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Original Article

Factors associated with recurrent appendicitis after successful treatment with antibiotics

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Abstract

Background: As more patients with appendicitis are treated with antibiotics, factors associated with recurrence may help inform individualized prognostication and decision-making.

Methods: This cohort study, using data from the Comparison of Outcomes of Antibiotic Drugs and Appendectomy trial, examined patients treated with antibiotics who did not undergo appendicectomy in the first 30 days. Patients who had appendicectomy between 30 days and 1 year were compared with those who did not. Marginalized logistic regression models were used to calculate adjusted risk differences (RDs) to estimate the association between baseline patient factors and the risk of undergoing an appendicectomy between 30 days and 1 year.

Results: Of 601 patients treated with antibiotics who did not undergo appendicectomy within 30 days (mean age 38.0 years; 217 women (36.1 per cent)), 144 had an appendicectomy and 56 were lost to follow-up between 30 days and 1 year. The estimated rate of appendicectomy between 30 days and 1 year was 28.6 (95 per cent c.i. 25.0 to 32.8) per cent. After adjustment for other factors, nausea, vomiting, or anorexia at baseline presentation was associated with an increased rate of appendicectomy between 30 days and 1 year (adjusted RD 17.52, 95 per cent c.i. 8.64 to 26.40). The presence of an appendicolith (adjusted RD 3.64, −6.08 to 13.36), or an abscess, perforation, or fat stranding on initial imaging (adjusted RD −7.23, −17.41 to 2.95) was not strongly associated with appendicectomy between 30 days and 1 year.

Conclusion: Most factors commonly associated with appendicitis severity were not strongly associated with an increased risk of undergoing appendicectomy in the longer term after treatment with antibiotics.

Introduction

Antibiotics are a safe and effective treatment for acute appendicitis[1]. As more patients are treated successfully with antibiotics, clinicians will probably be increasingly asked about the longer-term likelihood of appendicitis recurrence or appendicectomy for any reason. Although the chance of appendicectomy during the index episode (0–30 days after initiating treatment) appears to be increased with radiographic evidence of appendicolith, and slightly with increasing appendiceal diameter[2,3], almost nothing is known about factors associated with appendicectomy after 30 days. This is an important knowledge gap because the incidence of appendicectomy in both European and US trials of antibiotics nearly doubles between 30 days and 2 years[4]. Understanding the individual-level chance of longer-term appendicectomy in patients who avoid appendicectomy during the index presentation and initial treatment interval (30 days) may be helpful for clinic-based decision-making about subsequent management.

The CODA (Comparison of Antibiotic Drugs and Appendectomy) trial[5] was the largest randomized study of antibiotics for appendicitis, and included patients with most types of appendicitis commonly treated by appendicectomy (for example, it included people with perforation and appendicolith, but excluded those with abscess or severe phlegmon). True recurrence is difficult to ascertain owing to lack of a standardized definition and logistical barriers to capturing such information; however, studying longer-term appendicectomy in patients who are initially treated with antibiotics can provide a useful and patient-centred clinical outcome that is well defined and easier to ascertain accurately.

In this secondary analysis of CODA data, the relationship between patient characteristics measured at baseline presentation and features of response to antibiotic treatment in the first 30 days with longer-term appendicectomy between 30 days and 1 year was assessed. The goal of this study was to explore associations that could potentially inform conversations about subsequent management in patients who had antibiotic treatment for appendicitis and who did not undergo appendicectomy by 30 days.

Methods

The protocol for the CODA trial was approved by institutional review boards at all 25 participating sites and all participants provided written informed consent. CODA followed the STROBE reporting guidelines, and was registered with ClinicalTrials.gov (NCT02800785).

CODA trial

CODA was a non-blinded RCT designed to assess whether antibiotic treatment for appendicitis was non-inferior to

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appendicectomy. It was conducted at 25 US medical centres, and included patients with imaging-confirmed appendicitis who were approached consecutively in emergency departments between 3 May 2016 and 5 February 2020. Information about the trial, protocols, and primary analysis have been published previously[4,5]. Briefly, patients were randomized in a 1 : 1 ratio to treatment with antibiotics or appendicectomy. Previously published papers have reported both short-term[5] and longer-term[4] appendicectomy rates in the group assigned to antibiotics, and examined factors associated with short-term appendicectomies (within 30 days)[2]. Study exclusion criteria and both treatments have been described previously[5].

