# Conservative versus surgical management of pediatric appendicitis

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# Introduction

In 1894, Charles McBurney became one of the first surgeons in the United States (U. S.) to describe and perform the surgical procedure known as an appendectomy, or removal of the appendix (McBurney, 1894). Over 120 years later, one of the classic signs of appendicitis in the clinical world is referred to as tenderness at "McBurney's point," which describes tenderness in the right lower portion of the abdomen located one third of the way between the anterior superior iliac spine and the umbilicus. A patient presenting with tenderness at this point along with other symptoms of appendicitis, almost always warrants an urgent surgical consult. In the ever-changing medical world, the procedure has been modified over time and new laparoscopic methods have been developed; but for over a century, appendectomy has remained the standard of care for patients presenting with appendicitis (Brogden & Streets, 2013).

The appendix is a small organ located in the right lower quadrant of the abdomen. The organ is a blind pouch, as the only opening is at the attachment to the cecum, which marks the beginning of the colon, or large intestine. Appendicitis is the medical term for inflammation of the appendix. Although the entire spectrum of etiologic causes of appendicitis is still unknown, direct obstruction of the lumen and infection are known triggers. Impacted stool, also known as an appendicolith, is one of the main culprits of appendiceal obstruction. An obstruction of the lumen, where it attaches to the cecum, becomes problematic in this blind-pouched organ by increasing pressure within it and setting the stage for inflammation. Furthermore, an obstruction impedes blood flow within the organ, limiting oxygen delivery and resulting in ischemia (Brogden & Streets, 2013). Infection of the appendix by bacteria, viruses, parasites, and/or fungal organisms can also rapidly induce inflammation. Lymphoid hyperplasia, a common response of the body to infection, can secondarily cause obstruction to the lumen (Lamps, 2010).

Without intervention, uncontrolled inflammation and ischemia have the potential to continue in either mechanism, which eventually leads to necrosis and/or perforation of the appendix. If appendicitis is not treated early, necrosis and perforation can lead to further medical problems that are difficult to treat including abscess formation, peritonitis, and sepsis (Brogden & Streets).

Appendicitis classically manifests initially as pain in the periumbilical region due to the origination of the appendix from this region during embryologic development. As inflammation within the appendix continues, pain tends to migrate to the right lower quadrant of the abdomen. Due to appendiceal inflammation irritating adjacent structures, including the parietal peritoneum, pain is localized to this region. Other signs and symptoms include: fever; nausea; vomiting; tachycardia; pain that is worsened with movement; and tenderness at McBurney's point. In addition, clinicians are trained to perform a variety of physical examination maneuvers including obturator, psoas, and Roving's signs which all increase the clinical suspicion of appendicitis when they are positive (Brogden & Streets, 2013). Many clinicians also order hematologic laboratory studies to assess for the presence of inflammation, such as an increase in white blood cell (WBC) count and elevated C-reactive protein (CRP). Although these laboratory tests may support the diagnosis, they are not specific in confirming it. Imaging such as ultrasounds and/or computed tomography (CT) scans may be used, depending on the facility and the clinician's preference. However, both of these studies have downfalls as sometimes the appendix is not visualized by ultrasound and CT scans expose the patient to radiation. Clinicians may also use different scoring systems such as the Alvarado Score or Pediatric Appendicitis Score to assist in the diagnosis. These scoring systems assign a specific number of points to specific signs, symptoms, exam findings, and laboratory values to help determine the likelihood a patient has appendicitis. One study comparing these two scoring systems in children found the Alvarado

Score to have an 89% sensitivity and a 59% specificity and the Pediatric Appendicitis Score to have a sensitivity of 86% and a specificity of 50% (Pogorelic, Rak, Mrklic, & Juric, 2015). Although appendicitis has been treated for over a century by appendectomy, the pre-operative diagnosis remains clinical. No single sign, symptom, laboratory finding, imaging study, or scoring system is 100% specific to the diagnosis. Rather, synthesis of pieces of information in combination with experience, guide clinicians in making the diagnosis. It is not until after the appendectomy when histological examination of the appendix in the laboratory is confirmatory.

Approximately 7 to 10% of the population in the U.S. will develop acute appendicitis within their lifetime, making it the most common surgical emergency involving the abdomen (Goldman & Schafer, 2012). Over 59,000 children are admitted to the hospital each year with this diagnosis, with the occurrence peaking in the age group of 10 to 14 years (Wier, Yu, Owens, & Washington, 2013). Although the open approach to appendectomy described by McBurney over a century ago is less commonly used today, appendectomy still remains the standard of care for patients with appendicitis. The laparoscopic approach has increased in popularity over time as it is considered to be a minimally invasive surgery. Instead of making one large incision, one to three smaller incisions are made in a laparoscopic procedure. These smaller incisions are typically between a half-centimeter to 1.5 centimeters in length, depending on the tools the surgeon uses. Instead of retracting tissue back to visualize the appendix, a small scope video camera is inserted into one of the incision sites and other surgical instruments are inserted through the other incisions to perform the procedure. This approach has become an attractive option for surgeons due to decreased wound infections. Smaller incision sites make this procedure cosmetically more appealing to patients as well, especially in the younger population (Shalak, Almulhim, Ghantous, & Yazbeck, 2009). The use of the laparoscopic method in the pediatric population has climbed from approximately 22.2% of cases in 1999 to 90.8% of cases in 2010. In the U.S. today, open appendectomy is typically reserved for more complicated cases of appendicitis. National data from 2010 also reports wound infection incidence in approximately 3.1% of laparoscopic procedures versus 10% of open appendectomies. Incidence of post-operative bowel obstruction due to adhesions was also lower following laparoscopic procedures at a rate of 3.5% versus 8.8% with open procedures (Gasior et al., 2012). A single institution study that included 177 pediatric patients analyzed the hospital course and complication rate between patients undergoing open versus laparoscopic appendectomy. Each surgical group was further subdivided to include three groups of patients: those with simple appendicitis, perforated appendicitis, and appendicitis with an abscess. Results showed no significant difference in length of hospital stay or need for intravenous (IV) analgesia between patients undergoing laparoscopic versus open appendectomy in any of the three subgroups ($p > 0.05$). Incidence of minor complications was significantly lower in patients with perforated appendicitis that underwent laparoscopic appendectomy ($p < 0.05$), while no significant difference was seen in the other two subgroups. In regards to major complications, the subgroup with perforated appendicitis that underwent laparoscopic appendectomy had a lower incidence than those who underwent open appendectomy ($p < 0.05$). No significant difference was observed in the other two subgroups (Tsai, Lee, & Huang, 2012). These benefits of the laparoscopic procedure attributed to its role in becoming the standard of care for pediatric patients with appendicitis (Gasior et al.).

