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Methods of Conservative Antibiotic Treatment of Acute Uncomplicated Appendicitis: A Systematic Review

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Abstract

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 PRISMA guidelines.

Results

Thirty-four studies involving 2944 antibiotic-treated participants were identified. The greatest experience with conservative treatment is in persons 5-50 years of age. In most trials, imaging was employed 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 7-10 days. Approaches ranged from 3-day hospitalization on parenteral agents to same-day hospital or ED discharge of stable patients with outpatient oral antibiotics. Minimal time allowed before response was evaluated varied from 8-72 hours. Although pain was a common criterion for non-response and appendectomy, analgesic regimens were poorly described. Trials differed in use of other response indicators, i.e., WBC, CRP, and re-imaging. Diet ranged from restriction for 48 hours to as tolerated. Initial response rates were generally >90% and most improved by 24-48 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, 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.

Study Type

Systematic review

Level of Evidence

Level II

Key Words

appendicitis, non-operative, conservative, antibiotics, uncomplicated, appendectomy, methods, systematic, review

Introduction

Acute appendicitis is the most common reason for an emergency abdominal surgery, with a lifetime appendectomy risk of 12% for males and 23% for females.¹ Although conservative (i.e., non-operative) treatment of acute uncomplicated appendicitis with antibiotics has yet to be routinely recommended over appendectomy, and evidence gaps exist that are being addressed in ongoing trials, this management is becoming increasingly accepted as a reasonable option for patient shared decision-making. In a 2016 guideline, the World Society of Emergency Surgery concluded that antibiotic therapy can be successful in selected patients with uncomplicated appendicitis who wish to avoid surgery (level of evidence 1; grade of recommendation, A).² A 2014 survey of Irish surgeons found that about one-fifth routinely treat appendicitis non-operatively.³ However, little clinical guidance exists for practitioners in terms how non-operative treatment is administered so they can best select and inform patients and provide care to achieve similar efficacy and safety as established in published trials.

Since the mid '1990s, eight randomized controlled trials (RCTs) have investigated conservative antibiotic treatment in comparison to urgent appendectomy for acute uncomplicated appendicitis.⁴⁻¹¹ In 2015, Salminen et al.⁹ reported by far the largest RCT, which involved 530 adults, and found fewer complications, 6% initial antibiotic non-response and 23% 1-year recurrence rates, and 12 fewer disability days compared to mostly open appendectomy. Meta-analyses that included this trial found conservative treatment associated with similar or fewer total complications as surgery and concluded that it can be offered to patients.¹²⁻¹⁷

We report results of a search of all published trials describing the methods of conservative treatment of acute uncomplicated appendicitis. This systematic review describes specific components of medical management that may affect outcomes including patient selection, imaging, antibiotics, pain and diet management, criteria for antibiotic non-response and appendectomy, disposition, and follow-up. We summarize the details of medical management, describe the range of approaches, critically evaluate this management in the context of applicable guidelines and related research, and identify areas of uncertainty.

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 non operative OR nonoperative OR non-operative OR conservative) AND (appendicitis). References in the selected publications, including reviews, were searched for additional studies. Two reviewers (clinician and non-clinician) independently 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, non-comparative; retrospective, non-comparative; and RCT comparing antibiotic treatment vs. supportive care. The following information was extracted: number of participants that received conservative treatment, ages, patient selection including clinical and imaging criteria, antibiotic regimen, pain and diet management, criteria for initial antibiotic non-response, initial response rate, hospital discharge criteria, and follow-up. In some cases, authors were contacted for clarification.

Results

Search results

PUBMED and EMBASE identified 2510 and 5334 references, respectively, of which 192 were considered potentially relevant based on their title and 35 met selection criteria (Figure 1. PRISMA diagram).^{4-11,18-44} One RCT was excluded due to subsequent retraction.⁴⁴

Table 1 summarizes all 34 studies of conservative antibiotic treatment identified and details of medical management provided to a total of 2944 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 non-comparative (1318),²²⁻³² 10 retrospective

non-comparative 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 5-50 years of age. There is only one RCT in children, which involved 24 antibiotic-treated participants.¹⁰ The largest pediatric experience is a prospective, non-comparative trial in 362 antibiotic-treated children aged 3-16 years.³² Few data are available on children <5 years of age. Among pediatric trials with available data, the range of minimal ages of enrolled patients was 1-7 years and mean or median age was 9-14 years. Studies did not enroll many elderly. There is one prospective, non-comparative trial of 26 participants ≥ 80 years of age managed conservatively.³⁴ Excluding this study, among adult trials with available data, the range of maximal ages was 60-79 years and mean or median age was 26-38 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 of 34 (94%) studies^{4,5,8-11,18-36,37-43} (not specified in one study⁶). 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 non-comparative trial of 20 pregnant women that reported outcomes in mothers similar to those observed among non-pregnant adults, and no obstetrical or fetal complications.²⁸

