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ORIGINAL ARTICLE

Amoxicillin Plus Clavulanic Acid Versus Appendicectomy for Treatment of Acute Uncomplicated Appendicitis

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ABSTRACT
Acute appendicitis is the most common indication for surgery in patients admitted to hospital for acute abdominal pain. In about 20% of cases, acute appendicitis is complicated, leading to local or diffuse peritonitis mostly. Although urgent appendicectomy is still the recommended treatment for acute uncomplicated appendicitis and also antibiotic treatment can cure acute appendicitis or can be the first line of treatment. In the Current study we assessed the efficacy of amoxicillin plus clavulanic acid by comparison with emergency appendicectomy for treatment of patients with uncomplicated acute appendicitis. In this Study open-label, non-inferiority, randomized trial, adult patients (aged 18–68 years) with uncomplicated acute appendicitis, as assessed by CT scan, were enrolled at Pakistan Instiute of Medical Sciences (PIMS) Hospital Islamabad Pakistan. A computer-generated randomization sequence was used to allocate patients randomly in a 1:1 ratio to receive amoxicillin plus clavulanic acid (3 g per day) for 8–15 days or emergency appendicectomy. The primary endpoint was occurrence of post intervention peritonitis within 30 days of treatment initiation. Non-inferiority was shown if the upper limit of the two-sided 95% CI for the difference in rates was lower than 10 percentage points. Both intention-to-treat and per-protocol analyses were done. The Current research Result show that Of 243 patients randomised, 123 were allocated to the antibiotic group and 120 to the appendicectomy group. Four were excluded from analysis because of early dropout before receiving the intervention, leaving 239 (antibiotic group, 120; appendicectomy group, 119) patients for intention-to-treat analysis. 30-day post intervention peritonitis was significantly more frequent in the antibiotic group (8%, n=9) than in the appendicectomy group (2%, n=2; treatment difference 5·8; 95% CI 0·3–12·1). In the appendicectomy group, despite CT-scan assessment, 21 (18%) of 119 patients were unexpectedly identified at surgery to have complicated appendicitis with peritonitis. In the antibiotic group, 14 (12% [7·1–18·6]) of 120 underwent an appendicectomy during the first 30 days and 30 (29% [21·4–38·9]) of 102 underwent appendicectomy between 1 month and 1 year, 26 of whom had acute appendicitis (recurrence rate 26%; 18·0–34·7).The Current result conclude that Amoxicillin plus clavulanic acid was not non-inferior to emergency appendicectomy for treatment of acute appendicitis. Identification of predictive markers on CT scans might enable improved targeting of antibiotic treatment.
Keywords: Amoxicillin, clavulanic acid versus appendicectomy

INTRODUCTION
Acute appendicitis is still the most common indication for surgery in patients admitted to hospital for acute abdominal pain. In about 20% of cases, acute appendicitis is complicated, leading to local or diffuse peritonitis [1]. Although urgent appendicectomy is still the recommended treatment for acute uncomplicated appendicitis, several studies, including four randomised trials [2].Different Study suggested that antibiotic treatment can cure acute appendicitis or can be the first line of treatment [3]. The current strategy for treatment of acute appendicitis has not been altered [4]. Although emergency appendicectomy is well tolerated by most patients, it is nevertheless associated with a risk of postoperative complications in about 2–23% of patients [5]. Additionally, over 10 years, 3% of patients undergoing appendicectomy were readmitted for intestinal obstruction directly related to postoperative adhesions [6].Avoidance of emergency appendicectomy in patients with uncomplicated appendicitis, who otherwise would have had surgery, would therefore improve the risk–benefit ratio of acute-appendicitis treatment. In the Present Study we compared the results of treatment with amoxicillin plus clavulanic acid with emergency appendicectomy in a group of patients with uncomplicated acute appendicitis as assessed by CT.