Mortality due to appendicitis and complications related to the disease remained low worldwide over the past several decades. Data from 1990 and 2010 showed mortality rates of 0.7 and 0.5 persons per 100,000 worldwide population respectively (Stewart et al., 2014). Early recognition and prompt surgical appendectomy is successful in treating this disease process, however, morbidity and complications related to surgery still pose risks, which require consideration. All surgical procedures also involve risks associated with general anesthesia, bleeding, and injury or damage to adjacent organs, with intestines being most at-risk with appendectomies. Minor complications related to abdominal surgeries include development of a post-operative paralytic ileus, nausea, vomiting, diarrhea, and abdominal distension. Potential for major complications, even with minimally invasive laparoscopic surgery include wound infections and bowel obstruction. Development of a post-operative intra-abdominal abscess is another serious complication to consider (Tsai et al., 2012). Despite all of the potential risks of surgical procedures, a number of these procedures are routinely performed unnecessarily. The challenges in making the pre-operative diagnosis lead to some patients undergoing an appendectomy, only to reveal a histologically normal appendix.

One single institution study used a modified Alvarado Score on consecutive pediatric patients, ages four to 15 years, that presented with signs and symptoms suspicious for appendicitis. Based on the total number of points for each sign and symptom consistent with appendicitis, patients were assigned to one of three groups. Patients were assigned to group I if they had a score of four or less and were sent home with discharge instructions to return if symptoms persisted or worsened. Group II patients included patients that had a score of five or six. These patients were admitted for observation and re-evaluated. Patients were assigned to group III if they had a score of seven or higher; these patients were taken to surgery. Breakdown of each group included five patients in group I, 21 patients in group II, and 64 patients in group III. Nine of the patients in group II had a score of seven or higher upon re-evaluation and were taken to surgery. A total of 73 patients underwent appendectomy, and findings from the operation and histopathological report confirmed the diagnosis in 68 of these patients. The remaining five patients were found to have a histologically normal appendix, which makes the negative appendectomy rate almost 7%. In addition, two cases of appendicitis were missed with patients being sent home and subsequently returning and undergoing appendectomy at a later time (Shera, Nizami, Malik, Naikoo, & Wani, 2011).

Another single-institution study included patients of all ages over a 13-month period that presented to the emergency department with abdominal pain. History and physical examination suggested appendicitis in 164 of these patients. Diagnostic imaging was utilized in the majority of patients, with ultrasound as the modality of choice. In several cases, CT was used as first-line at the discretion of the radiologists due to body habitus of the patients. A CT scan was performed in addition to ultrasound if results were inconclusive. After clinical evaluation, three patients were taken immediately to surgery without imaging due to high clinical suspicion of appendicitis. The majority of imaging studies were performed on the day that the patient presented to the emergency department. However, several patients were observed overnight and re-evaluated in the morning, which subsequently lead to three home discharges and the remainder undergoing imaging. A total of 158 of 164 patients who were suspected to have appendicitis on presentation to the emergency department underwent an imaging study, and in total 29 CT scans were performed. Surgery was performed on 119 patients, with 114 cases confirmed by the pathologic examination. One patient was found to have a Meckel’s diverticulum and the appendix was not resected. Four patients that underwent appendectomy, the operative findings and pathological report failed to show evidence of appendicitis. Negative appendectomy rate in this study was 3.3% and a total of 4.2% of patients underwent surgery unnecessarily (Toorenvliet et al., 2010). Although appendectomy is the current gold standard for the disease process and has become a routine procedure, its potential risks and adverse effects should not be overlooked, especially when patients are still needlessly undergoing the procedure.

Over the past several decades, research trials were conducted challenging the need for routine appendectomy for suspected appendicitis. A number of studies compared the effectiveness of solely broad-spectrum antibiotics and conservative measures to surgery, while others have investigated the role of initial conservative measures with a delayed or interval appendectomy. A review of the current literature will evaluate the role of conservative medical management alone or in combination with interval appendectomy. This review will continue to focus on the pediatric population, as appendectomy is one of the most common surgical procedures performed in children. Can medical management alone or in combination with interval appendectomy replace the concept of acute appendicitis as a surgical emergency in the pediatric population?

# Literature Review

## The Importance of Prompt Treatment of Appendicitis

Time is of the essence in the diagnosis of appendicitis, as delaying treatment allows the inflammatory process to progress rampantly. Data from the Kids' Inpatient Database (KID) and Nationwide Inpatient Sample (NIS) support the fact that delay of treatment increases perforation rates. These databases encompass data from a variety of hospitals across the nation including urban, rural, teaching, and non-teaching facilities. One retrospective study included 232,732 children with a diagnosis of acute appendicitis from 1998 to 2008 from these databases. Records were analyzed to compare hospital admission to operation time and rates of appendiceal perforation. The breakdown of the number of operations performed each day for children and adults is not provided in the study. However, it is reported that approximately 81% of surgical procedures were performed the same day the patient presented to the emergency department. The percentage of procedures decreased with each subsequent day, with 15.8% on day two, 1.7% on day three, and 0.8% by day eight. In pediatric patients, 28.9% of those that underwent surgery on the day of presentation had a perforated appendicitis. The proportion of perforated appendices increased each day with nearly 60% by day four and approximately 84% by day eight (Papandria et al., 2013). One limitation to this study is that reasons for delay in surgical treatment are not identified. Possibilities include but are not limited to: lack of staff or surgeon availability; incorrect initial diagnosis; or differences in clinical judgment. Additionally, this study does not provide information regarding the clinical management of patients until their surgery, if it was delayed. As these patients were managed at a variety of hospitals across the nation, the medical management they received while waiting surgery was not likely uniform. Although this study validates the importance of prompt recognition and treatment of the disease process, it does not negate the possibility of alternative treatment options.

