Methods of conservative antibiotic treatment of acute uncomplicated appendicitis: A systematic review

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BACKGROUND: Meta-analyses and a recent guideline acknowledge that conservative management of uncomplicated appendicitis with antibiotics can be successful for patients who wish to avoid surgery. However, guidance as to specific management does not exist.

METHODS: PubMed and EMBASE search of trials describing methods of conservative treatment was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.

RESULTS: Thirty-four studies involving 2,944 antibiotic-treated participants were identified. The greatest experience with conservative treatment is in persons 5 to 50 years of age. In most trials, imaging was used to confirm localized appendicitis without evidence of abscess, phlegmon, or tumor. Antibiotics regimens were generally consistent with intra-abdominal infection treatment guidelines and used for a total of 7 to 10 days. Approaches ranged from 3-day hospitalization on parenteral agents to same-day hospital or ED discharge of stable patients with outpatient oral antibiotics. Minimum time allowed before response was evaluated varied from 8 to 72 hours. Although pain was a common criterion for nonresponse and appendectomy, analgesic regimens were poorly described. Trials differed in use of other response indicators, that is, white blood cell count, C-reactive protein, and reimaging. Diet ranged from restriction for 48 hours to as tolerated. Initial response rates were generally greater than 90% and most participants improved by 24 to 48 hours, with no related severe sepsis or deaths. In most studies, appendectomy was recommended for recurrence; however, in several, patients had antibiotic retreatment with success.

CONCLUSION: While further investigation of conservative treatment is ongoing, patients considering this approach should be advised and managed according to study methods and related guidelines to promote informed shared decision-making and optimize their chance of similar outcomes as described in published trials. Future studies that address biases associated with enrollment and response evaluation, employ best-practice pain control and antibiotic selection, better define cancer risk, and explore longer time thresholds for response, minimized diet restriction and hospital stays, and antibiotic re-treatment will further our understanding of the potential effectiveness of conservative management. (J Trauma Acute Care Surg. 2019;86: 722–736. Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Systematic review, level II.

KEY WORDS: Appendicitis; nonoperative; conservative; antibiotics; uncomplicated.

PATIENTS AND METHODS

Data Sources and Searches

A literature search was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines using PUBMED (1966) and EMBASE (1947) databases for studies published in English and non-English languages through April 29, 2018, using the keywords (antibiotic or antibiotics or nonoperative or non operative or non-operative or conservative) and (appendicitis). References in the selected publications, including reviews, were searched for additional studies. Two reviewers (clinician and nonclinician) independently submitted responses for each study.
searched these databases, then reached consensus on potentially relevant publications, and evaluated candidate articles for final inclusion.

Study Selection and Criteria

Only full-text articles of trials that described initial conservative management of acute uncomplicated appendicitis were considered relevant. Studies with poorly characterized study populations were excluded. All study designs were allowed.