Imaging

Thirty-three (97%) of 34 trials used ultrasound or CT imaging to evaluate the diagnosis of appendicitis and exclude findings of complicated appendicitis^{4,6-11,18-43}; ultrasound was used exclusively in five pediatric trials,^{30,33,36-38} three adult trials,^{4,29,31} and one with children and adults.²² Twenty (59%) studies 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.^{10,11,30} 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 maximal appendiceal diameter)^{4-6,23,24,35,42} or included all patients with appendicitis while reporting subgroups.⁷ 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 >11 mm. Appendicolith was an exclusion criterion in some studies,^{9,18,23,27-30,32,33,39,40,42,43} and was associated with antibiotic non-response or recurrence in some trials^{10,19,21,35,37,41} and not in others.^{4-8,11,20,22,24-26,31,32,33,34,36,38} Imaging findings suggestive of tumor were exclusion criteria in some adult trials,^{8,9,11,24,31} with criteria either unspecified or based on an appendiceal diameter >15 mm.⁸ One trial compared conservative antibiotic treatment to supportive care and used more selective CT criteria (e.g., no more than mild fat infiltration).⁴³ Some RCTs in adults did not use any imaging⁵ or used ultrasound selectively,⁷ with rates of unnecessary surgery as high as 11%.⁷

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 mild-to-moderate community-acquired intra-abdominal infections.^{45,46} Initial parenteral antibiotic regimens used included a second- or third-generation cephalosporin (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 cephalosporin plus metronidazole, and amoxicillin-clavulanate. Five (15%) trials used intravenous and oral amoxicillin-clavulanate (or ampicillin-sulbactam),^{8,24,20,33,42} which are recommended against by IDSA and SIS guidelines. In three pediatric trials, ciprofloxacin was used.^{10,18,19} One pilot RCT allowed outpatient management facilitated by administration of long-acting ertapenem.¹¹ Daily-dosed ceftriaxone and metronidazole have also been used.^{21,37,32,40,41} Conservatively managed patients have been shown to experience more, mostly mild, antibiotic-related side effects compared to appendectomy patients.¹¹

Total intravenous and oral antibiotic duration ranged from 4-15 days. The most common total antibiotic duration was 10 days, which was used in 12 (35%) trials^{4,6,9,10,11,18,19,21,22,29,31,39}; seven (21%) trials used 7 days.^{20,24,27,30,36,40,41} The shortest duration was 4 days, used in four (12%) trials.^{25,28,34,43}

Pain control

Although worsening or persistent pain were criteria for antibiotic non-response 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 (9%) trials used a non-steroidal anti-inflammatory drug (NSAID),^{6,22,29} diclofenac, as a scheduled regimen, two (6%) used morphine^{4,20} and one (3%) an unspecified narcotic⁴⁰ as needed, and one (3%) used paracetamol and dextropropoxyphene for outpatients.⁴

Diet

Participants were prohibited oral intake 12 hours in two (6%) studies,^{12,18} 24 hours in nine (26%) studies,^{5,7,10,25,27,28,34,37,43} and 48 hours in one (3%) study,³³ and allowed diet as tolerated in seven (21%; four pediatric and three adults trials)^{11,20,21,23,26,32,40}; diet was unspecified in 15 (44%) studies.^{4,6,8,9,22,24,29-31,35,36,38,39,41,42}

Response to treatment

Rates of initial clinical response during the index hospitalization was $\geq 88\%$ in 27 (79%) studies^{4-11,18,20,22-27,29-34,36-38,42,43} There were four (12%) outlier studies with rates in the 60-70% range.^{19,21,35,40} Among 2944 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 (24%) trials evaluated response within 24 hours,^{9,18-22,36,38} eight (24%) between 24 and 48 hours,^{5,7,28,32,35,39,41,42} five (15%) after 48-72 hours,^{8,11,24,27,33} and in 13 (38%)

this was unspecified.^{4,6,10,23,25,26,29-31,34,37,40,43} Studies also varied in the specific criteria for antibiotic non-response. 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 24 hours in 16 consecutive antibiotic-randomized patients; all initially received one dose of a long-acting antibiotic. The Alvarado score contains components that clinicians might use to follow the progress of an antibiotic-treated patient, i.e., fever, nausea, tenderness, and leukocytosis.⁴⁷ Most participants substantially improved over the first day. A few participants had lower scores that stayed constant over 1 day, but ultimately their symptoms resolved. At 2 days, 3-5 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 60-70% range^{19,21,35,40} to 30 (88%) trials with rates $\geq 80\%$ ^{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% vs. 27%; inclusion of patients with appendicolith or

unspecified, 75% vs. 60%; use of a guideline non-recommended intravenous and oral antibiotic or unspecified, 25% vs. 17%; total antibiotic duration <7 days or unspecified, 25% vs. 23%; no oral intake allowed or unspecified, 50% vs. 83%; and allowed time for clinical response ≤ 24 hours or unspecified, 75% vs. 62%, respectively.