One retrospective single institution study analyzed a variety of time intervals to determine if a delay in appendectomy had an effect on the rate of surgical site infection in children. This study included 1,388 pediatric patients up to age 18 years over a two-year period. In this study, patients were treated with antibiotics on admission until the time of surgery. The IV antibiotics included piperacillin/tazobactam or clindamycin and gentamycin in the case of a penicillin allergy. The patients were retrospectively divided into two groups, with 919 cases (66%) classified as simple appendicitis (SA). The remaining 469 cases (34%) were classified as complex appendicitis (CA), which was defined as the discovery of gangrene or perforation by the surgeon. Time variables of interest in this study were: time from start of symptoms to operation; emergency department (ED) triage to operation; and time from admission to the surgical service to operation. Results from this study did not indicate significant differences in surgical site infections with various time intervals from time of ED triage ($p = 0.51$) or surgical admission ($p = 0.997$) to operation. Time intervals from triage time to operation included four-hour intervals from less than four hours to greater than 16 hours. Time intervals from surgical admission to operation included three-hour intervals from less than three hours to greater than 12 hours. Surgical site infection rates significantly increased with length of time between the start of symptoms and the operation, with time intervals ranging from less than 12 hours to greater than 60 hours ($p < 0.0001$). Individual p-values for the SA and CA group were 0.048 and 0.002, respectively. However, when multivariable logistic regression models were performed separately on both groups, this significant difference only persisted in the CA group. This study also analyzed a variety of secondary factors and patient characteristics. Laparoscopic operation was the most common type of procedure in the study. However, significantly more patients in the CA group underwent an open procedure or had a laparoscopic converted to an open procedure. The laparoscopic procedure was successfully performed in 94.1% of the SA group and 84.7% of the CA group ($p < 0.0001$). Univariable analysis results indicated that significantly more surgical site infections occurred in patients who underwent an open or laparoscopic converted to open procedure ($p < 0.0001$). Surgical site infection rate for the study group as a whole was 5.1%. Out of the 126 patients that underwent open or laparoscopic converted to open, 11.1% developed a surgical site infection as opposed to only 4.5% of the 1,262 patients that underwent a laparoscopic procedure. Furthermore, multivariable analysis indicated that those in the CA group had an odds ratio of 1.75 if they had an open procedure and 7.68 if they underwent a laparoscopic conversion to open procedure of developing an infection. Results also indicated a significantly higher average WBC count in the CA group versus the SA group, at 17.4 versus 13.5 thousand cells per micro liter, respectively. For every 1,000 white blood cell increase per micro liter, univariable analysis indicated a 1.06 odds ratio ($p = 0.01$) of developing an infection. Although the number of obese patients is not provided in the study, the authors report univariable analysis to show that obesity had a 2.6 odds ratio ($P = 0.04$) with surgical site infection. Multivariable analysis of the CA group also indicated that those with a gastrointestinal comorbidity had a 4.76 odds ratio ($p = 0.02$) of developing an infection (Boomer et al., 2014). Although several factors in this study are associated with increased surgical site infection rates, it is notable that the only time variable associated with the increase in rate is delay in presentation, and this is the only time delay where patients are not receiving any antibiotics.

Stahlfeld, Hower, Homitsky, and Madden (2007) similarly sought to determine the effects of delaying appendectomy while administering IV antibiotics and hydration. This study is not specific to the pediatric population as it includes patients from 16 to 85 years. This retrospective single institution study included 71 patients that presented to the Emergency Department over a 26-month period. All patients in this study underwent a CT scan to support clinical diagnosis of acute appendicitis. Only non-complicated cases were included in this study, as any patient that had evidence of a perforation or other complications were excluded. Patients were divided into two groups: the 53 patients in group A underwent appendectomy within ten hours of CT diagnosis and the 18 patients in group B underwent appendectomy greater than ten hours after CT diagnosis. No significant difference existed in average white blood cell count and temperature between the two groups. The average time between CT scan and start of operation for group A was 3.18 hours, with a standard deviation of 2.38 hours. The average for group B was 15.8 hours, with a standard deviation of 5.50 hours. Results showed no significant difference in rates of wound complications, length of hospital stay, operative time, or documented antibiotic use between the two groups. Delayed operation in group B did not result in any perforations at the time of surgery. Although the following parameters were not statistically significant, patients in group B had fewer laparoscopic to open appendectomy conversions, fewer wound infections, required less narcotics for pain control, and tolerated a regular diet sooner post-operatively versus group A. The findings of both Boomer et al. (2014) and Stahfeld et al. suggest that medical management with antibiotics while waiting for surgery does not lead to increased rates of adverse events. Increased rates of surgical site infection were associated only with delay in presentation, but not delay in operation after initiation of antibiotic therapy (Boomer et al.). Furthermore, delaying surgery while initiating antibiotic therapy did not lead to increased rates of perforation or other identified adverse effects (Stahlfeld et al.). These findings suggest that timely antibiotic therapy is able to control the inflammatory process of appendicitis.

