

The initial hospital stay was significantly shorter in the antibiotic group (mean 3.6 vs. 4.8 days, median 3 days, $p = 0.03$) (Table 3). 9/48 (18.8%) patients with primary antibiotic treatment were re-admitted during the 1-year follow-up (7 patients for secondary appendectomy, one patient because of colitis, and three patients because of non-specific abdominal

Table 1 Patient characteristics at time of inpatient admission

	Primary antibiotic group ($n = 54$)	Primary appendectomy group ($n = 70$)	Mean difference (95% CI)	p value
Sex	n (%)	n (%)		0.14
Male	26 (48.1)	43 (61.4)		
Female	28 (51.9)	27 (38.6)		
CT scan performed	4 (7.4)	11 (15.7)		
	Mean \pm SD	Mean \pm SD		
Age [years]	34.8 \pm 15.1	44.1 \pm 19.8	9.3 (3.2–15.4)	0.004
CRP [mg/l]	35.4 \pm 35.7	88.8 \pm 86.7	53.4 (30.7–76.1)	< 0.001
Leukocyte count [$\times 10^9/l$]	11.8 \pm 3.6	14.5 \pm 5.2	2.7 (1.1–4.2)	0.001
Creatinine [mg/dl]	0.9 \pm 0.2	1.0 \pm 0.4	0.1 (0–0.2)	0.02
Body temperature [$^{\circ}\text{C}$] ^a	36.9 \pm 0.86	36.9 \pm 0.78	0.02 (-0.3–0.3)	0.91
Maximum pain intensity [NRS] ^b	4.3 \pm 2.7	4.5 \pm 2.2	0.2 (0.8–1.2)	0.73

SD = standard deviation, CRP C-reactive protein

^a This information was available from 49/54 patients (antibiotic group) and from 65/70 patients (surgical group)

^b This information was available from 42/54 patients (antibiotic group) and from 50/70 patients (surgical group)

Table 2 Comparison of patient characteristics between all groups (primary and secondary appendectomy and successful antibiotic treatment)

	Successful conservative treatment ($n = 37$) ^a	Secondary appendectomy ($n = 11$) ^b		Primary appendectomy ($n = 70$) ^c	
Sex	n (%)	n (%)		n (%)	
Male	15 (40.5)	8 (72.7)		43 (61.4)	
Female	22 (59.5)	3 (27.3)		27 (38.6)	
	Mean \pm SD (median)	Mean \pm SD (median)	p value ^d (95% CI)	Mean \pm SD (median)	p value (95% CI)
Age [years]	32.5 \pm 11.7	44.4 \pm 20.8	0.13 (–1–24.8)	44.1 \pm 19.8	<0.001 ^e (5.6–17.6)
CRP [mg/l]	35.7 \pm 36.9	44 \pm 38.2	0.37 (17.2–33.8)	88.8 \pm 86.7	<0.001 ^e (29.3–76.9)
Leukocyte count [$\times 10^9$ /l]	11.4 \pm 3.6	13.2 \pm 3.6	0.15 (–0.7–4.3)	14.5 \pm 5.2	<0.001 ^e (1.4–4.8)
Creatinine [mg/dl]	0.9 \pm 0.2	1.1 \pm 0.3		1.0 \pm 0.4	
Body temperature [°C]	37 \pm 0.8	36.9 \pm 1.3		36.9 \pm 0.78	
Cumulative duration of hospitalization (after 1-year follow-up) [days]	3.1 \pm 1 (3)	8.1 \pm 7.4 (6)		4.8 \pm 3.9 (3)	0.001 ^f (–1.2–7.8)
	n (%)	n (%)		n (%)	
Overall complication rate (after 1-year follow-up)	9 (24.3)	1 (9.1)		19 (27.1)	0.28 ^f (–2–38)
Type of appendectomy					
Open		0 (0)		14 (20.3)	
Laparoscopically		11 (100)		52 (75.4)	
Converted		0 (0)		3 (4.3)	
Type of acute appendicitis ^g					
Phlegmonous/ulcero-phlegmonous		6 (66.7)		39 (55.7)	
Complicated		2 (22.2)		21 (30)	
Other diagnosis					
Appendiceal neoplasia		0 (0)		1 (1.4)	
Chronic-recurrent appendicitis		0 (0)		4 (5.7)	
Normal appendix		1 (11.1)		5 (7.1)	