Outcome

The primary outcome of this secondary analysis was appendicectomy for any reason between 30 days and 1 year after randomization. Appendicectomies were reported by patients via surveys. Participants were designated as lost to follow-up (missing) at the time of a particular survey if an appendicectomy was not reported in a previous survey, participants did not respond to any surveys thereafter, and appendicectomy was not documented in the health record. When an appendicectomy was reported but the date of the operation could not be obtained, the median time between surveys was used to estimate the timing of the appendicectomy.

Patient factors

Baseline variables measured at the time of study enrolment were considered. These variables have been described previously[2], and include patient characteristics (age, sex, BMI), physiological/clinical (duration of symptoms, average pain in the previous 7 days, white blood cell (WBC) count, fever, and patient-reported nausea, vomiting, or anorexia), and radiological (appendiceal diameter, appendicolith, and perforation, abscess, or fat stranding) factors. Some postbaseline patient factors were also considered in this analysis. Whether patients were prescribed additional antibiotics in the first 30 days after randomization was determined from the survey question 'Since the initial treatment of your appendicitis with antibiotics, have you had to have an additional course of antibiotics for appendicitis?' (yes or no). Patients who answered 'yes' in the 1-, 2-, or 4-week surveys were counted as having had additional antibiotics in the first 30 days. Participants were counted as not having had additional antibiotics if they did not answer 'yes' in any of the three surveys and returned a 4-week survey. Whether patients had an abscess (including intra-abdominal abscess, abscess drainage procedure, and organ space infection) within 30 days of randomization was determined from medical records.

Statistical analysis

The secondary analysis presented here includes only CODA participants randomized to antibiotics who did not have an appendicectomy within 30 days of randomization. Patients who were lost to follow-up at 30 days were also excluded. Baseline demographic and clinical characteristics were described using mean(s.d.) or median (i.q.r.) for continuous measures, and count and percentage for categorical variables. The association between each baseline characteristic and appendicectomy between 30 days and 1 year was measured as a risk difference (RD) with 95 per cent confidence interval. RDs were calculated by marginalizing a logistic regression model[6]. A model including all baseline factors listed above was used to calculate adjusted RDs. For any baseline characteristic whose adjusted RD had a confidence interval excluding 0, two Cox proportional hazards models were fit to better understand how associations might change over time: one examining appendicectomies between 30 days and 1 year, and the other examining appendicectomies between 30 days and 3 years. The reported HRs were adjusted for the same baseline characteristics accounted for in the adjusted RD. The longer 3-year time frame was used only in this secondary analysis because of the increase in missing appendicectomy status over time (374 of 601 lost to follow-up by 3 years) (*Fig. 1*).

To better understand the baseline factors that were treated as continuous variables in the primary models, rates of appendicectomy within quartiles were reported. Associations were visualized using locally estimated scatterplot smoothing curves, which fit a smooth curve to summarize trends without imposing cut-off points or restrictive models.

Where appropriate, missing data on appendicectomy status and other patient characteristics were imputed using multivariate imputation by chained equations[7]; *Table 1* shows details of missing data. The imputation process included the primary outcome of appendicectomy between 30 days and 1 year, patient factors of interest, and other measures reported by the participants (*Appendix A*). Estimates were pooled across 20 imputation sets using Rubin's rules[8].

In a planned sensitivity analysis, RDs and adjusted RDs were recalculated using only appendicectomies between 30 days and 1 year for which appendicitis had been confirmed by a pathology report and excluding appendicectomies that were performed primarily for non-clinical reasons (*Appendix B*).

All analyses were undertaken using R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). Data were analysed from November 2021 to April 2022.

Approach to inference

This was a secondary analysis of the CODA trial, and the primary analysis of this study was planned before examining any of the relevant associations. This study was exploratory, and did not involve prespecified hypotheses regarding specific patient or disease factors. No formal hypothesis testing was employed in this analysis and *P* values for associations were not reported. Associations were interpreted primarily using the calculated adjusted RDs and 95 per cent confidence intervals. Where the point estimate and confidence interval did not include clinically meaningful RDs, this was interpreted as indicating no association between the patient factor and the outcome. Where confidence intervals were wide and included clinically meaningful as well as what might be considered to be clinically irrelevant RDs or no association, this was interpreted as providing no strong evidence of an association between the factor and the outcome; however, the present analysis cannot rule out a clinically meaningful association. Where point estimates and confidence intervals included clinically meaningful values only, this was interpreted as providing preliminary evidence for a clinically relevant association.