MATERIAL AND METHODS
Patients Selection: We undertook an open-label, non-inferiority, randomised controlled trial. The study took place at Pakistan Instiute of Medical Sciences (PIMS) Hospital Islamabad Pakistan and this research was approved by the Research and Administration committee of Hospital. All patients provided signed, informed consent.

All adults examined in the emergency department and suspected to have an acute appendicitis were assessed for possible inclusion in the study. Patients were excluded if one of the following criteria were present, age less than 18 years (no upper age limit), antibiotic treatment 5 days before, allergy to β-lactam antibiotics, known intolerance to amoxicillin plus clavulanic acid (nausea, vomiting), receiving steroid or anticoagulant treatments, past history of inflammatory bowel disease, pregnancy or a positive pregnancy test, life expectancy less than 1 year, allergy to iodine or blood creatinine 200 μmol/L or more, or inability to understand information about the protocol or to sign the consent form. Patients eligible for inclusion to the study were informed of the protocol and invited to participate. After informed consent was obtained, a CT scan was done. Diagnosis of uncomplicated appendicitis was assessed by CT imaging. An emergency radiologist in the hospital where the patient was admitted did a CT scan of patients' appendices according to the standard protocol of the hospitals. CT imaging was done with a 16-multidetector CT scanner. A final diagnosis of uncomplicated acute appendicitis required clear visualization of the appendix (appendix diameter >6 mm and no opacification of the appendix in patients with enema), and absence of any of the three following criteria of complicated appendicitis with peritonitis: extra luminal gas, periappendiceal fluid, or disseminated intraperitoneal fluid. An appendix diameter greater than 15 mm was a criterion for exclusion from the study, because of risk of malig nancy.11 Caecal-wall thickening, inflammation of periappendiceal fat, and presence of intraluminal stercoliths were also recorded, but were not exclusion criteria.

Randomization and masking: When a diagnosis of uncomplicated acute appendicitis acute appendicitis was made, patients were individually assigned to undergo either appendicectomy or treatment with amoxicillin plus clavulanic acid. The computer-generated randomization code was produced by the trial statistician. To ensure balance between the numbers in each group, block sizes of four were generated for allocation of patients to one of the two treatment groups. The randomization procedure was stratified by site, with an equal allocation ratio. Opaque, sealed, and sequentially numbered envelopes were provided to each trial site. To enroll a patient, an independent pharmacologist opened the next consecutively numbered envelope.

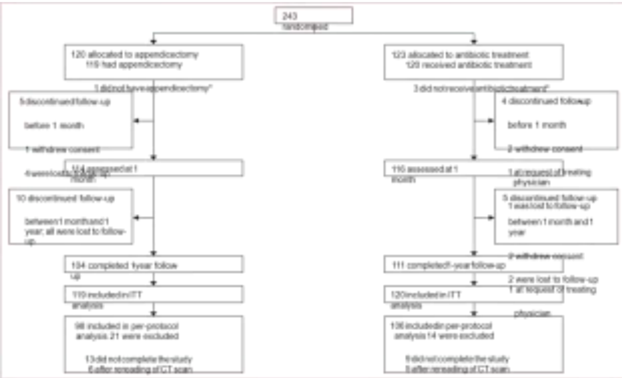

Figure1: Trial Profile. ITT=intention to treat. *Withdrew consent before starting treatment

