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A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis

The CODA Collaborative*

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Background

- Appendectomy is the standard treatment for appendicitis
- Antibiotics can be an alternative in uncomplicated appendicitis

- Within one year, 27.3% of patients who received antibiotics underwent appendectomy[1]

1) Salminen P. et al, Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical trial. JAMA. September 25, 2018. Volume 320;12. 125-1265

Methods

- Multicenter study in 25 hospitals in the US
- Adults > 18y with appendicitis confirmed on imaging
- Subgroup of patients with appendicolith was included

- Exclusion criteria: septic shock, diffuse peritonitis, recurrent appendicitis, severe phlegmone on imaging, walled-off abscess, free air or more than minimal free fluid, evidence suggestive of neoplasm

Treatments

- <u>Antibiotics:</u>
  - I.V. formulation for at least 24h followed by pills for a 10-day total course
  - Appendectomy recommended if diffuse peritonitis or septic shock developed or worsening of signs and symptoms after 48h

- <u>Surgery:</u>
  - Open and laparoscopic approaches were allowed

Figure S1. Most common antibiotics in the CODA trial

For initial intravenous use (at least 24 hours)

ertapenem
cefoxitin
or
metronidazole ***plus one of the following***
- ceftriaxone
- cefazolin
- levofloxacin

For oral use (remainder of 10 total days)

metronidazole ***plus one of the following***
- ciprofloxacin
- cefdinir

Outcomes

- Primary outcome was 30-day health status (EQ-5D)
- Secondary outcomes included patient-reported resolution of symptoms, serious adverse events, surgical complications, *C. difficile* infections, reactions to antibiotics and appendectomy in the antibiotics group