Data Extraction

Studies were included in data extraction if they reported methods of conservative management. Studies were categorized as follows: RCT, prospective, comparative; prospective, noncomparative;
| Study | No. Antibiotic Treated | Age Range (Average), y | Inclusion Criteria | Imaging | Clinical Exclusion Criteria | Imaging Exclusion Criteria | IV and Oral Antibiotics |
|-------|------------------------|------------------------|-------------------|---------|-----------------------------|---------------------------|------------------------|
| RCTs vs. appendectomy (n = 791) | | | | | | | |
| Eriksson and Granstrom⁴ (1995) | 20 | 18–53 (28) | WBC, CRP | US | Abdominal pain >24 h, diffuse peritonitis | NS | IV and Oral: cefotaxime and tinidazole, oral—cefloxicin and tinidazole |
| Styrud et al.⁵ (2006) | 128 | 18–50 | CRP ≥1.0 mg/dL | None | Diffuse peritonitis | NA | IV and Oral: cefotaxime and tinidazole, oral—cefloxicin and tinidazole |
| Turhan et al.⁶ (2009) | 107 | 16–65 (31) | WBC | US and CT | NS | NS | IV and Oral: ampicillin and gentamicin and metronidazole, oral—NS |
| Hansson et al.⁷ (2009) | 119 | >18 (40) | Lab tests | Selective US and CT | None | None | IV and Oral: cefotaxime and metronidazole, oral—ciprofloxacin and metronidazole |
| Vons et al.⁸ (2011) | 120 | 18–68 (31) | NS | CT | Receiving steroid or anticoagulant, history inflammatory bowel disease, pregnancy, serum creatinine >200 μmol/L | Extraluminal gas, periappendiceal fluid, disseminated intraperitoneal fluid, appendix diameter ≤6 or >15 mm | IV and Oral: amoxicillin/clavulanic acid |
| Salminen et al.⁹ (2015) | 257 | 18–60 (33) | WBC, CRP | CT | Serious systemic illness, pregnancy, serum creatinine >150 μmol/L, diffuse peritonitis | Appendicolith, perforation, abscess, tumor | IV and Oral: ertapenem, oral—levofloxicin and metronidazole |
| Svensson et al.¹⁰ (2015) | 24 | 6–15 (12) | WBC, CRP | US and selective CT | Diffuse peritonits, appendiceal mass | Appendiceal mass | IV and Oral: meropenem and metronidazole, oral—ciprofloxacin and metronidazole |
| Talan et al.¹¹ (2017) | 16 | 9–73 | NS | CT | High-risk diabetes, immunodeficiency, acute coronary syndrome, congestive heart failure, chronic liver disease, acute inflammatory bowel disease, malignancy, anti-coagulation, dialysis, pregnancy, diffuse peritonitis, sepsis | Complicated appendicitis, mass, mucocoele | IV and Oral: ertapenem, oral—cefotaxim and metronidazole |
| Prospective, comparative trials vs. appendectomy (n = 117) | | | | | | | |
| Minucci et al.¹² (2016) | 37 | 7–17 (11) | NS | US and/or CT | Chronic abdominal pain, abdominal pain >48 h, pregnancy, diffuse peritonitis, WBC >18,000/μL, CRP >400 mg/dL | Appendicolith, appendix diameter >11 mm, abscess, phlegmon, perforation | IV and Oral: piperacillin/tazobactam or ciprofloxacin and metronidazole, oral—amoxicillin/clavulanic acid or ciprofloxacin and metronidazole |
| Mahida et al.¹³ (2016) | 5 | 7–17 | NS | US and/or CT | Chronic abdominal pain, pregnancy abdominal pain >48 h, diffuse peritonitis, WBC >18,000/μL, CRP >400 mg/dL | No appendicolith, appendix diameter >11 mm, abscess, phlegmon, perforation | IV and Oral: piperacillin/tazobactam or ciprofloxacin and metronidazole, oral—amoxicillin/clavulanic acid or ciprofloxacin and metronidazole |
| Hartwich et al.¹⁴ (2016) | 24 | 5–18 (13) | NS | US and selective MRI | Symptoms >48 h, suspicion of perforated appendicitis | Abscess | IV and Oral: piperacillin/tazobactam, oral—amoxicillin/clavulanic acid or ciprofloxacin and metronidazole |
| Lee et al.¹⁵ (2018) | 51 | 3–17 (10) | Pediatric Appendicitis Score 26 | US or CT | Symptoms 25 d, pregnancy, immunodeficiency, cirrhosis, cognitive impairment, diffuse peritonits, severe sepsis or septic shock | Abscess >5 cm or perforation | IV and Oral: ceftriaxone and metronidazole or ciprofloxacin and metronidazole, oral—amoxicillin/clavulanic acid or ciprofloxacin and metronidazole or cefotaxim and metronidazole |
| Total Antibiotic Duration, d | Antibiotic Nonresponse/Appendectomy Criteria | Initial Antibiotic Response (No./Total [%]) | Discharge Criteria | Short-term Follow-up | Antibiotic Retreatment Allowed |
|-----------------------------|----------------------------------------------|--------------------------------------------|--------------------|----------------------|-------------------------------|
| 10                          | Morphine (in hospital, schedule NS), paracetamol and dextropropoxyphene (as outpatient) | 19/20 (95) NS                              | NS                 | Days 6, 10, and 30   | No                            |
| 12                          | NS                                           | 113/128 (88) No improvement after 24 h     | NS                 | Day 7                | No                            |
| 10                          | Scheduled diclofenac                         | 96/107 (90) Worsening symptoms confirmed by physical examination and US (time NS) | NS                 | Day 10               | Yes                           |
| 8–15                        | NS                                           | 106/120 (88) (to Day 30) No fever, pain, and digestive symptoms | NS                 | Days 8 and 15        | No                            |
| 10                          | NS                                           | 242/257 (94) Clinical progressive of infection, perforated appendix, or peritonitis after >12–24 h | NS                 | Day 7                | No                            |
| 10                          | NS                                           | 23/24 (96) Afebrile for 24 h, adequate pain relief with oral analgesia, tolerating diet, and mobile | NS                 | NS                   | No                            |
| 10                          | NS                                           | 16/16 (100) Hemodynamic stability, temperature <38.5°C; pain controlled with oral analgesics, and tolerating diet | NS                 | Days 2, 3–5, and 14  | Yes                           |
| 10                          | NS                                           | 35/33 (95) Improved and tolerating oral antibiotics after 24 h | NS                 | Days 2–5, and 10–14  | No                            |
| 10                          | NS                                           | 3/5 (60) Improved and tolerating oral antibiotics after 24 h | NS                 | Days 2–5, and 10–14  | No                            |
| 7                           | Morphine as needed                           | 21/24 (88) (within 7 d) Afebrile, diminished abdominal pain, tolerating diet after 8 h | NS                 | Days 2 and 30        | No                            |
| 10                          | NS                                           | 35/51 (69) Afebrile, tolerating diet, pain controlled | NS                 | Day 10–14, Day 30    | Yes                           |
TABLE 1. (Continued)