Procedure: Patients were admitted to hospital irrespective of the treatment assigned and were assessed twice a day while in hospital. They were discharged after resolution of pain, fever, and any digestive symptoms. Appendicectomy was done according to surgeons' standard practice (a McBurney incision or laparoscopy). Patients were given one injection of amoxicillin plus clavulanic acid (2 g) at induction of general anesthesia, but did not receive antibiotic treatment thereafter, unless complicated appendicitis was diagnosed during surgery, in which case patients were given postoperative antibiotics. Patients in the antibiotic treatment group received amoxicillin plus clavulanic acid (3 g per day for patients weighing <90 kg, and 4 g per day for patients ≥90 kg), given intravenously to those with nausea or vomiting, and orally to all others.12–14 This drug combination was chosen because of its efficacy for ambulatory treatment of uncomplicated sigmoiditis.13 If symptoms and abdominal tenderness did not resolve after 48 h, immediate appendicectomy was undertaken. If pain and fever resolved rapidly, patients were discharged. Patients continued the same antibiotic treatment at home, with the same dose, for 8 days, and were seen on day 8; persistence of pain or fever prompted a CT scan and possible appendicectomy. In the absence of these symptoms, a sustained high white-blood-cell count or a high C-reactive-protein concentration resulted in extension of antibiotic treatment for a further 8 days. Persistence of similar biological disorders on day 15 prompted appendicectomy without an additional CT scan. All patients were seen systematically in consultations on days 15, 30, 90, 180, and 360. Histological examination of the appendix was done after every appendicectomy. Definitive diagnosis of uncomplicated acute appendicitis was based on the presence of mucosal ulceration with neutrophil infiltration restricted to the mucosa, or with a transmural extension. The primary binary endpoint was occurrence of peritonitis within 30 days of initial treatment. In the antibiotic group, diagnosis of peritonitis was done either by appendicectomy when a complicated appendicitis was identified, or postoperatively by CT scan. In the appendicectomy group,

Histological examination of the appendix was done after every appendicectomy. Definitive diagnosis of uncomplicated acute appendicitis was based on the presence of mucosal ulceration with neutrophil infiltration restricted to the mucosa, or with a transmural extension. The primary binary endpoint was occurrence of peritonitis within 30 days of initial treatment. In the antibiotic group, diagnosis of peritonitis was done either by appendicectomy when a complicated appendicitis was identified, or postoperatively by CT scan. In the appendicectomy group, diagnosis of postoperative peritonitis was made with CT scan findings for patients with fever, abdominal pain, and high concentrations of white-blood cells and C reactive protein. Signs of localized postoperative peritonitis on CT scans were densification of soft tissue with or without organized fluid collection (abscess) of the right iliac fossa. Appendicectomy done within 30 days of treatment Initiation in the antibiotic group was

		Appendicectomy group (n=119)	Antibiotic treatment group (n=120)
Age (years)/Sex			
		34 (12)	31 (9)
Men		70 (59%)	73 (61%)
Women		49 (41%)	47 (39%)
Employment status full time or part time Body-mass index (kg/m2)		24·1 (4·1)	23·0 (3·8)
		87 (73%)	83 (69%)
Clinical symptoms on admission			
Full-time or part-time work	Sudden onset of pain*	59 (50%)	57 (48%)
	Mean pain score VAS (0–10)†	6·4 (2·1)	6·3 (1·9)
	Body temperature >37·5°C	32 (28%)	38 (32%)
	Biological ?ndings		
	Leucocytes (10⁹/L)	13·1 (3·4)	13·6 (3·6)
	High CRP concentration‡	78 (68%)	76 (68%)
	Additional CT ?ndings§		
	Local caecal-wall thickening	14 (13%)	17 (15%)
	In?ammation of periappendiceal fat	47 (44%)	49 (44%)
	Intraluminal stercolith	22 (21%)	19 (17%)

Table 1: Baseline characteristics of the intention-to-treat population

	Appendicectomy (n=119)	Antibiotic-treatment group (n=120)	Di?erence (95% CI) group
Primary endpoint events Incidence of			
30-day post-therapeutic peritonitis	2 (2%)*	9 (8%)†	5·8 (0·3 to 12·1)
peritonitis			
Complicated appendicitis with peritonitis identi?ed at surgery	21 (18%)‡	9 (8%)†	−10·1 (−18·7 to −1·7)
Postoperative peritonitis	2 (2%)‡	2 (2%)§	0 (−4·4 to 4·4)

Data are number unless otherwise stated. *In the appendicectomy group, two cases of postoperative peritonitis occurred; these patients had postoperative localised peritonitis successfully treated with antibiotics. †In the antibiotic group, complicated appendicitis with peritonitis was identified during appendicectomy performed within 30 days of treatment initiation in nine of 14 patients who did not show improvement. ‡Discovery of a complicated appendicitis with peritonitis in the appendicectomy group was not a primary endpoint. §Two patients in the antibiotic group, who underwent secondary appendicectomy, had postoperative peritonitis.

