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Study Title: Comparison of Medical and Surgical Treatment of Uncomplicated Acute Appendicitis in Children

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Purpose of the Study and Background

Purpose of the Study

Several prior studies have demonstrated that medical management of acute appendicitis in adults is a safe first-line therapy option. This study aims to determine whether non-operative management of uncomplicated acute appendicitis with antibiotics is non-inferior to operative management in a pediatric population.

Background

Appendicitis has traditionally been thought of as a surgical condition. Over the past ten years there have been several studies comparing medical and surgical management of acute appendicitis in adults which have demonstrated that medical management with antibiotics alone is a safe first-line option in adults with acute appendicitis.[1-4] Long-term follow-up of patients managed without surgery has also demonstrated longer-lasting safety of non-operative management of acute appendicitis in adults.[4] For pediatric patients, surgery is still the mainstay of treatment for uncomplicated appendicitis and perforated appendicitis. Recent prospective studies have demonstrated that non-operative management with antibiotics may be a feasible option for cases of uncomplicated acute appendicitis in children.[5,6] These studies, however, are limited by small sample sizes, and/or nonrandom treatment assignment.

The current standard of care for preoperative antibiotics in uncomplicated appendicitis includes a second or third generation cephalosporin with metronidazole if the cephalosporin does not provide adequate anaerobic coverage.[7] These antibiotics are used to control infection and bridge patients to surgery rather than to achieve true eradication of the infection. Additionally, these antibiotics prevent post-operative complications such as wound infections and intra-abdominal abscesses. Typically, patients receiving pre-operative antibiotics for appendicitis will receive them for at most 12-24 hours prior to surgery, the equivalent of 1-3 doses. For patients with beta-lactam or cephalosporin allergies the standard of care is ciprofloxacin with metronidazole. In patients with uncomplicated appendicitis operation adequately treats the infection, and post-operative antibiotics are rarely needed.

In prior studies conducted in children and adults the antibiotics used to treat uncomplicated appendicitis non-operatively were intravenous piperacillin/tazobactam or a carbapenem for at least 24 hours. For patients with beta-lactam allergies ciprofloxacin/metronidazole was typically used for the initial intravenous therapy.[2,5,6,8] This is followed by oral amoxicillin/clavulanate or a fluoroquinolone/metronidazole for a total antibiotic course of 7-10 days.[1-3,5,6,8] Piperacillin/tazobactam and carbapenems are broader in spectrum of coverage than the pre-operative antibiotics used per standard of care. For uncomplicated appendicitis managed operatively there is no difference in outcomes if broad-spectrum or narrow-spectrum pre-operative antibiotics are used.[9] Broad-spectrum antibiotics are used for non-operative management because infection control is dependent on strong therapeutic agents rather than a procedural

intervention. Given local *E. coli* resistance patterns to Augmentin, ciprofloxacin/metronidazole will be used as the first-line oral antibiotic combination in this study. These antibiotics will provide adequate gram-negative, pseudomonal and anaerobic coverage, as per guidance by a Pediatric Infectious Disease Specialist at NYU.

Study Design

This study will be a randomized controlled trial comparing non-operative management with antibiotics to surgical management of uncomplicated acute appendicitis. The hypothesis is that antibiotics are not worse than surgery for the treatment of uncomplicated appendicitis in children. The primary outcome will be survey scores on the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale Parent-proxy report. Secondary outcomes will include child scores on the PedsQL; length of stay; immediate, 1-week, 2-week, 30-day, and 60-day success of non-operative management; readmission rates for both groups; and long-term complications over one year.

Characteristics of the Research Population

Number of Subjects

A total of 190 subjects will be included in the study. This is based on validating statistics for the PedsQL Child Report and Parent-Proxy report.[10] Given the potential variability of response for subjects on the child report based on maturity of the subject, the Parent-Proxy report will be used as the primary outcome. For the Parent-proxy report the standard deviation of scores is 15.9 with an of mean clinically important difference (MCID) is 4.5 on the same 100-point scale. To establish non-inferiority the MCID will be used as a clinically acceptable margin of difference between the two treatment arms. The null hypothesis is that PedsQL scores for the non-operative management group will be lower than PedsQL scores for the operative management group by 4.5 points or fewer. The alternative hypothesis is that scores for the non-operative management group will be lower than scores for the operative management group by more than 4.5 points. Given our hypothesis that antibiotics alone are non-inferior to operative management, a significance level of $\alpha = 0.05$ ($Z_{1-\alpha} = 1.645$) and Power of 0.80 ($\beta = 0.20$, $Z_{1-\beta} = 0.84$), the expected sample size necessary for a non-inferiority trial is 77 per group, based on the formula for a one-tailed test: N (per group) = $(Z_{1-\alpha} + Z_{1-\beta})^2 * (SD/MCID)^2$. [1]The total sample necessary for the study would therefore be 154 subjects.