| Study, y* | No. Antibiotic Treated | Age Range (Average), y† | Inclusion Criteria‡ | Imaging | Clinical Exclusion Criteria§ | Imaging Exclusion Criteria | IV and Oral Antibiotics |
|-----------|------------------------|-------------------------|---------------------|---------|-----------------------------|---------------------------|-------------------------|
| Prospective, noncomparative trials (n = 1,318) | | | | | | | |
| Paudel et al.22 (2010) | 96 | 10–60 (26) | NS | Selective US | Diabetes, hypertension, diffuse peritonitis | Abscess | IV—ceftriaxone and metronidazole, oral—ceftriaxone and metronidazole |
| Park et al.12 (2011) | 107 | 5–86 (31) | Alvarado score 4–8 | US and selective CT | Diffuse peritonitis | Appendicolith, appendiceal diameter <6 or >10 mm | IV—unspecified 2nd generation cephalosporin and metronidazole, oral—NS |
| DiSaverio et al.24 (2014) | 159 | >14 | Alvarado score 5–9 or Appendicitis Inflammatory Response score 3–10 | Selective US and CT | Inflammatory bowel disease, pregnancy, diffuse peritonitis, sepsis | Large abscess, perforation, mass | IV and oral—amoxicillin/ clavulanic acid |
| Park et al.15 (2014) | 119 | 18–79 (37) | NS | US or CT | Heart disease, cerebral vascular disease, pregnancy | Appendiceal diameter >10 mm, extraluminal gas, intraperitoneal fluid, abscess | IV—unspecified 2nd generation cephalosporin and metronidazole, oral—NS |
| Tanaka et al.26 (2015) | 78 | 6–15 (10) | Unspecified laboratory tests | US and selective CT | Diffuse peritonitis | Abscess, phlegmon | IV—cefmetazole, then ampicillin/sublactam and cefazidime or meropenem if no improvement in WBC, oral—none given |
| Gorter et al.27 (2015) | 25 | 10–17 (14) | NS | US and selective CT or MRI | Diffuse peritonitis, sepsis | Appendicolith, perforation, abscess, phlegmon, mass, disseminated intraperitoneal fluid, extraluminal gas | IV—amoxicillin/clavulanic acid and gentamicin, oral—amoxicillin/ clavulanic acid |
| Joo et al.28 (2017) | 20 | 26–43 (33; pregnant women) | NS | US and selective MRI | Serious systemic disease | Appendicolith, appendix diameter <6.1 and >11 mm, perforation, abscess, phlegmon | IV—cefmetazole and metronidazole, oral—none given |
| Ali Memon et al.29 (2017) | 96 | 16–60 (26) | Alvarado score 5–7, WBC | US | Previous surgery, comorbidities | Appendicolith, perforation, abscess, phlegmon | IV—ciprofloxacin and metronidazole, oral—NS |
| Abbo et al.30 (2018) | 166 | 11 | CRP 5500 mg/dL | US | Diffuse peritonitis | Appendicolith, complicated appendicitis | IV—amoxicillin/clavulanic acid, oral—NS |
| Almaser et al.31 (2018) | 90 | 16–60 (34) | Alvarado score ≥5 | US | Symptoms >72 h, diabetes, hypertension, immunocompromised, pregnancy, diffuse peritonitis | Perforation, abscess, mass | IV—ceftriaxone and metronidazole, oral—ceftriaxone and metronidazole |
| Steiner et al.32 (2018) | 362 | 3–16 (11) | Pediatric Appendicitis Score ≥7 | US and selective CT | Symptoms ≥86 h, diffuse peritonitis | Appendicolith, appendiceal diameter ≥10 mm, abscess | IV—ceftriaxone and metronidazole, oral—amoxicillin/ clavulanic acid |
| Retrospective, noncomparative trials (n = 597) | | | | | | | |
| Abes et al.13 (2007) | 16 | 5–13 (9) | WBC | US | Abdominal pain >24 h, diffuse peritonitis, hemodynamic instability | Appendicolith, free fluid | IV—ampicillin/sublactam, oral—none given |
| Park et al.14 (2014) | 26 | 80–92 (84) | NS | US or CT | NS | Appendiceal diameter >10 mm, perforation, or abscess | IV—unspecified 2nd generation cephalosporin and metronidazole, oral—NS |
| Shindoh et al.55 (2010) | 224 | 17–49 (30) | WBC >9,000 µL, CRP >1.0 mg/dL | US and/or CT | Dementia or psychiatric disorders; pregnancy; diffuse peritonitis, sepsis; cardiac, respiratory, neurological complications; life-threatening conditions | None | NS |
| Armstrong et al.56 (2014) | 12 | <18 (12) | NS | US | Symptoms <48 h, diffuse peritonitis, hemodynamic compromise | Abscess, phlegmon | IV—ciprofloxacin and metronidazole or ampicillin, gentamicin, and metronidazole; oral—amoxicillin/ clavulanic acid |
| Total Antibiotic Duration, d | Analgesia     | Diet          | Antibiotic Nonresponse/Appendectomy Criteria | Initial Antibiotic Response (No./Total [%]) | Discharge Criteria | Short-term Follow-up | Antibiotic Retreatment Allowed |
|-----------------------------|---------------|---------------|---------------------------------------------|---------------------------------------------|-------------------|---------------------|-------------------------------|
| 10                          | Scheduled diclofenac | NPO (time NS) | No improvement within 24 h                  | 94/96 (98)                                  | NS                | Within 7 d           | NS                            |
| NS                          | NS            | As tolerated  | Worsening (time NS)                         | 97/107 (91)                                 | NS                | NS                  | Yes                           |
| 7                           | NS            | NS            | Diffuse peritonitis, imaging evidence of abscess, or lack of improvement or worsening after 5 d | 140/159 (88) (within 7 d)                   | NS                | Days 5, 7 and 15    | Yes                           |
| 4                           | NS            | NPO 24 h      | Worsening and WBC and CRP (time NS)         | 110/119 (93)                                | NS                | Days 7 and 30       | Yes                           |
| Until CRP decreased to <0.5 mg/dL | NS            | As tolerated  | NS                                          | 77/78 (99)                                  | CRP <0.5 mg/dL and no fever or abdominal pain | NS                  | No                            |
| 7                           | NS            | NPO 24 h      | Worsening or no improvement based on clinical findings, CRP, and repeat US after 72 h | 25/25 (100)                                  | Temperature <38°C, no more than mild pain, tolerating oral intake, and decreased WBC and CRP, and no signs of complex appendicitis on US after 72 h | Day 14              | No                            |
| 4                           | NS            | NPO 24 h      | Worsening symptoms and elevated WBC and CRP after 24 h | 17/20 (85)                                  | NS                | NS                  | Yes                           |
| 10                          | Scheduled diclofenac | NPO (time NS) | Worsening symptoms, WBC, and US (time NS)   | 86/96 (90)                                  | NS                | NS                  | NS                            |
| 7                           | NS            | NS            | Worsening fever and pain (time NS)          | 162/166 (98)                                | Clinical, WBC, and CPR improvement after 48 h | Day 7              | No                            |
| 10                          | NS            | NS            | No improvement or worsening (time NS)        | 80/90 (89)                                  | Improvement after 24 h | NS                | No                            |
| 3–11                        | NS            | As tolerated  | Persistent or worsening abdominal pain after 24–48 h | 343/362 (95%)                               | Afebrile for 48 h, tolerating diet, compliant with oral antibiotics, no abdominal pain or tenderness, and mobile | NS                | Yes                           |
| 4–7 (until abdominal tenderness resolved) | NS            | NPO 48 h      | Persistence of abdominal pain, no decrease in appendiceal diameter on US, and increase in WBC and temperature after 48 h | 15/16 (94)                                  | NS                | NS                  | Yes                           |
| 4                           | NS            | NPO 24 h      | Worsening symptoms and laboratory results (time NS) | 24/25 (95)                                  | Days 7 and 30     | Yes                | NS                            |
|                             | NS            | NS            | Worsening and/or inflammatory markers after 24 h | 133/224 (59)                                | NS                | NS                  | No                            |
| 7                           | NS            | NS            | Worsening or failure to improve over 24 h    | 11/12 (92)                                  | NS                | NS                  | No                            |
TABLE 1. (Continued)