Table 2: Incidence of primary endpoint events and complicated appendicitis with peritonitis and postoperative peritonitis within 30 days after the start of treatment in both groups (intention-to-treat population)

	Within 30 days (n=120)	Between 30 days and 1 year of follow-up (n=102)*
Number of patients (%; 95% CI)	14 (12%; 7·1–18·6)	30 (29%; 21·4–38·9)
Appendicitis (%; 95% CI) Complicated†	13 (11%; 6·4–17·7)	26 (25%; 18·0–34·7)
Uncomplicated	8	3
No appendicitis	4	23
Fibrous	1	4

*120 patients in the antibiotic-treatment group minus 14 patients who had an appendicectomy during the ?rst 30 days of follow-up and four who discontinued follow-up before 1 month. †Complicated appendicitis with peritonitis.

Table 3: Duration of post-therapeutic pain, hospital stay, and disability (intention-to-treat population)

	Appendicectomy	Antibiotic-treatment group (n=120)	p group (n=119)	treatment	value		
Duration of pain*	1·70 (1·67)	1·43 (1·35)	0·13	Duration of hospital stay	3·04 (1·30)	3·56 (4·87)	0·08
Duration of disability	10·45 (8·20)	9·82 (10·51)	0·25				

Data are mean (SD), p value (Wilcoxon test). Duration in days. *Pain as assessed with the visual analogue score =4.

Table 4: Aspects of appendices during appendicectomy done in 44 of 120 patients treated initially with antibiotics (intention-to-treat population

not a primary endpoint if complicated appendicitis with peritonitis was not identified at surgery. Secondary endpoints were the number of days with a post intervention visual-analogue-scale pain score ≥4 (on a 0–10 scale),[15] length of hospital stay and absence from work (total days including any additional hospital stays), incidence of complications other than peritonitis within 1 year (postoperative wound abscess, incisional hernia, adhesive occlusion), and recurrence of appendicitis after antibiotic treatment (appendicectomy done between 30 days and 1 year of follow-up, with a confirmed diagnosis of appendicitis).

Statistical analysis: This study was based on the notion that antibiotic treatment would not be inferior to appendicectomy in relation to the primary efficacy outcome with the use of a pre specified non-inferiority margin the upper limit of the 95% CI for the difference in rates would not exceed 10 percentage points. We calculated that a sample size of 200 patients would give a power of 80% to establish whether antibiotic treatment was not inferior to appendicectomy in relation to the 30-day incidence of postintervention peritonitis. This sample size took into account an expected 30-day incidence of peritonitis after appendicectomy for uncomplicated appendicitis of 2%,16,17 a non-inferiority margin of 10%, and a two-sided α risk of 0·05.18 However, we planned to enrol 250 patients because of the possible loss of patients after their inclusion. Study outcomes were assessed by both intention to treat and per-protocol analyses. The intention-to-treat population included all randomised participants who began a treatment (surgical treatment or at least one dose of antibiotics). A second reading of the CT scan was done later by an assigned non-emergency radiologist, who was masked to the patients' treatment or status, to confirm initial CT scan diagnosis of uncomplicated appendicitis made by the emergency radiologist. The per-protocol population included all patients who completed the study (1 year), and for whom the second reading of a CT-scan confirmed the diagnosis of uncomplicated appendicitis. The primary analysis in this non-inferiority trial compared the two study groups for the rate of peritonitis that occurred within 30 days of treatment initiation. The 95% CIs for absolute difference in percentages between the antibiotic-treatment group and the surgery group were estimated according to the methodology used by Altman and colleagues.19 Secondary binary endpoints were similarly analyzed. Wilcoxon tests were used to compare durations. Webappendix pp 1–2 shows management of missing data. All reported p values are two-sided and were not adjusted for multiple testing. We did additional post-hoc analyses. Factors predictive of complicated appendicitis in the appendicectomy group were calculated. For the antibiotic-treatment group, factors predictive of absence of improvement (patients needing appendicectomy during the first 30 days after start of antibiotic treatment, with a confirmed histological diagnosis of acute appendicitis), or of recurrence of appendicitis (patients needing appendicectomy between 30 days and 1 year, with a confirmed histological diagnosis of acute appendicitis) were also calculated. Univariate logistic-regression models were used to assess the association between these events and each patient's baseline clinical characteristics. We used R software (version 2.7.0) for all analyses