SD standard deviation, CRP C-reactive protein

^aData of body temperature relate to $n = 34$

^bData of body temperature relate to $n = 9$

^cData of body temperature relate to $n = 65$ and information about type of appendectomy to $n = 69$

^d p values relate to the comparison between secondary appendectomy group and successful conservative treatment group

^e p values relate to the comparison between primary appendectomy group and successful conservative treatment group

^f p values relate to the comparison between primary and secondary appendectomy group

^gHistopathological findings were available for all patients in the primary appendectomy group and for 9 patients in the secondary appendectomy group

pain). After 1 year, the cumulative hospital stay was not different between both groups (Table 3). In patients with secondary appendectomy, the cumulative duration of hospital stay was significantly longer ($p = 0.001$) than in patients with primary appendectomy (Table 2). No differences were found for pain intensity between both groups, neither on admission day nor during the hospital stay (Tables 1 and 3). In the primary antibiotic group, the mean overall duration of absence from work during 1-year follow-up was 5.4 days. In patients who

underwent secondary appendectomy, the mean cumulative duration of absence from work was 13.8 days.

Discussion

This study evaluated the feasibility, acceptance, safety, and effectiveness of antibiotic treatment for uncomplicated acute appendicitis in clinical practice outside of controlled trials.

Table 3 Secondary endpoints of both treatment groups

	Primary antibiotic group (<i>n</i> = 54) <i>n</i> (%)	Primary appendectomy group (<i>n</i> = 70) <i>n</i> (%)	Difference between both treatment groups (95% CI) Absolute difference	<i>p</i> value
Overall complication rate				
During hospital stay	1 (1.9)	19 (27.1)	25.2% (14–36)	< 0.001
During the follow-up of 1 year	10/48 (20.8)		6.3% (– 0.1–22)	0.43
	Mean ± SD (median)	Mean ± SD (median)	Mean difference	
Duration of primary hospital stay [days]	3.6 ± 3.2 (3)	4.8 ± 3.9 (3)	1.2 (0–2.5)	0.03
Cumulative duration of hospital stay (after 1-year follow-up) [days]	4.2 ± 4.1 (3) ^a	4.8 ± 3.9 (3)	0.6 (– 0.9–2.1)	0.46
Maximal pain intensity [NRS]				
Day 3 of hospital stay ^b	0.4 ± 0.8	1.1 ± 1.5	0.7 (0.2–1.2)	0.003
Total hospital stay ^c	4.2 ± 2.6	4.5 ± 2.2	0.3 (– 0.6–1.2)	0.59
Follow-up ^d				
1 week ^e	1 ± 1.3			
3 months ^f	0.4 ± 1.4			
1 year ^g	0.6 ± 1.8			

SD standard deviation, *NRS* numeric rating scale

^aData relate to 48/54 patients who were available for follow-up

^bThis information was available from 43/45 patients (antibiotic group) respectively 53/61 patients (appendectomy group). Patients who were discharged on day 3 were excluded from this analysis

^cData relate to 50/54 patients (antibiotic group) respectively 63/70 patients (surgery group)

^dNo comparative values were collected

^eInformation was available from 41/44 patients

^fInformation was available from 43/44 patients

^gInformation was available from 40/42 patients

The results show that there is broad acceptance for the antibiotic treatment approach in patients with uncomplicated acute appendicitis. Only single patients decided for surgical and against antibiotic treatment after evidence-based disclosure of potential advantages, disadvantages, and risks of both treatment approaches. About three-quarters (77.1%) of patients were successfully treated with antibiotics, and slightly less than a quarter (22.9%) of patients underwent secondary appendectomy within one year. These results are similar to those of the several available randomized trials [10–14].