| Study, y* | No. Antibiotic Treated | Age Range (Average), y† | Inclusion Criteria‡ | Imaging | Clinical Exclusion Criteria§ | Imaging Exclusion Criteria | IV and Oral Antibiotics |
|-----------|------------------------|-------------------------|--------------------|--------|-----------------------------|---------------------------|------------------------|
| Koke et al.27 (2014) | 125 | 1-15 (7) | WBC >9,000/uL, CRP >0.3 mg/dL, Pediatric Appendicitis Score ≥7 | US and selective CT | NS | Abscess | IV—cefepime, oral—cefaclor |
| Steiner et al.30 (2015) | 45 | 4-15 (9) | NS | US | Diffuse peritonitis | Abscess | IV—ceftriaxone and metronidazole, oral—amoxicillin/ clavulanic acid |
| Hasby and Kasou39 (2016) | 15 | (33) | Sepsis | US | Diffuse peritonitis | Appendicolith, abscess | IV—amoxicillin, gentamicin, and metronidazole, oral—amoxicillin and ciprofloxacin |
| Loftus et al.40 (2018) | 70 | 22-46 (35) | NS | CT | Pregnancy, Alvarado score >7 | Appendicolith, perforation, abscess | IV—ceftriaxone and metronidazole, oral—ciprofloxacin and metronidazole |
| Scott et al.41 (2018) | 50 | 7-12 (9) | Pediatric appendicitis score ≥6 | US or CT | Chronic abdominal pain, diffuse peritonitis, sepsis | Abscess | IV—piperacillin/tazobactam or ceftriaxone and metronidazole, oral—amoxicillin/ clavulanic acid |
| Horattas et al.42 (2018) | 14 | 18-52 (37) | NS | CT | Severe abdominal pain, diffuse peritonitis, immunocompromised, sepsis, temperature >37.8°C | Appendicolith, appendiceal diameter >11 mm, severe inflammation | IV—ampicillin/sulbactam or ceftriaxone and metronidazole, oral—amoxicillin/ clavulanic acid |
| Randomized trial vs. supportive care (n = 121) | 121 | 18-70 (38) | NS | CT | NS | Appendicolith, appendiceal diameter >11 mm, more than mild fat infiltration, perforation, abscess | IV—cefmetazole and metronidazole, oral—NS |

*Year of publication.
†If the specific age range of enrolled patients was not provided, the range allowed by entry criteria and/or mean or median age (in parentheses) is recorded.
‡An inclusion criterion of all studies was suspected acute appendicitis based on history and physical examination; any additional clinical criteria are provided.
§Many studies excluded patients who had prior appendicitis.
∥Short-term follow-up is a visit within 1 month. Days refer to day number following presentation (Day 1), unless specified otherwise.

CRP, C-reactive protein level; IV, intravenous; MRI, magnetic resonance imaging; NA, not applicable; NPO, nil per os (nothing by mouth); NS, not specified; US, ultrasound; WBC, white blood cell count.

RESULTS

Search Results

PUBMED and EMBASE identified 2,510 and 5,334 references, respectively, of which 192 were considered potentially relevant based on their title and 35 met selection criteria (Fig. 1, PRISMA diagram).4-11,18-44 One RCT was excluded because of subsequent retraction.44

Table 1 summarizes all 34 studies of conservative antibiotic treatment identified and details of medical management provided to a total of 2,944 antibiotic-treated participants.4-11,18-43 Reports were mostly from Europe, Asia, and the United States but also from Nepal,22 Pakistan,29 and Iraq.31 These trials ranged in evidence grade from level II (RCT with negative criteria) to level V (case series) and included eight RCTs4-11 (number antibiotic-treated, 791), four prospective comparative (117),18-21 11 prospective noncomparative (1,318),22-32 10 retrospective noncomparative studies (597),33-42 and one randomized single-blind (patients only) trial comparing conservative antibiotic treatment to supportive care (121).43

Patient Selection

Most published experience with conservative treatment is in healthy children and adults 5 to 50 years of age. There is only one RCT in children, which involved 24 antibiotic-treated participants.10 The largest pediatric experience is a prospective, noncomparative trial in 362 antibiotic-treated children aged 3 to 16 years.32 Few data are available on children younger than 5 years. Among pediatric trials with available data, the range of minimum ages of enrolled patients was 1 to 7 years and mean or median age was 9 to 14 years. Studies did not enroll many elderly. There is one prospective, noncomparative trial of 26 participants 80 years and older managed conservatively.34 Excluding this study, among adult trials with available data, the range of maximum ages was 60 to 79 years and mean or median age was 26 to 38 years.

Trials generally excluded patients with physical examination evidence of diffuse peritonitis, hemodynamic instability, or sepsis. The most common exclusion criterion was diffuse peritonitis.
by clinical examination or suggested by imaging, in 32 (94%) of 34 studies4,5,8–11,18–43 (not specified in one study).6 One RCT enrolled 369 unselected patients with appendicitis, which included 13 (3.5%) with diffuse peritonitis, and although there was crossover toward surgery, some participants were treated conservatively.7 Other common exclusion criteria were inflammatory bowel disease, pregnancy, and prior appendicitis. There is one prospective noncomparative trial of 20 pregnant women that reported outcomes in mothers similar to those observed among nonpregnant adults and no obstetrical or fetal complications.28

Imaging

Thirty-three (97%) of 34 trials used ultrasound or computed tomography (CT) imaging to evaluate the diagnosis of appendicitis and exclude findings of complicated appendicitis4,6–11,18–43; ultrasound was used exclusively in five pediatric trials30,33,36–38 three adult trials4,29,31 and one with children and adults.32 Twenty studies (59%) specifically excluded patients with any abscess,9,18–20,22,25–29,31,32,34,36–41,43 and three (9%) excluded patients with unspecified complicated appendicitis or mass.10,11,36 However, two (6%) included patients with a small abscess (i.e., <5 cm),21,33 and eight (24%) either did not specify (with exclusion in some based on a maximum appendiceal diameter)4,6,23,24,35,42 or included all patients with appendicitis while reporting subgroups.8 In one RCT of conservative treatment, among participants with a CT scan read as uncomplicated appendicitis, 18% of surgery-assigned patients had complicated appendicitis upon operation.8 Findings suggesting perforation were also common exclusion criteria, but these varied and included extraluminal gas, periappendiceal and intraperitoneal fluid (amount unspecified), and appendiceal diameter of greater than 11 mm. Appendicolith was an exclusion criterion in some studies9,18,23,27–30,32,33,39,40,42,43 and was associated with antibiotic nonresponse or recurrence in some trials8,19,21,35,37,41 and not in others.4–7,11,20,22,24–26,31,34,36,38 Imaging findings suggestive of tumor were exclusion criteria in some adult trials9,18,23,27–30,32,33,39,40,42,43 and associated with antibiotic nonresponse or recurrence in some trials8,9,21,35,37,41 and not in others.4–7,11,20,22,24–26,31,34,36,38

