

A Meta-Analysis of Antibiotics Versus Surgery for the Treatment of Acute Appendicitis

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Abstract: Appendectomy is the mainstay of treatment for acute appendicitis. Considering the complications of surgery, antibiotic treatment has also been gaining increasing interest in cases of acute appendicitis. This study aimed to compare the efficacy of antibiotics to surgery for acute uncomplicated appendicitis. The PubMed, Medline, Medscape and Cochrane databases were searched for studies comparing antibiotics versus surgery. The six outcome measures identified were thirty-day post-therapeutic peritonitis, length of hospital stay, prevalence of total complications, prevalence of normal appendix, prevalence of mean duration of pain and duration of disability. Five prospective RCTs with a total of 1430 patients (644 in the antibiotic group and 786 in the surgical group) were included in this study. Antibiotic treatment had a success rate of 75.3%. Regarding overall mean duration of disability, the antibiotic group had a significantly shorter duration of disability than that of the surgery group ($P < 0.05$). The total number of complications in the antibiotic group was 3.6% while that of the surgical group was 11.6%. The overall difference for mean duration of pain, and length of hospital stay between antibiotic therapy and surgery were not found to be statistically significant ($P > 0.05$). Although the conservative approach has a success rate lower than appendectomy, it is a possible alternative in certain clinical scenarios. Appendectomy remains the mainstay treatment for acute appendicitis. However, additional studies clarifying the certain etiologies of appendicitis that are responsive to antibiotic treatment are needed to further support its use.

Keywords: Acute, Appendicitis, Antibiotics, Surgery

1. Introduction

Acute appendicitis, first described by Fitz in 1886, is considered the most common cause of acute abdomen with a lifetime risk of approximately 7-8% [1-3]. Despite the fact that the exact etiology of acute appendicitis is not well understood, the majority of hypotheses suggest luminal obstruction of the appendix as the main etiology [3].

Appendectomy has been the gold standard treatment of acute appendicitis for more than 120 years since Mc Burney first explained it in 1889 [4]. It is one of the most common operations performed on the abdomen, with mortality rates ranging from 0.07% to 0.7% [5-7].

Mc Burney additionally recognized that the clinical course of appendicitis is variable, ranging from spontaneous resolution to appendiceal perforation. Hence, highlighting the need to perform immediate appendectomy in order to reduce mortality. Despite early intervention, the postoperative complications can range from 10%-19% and 30% for uncomplicated and complicated acute appendicitis, respectively [8-10]. The most frequent surgical complications being wound infection and intra-abdominal adhesions depending on the type of surgery used [11, 12].

The conservative treatment of acute appendicitis has long been appreciated since the 1950's. In 1953, Harrison reported successfully treating 42 out of 47 patients by antibiotics [13].

In 1956, Coldrey conducted a study to evaluate the efficacy of antibiotics in the treatment of acute appendicitis. He treated 137 patients with acute appendicitis non-operatively [14]. In 1979, combined traditional Chinese and Western medicine were used to treat 1200 patients with acute appendicitis, of whom 94.2% were treated successfully [15].

Several studies established the effectiveness of antibiotic therapy in the treatment of other intra-abdominal inflammatory conditions such as diverticulitis [16]. Furthermore, a common pathogenesis has been suggested between acute appendicitis and diverticulitis [17]. In this sense, the role of antibiotics in the treatment of acute appendicitis may have been overlooked.

Several retrospective studies demonstrated that antibiotics could be used as the sole treatment of uncomplicated acute appendicitis [18-20]. Nonetheless, the impact of antibiotics as a primary treatment of acute appendicitis has been controversial with systematic reviews and meta-analyses presenting inconsistent results [21-24].

The aim of this meta-analysis is to conclude if antibiotics can be used as a safe alternative to appendectomy in managing acute uncomplicated appendicitis, and to present the significant differences between the two modalities of treatment.

2. Materials and Methods

The study was registered to the Research Registry system with the Review Registry Unique Identifying Number: review registry 202 (www.figresearchregistry.com).