Discharge criteria and short-term follow-up

Seventeen (50%) trials described hospital discharge criteria.^{6-8,10,11,18-21,26,27,30-32,37,41,43} 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 1-3 days. One pediatric pilot trial allowed hospital discharge if the participant was afebrile and tolerated a diet after 8 hours of treatment²⁰ and one adult trial if there was improvement by the next morning.³¹ In one adult pilot RCT, 14 of 15 consecutive antibiotic-randomized adults achieved hemodynamic stability, temperature $<38.5^{\circ}\text{C}$, 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.¹¹ These patients were initially treated with a long-acting parenteral antibiotic, analgesics and anti-emetics 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 (35%) trials allowed patients with recurrent appendicitis to be re-treated with antibiotics, including among pregnant women.^{6,7,11,21,23-25,28,32,33,34,43} In the largest experience in adults, 14 of 22 participants with recurrence were re-treated with antibiotics, and in the largest pediatric experience, 30 of 75 children, in all cases successfully.^{24,32} 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 to 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 to surgery,¹²⁻¹⁷ 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.² 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) 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 non-comparative trials. In total, our search found 34 studies describing 2944 antibiotic-treated participants.^{4-11,18-42} 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 non-operative 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 findings of tumor or complicated appendicitis, such as phlegmon 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)^{21,35} 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,⁴⁸⁻⁵⁰ with one RCT reporting 18% of surgery-randomized patients having complicated appendicitis at operation.⁸ 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. Some RCTs in adults did not employ routine imaging,^{5,7} with an associated high rate of unnecessary surgery in one study.⁷ 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 non-response in some studies^{10,19,21,35,37,41} and not in others.^{4-8,11,20,22,24-26,31,32,33,34,36,38} 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 non-response. 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 non-traditional 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 non-appendicitis, leading to unnecessary care of what would otherwise be a self-resolving condition.⁵¹ One recent RCT reported comparable outcomes among participants treated with supportive care without antibiotics as with antibiotics.⁴³ 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 non-perforated). Further, 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 pre-surgery/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.^{45,46} 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 five (15%) trials,^{8,24,20,33,42} 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 non-inferiority of non-operative treatment.⁸ Inadequate in vitro activity of these antibiotics was cited as a trial limitation.⁵² However, antibiotic response rates in trials using these drugs were high, 88%-100%. Other trials used oral amoxicillin-clavulanic acid following improvement on a more broadly-active intravenous antibiotic regimen.^{18-21,27,32,36,38,41}

The most common total intravenous and oral antibiotic duration was 7-10 days. Four (12%) trials used only a 4-day duration.^{25,28,34,43} The Study to Optimize Peritoneal Infection Therapy (STOP-IT) 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.⁵³ As opposed to conservative management of appendicitis, all patients in the STOP-IT trial had source control. However, among studies of non-operative 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 (ESBL)-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.^{45,46} Several trials used broad-spectrum regimens such as piperacillin-tazobactam or meropenem,^{10,18-20,41} 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.⁵⁴ For example, concern about masking findings of rupture during antibiotic treatment may cause providers to under-treat 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 peritonitis.⁵⁵ Pre-appendectomy NSAID administration has been demonstrated safe and opiate-sparing.⁵⁶ Multimodal analgesia, using acetaminophen, NSAIDs, and opiates,⁵⁴ and scheduled as opposed to as needed administration, have been shown to optimize analgesia effectiveness.⁵⁷ Therefore, a scheduled oral or parenteral NSAID, as was used in a few trials,^{6,22,29} 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.