There are few studies in pediatric populations from which to generalize data about consent rates for randomization. The prior study conducted in children in the US was a parent-option format, and the consent rate for participation was 88%. Of the subjects and parents who agreed to participate 39% chose surgery, suggesting a non-operative approach is not significantly less favorable for parents. In adults, the more recent studies cite consent rates of participants at 80-90%. Expecting a 10-20% non-consent rate, a total of 190 patients would need to be enrolled to maintain the power of the study.

Patients will be identified for potential study inclusion upon consultation of the Pediatric Surgery team. Subjects will be recruited from all hospital sites covered by the pediatric surgical faculty at NYU. These sites include NYU Tisch Hospital, Bellevue Hospital, and Hackensack University Medical Center (HUMC) in New Jersey. Additionally, the pediatric surgeons cover consults from NYU Brooklyn and the NYU-run free-standing Cobble Hill Emergency Department. Patients under the age of 12 from these last two sites are transferred to Tisch Hospital for care, and will be

recruited at Tisch Hospital. Patients aged 13 and above will be recruited at the hospital where they initially present (NYU Brooklyn or Cobble Hill).

In the past year approximately 170 patients who would have been eligible for study enrollment presented to these facilities for treatment of acute appendicitis. 50% of subjects were treated at NYU Tisch Hospital, 35% at HUMC, and 15% at Bellevue. Using these proportions to estimate enrollment, 95 subjects are expected to be recruited from NYU, 67 from HUMC and 28 from Bellevue. The protocol has been submitted for independent review by the IRBs of these institutions. Approval of the study at HUMC is dependent on approval by the NYU IRB. When the study is approved by the IRB at HUMC a modification will be submitted to the NYU IRB, which will include the approval letter by the external site.

Gender of Subjects

Subjects of both genders are eligible for enrollment in the study. The gender distribution is not expected to favor either gender.

Age of Subjects

Subjects will be 6-17 years old. Prior studies comparing medical and surgical management of appendicitis in children used age criteria of 5-15 or 7-17 years of age. The incidence of appendicitis prior to the age of 5 is one to six cases per 10,000 children, making it a rare diagnosis in children under the age of 5. Peak incidence of acute appendicitis occurs in the second decade of life from 10-19 years of age. Younger children are more likely to present at a later stage of disease and are therefore less likely to improve with antibiotics alone. Given that individuals 18 and older at the time of presentation are treated by adult general surgeons, limiting age eligibility to individuals 6-17 years of age will capture the patients most likely to benefit from the intervention while simultaneously limiting the variability in surgical intervention.

Racial and Ethnic Origin

Participants of all racial and ethnic origins will be eligible for participation. The intended racial and ethnic distribution of subjects is not expected to vary significantly from that of the populations at the study sites.

Inclusion Criteria

Age 6-17, first episode of appendicitis, Pain < 48 hours, White blood cell count < 18,000, temperature < 103º F, radiographic evidence of acute appendicitis on ultrasound or CT without evidence of perforation, and appendiceal diameter < 11 mm, ability to take oral antibiotics

Exclusion Criteria

Prior antibiotic treatment for appendicitis, presence of medical condition prohibiting surgical therapy, radiographic or clinical evidence of abscess or perforation, appendiceal mass, positive pregnancy test, other diagnosis equally as likely as appendicitis, pain for ≥ 48 hours, white blood cell count ≥ 18,000, temperature ≥ 103º F, or appendiceal diameter ≥ 11 mm, inability to take oral antibiotics.

Vulnerable Subjects

The study population will include the vulnerable population of children. This is necessitated by the primary aim of the study, to determine whether medical management of acute appendicitis is superior to surgical management in a pediatric population. The study is designed to limit subjects to those who are likely to benefit from the treatment offered.

Methods & Procedures

Methods & Procedures

Patients for whom the Pediatric Surgery team is consulted for abdominal pain suspicious for acute appendicitis will be screened for inclusion/exclusion criteria. Eligible participants will have a diagnosis of acute appendicitis made by an attending pediatric surgeon on the basis of history and physical exam, with confirmatory imaging. The consent process will be conducted by the attending pediatric surgeon, all of whom are listed on this study, with the patient and their parent/guardian. Assent from the subject will be obtained independently of consent from their representative.