Comparing Treatment Methods for Uncomplicated Acute Appendicitis

Hartwich, Luks, Watson-Smith, Kurkchubasche, Muratore, Wills and Tracy (2016) performed a prospective study involving children with non-complicated acute appendicitis, giving patients and their families a choice of either surgery or medical management for first-line treatment. Patients were excluded if symptoms had begun greater than 48 hours prior to presentation, imaging that suggested an abscess, suspicion of perforation, significant comorbidities, allergy to penicillin, patients unable or unwilling to complete the course of oral antibiotics and inability to return to the hospital promptly if symptoms continued or recurred. A total of 74 children from five to 18 years met inclusion criteria and participated in this study. Twenty-four children chose conservative management and 50 chose operative management. It is not specifically stated in the article, but the laparoscopic method was most likely performed. No significant difference in age, gender, distribution, WBC count, or duration of symptoms existed between either group. Medical management was initiated with two doses of IV piperacillin-tazobactam six to eight hours apart. Patients were re-evaluated at the time of the second antibiotic dose and if objectively better, they were discharged home with a seven-day course of oral amoxicillin-clavulanate. Signs of objective improvement sought in this study included being afebrile, ability to tolerate an oral diet, and diminished abdominal pain. This study defined both early and late failures of medical management. Early failure was defined as patients that did not show objective improvement within eight hours of initiation of therapy, or had recurrence of symptoms within seven days while taking oral antibiotics. All patients found to have an early failure of medical management underwent an immediate appendectomy. Late failures were defined as patients that developed recurrent symptoms after completing the antibiotic regimen. On presentation, it was at the discretion of the surgeon to evaluate the patients with imaging and operate if clinical and/or radiologic evidence suggested recurrent appendicitis. Early failure occurred in three patients, and two patients experienced late failures at 43 and 52 days post discharge. An additional two patients chose to undergo an interval appendectomy after recovery from appendicitis; pathological analysis determined both to be histologically normal, with no signs of inflammation. It is reported that no major complications occurred in any patients in this study and an appendectomy performed for failure or recurrence did not differ subjectively from those who initially chose appendectomy. At an average follow-up of 14 months, 17 patients still had their appendix. Cost and utility were secondary factors evaluated in this study. Included in the cost analysis was money spent to account for the nursing staff, time and treatment in the emergency room, pharmacy, laboratory studies, radiographic imaging, surgery and anesthesia. Excluded from this analysis were surgeon's, anesthetist's and hospital fees. Average cost per patient was significantly lower in patients that chose initial conservative measures, inclusive of the patients that experienced recurrences or opted for interval appendectomy ($p < 0.01$). Average cost for this group was $2,771 with a standard deviation of $816, while the average of the group that underwent urgent appendectomy was $4130 with a standard deviation of $990. Utility was measured using the PedsQL 4.0 Generic Core Scales questionnaires, and was completed by all parents and patients over the age of seven years. The questionnaire consists of 23 items divided into four categories: physical functioning, emotional functioning, social functioning, and school functioning. Quality-adjusted life years (QALY) is the norm for quantifying utility, but because appendicitis is unlikely to affect a patient greater than one month, quality-adjusted life month (QALM) was used in this case. Patients from the group that initially chose conservative management were given a second questionnaire if they underwent a delayed appendectomy for any reason, and the average score was used. A QALM score of 1 indicates the perception of perfect health. Highest QALM scores were calculated in patients that completed successful conservative management without an appendectomy, with scores being 0.904 and 0.928, respectively. Parents and patients in the group that underwent urgent appendectomy had average scores of 0.856 and 0.854, respectively. Scores were the lower than those of urgent appendectomy for both patients and parents if the child underwent appendectomy for any reason after initial conservative management. Overall, patients that were initially managed conservatively, regardless of their outcome, had a significantly higher utility reported by QALM scores ($p < 0.001$), while scores of the parents did not significantly differ (Hartwich et al., 2016). Evidence from this study suggests that conservative management is more cost effective and results in greater utility as rated by the patient. Approximately 21% of patients failed initial measures due to early or late recurrences. At average follow-up of 14 months, 17 out of 24 or approximately 71% of patients still had their appendix, and the other two patients that underwent elective appendectomy were found to have normal appendices at this time.

A second prospective, single institution study analyzed patient and family choice in management for uncomplicated acute appendicitis established similar results. This study included patients from seven to 17 years of age over a five-month period that had abdominal pain for no more than 48 hours prior to presentation, WBC less than 18,000, and surgeon evaluation and radiographic imaging consistent with appendicitis without rupture, appendicolith, abscess or phlegmon and an appendiceal diameter of 1.1cm or less. A total of 102 patients were included with 65 that chose laparoscopic surgery and 37 that chose conservative management. Antibiotic therapy was administered for a minimum of 24 hours and consisted of IV piperacillin-tazobactam; in the case of an allergy, metronidazole or ciprofloxacin were substituted. Oral intake was withheld for 12 hours, and if patients showed signs of clinical improvement, their diet was advanced. Once a patient was able to tolerate a regular diet, IV antibiotics were discontinued and patients were discharged with a 10-day course of amoxicillin-clavulanate (or ciprofloxacin and metronidazole if allergic). Objective signs of clinical improvement that were evaluated included decreased abdominal pain or tenderness, improvement of fever, and cessation of nausea and/or vomiting. Any patient that was found to have signs of clinical worsening as an inpatient, failed to improve within 24 hours, or presented after discharge with recurrent clinical findings of appendicitis underwent timely appendectomy. Patients that opted for surgery were also started on IV antibiotics and were operated on within 12 hours of presentation. Results of initial conservative management are as follows: two patients failed to improve or showed signs of clinical worsening, two patients had recurrences within 30 days of discharge, and five more had recurrences between 30 days and one year. By one-year post discharge, 28 of 37 or approximately 75.7% of patients still had their appendix, and at the median final follow up of 21 months the number of patients with their appendix remained unchanged. No post-operative complications occurred in patients that required an appendectomy from those initially managed conservatively, while the postoperative complication rate in patients choosing surgery was 7.7%. Two major complications occurred with one hospital readmission and one re-operation. Rates of complicated appendicitis were not significantly different between groups ($p = 0.15$), with one out of 37 patients in the initial conservative treatment group and eight out of 65 patients in the surgery group. Four of the patients that underwent immediate appendectomy had a histologically normal appendix on pathological examination. Therefore, the negative appendectomy rate was 6.2% for this group, while this never occurred in the group initially managed by conservative measures. Although the non-operative group was found to have significantly longer median hospital stay ($p < 0.001$) at 37 versus 20 hours, healthcare costs were significantly lower with a median of $4219 versus $4992 ($p = 0.01$). Cost in this study included hospital charges from initial presentation through all clinical encounters related to appendicitis over a one-year period, with direct and indirect charges that were self-reported. Finally, the health-related quality-of-life (HRQOL) was measured at one year follow up to measure disability days for the patients and their parents. Days that the child did not participate in all of their normal activities was considered to be a disability day, examples include participation in gym, recess, sports and other extra-curricular activities. Disability days for parents were recorded as the number of days that their normal schedule was disrupted due to their child's diagnosis of appendicitis and any complications associated with it. No significant difference was found between parents or children of opposite treatment groups (Minneci et al., 2015).