| Total Antibiotic Duration, d | Analgesia | Diet | Antibiotic Nonresponse/Appendectomy Criteria | Initial Antibiotic Response (No./Total [%]) | Discharge Criteria | Short-term Follow-up|| Antibiotic Retreatment Allowed |
|-----------------------------|-----------|------|--------------------------------------------|------------------------------------------|-------------------|-----------------|-----------------|-------------------------------|
| 2 or 5 if CPR >1.0 mg/dL after 2 d IV antibiotics | NS | NPO 24 h | NS | 125/125 (100) | No abdominal pain, temperature <37.0°C, and no increase WBC or CRP level | NS | No |
| 8–10 | NS | NS | Worsening or no clinical and WBC response within 12–24 h | 42/45 (93) | NS | Day 7 | No |
| 10 | NS | NS | Temperature >38°C, no clinical improvement, or WBC 2×10⁶/m/dL or CRP level ≥500 mg/dL after 24 h | 12/15 (80) | NS | NS | NS |
| 7 | NS narcotic as needed | As tolerated | Worsening, increased WBC (time NS) | 33/51 (65) | NS | NS | NS |
| 7 | NS | NS | Worsening, persistent fever, increased WBC, or no improvement after 24 h | 40/50 (80) | Adiblile, tolerating diet, and pain resolved after 24 h | NS | No |
| 8–12 | NS | NS | No improvement, WBC after 24–48 h | 14/14 (100) | NS | NS | NS |
| 4 | NS | NPO 24 h | Worsening symptoms and laboratory results (time NS) | 112/121 (93) | Symptom resolution, no fever, and improved WBC and CRP | Days 7 and 30 | Yes |

Antibiotics

Most antibiotic regimens were consistent with 2010 and 2017 Infectious Diseases Society of America (IDSA) and Surgical Infection Society (SIS) guidelines for treatment of appendicitis4–6,23,24,35,42 or included all patients with appendicitis while reporting subgroups.8 In one RCT of conservative treatment, among participants with a CT scan read as uncomplicated appendicitis, 18% of surgery-assigned patients had complicated appendicitis upon operation.8 Findings suggesting perforation were also common exclusion criteria, but these varied and included extraluminal gas, periappendiceal and intraperitoneal fluid (amount unspecified), and appendiceal diameter of greater than 11 mm. Appendicolith was an exclusion criterion in some studies9,18,23,27–30,32,33,39,40,42,43 and was associated with antibiotic nonresponse or recurrence in some trials8,19,21,35,37,41 and not in others.4–7,11,20,22,24–26,31,34,36,38
**Temperature:** (points): right lower quadrant tenderness (0/2); elevated modified Alvarado score consists of the following components.

- Temperature ($\geq 37.3^\circ C$ or 99.1$^\circ F$) (0/1);
- Rebound tenderness (0/1);
- Anorexia (0/1); nausea or vomiting (0/1);
- Leukocytosis level of $> 10,000$ cells/$\mu L$ (0/2);
- Polymorphonuclear cell count of greater than 75% (0/1).

The modified score does not include migration of pain to the right lower quadrant since this variable would not be applicable for comparison of serial scores among a cohort of patients with imaging-confirmed appendicitis. The maximum modified Alvarado score is 9 instead of 10 for the original score. There was no change in score between Day 1 and Day 2 scores for patient numbers 15 and 16. Permission was obtained from Elsevier to reprint this figure, which is from Talan et al.

### Anti-Inflammatory Drugs

Mild-to-moderate community-acquired intra-abdominal infections.\(^4\,5\,6\) Initial parenteral antibiotic regimens used included a second- or third-generation cefalosporin (e.g., cefmetazole, cefotaxime, or ceftriaxone) plus metronidazole (or tinidazole) or single-agent regimens of amoxicillin-clavulanate (or ampicillin-sulbactam), piperacillin-tazobactam, or a carbapenem (ertapenem or meropenem). Oral (and alternative parenteral) regimens, started upon hospital discharge, included a fluoroquinolone or an advanced generation cefalosporin plus metronidazole, and amoxicillin-clavulanate. Four trials (12%) used intravenous and oral amoxicillin-clavulanate (or ampicillin-sulbactam),\(^8\,24\,33\,42\) which are recommended against by IDSA and SIS guidelines.

In three pediatric trials, ciprofloxacin was used.\(^10\,18\,15\) One pilot RCT allowed outpatient management facilitated by administration of long-acting ertapenem.\(^11\) Daily-dosed ceftriaxone and metronidazole have also been used.\(^21\,32\,38\,44\) Conservatively managed patients have been shown to experience more, mostly mild, antibiotic-related side effects compared with appendectomy patients.\(^11\)

Total intravenous and oral antibiotic duration ranged from 4 to 15 days. The most common total antibiotic duration was 10 days, which was used in 12 trials (35%).\(^6\,9\,11\,18\,19\,21\,22\,29\,31\,39\); seven trials (21%) used 7 days.\(^1\,20\,24\,27\,30\,36\,40\) The shortest duration was 4 days, used in four trials (12%).\(^25\,28\,34\,43\)

### Pain Control

Although worsening or persistent pain were criteria for antibiotic nonresponse leading to appendectomy, pain control regimens generally were not specified in published trials, with only six (18%) reporting analgesia\(^4\,6\,20\,22\,29\,40\) and none describing extent of pain control. Three trials (9%) used a nonsteroidal anti-inflammatory drug (NSAID), di clofenac, as a scheduled regimen, two (6%) used morphine,\(^4,20\) and one (3%) an unspecified narcotic, \(^40\) as needed, and one (3%) used paracetamol and dextropropoxyphene for outpatients.\(^4\)

### Diet

Participants were prohibited oral intake 12 hours in two studies (6%),\(^12\,18\) 24 hours in nine studies (26%),\(^5,7,10,25,27,28,34,37,43\) and 48 hours in one study (3%).\(^33\) and allowed diet as tolerated in seven (21%), four pediatric and three adult trials\(^1,10,21,23,26,32,40,\) diet was unspecified in 15 studies (44%).\(^4\)