It is unclear how diet strategies relate to outcomes. While diet approaches varied and included restricting intake to nothing by mouth 8-48 hours, early introduction of oral fluids and a diet as tolerated was employed in about one-third of trials in which this was specified,^{11, 20,21,23,26,32,40} 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,^{5,7-9,11,18-22,24,27,28,32,33,35,36,38,39,41,42} 38% allowed >24-48 hours^{5,7,28,32,35,39,41,42} and 24% >48-72 hours,^{8,11,24,27,33} with no related deaths or cases of progression to severe sepsis. Compared to 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 non-operatively, mean time to resolution of fever and leukocytosis was approximately 3 days, and the success rate was >95%.⁵⁸ 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 1-2 days.^{4,11,22,37} Since both providers and

patients need to know what to expect with conservative care, including atypical responses, additional clinical response data and other patient-related outcomes from future trials would be helpful. Patients with perforation, not identified on CT, which may occur in about 20%,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 non-responders than surgery-randomized patients¹² (and higher antibiotic non-response rates among those with conditions correlated 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 <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 10-25% of medically-treated patients experience recurrence over the next year.¹²⁻¹⁷ It appears that almost all recurrences happen in the first two 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. revealed appendectomy rates of 0.27 (includes 6% initial non-response rate), 0.34, 0.35, 0.37, and 0.39, respectively; no patient had a complication related to delay in surgery.⁶⁰ In most trials, appendectomy was done for patients with recurrence. However, in about one-third, participants were offered antibiotic re-

treatment, which had good success, although selection criteria for this approach were not described.^{6,7,11,21,23-25,28,32,33,34,43}

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. found 4 (1.5%) of 272 surgery-assigned patients had an appendiceal tumor.⁶⁰ The rate, 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 re-imaging. For conservatively-treated patients >40 years of age with complicated appendicitis who remain asymptomatic, selective re-imaging 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, i.e., antibiotics, pain and diet management, response criteria, and follow-up strategies have been compared together vs. 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 been demonstrated feasible¹¹ and is now incorporated in the methods of a ongoing multi-center 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" [Junichi Shindoh, MD, PhD, May 27, 2018] 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, employ best-practice pain control and antibiotic selection, 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.

ACCEPTED

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FIGURE TITLES AND LEGENDS

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart: selection of relevant studies

Figure 2. Modified Alvarado scores* at Day 1 and Day 2 for 16 participants with the diagnosis of acute uncomplicated appendicitis randomized to antibiotics-first treatment.¹¹

Figure 2. * The modified Alvarado score consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature ($\geq 37.3^{\circ}\text{C}$ or 99.1°F) (0/1); rebound tenderness (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis $>10,000$ cells/ μL (0/2); polymorphonuclear cells $>75\%$ (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 number #15 and #16.

[Permission was obtained from Elsevier to reprint this figure, which is from reference #11.]