Although the total number of patients with acute non-complicated appendicitis that were managed conservatively was relatively small, with 24 in the study by Hartwich et al. (2016) and 37 in the study by Minneci et al. (2015), findings between the two studies were consistent. The study period for Minneci et al. was longer with average follow-up until 21 months versus 14 months, but no incidents of appendicitis recurred after one-year. By the end of each study period, patients that either failed conservative management or had a recurrence of appendicitis was only 20.8% in the study by Hartwich et al. and 24.3% in the study by Minneci et al. Furthermore, neither study observed any major complications in those that underwent initial conservative management, even in those that it was unsuccessful or experienced recurrences. Of the patients that underwent immediate appendectomy in the study by Minneci et al., 7.7% had major complications, even with the laparoscopic approach. Additionally, the negative appendectomy rate was 6.2%. Both studies found total healthcare cost to be significantly lower for patients that were managed conservatively, and utility to be similar between groups. These two studies present several motives to further consider conservative management in patients with uncomplicated acute appendicitis.

Unique from other studies with patient/family decision-making, a pilot randomized controlled trial was performed at a single institution in Sweden. Patients between the ages of five to 15 years of age that agreed to participate were enrolled between February and October of 2012. Patients were excluded if clinical signs or imaging suggested perforation or if they had ever undergone prior non-operative treatment for appendicitis. Approximately 40% of patients asked to participate in this study consented, with a total of 50 children that were successfully randomized into treatment groups and followed through with the study. All patients received an initial ultrasound, an additional one ultrasound and four CT scans were performed in cases when the appendix was not visualized on the initial imaging study. Patients who were randomized to conservative treatment were treated with IV meropenam and metronidazole. Intravenous antibiotics were discontinued when the patient was able to tolerate an oral diet, and at this time therapy was switched to oral antibiotics that included ciprofloxacin and metronidazole. Both treatment groups were discharged from the hospital upon the same standards, which included: able to tolerate a light diet, afebrile for 24 hours, pain controlled adequately by oral analgesics and the patient had resumed mobility. Of the 26 patients that underwent appendectomy, no significant complications occurred. In the conservatively treated group, two major complications occurred. The first occurred, two days after commencing treatment when symptoms had not improved and an appendectomy was performed. However, it turned out that this patient had been misdiagnosed. Although the patient did have a macroscopic appendix, pathology results were negative for appendicitis and the patient was diagnosed with mesenteric lymphadenitis. The second complication occurred nine days after beginning treatment, when a patient presented to the emergency department with abdominal pain. This patient was found to have a walled-off perforated appendix and received surgery. All patients received follow-up for one year after their initial treatment. Over the course of the year, an additional seven patients underwent an appendectomy. One patient was confirmed to have recurrent acute appendicitis at nine months after enrollment. One patient underwent appendectomy due to parental request, although the patient was asymptomatic and a normal appendix was confirmed. Five additional children that were evaluated throughout the year for mild abdominal pain underwent appendectomies at the discretion of their parents and the surgeon. All five of the appendices were found to have some degree of fibrosis, but none were inflamed. At the end of the one-year study period, 15 out of 24 patients, or approximately 62%, that underwent initial conservative treatment still had their appendix. Agreeable with the cost analysis by Hartwich et al. (2016) and Minneci et al. (2015), cost for initial inpatient stay was significantly lower in the group that was managed conservatively ($P < 0.0001$). When cost for the entire year was analyzed there was no significant difference ($p = 0.11$), although costs for the group initially treated non-operatively, remained lower at $34,587 versus $45,805 for the operative group. Length of hospital stay was also analyzed and found to be significantly longer for patients in the conservative management group with a median time being 51.5 hours versus 34.5 hours for those in the surgery group ($p = 0.0004$). (Svensson et al., 2015). Overall, because this is a study and there are not yet standard guidelines regarding medical management of appendicitis and re-evaluation of abdominal pain, the threshold for operation on these patients was very low. Six out of the nine patients that underwent appendectomy during the follow-up period did not have recurrent appendicitis. However, it was noted that five of them did have some degree of fibrosis, which should pose further investigation.

A single institution study in Ontario, Canada from May 2012 to February 2013 enrolled children less than 18 years with uncomplicated acute appendicitis that agreed to non-operative management. Inclusion criteria consisted of: “classic presentation” of appendicitis, imaging that supported the diagnosis, and symptoms beginning less than 48 hours prior to presentation. Findings of a phlegmon or abscess on imaging or hemodynamic compromise were exclusion criteria. Data for the group that underwent surgery was obtained by a retrospective chart review of patients with non-complicated acute appendicitis who were operated on by the same surgeon between January and October of 2011. These patients were administered a single dose of antibiotics, which is not named in the study, proceeding a laparoscopic appendectomy. Patients that opted for conservative management received IV ciprofloxacin and metronidazole or IV ampicillin, gentamycin and metronidazole. Clinical signs of worsening or failure to improve within 24 hours warranted immediate operation. At the time of hospital discharge, patients were prescribed oral amoxicillin-clavulanate for a total of one week of antibiotic treatment. Both the operative and non-operative group included 12 patients. Average follow-up time for this study was six and a half months for patients that underwent medical management and six months for those that underwent surgery. Of the patients that were treated non-operatively, two failed initial treatment. One patient failed to improve within 24 hours while in the hospital and required appendectomy. A second patient was sent home and completed the course of oral antibiotics. However, at a six-week follow-up, the patient reported that abdominal pain had not resolved and elected for an outpatient appendectomy. It was notable that an appendicolith was discovered and the patient’s symptoms subsided following surgery. Seven months post-discharge, one patient experienced recurrent appendicitis and required an appendectomy. At the end of the follow-up time period, nine out of 12 or 75% of patients still had their appendix. They were offered, but none elected for an interval appendectomy. The only complication for this group of patients noted in the study is that one patient developed a deep surgical site infection. The infection occurred in the patient that failed to improve non-operative management and received an appendectomy on admission. Two patients from the operative group developed infections, with one being a deep and the other being a superficial surgical site infection. No invasive procedures were required for patients in either group that developed an infection, although both deep surgical site infections required hospital re-admission. The patient from the initial operative group that developed a deep surgical site infection required a second hospital re-admission. Average length of hospital stay including readmissions was not significantly different between treatment groups, with 1.8 days for the non-operative group versus 1.7 days for the operative group ($p = 0.97$). Subsequent emergency department visits included four visits from the non-operative group and two visits from the operative group ($p = 0.51$). Although not significant, patients in the non-operative group were likely to fear recurrent appendicitis with any gastrointestinal symptom, which may have led to a lower threshold for presentation to the emergency department. Although this was a small study group, no significant difference existed in post-treatment complications. Similar to Svennson et al. (2015), no significant difference in length of hospital stay existed between groups. Seventy-five percent of patients that underwent non-operative therapy had their appendix at average follow-up of six months and only one versus two surgical site infections occurred in this group. Additionally, patients from the initial non-operative group that required appendectomy did not have any evidence of perforation and no subjective difficulty in regards to the procedures were reported (Armstrong, Merritt, Jones, Scott, & Butter, 2014).