The main criticism concerning conservative treatment of acute appendicitis is the possibility of recurrent appendicitis with a potentially ensuing higher risk of severe complications [5, 19, 20]. Based on the results of the present study regarding complication rates, this criticism does not seem justified. After one year, the incidence and severity of complications were low both in all patients treated with antibiotics as well as specifically in those requiring secondary appendectomy. In particular, there was only one surgery-associated complication in patients who underwent secondary appendectomy, while all other complications were related to antibiotics. There was a non-significantly lower incidence of complications in the

secondary appendectomy group compared to the primary appendectomy group. However, this comparison is susceptible to bias because the primary surgery group contained a considerable proportion of patients with suspected complicated appendicitis, even if this diagnosis was confirmed intraoperatively in less than one-third of patients. One can therefore conclude that secondary appendectomy after failure of antibiotic treatment does not convey an elevated perioperative risk. The results reflect those of randomized trials, in which there was no higher incidence of complications in patients treated with antibiotics or in patients who underwent secondary appendectomy [10, 12–14, 5]. Only one study [11] showed a higher incidence of complications in the antibiotic group.

The present study can only partially confirm the postulated benefits of conservative treatment (shorter hospitalization, faster convalescence). The duration of primary hospital stay was longer in both groups compared to results of previous studies [12–14]. Probably, this can at least to some extent be attributed to a priori defined days for discharge in the treatment protocols of the single trials [5]. In the present study, discharge was recommended to patients treated with antibiotics after three days. For patients undergoing primary

appendectomy, there were no clear recommendations regarding timing of discharge. Considering that only a few patients underwent secondary appendectomy during the initial hospital stay and this occurred early after starting the therapy, the duration of hospitalization for antibiotic therapy might be shortened or it could even be carried out as outpatient treatment in selected patients. From the available randomized trials, only Vons et al. [11] reported the overall length of hospital stay including readmissions up to 1 year (mean stay 3.96 days in the appendectomy group vs. 3.04 days in the antibiotic group). This is shorter than in the present study. Here, the duration of absence from work in patients treated with antibiotics was short. Only in patients who underwent secondary appendectomy, it was extended. A comparison with the primary appendectomy group was not possible due to missing data for this endpoint in the latter. In comparison with results from randomized trials [10–13], the duration of absence from work was short; however, such comparisons across different contexts and health care systems are susceptible to misinterpretations.

Another disadvantage of antibiotic treatment is that possible appendiceal neoplasia remains untreated. This entity is rare but often mimics symptoms of acute appendicitis [5, 21]. A population-based study [22] found that 3.24% of patients diagnosed with complicated acute appendicitis and 0.87% of patients diagnosed with uncomplicated acute appendicitis actually had appendiceal neoplasia [5, 22]. In the present study, one patient in the primary surgical group had appendiceal neoplasia. In the secondary appendectomy group, no patient was found to have appendiceal neoplasia. To minimize the risk of leaving appendiceal neoplasia unresected, preoperative diagnosis plays a crucial role. In the presence of suspicious findings, appendectomy should be recommended. However, other differential diagnoses such as right colonic diverticulitis, Meckel's diverticulitis, pelvic inflammatory disease, or right pyelonephritis must be considered in the diagnosis of acute appendicitis and decision for antibiotic therapy.

A further disadvantage of antibiotic therapy is the possible development of antibiotic resistance on an individual or population level. Neither in this nor in previously published studies, long-term effects of widespread antibiotic treatment, such as drug resistance, are accounted for [5]. To assess possible effects of antibiotics on the population-related resistance situation, antibiotic therapy of acute appendicitis is not sufficiently widespread.

Perhaps the most important aspect regarding the decision between a medical or surgical treatment remains the patient's preference. Even if appendectomy is a safe and definitive treatment for acute appendicitis, surgery and the associated general anesthesia are considered stressful and affecting by many people. For such patients, surgery might potentially have a higher negative impact on quality of life than a drug therapy, even when the outcome of surgery is expected to be

good with no complications encountered. On the other side, there might be patients who rate their quality of life lower after conservative treatment because of a persisting risk of recurrent appendicitis [5]. Several studies showed that patient preferences on the choice of treatment for appendicitis differ in relation to socioeconomic factors and medical history [5, 19, 20]. Patients diagnosed with uncomplicated acute appendicitis should be informed in an unprejudiced and impartial way about the possibility of both treatment approaches under consideration of the available evidence.

