PROTOCOL

PROTOCOL TITLE	A prospective randomized trial of antibiotic duration in post-appendectomy abscess
PROTOCOL NUMBER	17-055
STUDY DESIGN (PHASE)	Prospective randomized
PROTOCOL VERSION	Version 5 Dated September 25, 2019
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SPONSOR	Craig Egan, MD Phoenix Children's Hospital 1919 East Thomas Road Phoenix, Arizona 85016
PRINCIPAL INVESTIGATOR	Craig Egan, MD

Absract

Appendicitis is a very common surgical problem in children. Although the rates of post-appendectomy abscess in simple appendicitis are less than 1%, the rates of post-appendectomy abscess in complicated appendicitis are not well-described.[5-8] Complicated appendicitis includes patients who present with a visible perforation and/or feces in the abdomen, a primary abscess, phlegmon, gangrene, or all of the above.[2-4] Research suggests that neither the type of the antibiotic therapy nor duration of treatment has a significant impact on reducing the risk of post-operative abscess for patients who present with any form of complicated appendicitis.[7] However, the lack of an evidence-based definition of perforated appendicitis has undermined the reliability of most research results because the study populations may have included non-complicated patients. In this study, we propose to assess the equivalence of an 8-day fixed course and a fixed 4-day course of antibiotics at drainage for perforated patients who develop a post-surgical abscess. We are proposing to study 342 pediatric patients (includes 10% oversampled) ages 2 to 17 years at institutions in the Western Surgical Pediatric Research Consortium (WSPRC) who are diagnosed with perforated appendicitis, treated laparoscopically, ***and form an abscess post-laparoscopy***. We hypothesize that the 8-day course of antibiotics is equivalent to the 4-day course on the primary clinical outcome (i.e., readmission rate) and secondary outcomes: length of stay (LOS) upon readmission; rate of abscess from drainage until 30 days after discharge, and wound infection from drainage until 30 days of discharge. This research will provide an ongoing contribution to the clinical management of complicated pediatric appendicitis and antibiotic stewardship.

A. Introduction/Background

In the United States, appendicitis is among the top five diagnoses for pediatric hospital admissions and accounts for 11.3 pediatric patients per 10,000 of the general population.[1] Generally, complicated appendicitis is associated with a higher risk of developing intra-abdominal abscess after appendectomy as compared to non-complicated appendicitis, where the rate of post-operative abscess is under 1%.[1] Approximately 20 to 35% of all children who present with appendicitis present with complicated appendicitis as defined by perforation, phlegmon, or abscess.[2–4] However, the reported risk of developing abscess after appendectomy in this patient group is less well described because researchers have not used one clear, consistent, evidenced-based definition of perforated appendicitis.[14, 16]

There is a growing body of research regarding the regimen of antibiotic treatment in adult patients with confirmed complicated appendicitis. Antibiotic treatments vary by hospital, clinical parameters, and patient condition.[12] A recent randomized, prospective pilot study

showed a short course of oral amoxicillin/clavulanate plus metronidazole was comparable to a standard 10-day IV antibiotic course for discharged patients.[9] Another study suggested that as long as oral intake was tolerated, patients could be discharged with a 7-day course of oral trimethoprim/sulfamethoxazole, regardless of the presence of leukocytosis or fever.[15] Another study showed no difference in clinical outcomes in an adult patient population where patients were randomized to a fixed 4-day treatment duration versus an 8-day regimen.[21] The study authors concluded that afebrile patients were at low risk for subsequent infections and may not have needed an antibiotic regimen at all.[14] These results support the overall conclusion that antibiotic regimen may not have a significant impact on reducing post-appendectomy abscess rates, even when controlling for variation in clinical parameters.[4,5,7,9-11,16,21] This research will contribute to the clinical management of perforated appendicitis in pediatric patients, post-laparoscopic abscess formation, and antibiotic stewardship.

B. Primary and Secondary Outcomes

The central hypothesis tested in this study is whether a 4-day antibiotics course is equivalent to an 8-day course for post-drainage primary and secondary clinical outcomes.