### Response to Treatment

Rates of initial clinical response during the index hospitalization were 88% or greater in 27 studies (79%);\(^1,11,18,20,22,27-29,34,36-38,42,43\) There were four (12%) outlier studies with rates in the 60% to 70% range.\(^19,21,35,40\) Among 2,944 antibiotic-treated patients, no related deaths or cases of progression to severe sepsis were reported.\(^4\,11,18-43\)

Trials differed regarding the time limit to demonstrate improvement before transition to appendectomy. Eight trials (24%) evaluated response within 24 hours,\(^5,18-22,36,38\) eight (24%) between 24 and 48 hours,\(^5,7,28,32,35,39,41,42\) and five (15%) after 48 to 72 hours.\(^8,11,24,27,33\) and in 13 (38%), this was unspecified.\(^4,6,10,25,26,29-31,34,37,40,\) Studies also varied in the specific criteria for antibiotic nonresponse. Most trials indicated no improvement or worsening as criteria. Some trials further required concurrent increase in total white blood cell count or C-reactive protein levels, and/or abnormal findings on repeat imaging.

There is a paucity of data on time course of clinical response to antibiotics. In one adult trial, mean total white blood cell count decreased to normal within 1 day.\(^4\) One pediatric trial reported that the mean duration of fever in the antibiotic group was about 1 day.\(^37\) One adult trial described that appetite returned in 55% of participants by 18 hours and 98% by 24 hours.\(^22\) In one pilot RCT, individual participant responses were described over the first 24 hours of antibiotic treatment.\(^11\) Figure 2 shows Alvarado scores initially and after approximately 1 day, 2 days, 3 to 5 days, 2 weeks, and 1 month, the proportion participants who were pain-free was 31%, 63%, 75%, and 88%, respectively.

We explored comparison of four (12%) outlier studies with initial antibiotic response rates in the 60% to 70% range\(^19,21,35,40\) to 30 trials (88%) with rates 80% or greater\(^1,18,20,22-34,36-39,41-43\) with regard to components of conservative management that might affect outcomes: inclusion of patients with abscess or unspecified, 50% versus 27%; inclusion of patients with appendicolith or unspecified, 75% versus 60%; use of a guideline nonrecommended intravenous and oral antibiotic or unspecified, 25% versus 17%; total antibiotic duration of less than 7 days or unspecified, 25% versus 23%; and allowed
time for clinical response less than or equal to 24 hours or unspecified, 75% versus 62%, respectively.

**Discharge Criteria and Short-term Follow-up**

Seventeen trials (50%) described hospital discharge criteria. Studies generally required improvement, control of pain with oral analgesics, and some, resolution of fever. Most studies mandated that antibiotic-treated participants be hospitalized for a minimum of 1 to 3 days. One pediatric pilot trial allowed hospital discharge if the participant was afebrile and tolerated a diet after 8 hours of treatment and one adult trial if there was improvement by the next morning. In one adult pilot RCT, 14 of 15 consecutive antibiotic-randomized adults achieved hemodynamic stability, temperature less than 38.5°C, pain control with oral analgesics, and tolerance for oral fluids and medications and were discharged from the emergency department; all were successfully managed as outpatients and had symptom resolution. These patients were initially treated with a long-acting parenteral antibiotic, analgesics and antinauseas as needed, and then observed for at least 6 hours before discharge. Among all studies, follow-up, when specified, occurred as a visit and/or by telephone or email, with contact usually within the first week and additional visits up to 30 days following hospital discharge.

**Recurrence and Long-term Follow-up**

In most studies, appendectomy was recommended for antibiotic-treated patients who initially had symptom resolution and experienced recurrence. Twelve trials (35%) allowed patients with recurrent appendicitis to be retreated with antibiotics, including among pregnant women. In the largest experience in adults, 14 of 22 participants with recurrence were retreated with antibiotics, and in the largest pediatric experience, 30 of 75 children, in all cases successfully. No study described a long-term follow-up strategy, such as with regard to possible missed appendiceal cancer.

**DISCUSSION**

The role of conservative antibiotic treatment for initial management of acute uncomplicated appendicitis is an area of continued controversy. Because of evidence gaps, it has not generally been concluded that antibiotic treatment should routinely replace surgery. These gaps include few data outside healthy young adults, limited comparison with laparoscopic surgery, and incomplete assessment of patient-related and long-term outcomes. Meta-analyses have found conservative treatment associated with similar or fewer complications overall compared with surgery, and a recent guideline now acknowledges that this management can be successful for selected patients who wish to avoid surgery and accept the possibility of recurrence. However, guidance does not exist to best advise patients and provide this care. This systematic review describes the patient selection criteria and range of medical treatments used in published trial methods of conservative antibiotic management of acute uncomplicated appendicitis. While RCT (level II; RCTs with some negative criteria) evidence of comparative effectiveness of conservative treatment in relation to urgent appendectomy exists, the full body of experience includes other prospective and retrospective, comparative and noncomparative trials. In total, our search found 34 studies describing 2,944 antibiotic-treated participants.

For patients, this summary facilitates discussion about the extent to which their clinical profile is supported by trial experience and what they should expect should they choose nonoperative treatment. For providers, this review identifies common patterns of specific care components in order to guide their management. Most trials of conservative treatment used ultrasound or CT imaging to evaluate the diagnosis of appendicitis and exclude patients with findings of or abscess. No consensus exists regarding definitions of complicated appendicitis and its complement and studies varied regarding specific criteria to distinguish these entities. For example, some studies excluded patients with any evidence of perforation or abscess. Others allowed small lesions (e.g., abscess <5 cm) consistent with a functional definition of uncomplicated appendicitis as appendicitis that would otherwise receive urgent appendectomy and complicated appendicitis as appendicitis accompanied by a major abscess or phlegmon that would preclude surgery (other than percutaneous drainage) or perforation with diffuse peritonitis that would require urgent operation. Both ultrasound and CT imaging correlate poorly with operative findings with one RCT reporting 18% of surgery-randomized patients having complicated appendicitis at operation. However, since antibiotic treatment without surgery is a standard approach for treatment of appendicitis accompanied by major phlegmon or abscess because of a high success rate and avoidable ileocecectomy, this may not be an important distinction other than the expected response time and a potentially increased risk of occult malignancy. Some RCTs in adults did not use routine imaging with an associated high rate of unnecessary surgery in one study. Patients diagnosed with uncomplicated appendicitis based only on clinical evaluation who do not respond to antibiotics must be considered to have other conditions such as complicated appendicitis, tumor, inflammatory bowel disease, or gynecological disorders.