Subjects will be randomized to receive either medical therapy or surgical intervention. Randomization will be achieved using a permuted block protocol. Blocks will be determined and treatments within a block will be assigned for each block prior to the start of the study. Upon enrollment, the treatment arm of each subject will be assigned as per the pre-determined order.

Subjects in both treatment arms will be maintained with intravenous fluids and no oral intake from the time of identification. If it has not already been done by the Pediatric Emergency Department team, a CBC with differential and C-reactive protein level (CRP) will be drawn. All potential subjects will receive piperacillin/tazobactam as antibiotic therapy at the time of diagnosis. Ciprofloxacin/metronidazole will be used in penicillin-allergic subjects. Patients often present with acute appendicitis during evening hours, making the time from initial evaluation to surgery approximately 12-24 hours. Starting all patients on the same antibiotics after initial evaluation will allow all potential subjects to receive identical initial treatment while still allowing potential subjects and their representatives ample time to consider participation in the study.

Subjects in the medical therapy arm will be treated with piperacillin/tazobactam for at least 24 hours. Ciprofloxacin/metronidazole will be used in penicillin-allergic patients. Subjects will be maintained on nothing by mouth with intravenous fluids for at least 12 hours. During this time their pain, and vital signs will be monitored every 4 hours as per standard of care. Specific attention will be paid to trends in pain levels, temperature and heart rate. If they show improvement in abdominal pain, they may be advanced to a diet.

After 24 hours of IV antibiotic administration a repeat CBC with differential and CRP will be drawn. Subjects will be transitioned to oral antibiotics when they have been afebrile for 24 hours on IV antibiotics, and they have a normal WBC or decrease in CRP by ≥ 15%. If patients have not achieved these clinical milestones after 48 hours of IV antibiotics, they will have an appendectomy. All patients will receive one dose of oral ciprofloxacin/metronidazole and be observed to assess tolerance prior to discharge. Subjects tolerating oral antibiotics will be discharged on oral antibiotics for a total 10-day course when they have adequate pain control and are ambulating. If oral ciprofloxacin is not a feasible option (if prohibitively expensive due to lack of coverage by insurance or unavailable due to pharmacy stock or compounding issue), the patients will be discharged on a regimen of oral Augmentin. All patients' insurance coverage will be checked for oral ciprofloxacin and metronidazole coverage prior to switching to oral Augmentin so as to limit the patients' exposure to different antibiotics within a short period of time. Augmentin offers similar coverage to ciprofloxacin and is readily available, and prior studies have found that Augmentin is non-inferior to emergency appendectomy for the treatment of acute appendicitis, in both children and adults. [11-14]

Failure of antibiotic therapy will be defined as lack of improvement in pain or vital signs, persistent fever, failure to normalize WBC, uptrending or < 15% decrease in CRP, or worsening clinical

exam after 48 hours of treatment with intravenous antibiotics. These patients will have an appendectomy.

Subjects in the surgical treatment arm will receive intravenous antibiotics until the time of operation, and will be maintained on intravenous fluids and no oral intake until they undergo appendectomy as per standard of care. Appendectomy will occur within 24 hours of enrollment. Subjects in the surgical treatment arm will receive post-operative antibiotics as per standard of care.

Follow-up will occur on the following schedule:

24 hours after discharge: Subjects will receive a phone call from the research team to ensure they were able to obtain and start outpatient oral antibiotics.

1 week after discharge: Subjects will receive a phone call from the research team to assess recovery, and return to school (subjects) or work (parents). Subjects in the medical treatment arm will be asked about whether they have been taking antibiotics appropriately, and whether they have developed complications such as recurrence of appendicitis.

2 weeks after discharge: Subjects will receive a phone call from the research team to evaluate whether they recovered from treatment, whether they experienced any complications, and when they returned to school/work. For subjects in the surgical treatment arm complications include abscess development and wound infections. The primary complication for subjects in the medical treatment arm is recurrence of appendicitis.

30 days after discharge: Subjects and their parents/guardians will present for an office visit. For subjects in the surgical arm this is a standard post-operative visit. For subjects in the medical treatment arm this will be the equivalent post-treatment evaluation. Subjects and their representatives will be given the PedsQL Generic Core Scale to complete at this visit.The PedsQL Generic Core Scale is a validated instrument available in multiple languages to assess quality of life in pediatric patients, with a parent-proxy report available. The instrument is designed for pediatric patients with different version of the form available for self-report and parent-report based on subject age. This is considered to be the best quality-of-life assessment tool in the pediatric population. A surgery-specific or appendicitis-specific scale is not available, so the generic core scale will be used. This instrument assesses daily physical, emotional, social and school functioning.