FIGURE 1

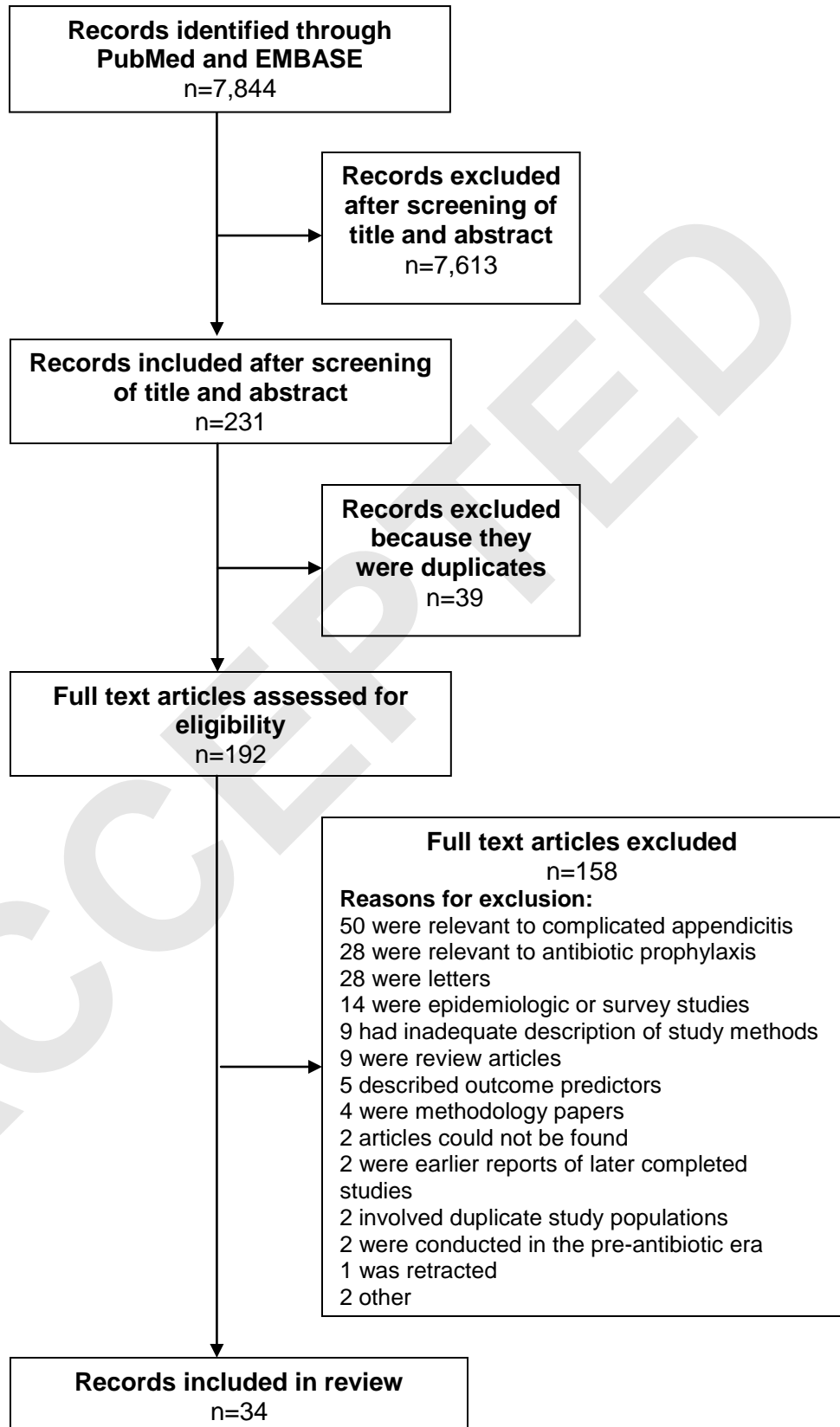


FIGURE 2

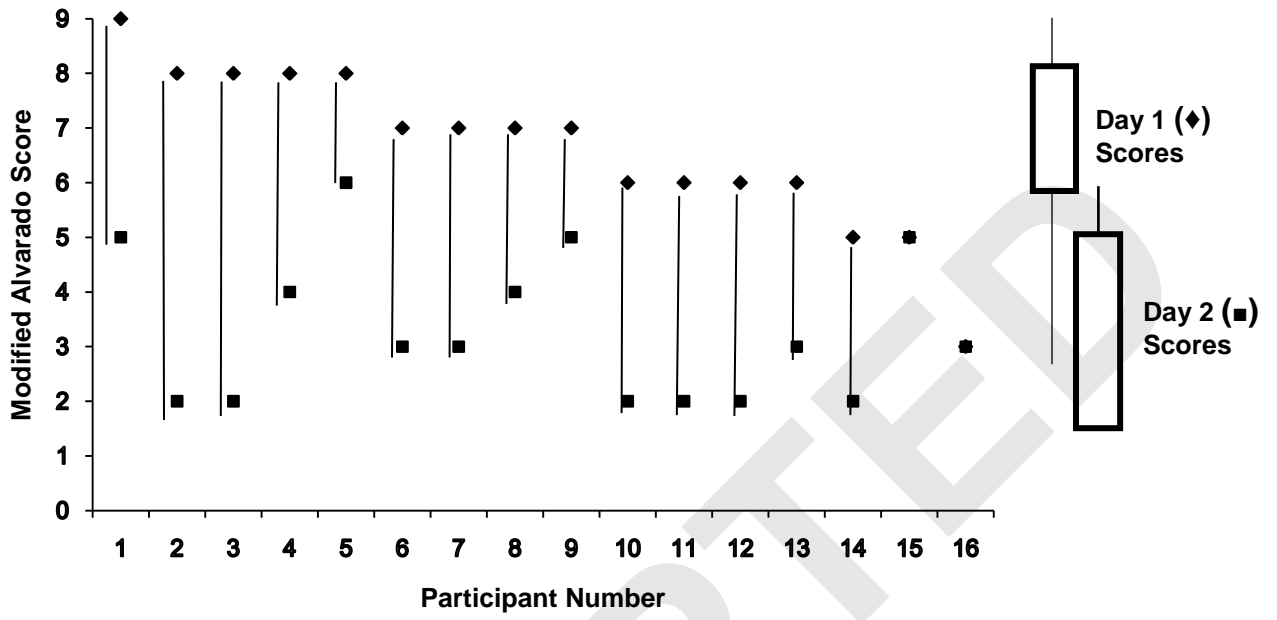


Table 1. Selection criteria and specific management of patients receiving conservative antibiotic treatment of acute uncomplicated appendicitis in published studies