Imaging-identified appendicolith was associated with antibiotic nonresponse in some studies and not in others. In all trials, clinicians who assessed response were not blinded to baseline findings. It is possible that knowledge of the recognized association of appendicolith with perforation may have biased subsequent evaluation and led to a false association with nonresponse. Lack of blinding of the clinicians evaluating antibiotic response to findings on presentation is a general limitation of past studies to allow identification of response predictors. Also, studies generally did not describe all qualifying patients and compare characteristics of those enrolled and not enrolled to identify potential selection biases. If patients with more mild illness tended to be enrolled, either generally or among subgroups perceived as high risk (e.g., those with appendicolith, leukocytosis, severe pain), as might occur with a nontraditional treatment approach, then response rates could be inflated and differences associated with certain findings obscured.

It has been suggested that increased use of imaging may be identifying appendicitis at an earlier stage than in the past, and also misidentifying nonappendicitis, leading to unnecessary care of what would otherwise be a self-resolving condition. One recent RCT reported comparable outcomes among participants.
treated with supportive care without antibiotics as with antibiotics. However, in this study, participants were selected as low-risk based on clinical and CT criteria (e.g., no more than mild fat infiltration), as well as their and their physician's willingness for enrollment, and accounted for only about 20% of all presenting patients with presumed appendicitis (whereas at operation, about 80% are nonperforated). Furthermore, there was no surgery control arm to confirm the existence and severity of appendicitis. Despite this one intriguing study, considering the recognized life-threatening complications of appendicitis in the presurgery/antibiotic era and absence of serious septic events reported in conservative treatment trials, if surgery is not performed, antibiotic treatment remains prudent.

Antibiotic treatment used in most trials was consistent with 2010 and 2017 IDSA and SIS guidelines for mild-to-moderate community-acquired intra-abdominal infections. These guidelines are based on clinical trials of antibiotics for patients with a range of intra-abdominal infections, including complicated appendicitis, and in vitro activity. One exception is that ampicillin-sulbactam and amoxicillin-clavulanic acid were used in four trials (12%) but are recommended against by guidelines because of high Escherichia coli resistance rates and inferior clinical outcomes in comparative trials. One RCT that used intravenous and oral amoxicillin-clavulanic acid could not demonstrate noninferiority of nonoperative treatment. In vitro activity of these antibiotics was cited as a trial limitation. However, antibiotic response rates in trials using these drugs were high, 88% to 100%. Other trials used oral amoxicillin-clavulanic acid following improvement on a more broadly active intravenous antibiotic regimen.

The most common total intravenous and oral antibiotic duration was 7 to 10 days. Four trials (12%) used only a 4-day duration. The Study to Optimize Peritoneal Infection Therapy trial demonstrated that antibiotic treatment for a median of 4 days (i.e., 2 days after symptom resolution) resulted in similar outcomes as treatment for a median of 8 days among patients with intra-abdominal infection. As opposed to conservative management of appendicitis, all patients in the Study to Optimize Peritoneal Infection Therapy trial had source control. However, among studies of nonoperative treatment of appendicitis, lower initial antibiotic response rates did not appear to be associated with shorter treatment duration, suggesting a shorter antibiotic course may be possible.

Guidelines do not recommend broad-spectrum regimens with activity against Pseudomonas aeruginosa and fluoroquinolone-resistant and extended-spectrum β-lactamase–producing bacteria for patients with mild-to-moderate community-acquired infections unless antimicrobial resistance risk factors exist, such as recent antimicrobial exposure, past infection with a resistant strain, or high prevalence of resistance in the patient's community or in recent areas of travel. Several trials used broad-spectrum regimens such as piperacillin-tazobactam or meropenem, which are discouraged by guidelines to promote antibiotic stewardship.

A major limitation of most past trials is absence of any specific pain control protocol or description of the extent to which pain control was achieved. Persistent or worsening symptoms were consistent criteria for transition to appendectomy, and inadequate analgesia could confound evaluation of antibiotic effectiveness. Related pain management research and guidelines may inform optimal care. For example, concern about masking findings of rupture during antibiotic treatment may cause providers to undertreat pain. However, it has been established that pain control for suspected appendicitis can be achieved safely, including with opiates if necessary, without adversely affecting diagnostic accuracy or obscuring findings of perforation. Preappendectomy NSAID administration has been demonstrated safe and opiate sparing. Multimodal analgesia, using acetaminophen, NSAIDs, and opiates, and scheduled as opposed to as needed administration, have been shown to optimize analgesia effectiveness. Therefore, a scheduled oral or parenteral NSAID, as was used in a few trials, and/or acetaminophen, and as needed opiates to control pain while treating with antibiotics can be expected to optimize pain control and limit unnecessary opiate use.

While diet approaches varied and included restricting intake to nothing by mouth 8 to 48 hours, early introduction of oral fluids and a diet as tolerated was used in about one third of trials in which this was specified, appears safe, and may promote comfort and earliest discharge.

The optimal time to allow for an antibiotic response is unknown. However, of 21 trials that specified response time threshold, 38% allowed more than 24 to 48 hours, and 24% more than 48 to 72 hours, with no related deaths or cases of progression to severe sepsis. Compared with patients with uncomplicated appendicitis, those with complicated appendicitis appear to take longer to respond to antibiotics. For example, in one series of 88 patients with perforated appendicitis complicated by abscess who were treated nonoperatively, mean time to resolution of fever and leukocytosis was approximately 3 days, and the success rate was greater than 95%. In the few trials that described time to response to conservative antibiotic treatment for patients with clinical- and imaging-diagnosed uncomplicated appendicitis, most participants responded within