Results

Of the 776 participants randomized to antibiotics, 175 were excluded from this analysis because they underwent appendicectomy within the first 30 days (155 participants) or were lost to follow-up so the appendicectomy status at 30 days was unknown (20) (*Fig. 1*). Of the 601 participants eligible for this analysis, 144 had an appendicectomy and 56 were lost to

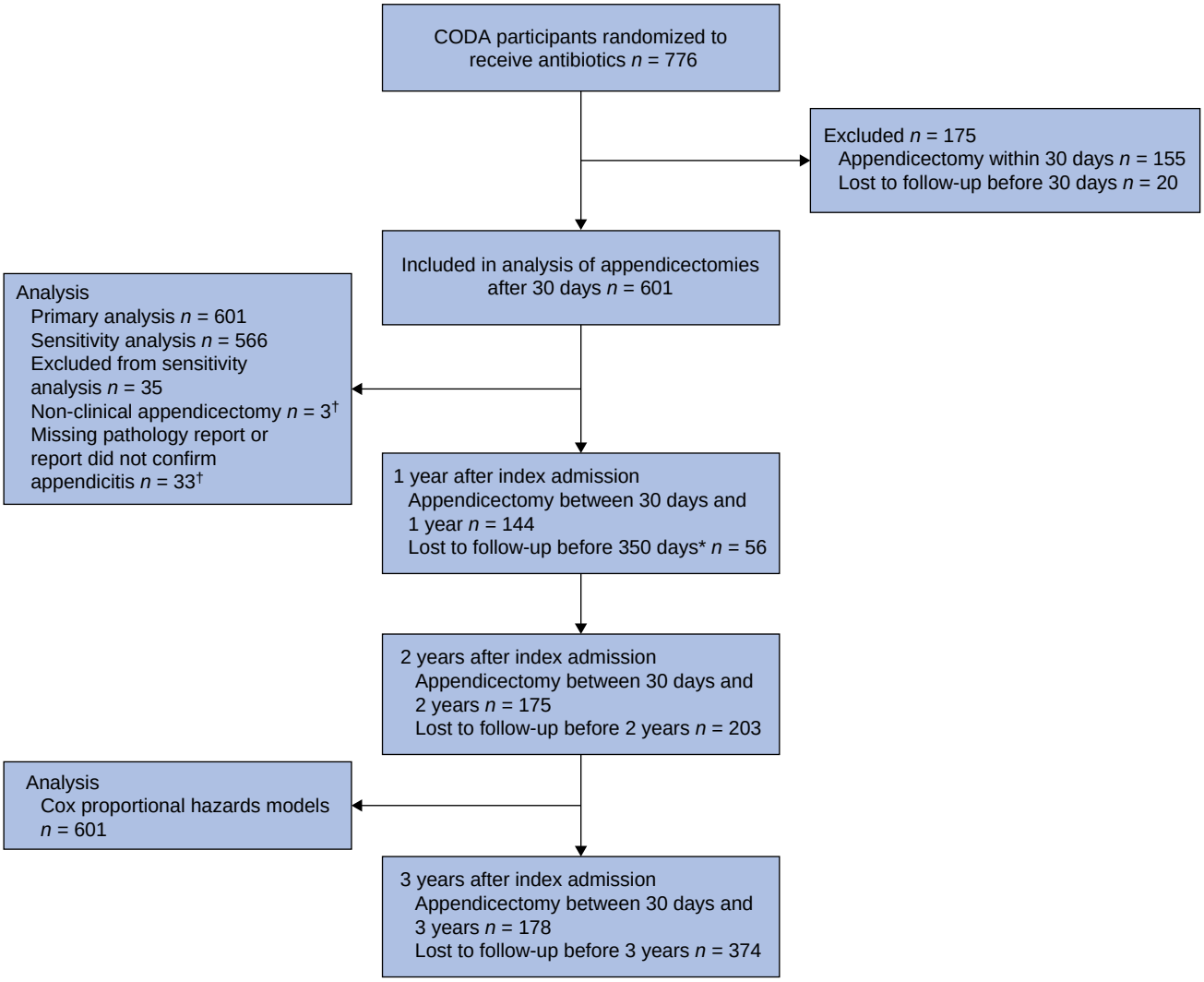

Fig. 1 Exclusion criteria and relevant participant follow-up for analyses of CODA trial participants who consented to randomization and were assigned to receive antibiotics