Primary outcomes:

- readmission rate

Secondary Outcomes:

- length of stay (LOS)
- rate of post-drainage surgical site infection until 30 days after discharge
- rate of post-drainage abdominal abscess until30 days after discharge
- secondary site infections

C. Methods

C.1. Study Design

This research proposes a randomized, prospective, equivalence trial design to test the research hypothesis. This study will demonstrate no difference in clinical outcomes between the 4-day antibiotic course and the 8-day course. The study will include 342

pediatric patients (includes 10% oversampled) ages 2 through 17 years treated from February 1, 2019 onward until the study cohorts have been filled. This study is based on an expectation of 90% success (10% readmitted) in arm A=10% and expectation of 90% success (10% readmitted) in arm B =10%. The clinical difference in primary outcome between the two groups that we are prepared to accept is equal or greater than 10% (i.e., clinically, we are willing to accept 10 children per 100 who may have benefited from the long course but received a short course to achieve 90% of children who received the short course and would not have benefitted from a long course). The sample size needed to attain a power of 0.80 at alpha=0.05 is 342 (171 in each arm, which includes a 10% attrition rate). The risk of type I error is 1-0.95 (alpha=0.05); power=0.80. The study will proceed until 171 patients are consented for each arm. Study personnel will perform an interim analysis of the data approximately halfway through study enrollment.

Definition of perforated appendicitis - Perforated appendicitis is defined as a visible hole or feces found in the abdomen at laparoscopy***. For purposes of research, either the hole or feces is photographed, and"hole," "feces/stool in the abdomen," or other note describing perforation will need to be specifically described in the operative report.*** Based on estimates from the Division of Pediatric Surgery, PCH performs approximately 1000 laparoscopic appendectomies annually. Approximately one-third of these appendectomies (300) are perforated; about 10%-20% of these 300 perforated patients (30-60) will develop a post-surgical abscess treated with a percutaneous drain and IV antibiotics.

Screening - The study population is comprised of patients who, upon admission, are diagnosed with perforated appendicitis and who, after laparoscopy, form an abscess (while still in hospital or discharged and then readmitted with abscess), and are treated with percutaneous drainage and IV ceftriaxone/metronidazole or other broad spectrum antibiotic equivalent per hospital standard of care. Screened patients will be assigned a screening ID, which will be maintained in a screening log.

Randomization - Once eligibility for study inclusion is determined at the time of drainage, the patient will be consented by the principal investigator or sub-investigator and assigned a study number. A block randomization strategy will be used based on a random number generator and applied after consent by site to assign patients to either the control (8-day) or experimental (4-day) arm of the study. All patients will be randomly assigned by patient study numbers. A current randomized trial underway at Phoenix Children's Hospital requires photography to confirm a diagnosis of perforation (IRB 17-011). We propose to follow the same approach for verifying perforated appendicitis across WSPRC institutions in this study. When possible, the hole or feces will be

photographed. If not, "hole," "feces/stool in the abdomen," or other note describing perforation will need to be specifically described in the operative report. The two study arms will include some patients with abscess that has been confirmed though CT or ultrasound as part of standard of care prior to study participation. We will include CT/ultrasound results as part of data collection.

Antibiotic regimen - All post-laparoscopic abscess patients will receive the standard of care for antibiotic therapy—IV ceftriaxone/metronidazole or other broad spectrum antibiotic equivalent —until afebrile (38.5° C) and tolerating food for 24 hours (i.e., without vomiting). CBC panels are also standard of care and may be drawn multiple times during the patient's stay. Standard of care at discharge includes prescribed oral, empiric, antibiotic therapy (PO), such as ampicillin/clavulanate or other broad spectrum antibiotic. The choice and the duration of broad spectrum antibiotic prescription are at the surgeon's discretion.

In this study, all patients will be treated with the hospital standard of care and receive in-patient treatment for abscess until afebrile and tolerating food for 24 hours. After percutaneous drainage of the abscess, the patient will be randomly assigned to receive either an 8-day regimen (arm A) or a 4-day regimen (arm B) of antibiotics (Diagram 1). Patients will remain on IV ceftriaxone/metronidazole or other broad spectrum antibiotic equivalent until afebrile and tolerating food for 24 hours. Patients will complete their assigned 4- or 8-day regimen with oral ampicillin clavulanate or other broad spectrum antibiotic equivalent. If patients are not afebrile at the completion of their assigned regimen, prescribing an extended course of antibiotics is at the discretion of the treating surgeon. A prescribed oral course of antibiotics may be finished in the hospital or at home if patient is discharged.