In the Netherlands, a multicenter prospective study was conducted over various time intervals between 2012 and 2014. Children from ages seven to 17 were included if clinical and ultrasound evidence indicated uncomplicated acute appendicitis. Criteria included localized tenderness in the right lower quadrant, normal to hyperactive bowel sounds, absence of a palpable mass, and no diffuse guarding. This study provided detailed ultrasound inclusion criteria, which were an appendix greater than 6mm that was non-compressible, hyperemia of the wall of the appendix, infiltration of surrounding adipose tissue and the absence of perforation, abscess, mass, phlegmon, extraluminal gas or disseminated peritoneal fluid. Allergy to any of the antibiotics in the non-operative protocol was an exclusion criteria. The protocol consisted of IV amoxicillin-clavulanate and gentamicin along with IV fluids. Patients were re-evaluated every six hours for signs of clinical deterioration, started on an oral diet after 24 hours, and underwent a repeat ultrasound at 48 hours. If at 48 hours patients met improvement criteria, they were started on oral amoxicillin-clavulanate and observed until discharge at 72 hours. Three patients did not meet all of the criteria and continued to receive IV antibiotics for an additional 24 hours, and all of them met the criteria to switch to oral antibiotics at that time. Criteria used to indicate that patients were clinically suitable for discharge included no signs of complex appendicitis on ultrasound, decreased CRP and WBC count from admission, patients that were ambulating, adequate oral intake, body temperature less than 38.8 Celsius and a score of less than four on the analog scale/comfort scale (which is not described further in the text). If criteria were not met, either laparoscopic or open appendectomies were performed at the discretion of the surgeon. A total of 25 patients met criteria and agreed to participate in the study. All were discharged at 72 hours from the hospital, and 23 were asymptomatic at 8-week follow-up. The remaining two patients underwent laparoscopic appendectomies at one and six weeks after admission. Both were found to have some degree of fibrosis but not re-current appendicitis. One of them was noted to have an appendicolith. Neither of these patients faced any medical or surgical complications (Gorter et al., 2015).

In Israel, a prospective study was performed from November 2013 through June 2014 at a single institution, including 45 children from four to 15 years with early acute appendicitis. All patients were evaluated with ultrasound and considered for the study if imaging was consisting with clinical signs of acute non-complicated appendicitis. This study differs from others, as the decision-making component between patients and families is not mentioned. Patients who met inclusion criteria were started on IV ceftriaxone and metronidazole. Patients were kept on this regimen for three to five days, and discharged home once asymptomatic with oral amoxicillin-clavulanate for an additional five days as long as their symptoms improved. If symptoms did not improve, patients underwent appendectomies. There was no control group of patients undergoing immediate appendectomy for comparison. Results indicated that 42 children were discharged home after improving on IV antibiotic therapy, while the remaining three underwent an appendectomy on admission due to any of the following: increased abdominal tenderness, increased temperature, and/or WBC count. These three operations found no incidence of perforation or necrosis and were followed by uneventful post-operative courses. Two weeks post-discharge, one patient was readmitted with abdominal pain and underwent an appendectomy, however, the pathology report was negative for appendicitis. A second patient experienced a true recurrence of appendicitis two months later, confirmed by appendectomy. At three-month follow-up appointments in clinic, no patients had evidence of surgical site infection and only two patients reported mild abdominal pain. Two patients at this time were lost to follow-up. A phone follow-up at six and 14 months post-discharge showed no further patients reported recurrence of disease (Steiner, Buklan, Stackievicz, Gutermacher, & Erez, 2015).