30-day follow-up will also determine the 30-day success of non-operative management and 30-day readmissions for participants in both groups.

30 days provides adequate time for subjects in both groups to recover from treatment and resume their pre-treatment level of activity. This will allow the survey to assess the extent to which subject/parent life was affected by appendicitis and treatment course. Given that the antibiotic treatment regimen for the non-operative arm in this study is expected to last 10 days, follow-up at a period shorter than 30 days may not allow enough time after completion of treatment to assess for the effect of treatment on patient life and return to pre-treatment functioning, which is part of the aim of the PedsQL survey

60 days after discharge: Subjects will receive a phone call from the research team to assess for complications as a result of treatment. For subjects in the medical treatment arm this will include recurrence of appendicitis and appendectomy during the 60-day follow-up period.

1 year following treatment; Subjects will receive a phone call from the research team. Long-term follow-up will occur via telephone at 1 year to determine whether subjects developed complications after the 60-day follow-up period, and whether subjects in the medical treatment

arm experienced recurrence of appendicitis, and/or had an appendectomy after the 60-day follow-up period.

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Data Analysis and Data Safety Monitoring

See above for rationale behind sample size determination. An intention-to-treat analysis will be performed based on the initial group a subject is randomized to. Survey result data will be analyzed using a one-tailed two-sample student's t-test to assess for non-inferiority of non-operative management. A chi-squared test will be used to compare readmission rates of the two groups. 95% confidence intervals will be established for immediate and 30-day success rates of non-operative management and need for interval appendectomy. Finally, the types of complications in each treatment group will be analyzed qualitatively. Subgroup analyses will be performed to determine whether there are differences in outcomes between patients based on the study site at which they are treated.

Given that surgery is the standard of practice for uncomplicated acute appendicitis in children, safety will be evaluated based on outcomes in the medical treatment arm. Data safety monitoring of the overall study will be the responsibility of Dr. Fisher. Tracy McTiernan, CPNP will be responsible for day-to-day review of study participants. She is a certified pediatric nurse practitioner and has been working with the pediatric surgery team at NYU for several years. For each patient enrolled records will be reviewed after 48 hours of admission to evaluate for complications within the immediate treatment period. These early complications will include reactions to antibiotics, and early failure of medical treatment requiring surgery during the initial hospital stay.

Outcomes will be monitored on a 6-month basis, with the start of the 6-month period being the first date of initial treatment. Adverse events during this 6-month period will include readmission, need for non-surgical invasive procedures such as drain placement by interventional radiology, failure of medical therapy requiring surgery, other complications of medical management such as allergic reaction, and overall length of stay. The study will be stopped early if greater than 25% of patients in the medical treatment arm require an invasive procedure (surgical or non-surgical) within this 6-month period.

Adverse events related to medical or surgical therapy will be reported to the IRB as soon as possible within 72 hours of their confirmed diagnosis. Often times children with acute appendicitis demonstrate natural variations in symptomatology that may appear to be complications at first, but resolve within 24 hours without intervention. Additionally, most complications of medical or surgical treatment of appendicitis are associated with low morbidity. Therefore, to allow proper diagnosis of a complication, without shielding the IRB from timely data nor placing the patient at unnecessary risk, a 72-hour reporting window after confirmed diagnosis is most appropriate."

Reports on decisions made as a result of safety monitoring review will be distributed to study sites via email. The email will contain a summary of adverse events and trends in the data to that point. The report will be sent to all investigators and support staff (surgical PAs and NPs) at all study sites. Information on individual patients will not be included in this email. Reports will be sent to all study sites and the IRB every 6 months.

Data Storage and Confidentiality

Subject data will be deidentified by assigning a unique study-ID to each subject which is linked to their medical record number. All data, including PedsQL survey scores will be stored in a REDCap database created specifically for this study. Paper surveys will be maintained in the study binder

in a locked cabinet in the Pediatric Surgery office. Only study personnel will have access to the data.

The key linking subject medical record numbers with study-IDs will be maintained in a separate REDCap registry accessible only by the study PI and Tracy McTiernan, CPNP.