*For the primary analysis, to allow for variation in when participants completed the 1-year survey, participants who did not report an appendicectomy and returned the 1-year survey between 350 and 365 days and were then lost to follow-up were counted as having no appendicectomy between 30 days and 1 year. Three participants were lost to follow-up between 350 and 365 days. †One participant was excluded based on both criteria. CODA, Comparison of Antibiotic Drugs and Appendectomy.

follow-up between 30 days and 1 year. Accounting for missing data with multiple imputation, the estimated rate of longer-term appendicectomy from 30 days to 1 year was 28.6 (95 per cent c.i. 25.0 to 32.8) per cent.

Among 601 patients (mean age 38.0 years, 217 women (36.1 per cent)), most clinical and sociodemographic characteristics were similar between the 144 patients who did and the 401 who did not undergo appendicectomy between 30 days and 1 year (*Table 1*). Of the 144 people who had an appendicectomy between 30 days and 1 year, pathology reports were available for review for 124 (86.1 per cent), of whom 114 (91.9 per cent) had acute appendicitis identified on the pathology report.

Nausea, vomiting, or anorexia at initial presentation

After adjusting for demographic and baseline clinical characteristics, only nausea, vomiting, or anorexia at initial presentation appeared to be associated with appendicectomy between 30 days and 1 year (*Table 2*). The adjusted risk of appendicectomy was 17.52 percentage points higher in the group that reported nausea, vomiting, or anorexia than in the group that did not (adjusted RD 17.52, 95 per cent c.i. 8.64 to 26.40). Specifically, patients who did not report nausea, vomiting, or anorexia at baseline presentation had a lower incidence of appendicectomy between 30 days and 1 year (*Table S1*). The adjusted HR for appendicectomy based on nausea, vomiting, or anorexia was 2.66 (95 per cent c.i. 1.37 to 5.17) for between 30 days and 1 year, and 1.73 (1.05 to 2.84) for between 30 days and 3 years. In the sensitivity analysis focused on pathologically confirmed appendicitis, the adjusted RD was 15.41 (7.12 to 23.70) (*Table S2*). *Appendix C*, *Table S3*, and Fig. S1 provide details about nausea, vomiting, and anorexia, and the association with appendicectomy.

White blood cell count at initial presentation

In the univariable model (*Table 2*), for each increase of 1000 per μl in WBC count, the risk of appendicectomy between 30 days and 1 year increased by 1.06 (95 per cent c.i. 0.14 to 1.97) percentage

Table 1 Demographic and clinical characteristics of participants randomized to antibiotics who did not undergo appendicectomy in the first 30 days, by appendicectomy status between 30 days and 1 year after randomization