Results

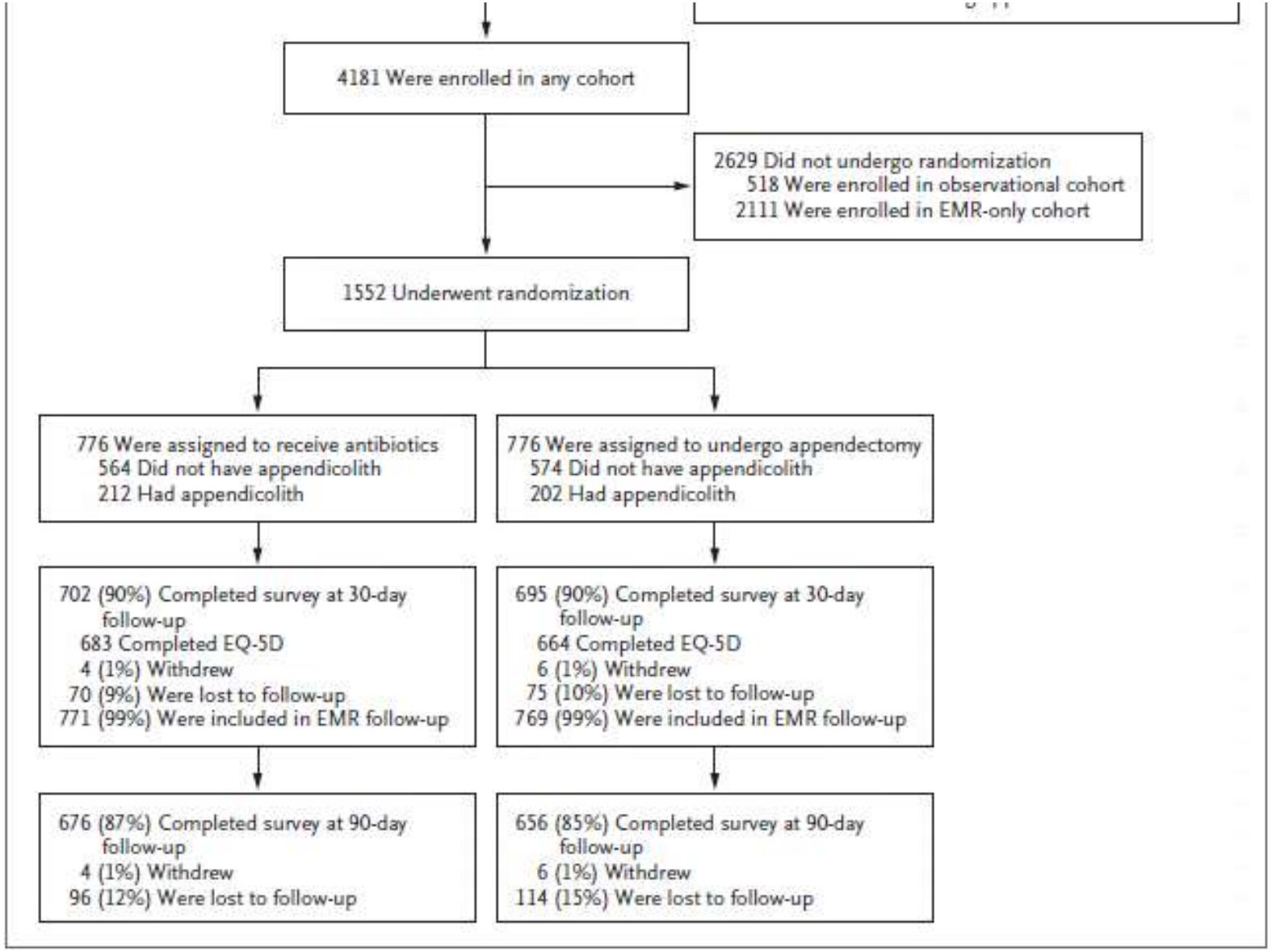
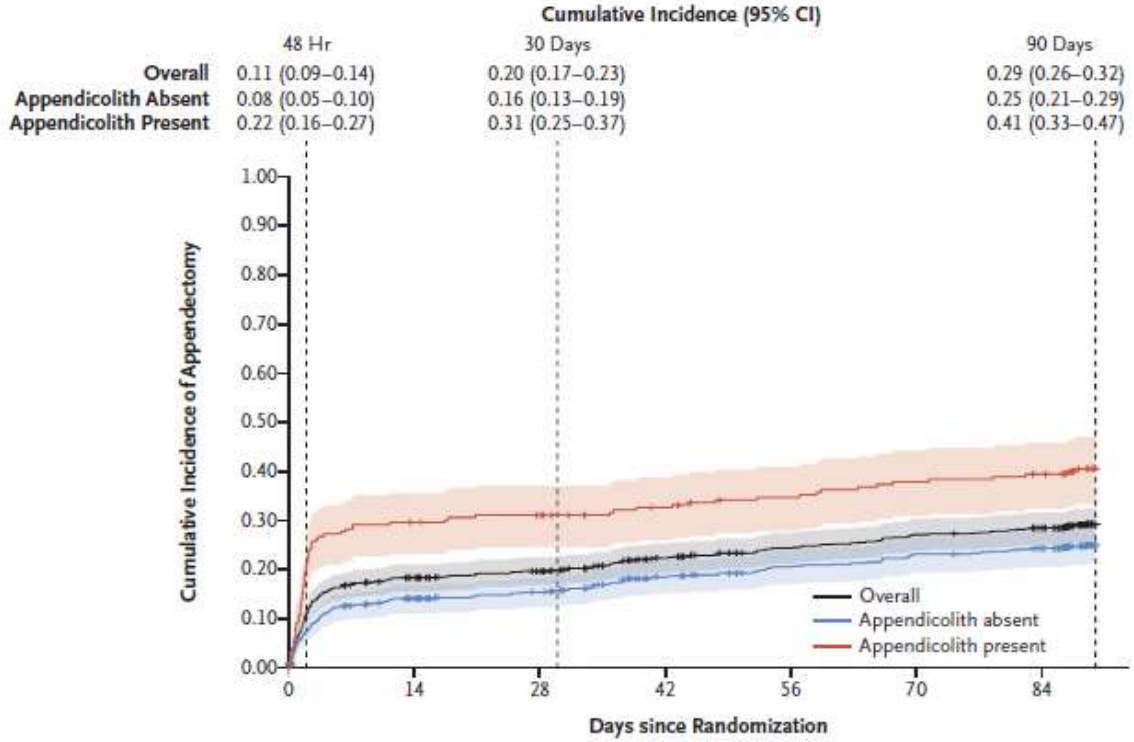

4181 Were enrolled in any cohort
2629 Did not undergo randomization
518 Were enrolled in observational cohort
2111 Were enrolled in EMR-only cohort
1552 Underwent randomization
776 Were assigned to receive antibiotics
564 Did not have appendicolith
212 Had appendicolith
776 Were assigned to undergo appendectomy
574 Did not have appendicolith
202 Had appendicolith
702 (90%) Completed survey at 30-day follow-up
683 Completed EQ-5D
4 (1%) Withdrew
70 (9%) Were lost to follow-up
771 (99%) Were included in EMR follow-up
695 (90%) Completed survey at 30-day follow-up
664 Completed EQ-5D
6 (1%) Withdrew
75 (10%) Were lost to follow-up
769 (99%) Were included in EMR follow-up
676 (87%) Completed survey at 90-day follow-up
4 (1%) Withdrew
96 (12%) Were lost to follow-up
656 (85%) Completed survey at 90-day follow-up
6 (1%) Withdrew
114 (15%) Were lost to follow-up