2.1. Data Sources

Prospective RCTs were selected for this study to evaluate

antibiotics versus surgery for the management of acute appendicitis. The PubMed, Medline, Medscape and Cochrane online library databases were systematically searched for articles published between 1990 and 2015. Publications in English Language were found using the following MESH phrase with Boolean operators: “Acute appendicitis AND (medical OR conservative OR non-operative OR antibiotics) AND (surgical OR appendectomy OR operative)”. Citations of the chosen articles were also manually screened for further potentially relevant articles.

2.2. Data Extraction

Four authors independently reviewed and crosschecked abstracts derived from the electronic library databases for relevance and extracted the data. Disagreements were resolved by discussion with a fifth author who supervised this process to ensure eligibility. A final consensus was reached after verifying all the papers provided by the authors.

2.3. Study Selection Criteria

All prospective RCTs comparing antibiotic therapy with appendectomy for patients with suspected acute appendicitis at initial presentation were eligible for inclusion. However, the inclusion criteria limited patients' age to those older than 16 years of either gender. Studies, which only enrolled patients with known complicated appendicitis, such as phlegmon or periappendiceal abscess at time of admission, were excluded. There were no restrictions on the type of antibiotic or duration of its use. Open or laparoscopic appendectomy was performed at the surgeon's preference (Figure 1).

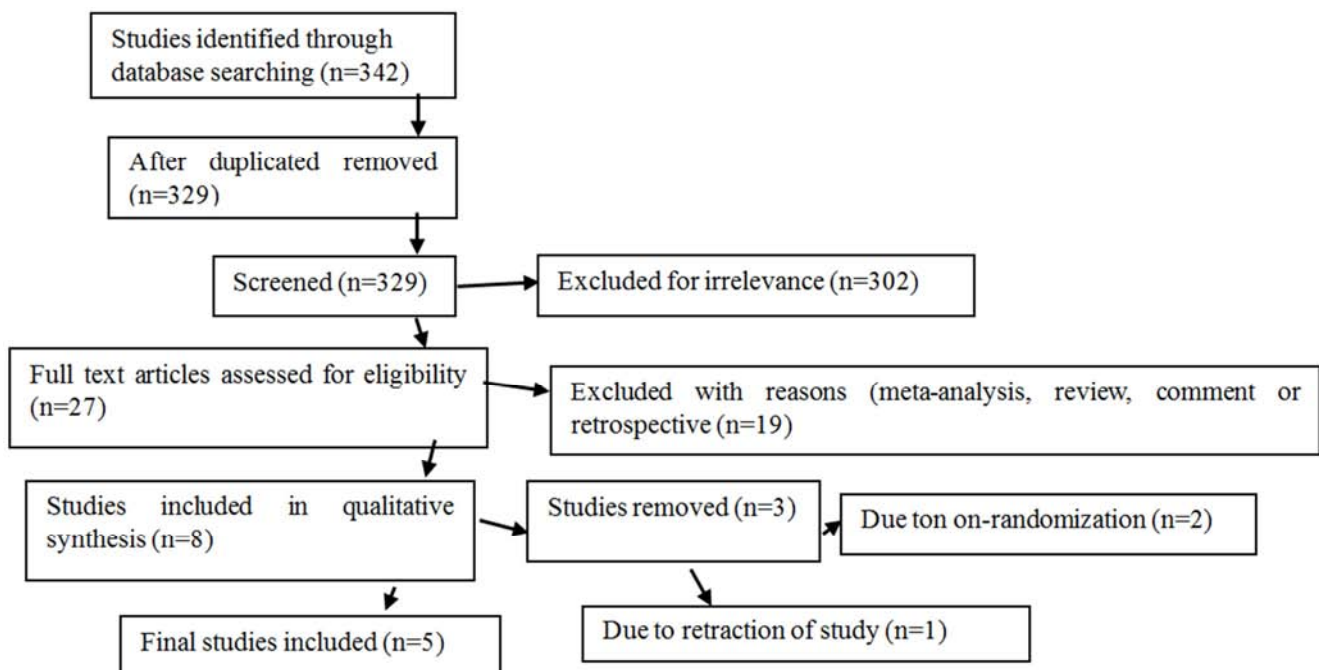


Figure 1. Prisma.