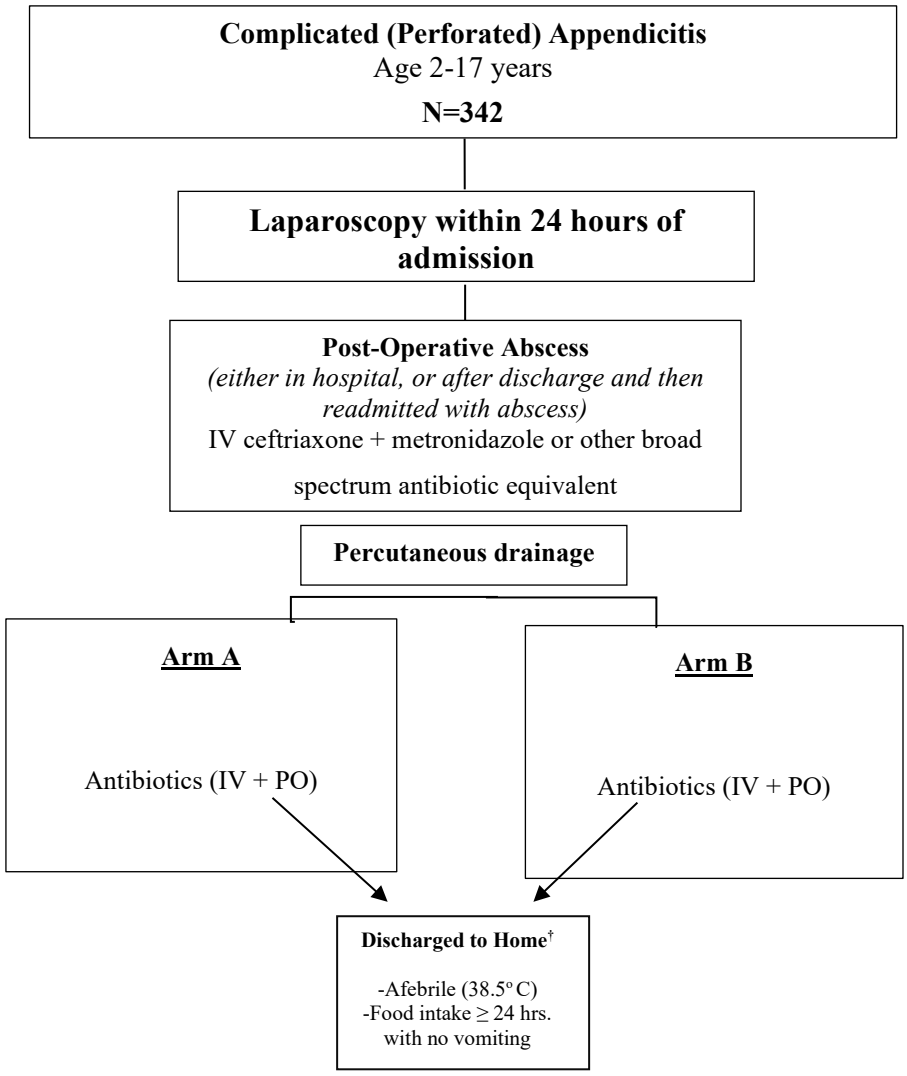
Ampicillin and clavulanate have been safely utilized in previous pediatric research.[5,10,14,11] These antibiotics have demonstrated clinical equivalence in both retrospective studies and prospective trials.[9,11] This randomized trial is the first to address duration of antibiotic treatment in pediatric patients diagnosed with perforated appendicitis and who form a post-laparoscopic abscess. Pediatric patients who are allergic to ampicillin will be prescribed another broad-spectrum antibiotic (e.g., gentamycin/clindamycin or ciprofloxacin) at the discretion of the treating surgeon.

Two arms are proposed for the study following the protocol implemented for adults in a recent randomized trial.[21] In the control arm, patients will be treated with an 8-day course of antibiotics, and in the experimental arm, patients will be treated with a 4-day course of antibiotics. The randomized trial should control for all confounding effects. In addition,

we will collect clinical data on the pre-operative, peri-operative and post-operative antibiotic treatment and number of days on antibiotic therapy prior to discharge to manage this potential confounder *post hoc*.