Risk/Benefit Assessment

Risk

Risks of medical therapy for appendicitis include necessarily longer initial hospital stay, readmission, treatment failure requiring surgery or another procedure during the initial presenting episode, recurrence of appendicitis at a later date, possible appendectomy after the initial treatment episode, and potential allergic reaction to antibiotics.

Risks of antibiotics depend on the specific agent used. Adverse effects of the antibiotics to be used in this study are as follows:

Piperacillin-Tazobactam

- GI reactions: diarrhea, nausea, vomiting, constipation, abdominal pain
- Local infusion reaction: rash and pruritus
- Pharyngitis
- Allergic reaction

Ciprofloxacin

- Musculoskeletal pain/joint sprains (With oral cipro, resolve within 30 days of end of treatment)
- GI reactions: diarrhea, vomiting, dyspepsia, abdominal pain
- Neurological events: dizziness, nervousness, insomnia, somnolence
- Rhinitis
- Rash

Metronidazole

- GI reaction: nausea, vomiting, diarrhea, abdominal pain, constipation
- Headache

Skin flushingAugmentin

- GI reaction: diarrhea, abdominal pain, nausea, vomiting
- Rash, urticaria
- Vaginitis
- Candidiasis

Risks of operative treatment include pain, bleeding, infection, and potential damage to surrounding structures, which are the standard risks of surgery. Common risks of anesthesia include pain, nausea and vomiting. Rare, more serious risks of anesthesia include allergic reaction to anesthetic agents, cardiovascular collapse, respiratory depression.

Protection Against Risks

Risks of medical therapy will be minimized by careful selection of subjects for enrollment and regular monitoring of pain, vital signs, and clinical exam during the period of IV antibiotic treatment to detect treatment failure early. Patients who experience an allergic reaction to antibiotics will treated for the reaction, switched to a different antibiotic combination and identified as a protocol violation.

Risks of operative treatment will be minimized by careful selection of subjects for enrollment, and having trained pediatric surgeons and pediatric anesthesiologists provide care for patients pre-, peri-, and post-operatively. Laparoscopic surgery minimizes the risks of pain, bleeding and infection, and is the standard of care for appendectomy. Open operations will only be performed if a laparoscopic approach is determined to be unsafe.

Potential Benefits to the Subjects

The benefits of medical treatment of appendicitis include avoidance of surgery and risks of surgery and anesthesia, quicker return to school and activity, and shorter parental leave.

Benefits of surgery include shorter initial hospital stay, decreased exposure to antibiotics, prompt resolution of the infection and decreased risk of recurrence.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

On an annual basis, the pediatric surgeons at NYU perform 170 appendectomies across 3 hospital settings (NYU Tisch Hospital, Bellevue Hospital, Hackensack University Medical Center in New Jersey) on patients who would be eligible for study inclusion. They also cover pediatric surgery consults from NYU Lutheran and the NYU-run Cobble Hill Emergency Department.

Any patient for whom the Pediatric Surgery service is consulted regarding possible appendicitis will be identified as a potential subject. Potential subjects will be screened for inclusion and exclusion criteria and will be recruited upon meeting these criteria. Given the urgent nature with which subjects present seeking treatment for appendicitis, it is not possible to adopt a more targeted recruitment strategy such as letters or phone calls to participants.

Upon meeting inclusion criteria, subjects and their parents will be informed about the study an its purpose, they will undergo the consent process, and will be provided up to 12 hours to consider participation prior to committing to a treatment plan, as detailed in the “Process of Consent” section below.

Process of Consent

Consent will be obtained by the attending physician on call. All of the pediatric surgeons at NYU are listed on this protocol. Subjects and their representatives will be taken to a private area for the consent process. They will be provided with a written version of the consent/assent document or a consent short form in their native language. An authorized interpreter will be used to help ensure clear communication and comprehension of the details of study participation whenever necessary.

The informed consent process will include explanation of the diagnosis of acute appendicitis and explanation that the purpose of the study is to compare the effectiveness of antibiotics and surgery for treating acute appendicitis. The consent process will specify that the treatment arm will be determined randomly, that participation in the study is voluntary, and that subjects can withdraw at any point in time.

While acute appendicitis is an urgent diagnosis, it is not an emergent diagnosis requiring an immediate trip to the operating room within the first few hours of presentation. There is typically a period of 6-12 hours between the time of diagnosis of acute appendicitis and the time that subjects must commit to a definitive treatment plan. The initial management will be identical for both treatment arms during this time period (fluid resuscitation, no oral intake and IV antibiotics). Subjects and parents will be informed about the study at the time of initial diagnosis, but the decision to enroll can be delayed up to 12 hours to allow subjects and parents adequate time to

consider participation without increasing risk of treatment failure, or progression to complicated appendicitis in either group.