Table 1. Sociodemographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Antibiotics (N=776)	Appendectomy (N=776)
Age — yr	38.3±13.4	37.8±13.7
Sex — no. (%)		
Female	286 (37)	290 (37)
Male	490 (63)	486 (63)
Gender different from sex assigned at birth — no. (%)	8 (1)	6 (1)
Race or ethnic group — no. (%)†		
White	461 (60)	449 (59)
Black	75 (10)	63 (8)
American Indian or Alaska Native	13 (2)	9 (1)
Asian	39 (5)	53 (7)
Native Hawaiian or Pacific Islander	4 (1)	3 (<1)
Multiple or other	176 (23)	185 (24)
Modified Charlson comorbidity index score‡	0.24±0.53	0.24±0.53
Body-mass index§	29.0±6.6	28.6±6.1
Duration of symptoms — days	1.8±3.6	1.6±1.6
Alvarado score¶	6.6±1.6	6.7±1.7
History of fever — no. (%)	194 (25)	185 (24)
Initial white-cell count — per μl	12,900±4000	13,400±4100
Imaging test — no. (%)		
Computed tomography alone	626 (81)	609 (78)
Ultrasonography alone	24 (3)	30 (4)
>1 Imaging test	125 (16)	137 (18)

Table 2. Intention-to-Treat Comparison of Patient-Reported Outcomes, Clinical Outcomes, Time Spent in Health Care Settings, and Missed Work.*

Outcome	Overall			Appendicolith Present			Appendicolith Absent		
	Antibiotics	Surgery	Effect (95% CI)	Antibiotics	Surgery	Effect (95% CI)	Antibiotics	Surgery	Effect (95% CI)
EQ-5D at 30 days†‡	0.92±0.13	0.91±0.13	0.01 (−0.001 to 0.03)§	0.92±0.14	0.92±0.13	−0.01 (−0.03 to 0.02)§	0.92±0.13	0.91±0.13	0.02 (0.003 to 0.03)§
Resolution of symptoms — no./total no. (%)¶‖									
By 7 days	350/714 (49)	344/688 (50)	0.99 (0.89 to 1.10)**	71/189 (38)	85/183 (46)	0.81 (0.64 to 1.03)**	279/525 (53)	259/505 (51)	1.04 (0.92 to 1.16)**
By 14 days	446/685 (65)	435/678 (64)	1.02 (0.94 to 1.10)**	103/182 (57)	102/176 (58)	0.98 (0.82 to 1.18)**	343/503 (68)	333/502 (66)	1.03 (0.94 to 1.12)**
By 30 days	462/676 (68)	466/663 (70)	0.97 (0.91 to 1.04)**	125/180 (69)	111/163 (68)	1.02 (0.88 to 1.18)**	337/496 (68)	355/500 (71)	0.96 (0.88 to 1.04)**
Days from randomization to discharge for index treatment — no. of days/ no. of participants (mean)†	1030/776 (1.33)	1010/776 (1.30)	1.00 (0.89 to 1.13)††	403/212 (1.90)	330/202 (1.63)	1.15 (0.89 to 1.47)††	626/564 (1.11)	679/574 (1.18)	0.92 (0.82 to 1.05)††
Any hospitalization after index treatment within 90 days — no./total no. (%)‖	154/635 (24)	32/613 (5)	4.62 (3.21 to 6.65)**	57/176 (32)	8/157 (5)	6.36 (3.13 to 12.90)**	97/459 (21)	24/456 (5)	4.02 (2.62 to 6.16)**
Days in hospital after index treatment within 90 days — no. of days/ no. of participants (mean)†	421/622 (0.68)	93/609 (0.15)	4.38 (2.49 to 7.73)††	191/166 (1.15)	37/156 (0.24)	4.55 (1.46 to 14.18)††	230/456 (0.50)	56/453 (0.12)	4.07 (2.24 to 7.41)††
Any visit to emergency department or urgent care clinic after index treatment within 90 days — no./ total no. (%)‖	55/618 (9)	26/604 (4)	2.07 (1.32 to 3.25)**	14/165 (8)	2/153 (1)	6.49 (1.50 to 28.09)**	41/453 (9)	24/451 (5)	1.70 (1.05 to 2.77)**
Visits to emergency department or urgent care clinic after index treatment within 90 days — no. of visits/ no. of participants (mean)†	66/615 (0.11)	24/599 (0.04)	2.64 (1.57 to 4.43)††	17/163 (0.10)	2/153 (0.01)	8.19 (2.03 to 33.00)††	49/452 (0.11)	22/446 (0.05)	2.15 (1.23 to 3.76)††
Days of missed work for participant within 90 days — no. of days/ no. of participants (mean)†	2516/478 (5.26)	4131/473 (8.73)	0.63 (0.51 to 0.77)††	743/121 (6.14)	1134/125 (9.07)	0.72 (0.48 to 1.09)††	1773/357 (4.97)	2997/348 (8.61)	0.60 (0.48 to 0.76)††
Days of missed work for caregiver within 90 days — no. of days/no. of caregivers (mean)†	679/509 (1.33)	1009/495 (2.04)	0.66 (0.48 to 0.91)††	242/137 (1.77)	213/126 (1.69)	1.04 (0.56 to 1.92)††	437/372 (1.17)	796/369 (2.16)	0.56 (0.38 to 0.82)††