2.4. Data Collection and Statistical Analysis

All analyses were performed using Comprehensive Meta-Analysis V3 (Trial) software. The meta-analysis was performed according to the recommendations of The Cochrane Collaboration and the Cochrane Handbook for Systematic Reviews of Interventions [25].

The summarized statistics of categorical outcomes are presented as risk ratios for complications and treatment efficacy. Risk ratio was preferred to odds ratio with 95% confidence intervals (CIs), as the latter is more appropriate for case-control studies. The Mantel-Haenszel method was used to combine the summarized statistics and assess the heterogeneity between studies by considering the " I^2 " method alongside the chi-square P value. Interpretation of the I^2 statistic was based on the guidelines in the Cochrane Handbook, in which 0% to 40% may be unimportant heterogeneity, 30%–60% indicates moderate, 50%–90% indicates substantial, and 75%–100% indicates considerable heterogeneity. When combining studies of this nature for meta-analysis, we assumed that variation existed between trials in both the design and the methodological quality, so we used a random effect model to provide a conservative estimate of the results. A fixed effect model was used when no heterogeneity existed.

Continuous variables, when the mean and SD were presented, were assessed using the weighted mean difference

(WMD) with the 95% CI and a random-effects model was used according to heterogeneity if significant heterogeneity was present. We present the results of statistical heterogeneity in the forest plots. We considered the results to be statistically significant at the P value less than 0.05 if the 95% confidence interval did not include the value "one" for risk ratio or the value "zero" for WMD.

3. Results

The PubMed, Medline, Medscape and Cochrane online library databases yielded 329 possibly relevant studies after duplicates removed. We excluded 321 papers, of which 302 were irrelevant and nineteen were meta-analyses, reviews, comments or retrospective studies. After further assessment, two out of the eight studies remaining were excluded due to non-randomization. A final study authored by Malik et al. [26] was excluded because it was retracted.

Five prospective RCTs [27-31] with a total of 1430 patients met the selection criteria and were eligible for inclusion. The number of patients, per protocol, allocated to the antibiotic group was 644, while 786 patients comprised the surgery group.

The characteristics of the studies included are summarized in Table 1. The treatment efficacy parameters dictated by each study is included in Table 2.

Table 1. Characteristics of included studies.

	Males/Females	Age	No. of Pts. in AG	No. of Pts. in SG	Methods of diagnosis	Treated successfully in AG
Erikson et al. (1995)	27/13	18-75	20	20	US, Chemistry	12 (60%)
Styrud et al. (2006)	252/0	18-50	128	124	US, Chemistry	113 (88.3%)
Hansson et al. (2009) ¹	195/174	>18	202	167	US/CT, Chemistry	83 (41.1%)
Hansson et al. (2009) ²	200/169	>18	119	250	US/CT, Chemistry	93 (78.2%)
Vons et al. (2011)	143/96	18-68	120	119	CT, Chemistry	81 (67.5%)
Salinen et al. (2015)	329/201	18-60	257	273	CT	186 (72.4%)
Total*			644	786		485 (75.3%)

Table 1. Continue.

	Normal appendix in SG	Hospital stay in SG (days)	Hospital stay in AG (days)	Follow-up period (months)	No. of Pts. lost to follow-up in AG	No. of Pts. lost to follow-up in AG
Erikson et al. (1995)	3	3.1	3.4	1	0	1
Styrud et al. (2006)	4	3	2.6	12	0	0
Hansson et al. (2009) ¹	2	2	3	12	10	28
Hansson et al. (2009) ²	30	2	3	12	10	28
Vons et al. (2011)	3	3.96	3.04	12	9	15
Salinen et al. (2015)	2	3	3	12	30	58
Total*	42 (5.3%)				49 (7.6%)	102 (13%)

AG: antibiotic group

SG: surgery group

1: Intention-to-treat

2: per-protocol

US: ultrasound

CT: computerized tomography

*: Total includes Hansson et al.'s per-protocol results only.