One study performed in Japan had a longer follow-up period than similar studies have reported. Patients and their families selected operative versus non-operative treatment. Similar to other studies, patients were excluded if they exhibited diffuse peritonitis or signs of abscess, phlegmon or other complications on imaging. Ultrasound was the imaging modality of choice to assist with diagnosis and was performed on all patients; CT scans were reserved for when the appendix was not visualized on ultrasound. Of the 164 patients that enrolled in this study, 86 opted for surgery and 78 opted for non-surgical management. Those that opted for surgery were treated with IV antibiotics until 48 hours after surgery, and discharged once tolerating oral intake, were afebrile and pain was controlled. In the non-operative group, IV cefmetazole was administered. If a patient's WBC did not decrease by at least 25% within two days, the antibiotic regimen was changed to sulbactam/ampicillin and ceftazidime. If no response, the third line antibiotic regimen was meropenem or imipenem/cilastatin and gentamicin. IV antibiotic treatment continued until CRP concentrations were below 0.5 mg/dL and patients were discharged in the absence of fever and abdominal pain. Reportedly, 66 out of 77 (85.7%) responded appropriately to the first-line antibiotic. The breakdown of patients that required second versus third line antibiotic treatment is not reported. However, an additional 13% of patients were successfully treated non-operatively after adjusting the antibiotic regimen. Only one patient was deemed to fail conservative management, and the success rate of non-operative treatment was 98.7%. This patient was the only one in the non-operative group that experienced complications during the treatment period, which lead to a perforated appendix. The only reported complications in the operative group were two cases of postoperative ileus that were managed conservatively. Average follow-up for this study was 4.3 years, and during this time, appendicitis recurred in 22 (28.6%) patients who were initially treated conservatively. Average time of recurrence was six months, although the range was 17 days to 39 months. Throughout the first year, 16 patients (20.8%) experienced recurrence, which accounted for approximately 73% of total recurrences during the study period. Data on each patient's WBC count on admission, maximum CRP level during treatment, diameter of appendix, length of hospital stay, and presence of appendicolith at time of diagnosis was analyzed. The presence of appendicolith was the only identified factor that showed a significant correlation with recurrence of appendicitis or patient requiring a subsequent hospital admission ($p = 0.049$). It was also noted that the one patient that failed initial conservative treatment was 1 of 19 that had an appendicolith, although this was not statistically significant in correlation with treatment failure ($p = 0.24$). All patients that experienced recurrent appendicitis were treated with laparoscopic appendectomy. This study went on to compare statistics from patients that were initially treated operatively versus those who were treated operatively for a recurrence. No significant differences existed in average operative time, length of hospital stay or postoperative complications. Several other factors were analyzed between initial operative and non-operative treatment groups, including length of hospital stay and patient satisfaction. Length of hospital stay was not significantly different between treatment groups ($P = 0.81$), with the average for the non-operative group being 6.6 days versus 6.5 days for the operative group. Length of stay in this study is overall longer than other comparable studies, which is due to a medical expense support system in Japan. The support system allows for longer hospital stays in a culture where parents traditionally expect their child to be free of disease at discharge. Satisfaction surveys were sent out greater than one year after a patient received initial treatment. Information regarding the questionnaire is not provided, but the maximal score was five. Response rate was 66.9% and there was no significant difference in number of responses received per treatment group. Satisfaction scores were significantly higher in the operative group (p = 0.029) with average scores being 4.7 versus 4.4 in the non-operative group. Within the non-operative group, there was no statistically significant difference in satisfaction scores between patients that experienced recurrence from those that did not (Tanaka et al., 2015). Of the three studies that analyzed utility, this is the only one that reports it to be higher in the operative group. Both Minneci et al. (2015) and Hartwhich et al. (2016) found parents and children to have no significant difference or rank non-operative as higher. This could be due to difference in utility questionnaires or cultural expectations. Overall, this study indicates the value of antibiotic therapy substitutions if appropriate response is not initially seen, a correlation between appendicoliths and recurrent appendicitis and that the majority of recurrences were within one year from initial diagnosis.

## Predictors of Non-operative Treatment Failure

Several studies have sought to identify factors linked to failure of conservative management or recurrence of appendicitis in cases of uncomplicated acute appendicitis in the pediatric population. Some have suggested a link between treatment failure and recurrent appendicitis and the presence of appendicolith. One prospective study performed at Nationwide Children's Hospital in Columbus, Ohio was designed to specifically include only patients with appendicitis that had an appendicolith. Children ages seven to 17 years were included that had non-complicated appendicitis as determined by evidence from laboratory studies, imaging and consistent clinical signs and symptoms as determined by the surgeon. The trial began in July 2014 and ended in March 2015 due to concerns for patient safety. Of the 14 patients that enrolled, only five opted for non-operative management. Of these five patients, two experienced failure of initial treatment, and underwent appendectomy after developing increased abdominal pain and tenderness. Eight months after initial treatment, a third patient experienced a recurrence. All three of these patients had confirmed acute appendicitis on pathological analysis. The antibiotic protocol that these patients received was similar to other studies, utilizing IV piperacillin-tazobactam for a minimum of 24 hours followed by a switch to oral amoxicillin-clavulanate. Those allergic to penicillin were treated with ciprofloxacin and metronidazole, with all patients to complete a seven-day total course of antibiotic therapy. In addition to the high failure rate of conservative management (60%), six out of nine (66%) patients in the operative arm were found to have complicated appendicitis. The complicated appendicitis cases included one case of gangrenous appendicitis and five cases of perforated appendicitis. This indicates that the pre-operative diagnosis of uncomplicated acute appendicitis was either incorrect or patients with appendicoliths transform quickly to complicated appendicitis. Inclusion criteria was similar to many prior studies: abdominal pain for 48 hours or less, white blood cell count less than 18,000 microliters, appendiceal diameter 1.1 cm or less and no evidence of rupture, abscess or phlegmon on ultrasound or CT, and a disposition from the surgeon after physical examination that was agreeable to the diagnosis (Mahida et al., 2016). Overall, this study was shown to be unsafe and suggests a high failure rate and recurrence rate in conservative management of pediatric patients with appendicitis and presence of an appendicolith.

Another study sought to identify predictive factors for recurrent appendicitis. This study was a retrospective chart review of patients that underwent conservative management for uncomplicated acute appendicitis between January 2002 and December 2010 in Mie, Japan. Inclusion criteria were as follows: right lower quadrant pain, WBC count greater than 9,000 per microliter and/or CRP greater than 0.3 mg/dl, ultrasound and/or CT findings to support the diagnosis and a score of seven or greater on the pediatric appendicitis score (Koike et al, 2014). The pediatric appendicitis score has a maximum of ten points; patients are assigned two points for tenderness over the right iliac fossa, two points for tenderness with hopping, cough and/or percussion in the right lower quadrant, and one point for fever, nausea and/or vomiting, anorexia, polymorphonuclear neutrophilia, leukocytosis and migration of pain. In this study, 125 patients were identified to have successfully undergone conservative management. The protocol in this study included a minimum of 48 hours of IV cefoperazone. IV hydration was provided, and patients were not to intake anything by mouth until at least the second day of admission. Discharge criteria included the absence of abdominal pain, body temperature less than 37 degrees Celsius and no increase in levels of inflammatory markers. The regimen in this study was unique in the fact that oral antibiotic therapy was only prescribed to those with a CRP greater than 1 mg/dL at discharge, with the antimicrobial agent being cefcapene pivoxil for only three additional days. Appendicitis recurred in 24 out of 125 patients, or approximately 19% between two and 36 months after treatment, with average recurrence at 12.6 months. A univariate analysis was performed on a multitude of factors to determine correlation with recurrent appendicitis. Analyzed factors included age, sex, pediatric appendicitis score on admission, signs and symptoms including nausea, vomiting, diarrhea, rebound tenderness, muscular guarding, clinical course including duration of fever and abdominal pain, inflammatory markers on admission including white blood cell count, neutrophil percent, CRP, radiographic findings including appendiceal diameter greater versus less than nine mm, presence of appendicolith and presence of intraluminal fluid. Univariate analysis found significant association with recurrence in the following factors: pediatric appendicitis score ($p = 0.0096$);