No. at Risk							
Overall	776	616	589	542	518	499	485
Appendicolith absent	564	470	448	411	394	381	371
Appendicolith present	212	146	141	131	124	118	114

Cumulative No. of Events							
Overall	0	141	151	170	184	203	212
Appendicolith absent	0	79	86	102	112	125	131
Appendicolith present	0	62	65	68	72	78	81

Figure 2. Cumulative Incidence of Appendectomy in the Antibiotics Group.

Plus signs indicate censoring because the participant withdrew or was lost to follow-up.

Table 3. Adverse Events and Complications at 90 Days.*

Event	Overall			Appendicolith Present			Appendicolith Absent		
	Antibiotics	Surgery	Effect (95% CI)†	Antibiotics	Surgery	Effect (95% CI)†	Antibiotics	Surgery	Effect (95% CI)†
Serious adverse events									
Participants with ≥1 event — no./total no. (%)	19/676 (3)	19/656 (3)	0.97 (0.52 to 1.80)	11/183 (6)	6/169 (4)	1.69 (0.64 to 4.48)	8/493 (2)	13/487 (3)	0.61 (0.25 to 1.45)
Total events — no. of events/no. of participants (events per 100 participants)	27/676 (4.0)	20/656 (3.0)	1.29 (0.67 to 2.50)	17/183 (9.3)	6/169 (3.6)	2.62 (0.95 to 7.24)	10/493 (2.0)	14/487 (2.9)	0.71 (0.28 to 1.76)
Unplanned hospitalization not for appendectomy	19/676 (2.8)	19/656 (2.9)	0.96 (0.48 to 1.91)	10/183 (5.5)	6/169 (3.6)	1.54 (0.55 to 4.30)	9/493 (1.8)	13/487 (2.7)	0.68 (0.26 to 1.80)
NSQIP-defined complications‡									
Participants with ≥1 event — no./total no. (%)	37/676 (5)	21/656 (3)	1.72 (1.02 to 2.90)	26/183 (14)	5/169 (3)	4.80 (1.89 to 12.22)	11/493 (2)	16/487 (3)	0.68 (0.32 to 1.45)
Total events — no. of events/no. of participants (events per 100 participants)	55/676 (8.1)	23/656 (3.5)	2.28 (1.30 to 3.98)	37/183 (20.2)	6/169 (3.6)	5.69 (2.11 to 15.38)	18/493 (3.7)	17/487 (3.5)	1.05 (0.45 to 2.43)
Site-related infectious complication§	33/771 (4.3)	21/769 (2.7)	1.54 (0.87 to 2.72)	22/210 (10.5)	7/200 (3.5)	2.99 (1.30 to 6.92)	11/561 (2.0)	14/569 (2.5)	0.80 (0.33 to 1.92)
Drainage procedure	17/676 (2.5)	3/656 (0.5)	5.36 (1.55 to 18.50)	12/183 (6.6)	1/169 (0.6)	11.08 (1.42 to 86.55)	5/493 (1.0)	2/487 (0.4)	2.47 (0.48 to 12.67)
Reaction to antibiotics that led to a health care encounter — no. of events/no. of participants (events per 100 participants)	22/676 (3.3)	1/656 (0.2)	21.36 (2.86 to 159.67)	6/183 (3.3)	0/169	NA	16/493 (3.2)	1/487 (0.2)	15.81 (2.07 to 120.50)
Clostridioides difficile colitis — no. of events/no. of participants (events per 100 participants)	4/676 (0.6)	4/656 (0.6)	0.99 (0.21 to 4.63)	0/183	0/169	NA	4/493 (0.8)	4/487 (0.8)	0.99 (0.21 to 4.63)

Discussion and limitations

- Antibiotics noninferior to appendectomy
- By week 1, resolution of symptoms was similar
- Patients with more severe appendicitis were included, which can explain higher incidence of appendectomy at day 90 and higher rate of perforation.

- Underrepresentation of recurrence and long-term complications
- Only 30% of eligible patients underwent randomization