Table 2. Treatment efficacy parameters.

	Treatment efficacy parameters in antibiotic group	Treatment efficacy parameters in surgery group
Erikson et al. (1995)	Decrease in pain using visual analogue scale, WBC levels, CRP values	Decrease in pain using visual analogue scale, WBC levels, CRP values
Styrud et al. (2006)	Improvement in symptoms with no local peritonitis	N/A
Hansson et al. (2009)	Definite improvement without the need for surgery within a median follow-up of one year	Confirmed appendicitis at operation or another appropriate surgical indication for operation
Vons et al. (2011)	Occurrence of peritonitis within 30 days	Occurrence of peritonitis within 30 days
Salinen et al. (2015)	Discharge from the hospital without the need for surgery and no recurrent appendicitis during 1 year follow up period	Successful completion of an appendectomy

CRP: c-reactive protein

The total number of complications in the antibiotic group is 3.6% which is significantly lower than that observed in the surgery group; 11.6%. However, when taking recurrence rate into account, the overall failure rate of antibiotic treatment reaches 21.9% (Table 3).

Heterogeneity is found for the prevalence of thirty-day post-

therapeutic peritonitis ($I^2 = 79.195\%$, $P = 0.002$). Because of this we used random model results. The prevalence of “thirty-day post-therapeutic peritonitis” was similar in both groups according to the random model (MH risk ratio = 3.216, 95% CI; 0.530-19.514, $P = 0.204$) (Table 4).

Table 3. Unsuccessful treatment in both groups.

	Number of recurrent cases in antibiotic group	Number of complications in antibiotic group	Antibiotic Failure (recurrences + complications)	Number of complications in surgery group
Erikson et al. (1995)	7 (35%)	1 (5%)	8 (40%)	2 (10%)
Styrud et al. (2006)	16 (12.5%)	4 (3.1%)	20 (15.6%)	17 (13.7%)
Hansson et al. (2009) ¹	14 (6.9%)	11 (5.4%)	25 (12.4%)	18 (10.8%)
Hansson et al. (2009) ²	15 (12.6%)	3 (2.5%)	18 (15.1%)	25 (10%)
Vons et al. (2011)	30 (25%)	9 (7.5%)	39 (32.5%)	2 (1.7%)
Salinen et al. (2015)	50 (19.5%)	6 (2.3%)	56 (21.8%)	45 (16.5%)
Total*	118 (18.3%)	23 (3.6%)	141 (21.9%)	91 (11.6%)

1: Intention-to-treat

2: per-protocol

*: Total includes Hansson et al.'s per-protocol results only

Table 4. Results for the prevalence of thirty-day post-therapeutic peritonitis.

Model	Study Name	Statistics for each study					Events / Total		MH risk ratio and 95% CI				
		MH risk ratio	LL	UL	Z-value	P-value	Antibiotic	Surgery	0.01	0.1	1	10	100
	Erikson et al. (1995)	3	0.129	69.52	0.69	0.493	1/20	0/20					
	Styrud et al. (2006)	30.1	1.817	496.6	2.38	0.017	15/128	0/124					
	Hansson et al. (2009)	0.756	0.528	1.083	-1.52	0.128	43/202	47/167					
	Vons et al. (2011)	4.463	0.985	20.22	1.94	0.052	9/120	2/119					
Fixed		1.187	0.859	1.639	1.04	0.300							
Random		3.216	0.530	19.51	1.27	0.204							

MH: Mantel-Haenszel; LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=79.195 (P=0.002)

The prevalence of “Normal appendix” was similar in both groups according to the random model (MH risk ratio = 2.964 95% CI; 0.901-9.748, $P = 0.074$). Heterogeneity was not found in the studies ($I^2 = 0.648\%$, $P = 0.389$) (Table 5).