	Overall ($n = 601$)	Appendicectomy between 30 days and 1 year	
		Yes ($n = 144$)	No ($n = 401$)
Sociodemographic factors assessed at baseline			
Age (years), mean(s.d.)	38.0 (13.2)	37.9 (13.3)	38.3 (13.1)
Sex ratio (M : F)	384 : 217	85 : 59	255 : 146
Race			
Multiple or other	126 (21.2)	25 (17.5)	88 (22.3)
White	370 (62.3)	96 (67.1)	244 (61.8)
Black	59 (9.9)	16 (11.2)	33 (8.4)
American Indian or Alaska Native	7 (1.2)	0 (0.0)	5 (1.3)
Asian	29 (4.9)	5 (3.5)	24 (6.1)
Native Hawaiian or Pacific Islander	3 (0.5)	1 (0.7)	1 (0.3)
Hispanic			
No	327 (54.4)	83 (57.6)	217 (54.1)
Yes	274 (45.6)	61 (42.4)	184 (45.9)
Preferred language			
English	422 (70.2)	98 (68.1)	282 (70.3)
Spanish	179 (29.8)	46 (31.9)	119 (29.7)
Health literacy help			
Never or rarely	478 (82.6)	114 (81.4)	323 (84.3)
Sometimes or more	101 (17.4)	26 (18.6)	60 (15.7)
Worried about bills			
No	174 (29.5)	44 (31.2)	111 (28.2)
Yes	416 (70.5)	97 (68.8)	282 (71.8)
Below federal poverty level or Medicaid beneficiary			
No	257 (56.1)	70 (61.9)	170 (55.9)
Yes	201 (43.9)	43 (38.1)	134 (44.1)
Modified Charlson Co-morbidity Index score, mean(s.d.)	0.2(0.5)	0.2 (0.5)	0.2 (0.5)
BMI (kg/m^2)			
< 25	139 (31.2)	35 (33.3)	96 (32.3)
25 to < 35	234 (52.5)	55 (52.4)	155 (52.2)
≥ 35	73 (16.4)	15 (14.3)	46 (15.5)
Clinical factors assessed at baseline			
Alvarado score, mean(s.d.)	6.5 (1.6)	6.8 (1.7)	6.4 (1.6)
Absolute neutrophil count (×1000/μl), median (i.q.r.)	10.3 (7.6–13.4)	11.0 (8.5–14.5)	10.0 (7.4–13.2)
Duration of symptoms (days)			
< 1	150 (25.0)	38 (26.4)	98 (24.4)
≥ 1	451 (75.0)	106 (73.6)	303 (75.6)
Pain score in previous 7 days, mean(s.d.)	5.3 (2.9)	5.5 (3.1)	5.2 (2.9)
WBC count (×1000/μl), mean(s.d.)	12.8 (4.0)	13.5 (4.3)	12.5 (3.9)
Fever			
None or not reported	458 (76.2)	109 (75.7)	311 (77.6)
Reported	143 (23.8)	35 (24.3)	90 (22.4)
Nausea, vomiting, or anorexia			
None or not reported	99 (16.5)	10 (6.9)	80 (20.0)
Reported	501 (83.5)	134 (93.1)	320 (80.0)
Imaging			
CT alone	483 (80.4)	113 (78.5)	325 (81.0)
Ultrasonography alone	18 (3.0)	4 (2.8)	13 (3.2)
> 1 imaging test	100 (16.6)	27 (18.8)	63 (15.7)
Appendicolith			
None or not reported	457 (76.0)	104 (72.2)	313 (78.1)
Reported	144 (24.0)	40 (27.8)	88 (21.9)
Appendiceal diameter (mm), mean(s.d.)	11.3 (2.8)	11.7 (2.5)	11.2 (2.8)
Perforation, abscess, or appendiceal fat stranding			
None or not reported	504 (86.9)	124 (88.6)	330 (85.7)
Reported	76 (13.1)	16 (11.4)	55 (14.3)
Postbaseline factors			
Additional antibiotics within 30 days			
No	525 (93.3)	123 (89.1)	359 (94.5)
Yes	38 (6.7)	15 (10.9)	21 (5.5)
Abscess within 30 days			
None or not reported	583 (97.5)	138 (95.8)	392 (98.5)
Reported	15 (2.5)	6 (4.2)	6 (1.5)

Values are *n* (%) unless otherwise indicated. The following data were missing for some participants: race (7), health literacy help (22), worried about bills (11), below poverty or Medicaid/state insurance (143), Charlson Co-morbidity Index score (3), BMI (155), Alvarado score (35), absolute neutrophil count (110), pain score in previous 7 days (16), white blood cell (WBC) count (3), nausea, vomiting or anorexia (1), appendiceal diameter (83), perforation, abscess or fat stranding (21), additional antibiotics within 30 days (38), abscess within 30 days (3). Appendicectomy status between 30 days and 1 year was missing for 56 participants; these participants are included in overall data only.

points; however the adjusted RD was 0.71 (−0.25 to 1.66). In analyses considering quartiles of WBC, the lowest quartile (10 000/μl or less) was associated with a rate of appendicectomy of 26.4 (95 per cent c.i. 19.7 to 35.3) per cent, and the highest quartile (over 15 300/μl) with an appendicectomy rate of 34.3 (27.1 to 43.4) per cent. *Table S1* and *Fig. S2* describe the association between WBC and appendicectomy (without assuming a linear relationship).

