AAHP Virtual Journal Club

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Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis

Background on appendicitis management

For years, appendectomy has been the mainstay treatment for appendicitis. There have been many trials evaluating the use of antibiotics compared to appendectomy, however, other trials have excluded potentially important subgroups including patients with an appendicolith.

This study looks at the treatment of appendicitis with antibiotics compared to appendectomy and has a subgroup to better understand management of patients with an appendicolith.

Design

This was a pragmatic, non-blinded, non-inferiority, randomized trial comparing 10-day antibiotic therapy with appendectomy in patients with appendicitis.

Key inclusion criteria were as follows:

- Consecutive English- or Spanish-speaking adults
- ≥18 years of age
- Appendicitis confirmed on imaging

Patients were randomized to receive an appendectomy or antibiotics. Patients assigned to the antibiotics group were to receive an intravenous formulation for 24 hours, followed by oral medication, for a duration of 10 days total. The antibiotics utilized were selected from the Surgical Infection Society and the Infectious Disease Society of America guidelines for intraabdominal infections.

The primary endpoint was 30-day health status assessed by the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.

This was used as the primary outcome because it was a validated measure of overall health status responsive to appendicitis treatment and the time period is typical for recovery from appendectomy.

This was different from other previous trials which utilized successful surgery and requirement of surgery within the following year as their primary outcome.

Secondary endpoints included the following:

- Patient-reported resolution of symptoms
- Serious adverse events
- National Surgical Quality Improvement Program (NSQIP) defined complications
- *Clostridioides difficile* infections
- Invasive procedures
- Appendiceal perforation

- Appendectomy in the antibiotics group

Subjects

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)
Hispanic ethnic group†	362 (47)	366 (47)
Primary language — no. (%)		
English	469 (60)	464 (60)
Spanish	267 (34)	267 (34)
Other	40 (5)	45 (6)
Insurance — no. (%)		
Commercial	323 (43)	317 (42)
Medicare or Tricare	89 (12)	89 (12)
Medicaid or other state program	134 (18)	131 (17)
Other or no coverage	213 (28)	217 (29)
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)

The baseline demographics as shown above were similar between the antibiotic and appendectomy groups. An appendicolith was identified by imaging in 27% of the participants. Nearly half (51%) of patients in the antibiotic group were admitted to the hospital for the index treatment compared to 95% of the surgery group that was admitted to the hospital.

Results

There was no difference in the primary endpoint of EQ-5D at 30 days, suggesting that use of antibiotics is non-inferior to appendectomy in treatment of appendicitis.

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 (0.008 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)††

There was shown to be no difference in the EQ-5D and symptoms at 30 days. Within 90 days, patients in the antibiotic treatment group had significantly more hospitalizations, days in the hospital, and number of visits to an emergency department or urgent care compared to the surgery group.

The surgery group, however, showed to have more days missed from work for themselves and their caregivers. This could reflect how minimally invasive the appendectomy was, and that patients often could recover at home opposed to in the hospital resulted in higher days missed for their caregivers.

These results were not shown to be different regardless of if an appendicolith was present or absent.

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 complications§	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)

There was no statistical difference in serious adverse events between the two groups.

The NSQIP-defined complications favored the surgery group, but were also non-specific with a high number needed to harm.

There were similar rates of *clostridioides difficile* between the two groups, maybe suggesting that the surgery group received perioperative antibiotics as a part of their treatment. However, it is not surprising that the number of antibiotic related reactions was higher in the antibiotic group. But the number needed to harm for this event was also fairly high.

Author's Concluding Statements

The author concluded stating for the treatment of appendicitis, antibiotics were non-inferior to appendectomy on the basis of results of a standardized measure of general health status, in the short term.

Secondary outcomes such as time spent in health care setting and missed work were noted as important considerations in decision making.

Appendicoliths are found in 20% of specimens and their effect on treatment success is unclear. Although it is related to a higher rate of complicated appendicitis.

Discussion

There was no difference in the primary endpoint of EQ-5D at 30 days, suggesting that the use of antibiotics is non-inferior to appendectomy in treatment of appendicitis. However, this endpoint is subjective and since this trial was not blinded there is a potential for these results to be skewed. This endpoint was also measured at 30 days which is a short time frame compared to previous literature which used a 12-month follow-up.

When looking at other results, within 90 days, it shows that the antibiotic treatment group had more hospitalizations, days in the hospital, and number of visits to an emergency department or urgent care when compared to the surgery group. However, days missed from work for the patient and caregiver was lower in the antibiotics group.

I found it strange that all data that could be directly measured by the investigators such as hospitalizations, days in hospital, and visits to emergency department favored the surgery group whereas subjective or patient given report such as EQ-5D, resolution of symptoms, and days missed from work favored the antibiotic group. I was unsure what to take away from these differences. Were the investigators favoring surgery or were they favoring antibiotic treatment?

Will I use this study to change how I practice?

My answer to this is no. I do not believe that this study showed non-inferiority of antibiotics to appendectomy for the treatment of appendicitis, with the exception of patient reported resolution of symptoms in the short-term.

I believe previous studies had more reliable outcomes and longer duration of patient follow-up than this study. These results are not significant enough to change practice when reviewing previously published literature.

References

1. Flum DR, Davidson GH, Monsell SE et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. N Engl J Med 2020;383:1907-19.