There is a low probability of study attrition or loss to follow-up. As the primary treatment provider in a study with a short (30-day) follow-up period for readmission, we do not expect significant attrition. Follow-up will entail tracking all patients from the initial study who return to the hospital for complications related to the procedure within 30 days of discharge. All complications, including those requiring readmission, will be included in the follow-up. All study patients will be assessed for primary and secondary clinical outcomes. Complications associated with surgically treated acute appendicitis based on the National Surgery Quality Improvement Program criteria (available at http://nsqip.healthsoftonline.com/hsi/) include (1) wound infection, (2) abscess, (3) post-discharge small bowel obstruction, (4) hernia, (5) length of hospital stay of greater than 4 days, and (6) death.

Diagram 1: Treatment arms for randomized trial of an 8-day antibiotic treatment vs. 4-day treatment of post-laparoscopic abscess formation in pediatric complicated (perforated) appendicitis.



* If febrile after assigned course of antibiotics (i.e., 8 days or 4 days) is completed, extended anitibotic treatment will be up to the treating surgeon.

†Patient may be discharged before 8- or 4-day course is completed and may finish antibiotics at home.

C.2. Inclusion/Exclusion

Inclusion criteria:

- All patients ages 2 through 17 years treated laparoscopically for perforated appendicitis after February 1, 2019 (where perforated appendicitis is defined as a photographed hole in the abdomen, as feces in the abdomen, or a specific description of either in the operative report), and who developed post-appendectomy abscess that was treated via percutaneous drainage.

Exclusion criteria:

- Patients who are treated for appendicitis without appendectomy or with a non-laparoscopic procedure (e.g., drainage only or open appendectomy);
- Patients being treated with antibiotics for a diagnosis other than abscess during their course of treatment (e.g., sinusitis along with abscess);
- Patients who are treated laparoscopically for perforated appendicitis with confirmed post-appendectomy abscess, but the abscess was not treated via percutaneous drainage;
- Patients who are immunocompromised;
- Patients with Crohn's disease, ulcerative colitis, or other clinical diagnoses that subject the patient to a high-risk of developing intra-abdominal abscess;
- Patients whom the surgeon believes should not participate for any reason.

C.3. Data Collection

Data will be collected prospectively for all study patients. Patients will be followed until 30 days post-discharge to assess clinical outcomes. The following will be collected: patient and demographic data (e.g., BMI, age, and gender), clinical data (e.g., antibiotic route, WBC, CBC pathology report, CT/ultrasound results, symptom duration, diffused vs. localized peritonitis, intra-abdominal contamination, maximum temperature prior to laparoscopy, LOS, and time to regular diet), and outcomes (e.g., abscess formation after drainage, re-hospitalization frequency and duration of each stay, secondary infections, and total number of visits after discharge). A CBC with differential will be collected at admission and post-laparoscopy if available. CT/ultrasound data will also be collected. For a complete list of variables, please refer to the data collection form included as part of the IRB application (RCT_Post_Appy_Abscess_DCF1).

It is estimated that it will take about 6 years for PCH to fill the study arms; interim analysis will be performed when study cohorts are half-filled. In order to complete this and other planned pediatric appendicitis studies more quickly, we are planning to add other study sites though the Western Surgical Research Consortium. The multisite approval process will be facilitated by Streamlined Multisite Accelerated Resources for Trials (SMART) IRB certification. With participation from the nine hospitals in the Western Surgical Research Consortium, we would expect to fill the trial cohorts in approximately 2 years.

C.4. Data Analysis Plan

The study will describe patient and clinical characteristics related to laparoscopy among study cohorts (e.g., age, BMI, gender, maximum temperature upon admission, diarrhea at presentation, duration of symptoms, and white blood cell count); patient recovery and abscess formation (e.g., time to abscess, abscess size if available, time to regular diet, and LOS after the drainage); primary clinical outcome (readmission); and secondary clinical outcomes (LOS, total visits after discharge, post-drainage occurrence of abscess, and post-drainage secondary infection).