rebound tenderness ($p = 0.0185$); muscle guarding ($p = 0.0096$); appendiceal diameter greater than 9 mm ($p = 0.0009$); intraluminal appendiceal fluid ($p < 0.0001$) and presence of appendicolith ($p = 0.0377$). Clinical course and inflammatory markers did not have any statistical significance in correlation with disease recurrence. Multivariate analysis of the potential predictive recurrence factors identified in the univariate analysis found only the presence of intraluminal appendiceal fluid to be an independent predictor of recurrence ($p = 0.0019$). Cumulative rates of recurrence over a three-year period were significantly higher in those that presented with intraluminal appendiceal fluid ($P < 0.0001$). Of the 37 patients found to have intraluminal fluid, 17 experienced recurrent appendicitis. Recurrence in this group was 45.9% versus only 7.95% of those who did not have intraluminal fluid. Cumulative analysis at one year was also statistically significant ($p < 0.00001$) with rates at 32.4% versus 5.68%. Additionally 88.2% (15 out of 17 patients) that had intraluminal fluid on initial presentation were found to also have it on recurrence (Koike et al., 2014).

## Discussion/Conclusion

Although the treatment of appendicitis has evolved over time from the open to laparoscopic approach, surgery remains the standard of treatment worldwide. The laparoscopic approach has maintained a very low mortality rate, results in less post-operative adhesions and wound infections and is less invasive. However, surgical risks of general anesthesia, bleeding, injury and damage to abdominal organs and development of an abscess remain significant complications. Additionally, even with a variety of disease-specific physical examination maneuvers, clinical scoring criteria and use of various imaging modalities negative appendectomies continue to occur, even in some cases where CT has been used. Several studies have demonstrated the importance of urgent treatment of the disease as delay increases perforation rates. However, studies performed by Stahlfeld et al. (2007) and Boomer et al. (2014) have supported the concept that administration of antibiotics and delaying surgery does not lead to negative consequences.

Several studies have investigated the role of treating non-complicated acute appendicitis conservatively with antibiotic therapy instead of surgery. The majority of studies reported follow-up periods of 14 months or less and had failure rates of 25% or less, which includes patients that did not respond to treatment or had a recurrence within the follow-up time frame. In several of the studies, there were asymptomatic patients that opted to have appendectomies at later times with no pathological abnormalities of their appendix. These cases are not included in the failure rates. One study by Svennson et al. (2015) had a failure rate of 39%, inclusive of five appendectomies that were negative for appendicitis but positive for fibrosis. Since these patients were symptomatic and did not have completely normal appendices they are counted as failures for the purpose of this review. The study by Tanaka et al. (2015) includes the most long-term follow-up period, lasting 4.3 years. Of the patients that experienced recurrence, 73% were within the first year. This study was also unique as it provided a second and third line antibiotic regimen for patients that did not clinically improve with the initial regimen. This approach resulted in the most successful initial success rate of 98.7%, exclusive of cases of recurrent appendicitis. This study shows that adjusting the antibiotic regimen increases success rates of non-operative treatment.

Overall, complications that resulted from non-operative treatment were low, and only two cases of perforated appendix occurred throughout the entire group of studies. In several studies, operative complications were more common (Armstrong et al., 2014; Minneci et al., 2015). Several studies have reported that an operation following failure of non-operative management did not subjectively differ or result in complications (Armstrong et al.; Svennson et al., 2015; Steiner et al., 2015). Furthermore, medical expenses have been comparable or less in patients that underwent non-operative management (Hartwich et al.; Minneci et al., 2016; Svenson et al.). In the studies performed in the United States, utility as rated by parents and children have either been higher or equal to that of operatively managed patients (Hartwich et al.; Minneci et al.).

Several studies have found significant correlations in factors that are associated with failure of non-operative management. The presence of appendicoliths in patients that failed non-operative management or experienced recurrences has been mentioned in several studies (Armstrong et al., 2014; Koike et al., 2014; Tanaka et al., 2015). The study by Mahida et al. (2016) that specifically sought a study population with appendicoliths was canceled due to concern for patient safety. Koike et al. was the only study group to mention a correlation with intraluminal appendiceal fluid and disease recurrence, however, it was the most significant factor on both univariate and multivariate analysis out of a variety of clinical factors that were investigated as possible predictors of recurrence.

Overall, this review shows that non-operative management of appendicitis is effective in the majority of cases. A variety of different antibiotics and regimens including length of treatment and dosage have been successful in treating the disease. Further research in this area should aim to establish the most effective regimen and encourage the use of a second and third line regimen as shown effective by Tanaka et al. (2015). Studies have shown that non-operative management is less effective in the presence of intraluminal fluid and appendicoliths. Evidence suggests that if either of these are detected on imaging, patients should undergo appendectomies as opposed to non-surgical management. Additional factors that may influence failure or recurrence should also be further investigated. Finally, Svensson et al. (2015) mentions patients that were treated non-operatively and had unresolved abdominal complaints until appendectomy. Although the appendices were not inflamed, a degree of fibrosis was discovered in five cases. Further research should be directed at uncovering reasons for this and long-term consequences of non-operative management of appendicitis. Excluding the study by Mahida et al. (2016), the present trials have shown to be safe through the follow-up periods described. Although the scope of this paper includes only the pediatric population and does not include cases of complicated or perforated appendicitis, there is evidence to suggest that non-operative management may be a plausible treatment option.

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Abstract

Objective: To determine if non-operative management of appendicitis is an effective treatment option for acute non-complicated appendicitis in the pediatric population. Method: MEDLINE, PubMed, Embase. Results: Failure rates varied from 9% to 39% over varied time intervals. Conclusion: Although further research is required, evidence suggests that non-operative management of acute non-complicated appendicitis is effective.

*Keywords: Non-operative management, Appendicitis, Antibiotic therapy, Pediatric appendicitis*