Table 2 Association between baseline patient factors and appendicectomy between 30 days and 1 year in univariable and multivariable models

	Unadjusted risk difference	Adjusted risk difference*
Age (for 1-year increase)	−0.003 (−0.30, 0.29)	−0.050 (−0.38, 0.28)
Sex (F *versus* M)	2.43 (−5.65, 10.52)	0.44 (−8.14, 9.03)
BMI (25 to < 35 *versus* < 25 kg/m^2)	2.19 (−6.59, 10.98)	2.59 (−6.22, 11.40)
BMI (≥ 35 *versus* < 25 kg/m^2))	5.04 (−5.67, 15.75)	5.85 (−5.55, 17.25)
Duration of symptoms (≥1 *versus* < 1 day)	−1.93 (−10.69, 6.83)	−0.79 (−9.85, 8.27)
Pain score in previous 7 days (for 1-point increase)	0.75 (−0.58, 2.08)	0.54 (−0.81, 1.89)
WBC count (for 1000/μl increase)	1.06 (0.14, 1.97)	0.71 (−0.25, 1.66)
Fever†	2.82 (−6.49, 12.14)	2.18 (−7.22, 11.58)
Nausea, vomiting, or anorexia†	18.29 (9.91, 26.67)	17.52 (8.64, 26.40)
Appendiceal diameter (for 1-mm increase)	1.16 (−0.26, 2.58)	0.93 (−0.72, 2.57)
Perforation, abscess, or appendiceal fat stranding†	−4.61 (−15.32, 6.10)	−7.23 (−17.41, 2.95)
Appendicolith†	6.25 (−2.94, 15.43)	3.64 (−6.08, 13.36)

Values in parentheses are 95% confidence intervals. All estimated risk differences are pooled estimates from multiply imputed data sets. *Adjusted for all factors listed in this table. †Compared with none or not reported. WBC, white blood cell.

Appendiceal diameter at initial presentation

In the univariable model (*Table 2*), for each increase of 1 mm in appendiceal diameter, the risk of appendicectomy between 30 days and 1 year increased by 1.16 (95 per cent c.i. −0.26 to 2.58) percentage points, and the adjusted RD was 0.93 (−0.72 to 2.57). Considering quartiles of diameter, the lowest quartile (9 mm or less) was associated with a rate of appendicectomy of 20.6 (95 per cent c.i. 14.5 to 29.5) per cent, and the highest quartile (over 13 mm) with an appendicectomy rate of 32.3 (24.2 to 43.2) per cent (*Table S1*). *Figure 2* shows the rate of eventual appendicectomy across different values of diameter. In the sensitivity analysis focused on pathologically confirmed appendicitis, there was a stronger association between diameter and appendicectomy between 30 days and 1 year (RD 1.37, 0.09 to 2.65, for a 1-mm increase); the adjusted RD was 1.15 (−0.32 to 2.63) (*Table S2*).

Other factors at initial presentation

Some factors that have been hypothesized to confer an increased risk of eventual appendicectomy, such as radiographic evidence of perforation, abscess or fat stranding, or the presence of an appendicolith, did not appear to have an association, with wide confidence intervals and a mix of no RD, small RD, and, in one instance, a potentially clinically relevant RD. Self-reported levels of pain in the 7 days before presentation were associated with a 1-point RD and confidence intervals that did not include clinically meaningful values (*Table 2*). Alternative summaries for the continuous factors age and pain score are available in *Table S1*, *Fig. S3* and *Fig. S4*.