The prevalence of “total complications” was similar in both groups according to the random model (MH risk ratio = 0.442, 95% CI; 0.178-1.101, $P = 0.080$). Heterogeneity is found in studies ($I^2 = 79.256\%$, $P = 0.001$) (Table 6).

The overall difference for length of hospital stay between antibiotic therapy and surgery is not found to be statistically significant (95% CI): 0.184 (-0.120, 0.488) $P = 0.236$. Heterogeneity is found in the studies ($I^2 = 40.011\%$, $P = 0.155$) (Table 7).

Table 5. Results for the prevalence of normal appendix.

Model	Study Name	Statistics for each study					Events / Total		MH risk ratio and 95% CI				
		MH risk ratio	LL	UL	Z-value	P-value	Antibiotic	Surgery	0.01	0.1	1	10	100
	Erikson et al. (1995)	7	0.385	127.3	1.32	0.189	3/20	0/20					
	Styrud et al. (2006)	0.323	0.013	7.85	-0.69	0.488	0/128	1/124					
	Vons et al. (2011)	10.9	0.610	195.1	1.62	0.104	5/120	0/119					
	Salminen et al. (2015)	2.656	0.520	13.56	1.17	0.241	5/257	2/273					
Fixed		3.274	1.147	9.35	2.22	0.027							
Random		2.964	0.901	9.75	1.79	0.074							

MH: Mantel-Haenszel; LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=0.648 (P=0.389)

Table 6. Results for the prevalence of total complications.

Model	Study Name	Statistics for each study					Events / Total		MH risk ratio and 95% CI				
		MH risk ratio	LL	UL	Z-value	P-value	Antibiotic	Surgery	0.01	0.1	1	10	100
	Erikson et al. (1995)	0.200	0.010	3.920	-1.06	0.289	0/20	2/20					
	Styrud et al. (2006)	0.342	0.139	0.839	-2.44	0.019	6/128	17/124					
	Hansson et al. (2009)	0.767	0.556	1.057	-1.62	0.105	51/202	55/167					
	Vons et al. (2011)	1.653	0.404	6.761	0.70	0.485	5/120	3/119					
	Salminen et al. (2015)	0.142	0.061	0.326	-4.59	0.001	6/257	45/273					
Fixed		0.503	0.383	0.661	-4.95	0.001							
Random		0.442	0.178	1.101	-1.75	0.080							

MH: Mantel-Haenszel; LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=79.26 (P=0.001)

Table 7. Results for the prevalence of length of hospital stay (days).

Model	Study Name	Statistics for each study						Sample Size		Difference in means and 95% CI				
		Difference in means	Standard error	LL	UP	Z-value	P-value	Antibiotic	Surgery	-1	-0.5	0	0.5	1
	Erikson et al. (1995)	-0.30	0.425	-1.13	0.53	-0.71	0.481	20	20					
	Styrud et al. (2006)	0.40	0.164	0.08	0.72	2.43	0.015	128	124					
	Hansson et al. (2009)	0.00	0.227	-0.45	0.45	0.00	1.000	202	167					
	Vons et al. (2011)	0.92	0.467	0.01	1.84	1.97	0.049	120	119					
	Salminen et al. (2015)	0.00	0.246	-0.48	0.48	0.00	1.000	257	273					
Fixed		0.21	0.110	-0.01	0.42	1.90	0.057							
Random		0.18	0.155	-0.12	0.49	1.19	0.236							

LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=79.26 (P=0.001)

The overall difference between antibiotic therapy and surgery is not statistically significant in terms of mean duration of pain (Difference in means = -1.170, standard error = 1.398, $P = 0.403$) (Table 8).

Regarding the overall mean duration of disability, the

antibiotic group has a statistically significant shorter duration of disability than that of the surgery group ($P = 0.047$). Heterogeneity is not found in these studies ($I^2 = 0\%$, $P = 0.348$) (Table 9).

Table 8. Results for the prevalence of mean duration of pain.