Study (year)*	No. antibiotic treated	Age range (average ; years)†	Inclusion criteria‡	Imaging	Clinical exclusion criteria§	Imaging exclusion criteria	IV and oral antibiotics	Total antibiotic duration (days)	Analgesia	Diet	Antibiotic non-response/appendectomy criteria	Initial antibiotic response (no./total [%])	Discharge criteria	Short-term follow-up	Antibiotic retreatment allowed
Randomized controlled trials vs. appendectomy (n = 791)															
Eriksson ⁴ (1995)	20	18-53 (28)	WBC; CRP	US	Abdominal pain >24 hours; diffuse peritonitis	NS	IV - Cefotaxime and Tinidazole; oral - Ofloxacin and Tinidazole	10	Morphine (in hospital, schedule NS) Paracetamol and Dextropropoxyphene (as outpatient)	NS	NS	19/20 (95)	NS	Days 6, 10, and 30	No
Slyrud ⁵ (2006)	128	18-50	CRP ≥1.0 mg/dL	None	Diffuse peritonitis	NA	IV - Cefotaxime and Tinidazole; oral - Ofloxacin and Tinidazole	12	NS	NPO 24 hours	No improvement after 24 hours	113/128 (88)	NS	Day 7	No
Turhan ⁶ (2009)	107	16-65 (31)	WBC	US and CT	NS	NS	IV - Ampicillin and Gentamicin and Metronidazole; oral - NS	10	Scheduled Diclofenac	NS	Worsening symptoms confirmed by physical examination and US (time NS)	96/107 (90)	Clinical improvement at day 3	Day 10	Yes
Hansson ⁷ (2009)	119	>18 (40)	Lab tests	Selective US and CT	None	None	IV - Cefotaxime and Metronidazole; oral - Ciprofloxacin and Metronidazole	10	NS	NPO 24 hours	At least 24 hours of antibiotics; otherwise NS	108/119 (91)	Clinical improvement by the next morning	NS	Yes
Vons ⁸ (2011)	120	18-68 (31)	NS	CT	Receiving steroid or anticoagulant; history inflammatory bowel disease; pregnancy; serum creatinine >200 µmol/L	Extraluminal gas; peri-appendiceal fluid; disseminated intraperitoneal fluid; appendix diameter ≤6 or >15 mm	IV and oral - Amoxicillin/clavulanic acid	8-15	NS	NS	No symptom resolution after 48 hours, or CT findings among patients with persistence of fever and pain at day 8, or persistence of elevated WBC or CRP at day 15	106/120 (88) (to Day 30)	No fever, pain, and digestive symptoms	Days 8 and 15	No
Salminen 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 - Ertapenem; oral - Levofloxacin and Metronidazole	10	NS	NS	Clinical progressive of infection, perforated appendix, or peritonitis after >12-24 hours	242/257 (94)	NS	Day 7	No
Svensson ¹⁰ (2015)	24	6-15 (12)	WBC; CRP	US and selective CT	Diffuse peritonitis; appendiceal mass	Appendiceal mass	IV - Meropenem and Metronidazole; oral - Ciprofloxacin and Metronidazole	10	NS	NPO 24 hours	NS	23/24 (96)	Afebrile for 24 hours, adequate pain relief with oral analgesia; tolerating diet, and mobile	NS	No
Talan ¹¹ (2017)	16	9-73	NS	CT	High-risk diabetes; immunodeficiency; acute coronary	Complicated appendicitis; mass;	IV - Ertapenem; oral - Cefdinir and Metronidazole	10	NS	As tolerated	Diffuse peritonitis, severe sepsis, or no improvement in abdominal pain, or	16/16 (100)	Hemodynamic stability, temperature	Days 2, 3-5, and 14	Yes