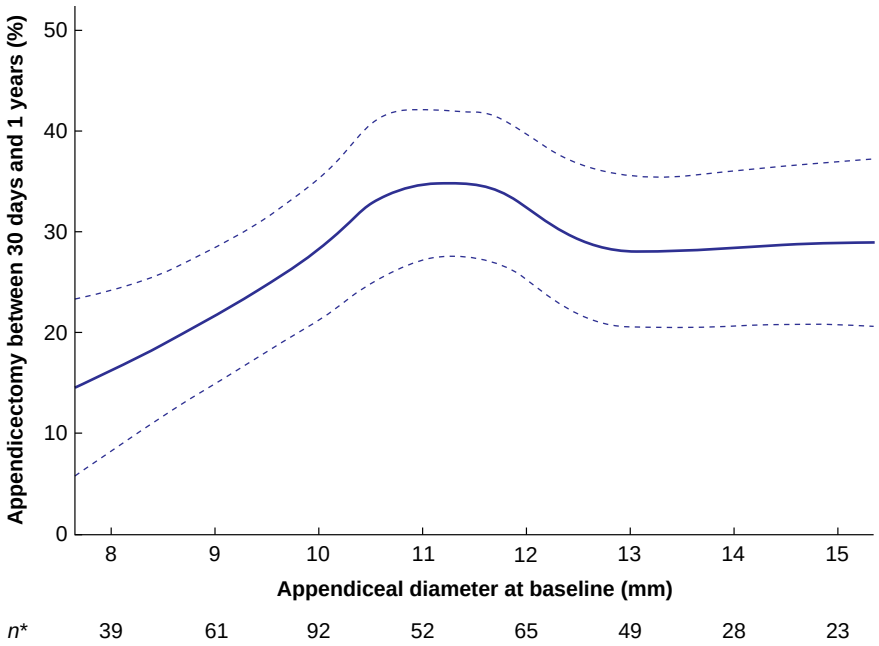

Fig. 2 Locally estimated scatterplot smoothing curve summarizing univariable association between appendiceal diameter at baseline and appendicectomy between 30 days and 1 year

Participants missing appendiceal diameter or appendicectomy status between 30 days and 1 year were excluded. *Number of participants falling into each level of appendiceal diameter, up to but not including the next highest integer; for example, there were 39 participants with an appendiceal diameter of 8.0–8.9 mm. Because of limited sample size to fit the locally estimated scatterplot smoothing curve, data for participants in the lower tail (22 participants with diameter less than 8 mm) and upper tail (40 participants with diameter greater than 15 mm) are not displayed here but were still used to inform the shape of this curve. These cut-off points were chosen based on the 10th and 90th percentiles of the data, but were not even because diameter was mostly reported to the nearest millimetre. Dotted lines represent 95% CIs.

Factors after initial presentation

A small group of participants were prescribed an additional course of antibiotics or underwent an abscess drainage procedure in the first 30 days and avoided appendicectomy in the index phase. Among the 601 participants who did not have an appendicectomy in the first 30 days, 38 had an additional course of antibiotics within 30 days; 40 (95 per cent c.i. 26 to 59) per cent of those who had additional antibiotics had an appendicectomy between 30 days and 1 year compared with 28 (24 to 32) per cent of those who did not have an additional course of antibiotics within the first 30 days. Fifteen participants had an abscess drained in the first 30 days and did not undergo appendicectomy within 30 days of randomization. Of these, 53 (30 to 94) per cent underwent appendicectomy from between 30 days and 1 year, whereas 28 (24 to 32) per cent of those who did not have an abscess drained underwent appendicectomy. The small number of participants with these characteristics precluded formal assessment by RDs or adjusted analyses.

Discussion

In this study of 601 participants randomized to treatment with antibiotics for acute appendicitis, who did not undergo appendicectomy within the first 30 days, the estimated risk of longer-term appendicectomy was 28.6 (95 per cent c.i. 25.0 to 32.8) per cent between 30 days and 1 year. Clinicians have suspected several factors—presence of an appendicolith, more severe presentations or evidence of abscess, perforation, or fat stranding on initial imaging—to be associated with an increased chance of appendicectomy in the longer term. Strong evidence supporting these associations was not found. Unexpectedly, the absence of reported nausea, vomiting, or anorexia at baseline was strongly associated with a lower rate of longer-term appendicectomy. Although evidence supporting a strong linear trend between appendiceal diameter and longer-term appendicectomy was not found, non-linear assessments suggested that a relationship may exist, most evident in the extremes of diameter (below 9 mm and above 15 mm), which are uncommon.

With evidence from several RCTs demonstrating that an antibiotic-first approach to acute appendicitis is both safe and effective[1,4,5,9], it is likely that more patients who are successfully treated with antibiotics will seek guidance regarding their chance of recurrent appendicitis. Although the outcome of longer-term appendicectomy is not equivalent to true recurrence, it is a pragmatic outcome because the occurrence of surgery at some time in the future is a meaningful outcome to patients who select antibiotics to try and avoid surgery. Understanding factors associated with longer-term appendicectomy may be important to facilitate effective decision-making. Clinicians have long suspected that a constellation of findings usually associated with appendicitis severity—perforation, appendicolith, raised WBC—may put patients at increased risk of appendicectomy after initiating antibiotics. This analysis has indicated that, in contrast to the primary analysis of the CODA trial[2,5], the effect of appendicolith is not relevant after 30 days. Contrary to the notion that so-called 'complicated appendicitis' confers a higher risk of recurrence, the presence of perforation, abscess, or fat stranding on initial imaging was not associated with increased rate of longer-term appendicectomy among those who did not have an appendicectomy in the first 30 days. The observation in the present study that these factors may have a negative association with appendicectomy raises the possibility that more severe inflammation results in scarring of the appendix which may make longer-term appendicectomy less likely.