Model	Study Name	Statistics for each study						Sample Size		Difference in means and 95% CI				
		Difference in means	Standard error	LL	UP	Z-value	P-value	Antibiotic	Surgery	-1	-0.5	0	0.5	1
	Erikson et al. (1995)	2.60	4.215	17.7	-5.66	0.62	0.537	20	20					
	Hansson et al. (2009)	-3.00	0.105	0.01	-3.21	-28.6	0.001	202	167					
	Vons et al. (2011)	-0.07	0.158	0.03	-0.38	-0.44	0.657	120	119					
Fixed		-2.10	0.087	0.01	-2.27	-24.1	0.001							
Random		-1.17	1.398	1.96	-3.91	-0.84	0.403							

LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=99.17 (P=0.0001)

Table 9. Results for the prevalence of duration of disability.

Model	Study Name	Statistics for each study						Sample Size		Difference in means and 95% CI				
		Difference in means	Standard error	LL	UP	Z-value	P-value	Antibiotic	Surgery	-8	-4	0	4	8
	Styrud et al. (2006)	-2.10	0.98	-4.03	-0.17	-2.14	0.033	128	124					
	Vons et al. (2011)	-0.63	1.22	-3.02	1.76	0.52	0.606	120	119					
Fixed		-1.52	0.77	-3.02	-0.02	-1.98	0.047							
Random		-1.52	0.76	-3.02	-0.02	-1.98	0.047							

LL: Lower Level; UL: Upper Level; CI: Confidence Interval; I-Square=0.00 (P=0.348)

4. Discussion

In this meta-analysis, a new and well-designed study published in 2015 [27] is taken into account. This study, by Salminen et al., involved the largest sample of patients of all

the discussed studies, making it more representative of the general population. In addition, a handful of outcomes are discussed in order to present a more comprehensive comparison of the treatment modalities.

Each of the selected studies adopted a different set of parameters to consider the treatment successful.

Improvement in symptoms, mainly pain, is used as an indicator for treatment efficacy in three studies. Two of these also used normal laboratory investigations, such as CRP and WBC count in addition to the decrease in the visual analogue scale as parameters. Lack of need for surgery throughout the follow-up period is another parameter used by both Hansson *et al.* and Salminen *et al.* As for surgery, success is mainly dependent on the completion of appendectomy and confirmation of appendicitis at operation, without the occurrence of peritonitis within thirty days (Table 2).

The success of antibiotic treatment for acute appendicitis ranges from 60% to 88.3% according to the randomized controlled trials at hand. As evident from this wide range, many variables can affect treatment efficacy including the definition of successful treatment, accuracy of diagnosis, type of antibiotics used and duration of follow up. A mean of 65.3% of patients allocated to the antibiotic group, per-intention-to-treat, were treated successfully. However, if the same parameter is calculated using the per-protocol values in the Hansson *et al.* study, the success rate of antibiotic treatment reaches 75.3%. Thus, values for complication and recurrence rates are calculated depending on per-protocol values only to avoid crossover of patients and to eliminate any failures that might have been successes had the involved physicians continued with the regimen dictated by the intention-to-treat groups. It is also observed that the 17.8% who presented with recurrent appendicitis after antibiotic treatment showed no chronic findings upon histopathological examination. Although the difference in the number of total complications between the two groups is statistically insignificant ($p = 0.08$), studies coincide that complications seen in patients allocated to the antibiotic group are less severe than those seen in the surgical group. Most complications seen in patients undergoing appendectomy were major, such as abscesses, small bowel obstruction, wound rupture and pulmonary embolism. As for patients allocated to the antibiotic group, complications were relatively minor including fungal infection, diarrhea and bladder dysfunction.

Three out of the fifteen patients who had recurrent appendicitis in the study conducted by Hansson underwent a second round of antibiotics, which led to complete resolution of the condition with no recurrence or complications in a one-year follow-up period. Although the patients with recurrent appendicitis in the Styrd *et al.* study underwent surgery, most of them requested to be treated with another course of antibiotics, indicating high patient satisfaction. Moreover, Eriksson *et al.* stated that patients given antibiotics before surgery did not have any postoperative infection. This suggests that antibiotic use can eliminate some of the complications associated with surgery and, possibly, delay surgery in uncomplicated cases.