| TABLE 2. Areas of Uncertainty for Conservative Antibiotic Treatment of Acute Uncomplicated Appendicitis |
|---------------------------------------------------------------|
| • Efficacy among young children, those with comorbidities, and the elderly; |
| • Efficacy among those with evidence of localized perforation on imaging but without major phlegmon or abscess; |
| • Efficacy in comparison to laparoscopic appendectomy; |
| • Randomized comparison of components of care (e.g., various antibiotic regimens); |
| • Independent baseline clinical and imaging predictors of initial antibiotic response (e.g., appendicolith); |
| • Description of initial clinical course of response to antibiotic treatment; |
| • Serial clinical and imaging findings and antibiotic duration threshold for transition to appendectomy that lead to optimal outcomes; |
| • Patient-related outcomes; |
| • Outcomes by anesthesia risk; |
| • Long-term risk of recurrence and factors that predict recurrence; |
| • Extent to which imaging can identify patients with a tumor such that these patients can be excluded from consideration of conservative treatment; |
| • Frequency of and risk factors for cancer of the appendix and course of patients with missed cancer who receive conservative treatment; |
| • Appropriate follow-up of conservatively-managed patients; and |
| • Effectiveness with pragmatic application in a wide range of settings. |
1 to 2 days.5,11,22,37 Since both providers and patients need to know what to expect with conservative care, including atypical responses, additional initial response data from future trials would be helpful. Patients with perforation, not identified on CT, which may occur in about 20% and reflect the degree to which patients with more advanced disease are included,8 likely take longer to respond to antibiotics than those without perforation. This may contribute to the observation of a slightly higher rate of complicated appendicitis found at surgery among antibiotic nonresponders than surgery-randomized patients12 (and higher antibiotic nonresponse rates among those with conditions associated with complicated appendicitis, e.g., appendicolith) and supports allowing a longer antibiotic trial (i.e., 72 hours) in those uncommon patients who are slow to respond and who still wish to avoid surgery, with ongoing careful monitoring. Although there were only four studies with low initial antibiotic response rates, these more frequently allowed less than 24 hours for response and did not exclude patients with small appendiceal abscess or appendicolith.19,21,35,40 The relationship of serial laboratory and imaging findings to antibiotic responsiveness has yet to be determined.

Following symptom resolution, about 10% to 25% of medically treated patients experience recurrence over the next year.12–17 It appears that almost all recurrences happen in the first 2 years.59,60 In one report, among 710 antibiotic-treated patients, cumulative probability of recurrence was 0.09, 0.12, 0.12, and 0.13 at 1, 2, 3, and 5 years, respectively.59 Five-year follow-up of 256 antibiotic-assigned patients in the RCT by Salminen et al.60 revealed appendectomy rates of 0.27 (includes 6% initial nonresponse rate), 0.34, 0.35, 0.37, and 0.39, respectively. Salminen et al.60 reported that the complication rate associated with appendectomy in the antibiotic group was similar to that in the group randomized to initial surgery. The 5-year overall complication rate was significantly less than the antibiotic than the surgery group, 6.5% vs. 24.4%, respectively. In most trials, appendectomy was done for patients with recurrence. However, in about one third, participants were offered antibiotic retreatment, which had good success, although selection criteria for this approach were not described.6,7,11,27,23–25,28,32–34,43

Studies have not described long-term care. Older adults are greater risk of occult appendiceal malignancy (for all primary neoplasms, mean age is 55 years), which has been estimated to occur in 0.9% of patients based on histopathological review of 7,970 appendectomy specimens.61,62 Studies of conservative management excluded patients with suspicion of tumor on imaging. Salminen et al.60 found 4 (1.5%) of 272 surgery-assigned patients had an appendiceal tumor (3 neuroendocrine tumors, and one polyp); no appendiceal tumors were discovered over 5 years in the antibiotic group. The rate, tumor types, risk factors, and course of occult malignancy require further investigation in a much larger number of patients. Patients reevaluated for recurrent abdominal symptoms may have tumor detected on reimaging. For conservatively treated patients older than 40 years with complicated appendicitis who remain asymptomatic, selective reimaging and colonoscopy have been suggested.63 Although conservatively treated patients with uncomplicated appendicitis appear to be a less risk of occult malignancy than those with complicated appendicitis, this may also be a reasonable follow-up approach for patients with uncomplicated appendicitis after successful antibiotic treatment, with appendectomy preferred for recurrence.

This systematic review has limitations. First, these were open trials in which enrollment and outcomes, such as antibiotic response, may have been influenced by provider and patient knowledge of and attitudes toward treatment assignments. Second, evidence gaps exist that preclude a full understanding of the comparative effectiveness of conservative treatment in relation to surgery so that shared decision-making can be well-informed. These areas of uncertainty are summarized in Table 2. Third, at the present state of investigation, conservative treatment is bundled, that is, antibiotics, pain and diet management, response criteria, and follow-up strategies have been compared together versus surgery; individual components of this care have yet to be subjected to randomized trials. However, in care of any complexity, many interventions are involved, and trials that may or may not attempt to control for various aspects of management still inform care. We can look for common approaches related to good outcomes in large numbers of patients to guide treatment as well as observed associations to generate hypotheses for future trials. Fourth, our search may not have identified all relevant trials, particularly non-RCTs since, to our knowledge, this is the first attempt to assemble all studies of conservative treatment. Fifth, over the approximately two-decade span of this research, comfort with conservative treatment has increased, and this review may not identify trends in care. For example, whereas requisite 3-day hospitalization was justified in the largest RCT to “ensure the safety of this unproved therapeutic modality,”64 emergency department discharge of stable patients has been demonstrated feasible11 and is now incorporated in the methods of a ongoing multicenter US trial (ClinicalTrials.gov, NCT02800785). Avoided or shortened hospitalization could substantially reduce costs and inconvenience. One author who was contacted about a study’s low initial response rate commented that it was done “in an era of aggressive (and sometimes) unnecessary surgery” (J. Shindoh, MD, PhD, May 2018, e-mail communication), and suspected success rates are currently higher.35 Finally, we also continue to learn more about possible functions of the appendix that may support or deem unnecessary its preservation, such as in cancer immunity65 and as a gastrointestinal microbiome reservoir.66

This systematic review identifies patient populations most studied and common selection criteria and care methods, provides critical analysis in the context of applicable clinical guidelines and related research, and highlights areas of uncertainty so that patients can be best informed and managed should they consider this approach and researchers can better target unanswered questions about this care. Future studies that address biases associated with enrollment and response evaluation, use best-practice pain control and antibiotic selection, better define cancer risk, and explore longer time thresholds for response, minimized diet restriction and hospital stays, and antibiotic retreatment will further our understanding of the potential effectiveness of conservative management.

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