There was a strong association between nausea, vomiting, or anorexia at baseline presentation, and the risk of longer-term appendicectomy. More specifically, the minority of participants without nausea, vomiting, or anorexia at index presentation (99 of 600 patients (16.5 per cent) in this analysis) had a lower risk of appendicectomy than the larger, more typical group that had nausea, vomiting, or anorexia. Nausea, vomiting, and anorexia are often associated with appendicitis, and may be linked to the underlying pathophysiology[10]. Given the growing evidence that some groups of patients with appendicitis recover without any treatment[11,12], identifying biological factors that decrease the risk of appendicectomy should be an important avenue for research; additional placebo-controlled trials should be undertaken to better understand the subgroup of patients who may be able to recover without antibiotic treatment. Although care must be taken in interpreting and using this finding, given the lack of a prespecified hypothesis regarding this association, the magnitude of the effect is notable. Lastly, although appendiceal diameter has been associated with the risk of primary non-response/early appendicectomy in several studies, including the CODA trial[2], only a modest relationship between increasing appendiceal diameter and longer-term appendicectomy was found. The Appendicitis Acuta II study[3] suggested that size over 15 mm increases the risk of short-term appendicectomy. In the present analysis, only 43 of 518 participants (8.3 per cent) had a diameter greater than 15 mm, precluding effective evaluation of the risk at this size.

This study has notable limitations. The analysis was restricted to patients who did not undergo appendicectomy in the first 30 days so, in considering these results for patients, the factors analysed should be interpreted as 'baseline variables among those who did not undergo appendicectomy in the first 30 days'. The application of these results in clinical conversations should be reserved for those who have recovered from an episode of appendicitis without appendicectomy by 30 days. The CODA trial was not designed nor adequately powered to assess the relationship between baseline characteristics and this outcome; in many instances, the confidence intervals around risk estimates are wide, and do not exclude clinically meaningful RDs. The analysis did not include patients with recurrences that were treated with antibiotics rather than appendicectomy after 30 days[13] because of concerns related to the fidelity of the diagnosis in this cohort as detailed information about clinical presentation at the time of subsequent appendicectomy was not available. Furthermore, the trial did not specify standardized criteria for pathological assessment of surgical specimens, instead relying on the interpretations of local pathologists, potentially leading to variability in rates of pathologically confirmed acute appendicitis. Some potentially important variables were limited by missing data or were too rare to analyse effectively in this study cohort. Nausea, vomiting, and anorexia are patient-reported symptoms that do not have validated clinical scales for analysis. Social factors that influence patients' access to care for follow-up episodes were not assessed, and these may have influenced whether participants underwent appendicectomy during follow-up. Finally, although the CODA study used the 30 days from randomization to distinguish the index episode of appendicitis from longer-term appendicectomy, this may not necessarily be

a biological distinction and there is no standard definition of appendicitis recurrence. Given the pragmatic design of the CODA trial, repeat CT was not required to confirm the resolution of index appendicitis and documentation of symptom resolution before longer-term appendicectomy was not required.

In conclusion, in this exploratory analysis of patients undergoing antibiotic treatment for appendicitis in the CODA trial, factors often used to characterize the severity of an appendicitis episode, such as the presence of abscess, perforation, fat stranding, or an appendicolith on initial CT or ultrasonography were not strongly associated with the risk of longer-term appendicectomy between 30 days and 1 year. The absence of nausea, vomiting, or anorexia at baseline and small appendiceal diameter may be associated with a lower chance of appendicectomy from 30 days to 1 year, but this finding was unexpected and should be confirmed in other cohorts. The lack of strong associations between longer-term appendicectomy and most baseline factors favours a more individualized decision-making process after initial successful management with antibiotics. Based on a patient's unique characteristics, priorities and preferences, these findings, in concert with previously published data[4] describing overall rates of appendicectomy from the time of initial presentation, may be used to guide either expectant management or potentially inform a patient's interest in elective surgery.

Collaborators

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Disclosure

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Deidentified, individual-participant data will be available at the end of the study. A data dictionary describing raw data fields and derived variables will be provided. The study protocol was published in *BMJ Open* (https://bmjopen.bmj.com/content/7/11/e016117). The statistical analysis plan and informed consent form will also be made available at the end of the study. The dates of availability, location of data, who will be able to request the data and how are pending, based on contracting with PCORI.

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