In spite of having the same length of hospital stay and duration of pain as the surgery group (Table 7 and 8), patients in the antibiotic group have a shorter duration of disability and are able to return to work earlier than their counterparts who underwent appendectomy (Table 9). These patients also

have a lower, faster declining WBC count, lower body temperatures and decreased incidence of local peritonitis. It can be also inferred that antibiotics significantly reduce the risks associated with surgery and eliminate those associated with anesthesia, which are a possibility in patients undergoing appendectomy. The study conducted by Hansson *et al.* showed that major complications found in the surgery group were three-fold those observed in the antibiotic group, with comparable conclusions in the other studies.

The selected studies used similar antibiotic regimens in the treatment of the conservative groups. During the hospital stay, which ranged from one to three days, three studies used a third generation cephalosporin, namely cefotaxime, in combination with either metronidazole or tinidazole. Vons *et al.* chose to administer amoxicillin and clavulanic acid to the antibiotic group. The decision was based on the findings of an earlier study, which proved that this combination is superior to other antibiotics when used in uncomplicated sigmoid diverticulitis [32]. However, it is worth noting that *E. coli*'s resistance to amoxicillin and clavulanic acid has been increasing over the past few years [33]. This might account for the high recurrence rate (25%) seen in this particular study. The most recent RCTs used ertapenem, following the previously published guidelines by the surgical infection society and the infectious diseases society of America for the management of intra-abdominal infection [34]. As for post-discharge antibiotics, four of the five selected studies used a combination of a second or third generation fluoroquinolone; ofloxacin, ciprofloxacin or levofloxacin, and a nitroimidazole; metronidazole or tinidazole [27-29, 31]. Vons *et al.* continued to use amoxicillin and clavulanic acid. These post-discharge antibiotics were given for a period ranging from 7 to 10 days. Therefore, it is worth mentioning that there is no consensus on the type of antibiotic to be used and is yet to be agreed upon.

Three of the studies did not use CT for diagnosis of acute appendicitis, inadvertently increasing the percentage of negative appendectomies. In Vons *et al.*, and Salminen *et al.*, CT was the main method of diagnosis, reducing the rate of negative appendectomy to 1.3%, compared to 9.4% in the studies that did not use CT for diagnosis. It has been suggested by Vons *et al.* that complications seen in patients who underwent appendectomy after failure of antibiotic treatment might have been already present and missed at the time of diagnosis. This is also supported by the fact that all the complications in the antibiotic group in Salminen *et al.*'s study were found during the primary hospital stay, while none were found in later recurring cases. Surgical complications as well as failure of antibiotics treatment were also thought to be associated with the presence of a stercolith in the appendix on CT. This further enhances the importance of CT scans for correct status evaluation; complicated versus uncomplicated, and consequently, for choosing whether patients are to be treated conservatively or operatively. A notable drawback of CT utilization would be the delay in antibiotic administration, ultimately leading to decreased efficacy.

While emergency appendectomy, for the time being,

remains the gold standard for treating acute appendicitis, the use of antibiotics can be seen as a reliable substitution in certain circumstances to reduce the risks associated with surgery. In addition, antibiotics can also be safely recommended for elderly, patients with comorbidities and obese patients instead of surgery, as operative morbidity is higher in these cases.

According to the data collected, 75.3% of acute appendicitis cases have proven to be successfully treated by antibiotics alone. The remaining 24.7% of cases, in which antibiotics were unsuccessful, raise the doubt that the etiologies of these cases may differ from those in which antibiotics were successful.

5. Conclusion

It is of major importance to know why antibiotic treatment fails in some cases. Therefore, we emphasize the need for upcoming studies to focus particularly on this topic. This may subsequently enable patient-targeted therapy according to the exact pathophysiology of acute appendicitis.

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