RESULTS

The figure shows the trial profile. 243 patients (aged 18–68 years) were enrolled into the study between March 11, 2016, and January 16, 2019. Four refused to participate in the trial shortly after randomization, therefore 239 patients constituted the intention-to-treat population. Table 1 shows baseline characteristics of these patients. Table 2 shows incidence of primary endpoints and incidence of complicated appendicitis with peritonitis and postoperative peritonitis within 30 days after the start of treatment in the intention-to-treat population. 30 day postintervention peritonitis was significantly more frequent in the antibiotic group than in the appendicectomy group 24 (10%) of 239 patients did not complete the 1-year study. 11 were excluded by re-reading of the CT-scan. The remaining 204 patients constituted the per-protocol population (figure; results are shown in webappendix pp 2–5). Primary endpoint data were missing for nine patients(four in the antibiotic group and five in the appendicectomy group). We did a sensitivity analysis to establish the effect of missing cases, excluding patients with missing data from the analysis. The rate of peritonitis within 30 days of treatment initiation remained higher in the antibiotic-treatment group than in the surgery group (difference 6·0 percentage points; 95% CI 0·3–12·5; Webappendix pp 5–6). For secondary endpoints, the median duration of severe pain, days in hospital, and absence from work did not differ between the two groups (table 3). Other postintervention complications included postoperative wound infection (two of 120 in the antibiotic group vs one of 119 in the appendicectomy group) and intestinal adhesive occlusion (one of 120 in the antibiotic group vs none in the appendicectomy group) during the 1-year follow-up. Incisional hernia did not occur in either group. No significant differences were identified between the two groups for any postintervention complications. Table 4 shows the aspects of the appendices assessed in patients who had appendicectomies treated initially with antibiotics in the intention-to-treat population. Those who underwent appendicectomy between 1 month and 1 year had the operation after a median of 4·2 months (range 1·2–11·1). Overall, 81 (68%) of 120 patients did not need an appendicectomy for acute appendicitis in the antibiotic group during the 1-year follow-up. Post-hoc analyses showed that laparoscopic or McBurney approach rates were similar in both groups (web appendix pp 6–7). Logistic-regression analyses showed that CT-scanner type (multidetector vs single detector) was not significantly associated with misdiagnosed complicated appendicitis (p=0·42; table 5). Presence of a stercolith on preoperative CT scan was the only factor associated with a significantly increased risk of complicated appendicitis (table 5, p<0·0001). In the antibiotic group, the presence of a stercolith was also the only factor associated with failure of antibiotic treatment for appendicitis (table 6, p=0·0072). In the subgroup of patients without visualization of a stercolith on initial CT scan, we identified no significant difference in the incidence of 30-day postintervention peritonitis between the two groups (difference 2·9 percentage points; 95% CI –3·0 to 9·2; webappendix p 7). No factors were associated with the recurrence of appendicitis. No adverse events were deemed by the investigator as being related to CT scanning or antibiotic treatment.