This study has some limitations. One limitation is its non-randomized design and that it is not an open-label, non-inferiority trial. The decision between conservative or surgical treatment was based on estimated severity of appendicitis and patient's preference. This explains the inhomogeneity between both groups. All patients with suspected complicated appendicitis (suspicion of perforation, peritonitis, abscess, and appendicolith) [15] underwent primary appendectomy. Therefore, the comparison of secondary outcomes may be biased between both groups. However, complicated appendicitis was confirmed intraoperatively in less than a third of patients. Consequently, most of the patients who underwent primary appendectomy probably would have been eligible for antibiotic treatment. The non-controlled study design can also be regarded as methodological strength because the results relate to antibiotic therapy of uncomplicated acute appendicitis in clinical practice outside controlled study conditions. This considerably enhances external validity. Another limitation is the small number of patients with secondary appendectomy. This decreases the statistical validity of the results in this group. The follow-up period of one year does not allow conclusions on long-term effects of antibiotic therapy. Results of the hitherto largest randomized controlled trial show that the incidence of secondary appendectomy increases to 39% within a follow-up period of five years [23]. As the results of this study and previous studies show, appendectomy remains the most effective treatment approach for acute appendicitis. In this context, differences between laparoscopic and open appendectomy regarding complications, pain intensity, duration of hospital stay, or duration of absence from work may be interesting. In the present study, however, the number of patients who underwent open appendectomy was too low for a meaningful comparison to patients who underwent laparoscopic appendectomy. Results of previous studies and meta-analyses comparing open versus laparoscopic appendectomy showed that the duration of hospitalization and the duration of convalescence was shorter in the laparoscopic appendectomy group, and that postoperative complications were comparable between both groups [24–26].

In summary, this study shows that antibiotic therapy constitutes a safe alternative treatment approach for selected patients with uncomplicated acute appendicitis. In clinical practice, outside controlled trials, there is broad acceptance of