Subjects and their representatives will be informed that participation will last one year from the date of enrollment, with follow-up intervals of 30-days, and 1 year after treatment. The details of study participation will be explained, including completion of the PedsQL Generic Core Scale at the 30-day follow-up point, as well as phone interviews at the 1-year follow-up points. The physician will explain the risks and benefits of medical treatment as well as the course of treatment should subjects choose not to participate. Finally, subjects and their representatives will be informed of how data collected for the purposes of the trial will be stored in order to maintain patient privacy.

Subjects and their representatives will be asked to demonstrate comprehension of the consent process prior to signing the consent/assent form for the study. Subjects who are 17 years of age at the time of enrollment will be asked to sign a consent form if they turn 18 during the study period. Signed forms will be kept in a regulatory binder to be stored in a locked cabinet in the Division of Pediatric Surgery office.

Subject/Representative Comprehension

Subjects and representatives will be asked to verbally describe the purpose of the study and risks and benefits of participation as well as alternate therapy options should they choose not to participate to confirm comprehension during the consent process. Subjects will be asked to assent to participation in addition to representative consent.

Consent Forms

Consent/assent forms attached.

Costs to the Subject

Subjects will incur the standard cost of treatment for appendicitis including the costs of treatment in the emergency room, imaging, and hospital stay as per their insurance company coverage. Patient in the non-operative treatment arm will incur the cost of both inpatient and outpatient antibiotics. All costs for treatment will be billed to subject insurance.

Payment for Participation

Subjects will not be paid for participation in the study.

Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan

Dr. Fisher will be responsible for overall study monitoring. Study monitoring will include site assessment review and staff training prior to initiation of the study. Interval visits will review sites for maintenance of study-related documents and assessment of study-related facilities. Interim monitoring visits will occur every 3-6 months based on the site activity. Other monitoring will occur as needed or requested.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/ECand University compliance and quality assurance groups of all study related documents. The investigator will also ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

References

1. Di Saverio S, Sibilio A, Giorgini E, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Annals of surgery.* 2014;260(1):109-117.
2. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *British Journal of Surgery.* 2009;96(5):473-481.
3. Hansson J, Körner U, Ludwigs K, Johnsson E, Jönsson C, Lundholm K. Antibiotics as First-line Therapy for Acute Appendicitis: Evidence for a Change in Clinical Practice. *World journal of surgery.* 2012;36(9):2028-2036.
4. McCutcheon BA, Chang DC, Marcus LP, et al. Long-term outcomes of patients with nonsurgically managed uncomplicated appendicitis. *J Am Coll Surg.* 2014;218(5):905-913.
5. Minneci PC, Sulkowski JP, Nacion KM, et al. Feasibility of a Nonoperative Management Strategy for Uncomplicated Acute Appendicitis in Children. *Journal of the American College of Surgeons.*219(2):272-279.
6. Svensson JF, Patkova B, Almstrom M, et al. Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial. *Annals of surgery.* 2015;261(1):67-71.
7. Nadler EP, Gaines BA. The Surgical Infection Society guidelines on antimicrobial therapy for children with appendicitis. *Surgical infections.* 2008;9(1):75-83.
8. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The appac randomized clinical trial. *JAMA.* 2015;313(23):2340-2348.
9. Kronman MP, Oron AP, Ross RK, et al. Extended- Versus Narrower-Spectrum Antibiotics for Appendicitis. *Pediatrics.* 2016;138(1).
10. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™* 4.0 as a Pediatric Population Health Measure: Feasibility, Reliability, and Validity. *Ambulatory Pediatrics.* 2003;3(6):329-341.
11. Hartwich J, Luks FI, Watson-Smith D, et al. Nonoperative treatment of acute appendicitis in children: A feasibility study. *Journal of pediatric surgery.* 2016;51(1):111-116.
12. Minneci PC, Mahida JB, Lodwick DL, et al. Effectiveness of Patient Choice in Nonoperative vs Surgical Management of Pediatric Uncomplicated Acute Appendicitis. *JAMA surgery.* 2016;151(5):408-415.
13. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet (London, England).* 2011;377(9777):1573-1579.
14. Gorter RR, van der Lee JH, Cense HA, et al. Initial antibiotic treatment for acute simple appendicitis in children is safe: Short-term results from a multicenter, prospective cohort study. *Surgery.* 2015;157(5):916-923.