					syndrome; congestive heart failure; chronic liver disease; acute inflammatory bowel disease; malignancy; anti-coagulation; dialysis; pregnancy; diffuse peritonitis; sepsis	mucocoele					temperature >38.5°C, or WBC <4,000 or >15,000/μL after 48 hours		<38.5°C, pain controlled with oral analgesics, and tolerating diet		
Prospective, comparative trials vs. appendectomy (n = 117)															
Minnecci ¹⁸ (2016)	37	7-17 (11)	NS	US and/or CT	Chronic abdominal pain; abdominal pain >48 hours; pregnancy; diffuse peritonitis; WBC >18,000/μL; CRP >400 mg/dL	Appendicolith; appendix diameter >11 mm; abscess; phlegmon; perforation	IV - Piperacillin/tazobactam or Ciprofloxacin and Metronidazole; oral - Amoxicillin/clavulanic acid or Ciprofloxacin and Metronidazole	10	NS	NPO 12 hours	Increased pain, signs of sepsis, or no clinical improvement within 24 hours	35/37(95)	Improved and tolerating oral antibiotics after 24 hours	Days 2-5, and 10-14	No
Mahida ¹⁹ (2016)	5	7-17*	NS	US and/or CT	Chronic abdominal pain; pregnancy abdominal pain >48 hours; ; diffuse peritonitis; WBC >18,000/μL; CRP >400 mg/dL	No appendicolith; appendix diameter >11 mm; abscess; phlegmon; perforation	IV - Piperacillin/tazobactam or Ciprofloxacin and Metronidazole; oral - Amoxicillin/clavulanic acid or Ciprofloxacin and Metronidazole	10	NS	NPO 12 hours	New or persistent pain, signs of sepsis, or nausea or emesis after 24 hours	3/5 (60)	Improved and tolerating oral antibiotics after 24 hours	Days 2-5, 10-14	No
Hartwich ²⁰ (2016)	24	5-18 (13)	NS	US and selective MRI	Symptoms >48 hours; suspicion of perforated appendicitis	Abscess	IV - Piperacillin/tazobactam; oral - Amoxicillin/clavulanic acid	7	Morphine as needed	As tolerated	Clinical worsening or lack of improvement within 8 hours	21/24 (88) (within 7 days)	Afebrile, diminished abdominal pain, tolerating diet after 8 hours	Days 2 and 30	No
Lee ²¹ (2018)	51	3-17 (10)	Pediatric Appendicitis Score ≥6	US or CT	Symptoms ≥5 days; pregnancy; immunodeficiency; cirrhosis; cognitive impairment; diffuse peritonitis; severe sepsis or septic shock	Abscess >5 cm or perforation	IV - Ceftriaxone or and Metronidazole or Ciprofloxacin and Metronidazole; oral - Amoxicillin/clavulanic acid or Ciprofloxacin and Metronidazole or Cefdinir and Metronidazole	10	NS	As tolerated	Clinical worsening or failure to improvement within 24 hours	35/51 (69)	Afebrile, tolerating diet, pain controlled	Day 10-14, Day 30	Yes
Prospective, non-comparative trials (n = 1318)															
Paude ²² (2010)	96	10-60 (26)	NS	Selective US	Diabetes; hypertension; diffuse peritonitis	Abscess	IV - Ceftriaxone and Metronidazole; oral - Cefixime and Metronidazole	10	Scheduled Diclofenac	NPO (time NS)	No improvement within 24 hours	94/96 (98)	NS	Within 7 days	NS
Park ²³ (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	NS	As tolerated	Worsening (time NS)	97/107 (91)	NS	NS	Yes

							NS								
DiSaverio 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	7	NS	NS	Diffuse peritonitis, imaging evidence of abscess, or lack of improvement or worsening after 5 days	140/159 (88) (within 7 days)	NS	Days 5, 7 and 15	Yes
Park ²⁵ (2014)	119	18-79 (37)	NS	US or CT	Heart disease; cerebral vascular disease; pregnancy	Appendix diameter >10 mm, extraluminal gas, intraperitoneal fluid; abscess	IV - Unspecified 2nd generation cephalosporin and Metronidazole; oral - NS	4	NS	NPO 24 hours	Worsening and WBC and CRP (time NS)	110/119 (93)	NS	Days 7 and 30	Yes
Tanaka ²⁶ (2015)	78	6-15 (10)	Unspecified lab tests	US and selective CT	Diffuse peritonitis	Abscess; phlegmon	IV - Cefmetazole, then Ampicillin/sulbactam and Ceftazidime or Meropenem if no improvement in WBC; oral - none given	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
Gorte 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	7	NS	NPO 24 hours	Worsening or no improvement based on clinical findings, CRP, and repeat US after 72 hours	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 hours	Day 14	No
Joo 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	4	NS	NPO 24 hours	Worsening symptoms and elevated WBC and CRP after 24 hours	17/20 (85)	NS	NS	Yes
Ali Memon 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	10	Scheduled Diclofenac	NPO (time NS)	Worsening symptoms, WBC, and US (time NS)	86/96 (90)	NS	NS	NS
Abbo ³⁰ (2018)	166	11	CRP ≤500 mg/dL	US	Diffuse peritonitis	Appendicolith; complicated appendicitis	IV - Amoxicillin/clavulanic acid; oral - NS	7	NS	NS	Worsening fever and pain (time NS)	162/166 (98)	Clinical, WBC, and CPR improvement after 48 hours	Day 7	No
Alnaser ³¹ (2018)	90	16-60 (34)	Alvarado score ≥5	US	Symptoms >72 hours; diabetes; hypertension; immunocompromised; pregnancy; diffuse peritonitis	Perforation; abscess; mass	IV - Cefotaxime and Metronidazole; oral - Ciprofloxacin and Metronidazole	10	NS	NS	No improvement or worsening (time NS)	80/90 (89)	Improvement after 24 hours	NS	No