DISCUSSION

Incidence of 30-day post intervention peritonitis, which was the main judgment criterion, was significantly higher in the antibiotic-treatment group than in the appendicectomy group. This study showed that antibiotic treatment with amoxicillin plus clavulanic acid was not non-inferior to emergency appendicectomy for treatment of acute uncomplicated appendicitis. Trials that show that acute appendicitis can be treated successfully with antibiotics2–5 were weakened by several design limitations. For example, diagnosis of uncomplicated appendicitis was not supported by systematic CT-scan assessment, although researchers claimed to have treated uncomplicated appendicitis alone [7]. Therefore, we tried to avoid these limitations in our study by using CT scans to select patients with uncomplicated appendicitis before randomization. Multiple detector CT scanning is generally accepted as the best investigation to diagnose acute appendicitis, because it has a high sensitivity and specificity [8]. Indeed, only 3% of patients allocated to surgery in our trial had no appendicitis, which compares favourably with the 10–15% reported in two previous studies [9,10]The study was limited by the short follow-up period. Recurrence of appendicitis might have continued after one year. Masking of participants or clinicians to treatment allocation was not possible, and research assessors were also not masked .In our trial, two-thirds of patients in the antibiotic group who needed an appendicectomy during the 30 days after treatment initiation had complicated appendicitis, consistent with previous studies [11,12]. This finding could be interpreted as a failure of the antibiotics to prevent complications after non-operated acute uncomplicated appendicitis; however, if this were the case, the rate of complicated appendicitis discovered during appendicectomy in the antibiotic group would be expected to be higher than that identified in the appendicectomy group. In fact, complicated appendicitis was less frequent in the antibiotic group than in the appendicectomy group (table 2). Alternatively, complicated appendicitis might already have been present in these patients at the time of randomization, despite not being diagnosed on CT scan, and some were successfully treated with amoxicillin plus clavulanic acid. Therefore, our finding that antibiotic treatment with amoxicillin plus clavulanic acid was inferior relative to appendicectomy in patients with uncomplicated acute appendicitis might be related to the small proportion of patients with complicated appendicitis who were erroneously included and randomised. Distinction between uncomplicated and complicated appendicitis remains difficult even with multiple-detector CT scans[13,14]Morphological diagnosis of appendiceal perforation depends on indirect but late signs, which are very specific but have a low sensitivity; however, Tsuboi and colleagues[15,16] have suggested that morphological diagnosis could be improved. Additionally, in our trial and other reports, visualization of a stercolith on the initial CT scan predicted both complicated appendicitis in patients treated with appendicectomy[17,18] and failure in the antibiotic group.24 Even though complicated appendicitis can also be cured with antibiotics, further trials of such treatment of acute appendicitis should focus on use of new diagnostic techniques for improved patient selection. The inferiority of antibiotic treatment versus appendicectomy could be also related to appendicitis resistant to amoxicillin plus clavulanic acid. Evidence shows that resistance of Escherichia coli to this antibiotic combination is increasing [19,20].Third-generation cephalosporins could be used, although they are not yet recommended[21]. Nearly a quarter of our patients who recovered after antibiotic treatment had recurrence of appendicitis; this finding is more than the 14% reported in previous studies[22,23]This difference could be explained by the high rate of patients lost to 1-year follow-up in previous trials[24,25]. Our results suggest that emergency appendicectomy remains the gold standard for treatment of acute uncomplicated appendicitis.

CONCLUSION

The Current result conclude that Amoxicillin plus clavulanic acid was not non-inferior to emergency appendicectomy for treatment of acute appendicitis. Identification of predictive markers on CT scans might enable improved targeting of antibiotic treatment and also our study Further suggest that that emergency appendicectomy remains the gold standard for treatment of acute uncomplicated appendicitis.

Conflicts of intrest: The Authors have no conflicts of intrest.

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