antibiotic therapy by patients with uncomplicated acute appendicitis. Nonetheless, for the definitive cure of acute appendicitis, appendectomy remains the most effective treatment approach. For patients treated with antibiotics, no higher risk of complications is to be expected compared to patients with primary appendectomy, even if secondary appendectomy becomes necessary. The decision regarding conservative or surgical treatment should be made after evidence-based discussion and under consideration of the patient's individual preferences. To obtain further long-term results regarding effectiveness of antibiotic therapy, trials with longer follow-up are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (ethical committee II of the Medical Faculty Mannheim of the University of Heidelberg [2015-906W-MA]) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV (1990) The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 132(5):910–925
2. Podda M, Cillara N, Di Saverio S, Lai A, Feroci F, Luridiana G, Agresta F, Vettoretto N (2017) Antibiotics-first strategy for uncomplicated acute appendicitis in adults is associated with increased rates of peritonitis at surgery. A systematic review with meta-analysis of randomized controlled trials comparing appendectomy and non-operative management with antibiotics. *Surgeon: J R Coll Surg Edinburgh Ireland* 15(5):303–314. <https://doi.org/10.1016/j.surge.2017.02.001>
3. Cervellin G, Mora R, Ticinesi A, Meschi T, Comelli I, Catena F, Lippi G (2016) Epidemiology and outcomes of acute abdominal pain in a large urban emergency department: retrospective analysis of 5,340 cases. *Ann Transl Med* 4(19):362. <https://doi.org/10.21037/atm.2016.09.10>
4. Fagerstrom A, Paajanen P, Saarelainen H, Ahonen-Siirtola M, Ukkonen M, Miettinen P, Paajanen H (2017) Non-specific abdominal pain remains as the most common reason for acute abdomen: 26-year retrospective audit in one emergency unit. *Scand J Gastroenterol* 52(10):1072–1077. <https://doi.org/10.1080/00365521.2017.1342140>
5. Prechal D, Damirov F, Grilli M, Ronellenfitsch U (2019) Antibiotic therapy for acute uncomplicated appendicitis: a systematic review and meta-analysis. *Int J Color Dis* 34(6):963–971. <https://doi.org/10.1007/s00384-019-03296-0>
6. Treutner KH, Schumpelick V (1997) Epidemiology of appendicitis. *Der Chirurg; Zeitschrift für alle Gebiete der operativen Medizin* 68(1):1–5
7. Sakorafas GH, Mastoraki A, Lappas C, Sampanis D, Danias N, Smyrniotis V (2011) Conservative treatment of acute appendicitis: heresy or an effective and acceptable alternative to surgery? *Eur J Gastroenterol Hepatol* 23(2):121–127. <https://doi.org/10.1097/MEG.0b013e32834233b6>
8. Harrison PW (1953) Appendicitis and the antibiotics. *Am J Surg* 85(2):160–163
9. Coldrey EJJCS (1959) Five years of conservative treatment of acute appendicitis 32(3):255–261
10. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Tuominen R, Hurme S, Virtanen J, Mecklin JP, Sand J, Jartti A, Rinta-Kiikka I, Grönroos JM (2015) Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA* 313(23):2340–2348. <https://doi.org/10.1001/jama.2015.6154>
11. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, Karoui M, Alves A, Dousset B, Valleru P, Falissard B, Franco D (2011) Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 377(9777):1573–1579. [https://doi.org/10.1016/s0140-6736\(11\)60410-8](https://doi.org/10.1016/s0140-6736(11)60410-8)
12. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, Rex L, Badume I, Granström L (2006) Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 30(6):1033–1037. <https://doi.org/10.1007/s00268-005-0304-6>
13. Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K (2009) Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 96(5):473–481. <https://doi.org/10.1002/bjs.6482>
14. Eriksson S, Granstrom L (1995) Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 82(2):166–169
15. Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT (2015) Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet (London, England)* 386(10000):1278–1287. [https://doi.org/10.1016/s0140-6736\(15\)00275-5](https://doi.org/10.1016/s0140-6736(15)00275-5)
16. Sippola S, Gronroos J, Tuominen R, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T, Hurme S, Salminen P (2017) Economic evaluation of antibiotic therapy versus appendicectomy for the treatment of uncomplicated acute appendicitis from the APPAC randomized clinical trial. *Br J Surg* 104(10):1355–1361. <https://doi.org/10.1002/bjs.10575>
17. Elder DP, Kuentz M, Holm R (2016) Antibiotic resistance: the need for a global strategy. *J Pharm Sci* 105(8):2278–2287. <https://doi.org/10.1016/j.xphs.2016.06.002>
18. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240(2):205–213
19. Kadera SP, Mower WR, Krishnadasan A, Talan DA (2016) Patient perspectives on antibiotics for appendicitis at one hospital. *J Surg Res* 201(2):253–257. <https://doi.org/10.1016/j.jss.2015.11.016>
20. Hanson AL, Crosby RD, Basson MD (2018) Patient preferences for surgery or antibiotics for the treatment of acute appendicitis. *JAMA Surg* 153(5):471–478. <https://doi.org/10.1001/jamasurg.2017.5310>
21. Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C 3rd, Memis B, Adsay V, Bekaii-Saab T, El-Rayes BF (2017) Appendiceal mucinous neoplasms: diagnosis and management. *Oncologist* 22(9):1107–1116. <https://doi.org/10.1634/theoncologist.2017-0081>
22. Lietzen E, Gronroos JM, Mecklin JP, Leppaniemi A, Nordstrom P, Rautio T, Rantanen T, Sand J, Paajanen H, Kaljonen A, Salminen P (2019) Appendiceal neoplasm risk associated with complicated acute appendicitis—a population based study. *Int J Color Dis* 34(1):39–46. <https://doi.org/10.1007/s00384-018-3156-x>
23. Salminen P, Tuominen R, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T, Hurme S, Mecklin JP, Sand J, Virtanen J, Jartti A, Gronroos JM (2018) Five-year follow-up of antibiotic

- therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA* 320(12):1259–1265. <https://doi.org/10.1001/jama.2018.13201>
24. Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K (2012) Meta-analysis of the results of randomized controlled trials that compared laparoscopic and open surgery for acute appendicitis. *J Gastrointest Surg* 16(10):1929–1939. <https://doi.org/10.1007/s11605-012-1972-9>
25. Li X, Zhang J, Sang L, Zhang W, Chu Z, Li X, Liu Y (2010) Laparoscopic versus conventional appendectomy—a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 10:129. <https://doi.org/10.1186/1471-230x-10-129>
26. Khalil J, Muqim R, Rafique M, Khan M (2011) Laparoscopic versus open appendectomy: a comparison of primary outcome measures. *Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association* 17(4):236–240. <https://doi.org/10.4103/1319-3767.82574>

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