Steiner ³² (2018)	362	3-16 (11)	Pediatric Appendicitis Score ≥7	US and selective CT	Symptoms ≥36 hours; diffuse peritonitis	Appendicolith; appendiceal diameter ≥10 mm; abscess	IV - Ceftriaxone and Metronidazole; oral - Amoxicillin/clavulani c acid	3-11	NS	As tolerate d	Persistent or worsening abdominal pain after 24- 48 hours	343/362 (95%)	Afebrile for 48 hours, tolerating diet, compliant with oral antibiotics; no abdominal pain or tenderness, and mobile	NS	Yes	
Retrospective, non-comparative trials (n = 597)																
Abes ³³ (2007)	16	5-13 (9)	WBC	US	Abdominal pain >24 hours; diffuse peritonitis; hemodynamic instability	Appendicolith; free fluid	IV - Ampicillin/ sulbactam; oral - none given	4-7 (until abdominal tendernes s resolved)	NS	NPO 48 hours	Persistence of abdominal pain, no decrease in appendiceal diameter on US, and increase in WBC and temperature after 48 hours	15/16 (94)	NS	NS	Yes	
Park ³⁴ (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	4	NS	NPO 24 hours	Worsening symptoms and laboratory results (time NS)	24/25 (95)	NS	Days 7 and 30	Yes	
Shindoh ³⁵ (2010)	224	17-49 (30)	WBC >9000/ 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	NS	NS	NS	Worsening and/or inflammatory markers after 24 hours	133/224 (59)	NS	NS	No	
Armstrong ³⁶ (2014)	12	<18 (12)	NS	US	Symptoms <48 hours; diffuse peritonitis; hemodynamic compromise	Abscess; phlegmon	IV - Ciprofloxacin and Metronidazole or Ampicillin, Gentamicin, and Metronidazole; oral - Amoxicillin/clavulani c acid	7	NS	NS	Worsening or failure to improve over 24 hours	11/12 (92)	NS	NS	No	
Koike ³⁷ (2014)	125	1-15 (7)	WBC >9000/ μL; CRP >0.3 mg/dL; Pediatric Appendicitis Score ≥7	US and selective CT	NS	Abscess	IV - Cefoperazone; oral - Cefcapene	2 or 5 if CPR >1.0 mg/dL after 2 days IV antibiotics	NS	NPO 24 hours	NS	125/125 (100)	No abdominal pain, temperature <37.0°C, and no increase WBC or CRP level	NS	No	
Steiner ³⁸ (2015)	45	4-15 (9)	NS	US	Diffuse peritonitis	Abscess	IV - Ceftriaxone and Metronidazole; oral - Amoxicillin/clavulani c acid	8-10	NS	NS	Worsening or no clinical and WBC response within 12-24 hours	42/45 (93)	NS	Day 7	No	
Hasby ³⁹ (2016)	15	(33)	Sepsis	US	Diffuse peritonitis	Appendicolith; abscess	IV - Amoxicillin, Gentamicin, and Metronidazole; oral - Amoxicillin and Ciprofloxacin	10	NS	NS	Temperature >38°C, no clinical improvement, or WBC ≥12,000/ μL or CRP level ≥500 mg/dL after 24 hours	12/15 (80)	NS	NS	NS	

Loftus ⁴⁰ (2018)	70	22-46 (35)	NS	CT	Pregnancy; Alvarado score >7	Appendicolith; perforation; abscess	IV - Ceftriaxone and Metronidazole; oral - Ciprofloxacin and Metronidazole	7	NS narcotic as needed	As tolerate d	Worsening, increased WBC (time NS)	33/51 (65)	NS	NS	NS
Scott 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/clavulani c acid	7	NS	NS	Worsening, persistent fever, increased WBC, or no improvement after 24 hours	40/50 (80)	Afebrile, tolerating diet, and pain resolved after 24 hours	NS	No
Horattas 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 Ciprofloxacin and Metronidazole; oral - Amoxicillin/clavulani c acid	8-12	NS	NS	No improvement, WBC after 24-48 hours	14/14 (100)	NS	NS	NS
Randomized trial vs. supportive care (n = 121)															
Park ⁴³ (2017)	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	4	NS	NPO 24 hours	Worsening symptoms and laboratory results (time NS)	112/121 (93)	Symptom resolution, no fever, and improved WBC and CRP	Days 7 and 30	Yes

Abbreviations: CRP = C-reactive protein level; CT = computed tomography; MRI = magnetic resonance imaging; NA = not applicable; NPO = nil per os (nothing by mouth); NS = not specified; US = ultrasound; WBC = white blood cell count

* 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.

Table 2. Areas of uncertainty for conservative antibiotic treatment of acute uncomplicated appendicitis

- Efficacy among young children, those with co-morbidities, 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.