All data will be described using descriptive statistics, including means, standard deviation, and proportions. Differences among treatment cohorts and on clinical outcomes will be assessed using parametric and non-parametric tests as appropriate. Factors confounding outcomes will be identified *a priori* from research and empirically via correlational analysis for continuous measures or through non-parametric techniques for discrete variables with a Bonferroni correction for multiple comparisons among families of statistical tests. Binomial logistical regression will also be used where appropriate. Unadjusted odds ratios will be used to identify variables of interest and confounding effects for discrete dependent variables of interest. Adjusted odds ratios will be used to compare differences among study cohorts and covariates (e.g., age, gender, white blood cell count, and BMI), interactions, and confounders as appropriate. Statistical significance will be defined as an alpha of 0.05, with two-sided alternative hypothesis and a Bonferroni correction for multiple comparison. Data analysis will be performed using SPSS and R.

Interim Analysis - At approximately the halfway point of the study (i.e., 171 patients per arm), study personnel will undertake an interim analysis.

D. Benefit and Risk Assessment

D.1. Risk Assessment:

This study poses minimal risk. There are no additional expected risks of this study related to the trial protocol. The study protocol aligns to the current hospital standard of care at diagnosis, treatment, and discharge. This study excludes any patient who possesses a higher than normal risk of abscess formation. The study also excludes any patient the surgeon believes should NOT participate for any reason.

Hospital standard of care currently diagnoses acute perforated appendicitis via laparoscopy, which minimizes the risk of over-inclusion (e.g., including a patient who does not have perforated appendicitis and post-appendectomy abscess). Photographing at laparoscopy when possible also minimizes risk of inadvertent exclusion because patients may be asymptomatic for perforation at the time of laparoscopy. The engagement and involvement of pediatric surgeons (multiple surgeons at each institution when possible) will assure patient safety during the trial. Physician training on the protocol will also contribute to study safety and consistency. Finally, we will also follow strict study oversight protocol, including adverse event reporting and in accordance with Good Clinical Practices (GCP) research guidelines.

This study does not require new or unique diagnostic procedures other than those already in use under hospital standard of care. In this study protocol, there are no changes to the standard of care for treatment of post-laparoscopy abscess formation—which currently includes IV antibiotics and percutaneous drainage until afebrile and tolerating food intake for at least 24 hours—and then discharge to home with an oral antibiotic. All study patients receive the standard of care until afebrile and eligible for discharge to home. At discharge, standard of care requires attending physicians to determine the regimen for patients who have received treatment for post-appendectomy abscess. The principal investigator, Dr. Craig Egan, along with other study investigators and research coordinators, will provide study oversight. He and the study investigators will also jointly determine if interim analyses support closing the study, completing the study, or adding another study arm. Specifically, study investigators are considering proposing no antibiotic at drainage if this study is successful.

As with any data collection, there is a risk of breach of confidentiality and protected health information (PHI). This risk will be minimized by the following measures:

1) Subject identity will be protected and kept confidential by storing all research records in a password-protected file on a HIPAA-compliant, cloud-based server (REDCap), with access limited to study personnel;
2) Subject informed consent/assent statements will include detail on confidentiality and protection of confidential health records;
3) The compiled data used for analysis will have limited PHI and will not be directly linkable to individual subjects;
4) Manuscripts prepared for presentation and journals will be aggregated and will not contain any individual PHI or identifiable patient data.

D.2. Benefits Assessment:

There will be no direct patient benefit from this study. This research will benefit clinical management by evaluating whether patients achieve significant differences in primary and secondary clinical outcomes based on duration of antibiotic treatment at abscess drainage. The study results may help lower costs for post-appendectomy patient care, improve infection management, and contribute to antibiotic stewardship.

E. Confidentiality and Protection of Human Subjects

E.1. Data Protection, Privacy, Storage, and Security

In accordance with standards for human subjects review, the research study team will adhere to precautions to protect participant privacy and confidentiality of information. Trauma Research will hold the master key of participant names and unique identifiers for use in tracking cases, connecting to data from electronic health records (EHRs), and de-identifying data. All data will be collected by Trauma Research, de-identified, and entered into an encrypted, cloud-based, HIPPA-compliant server (REDCap). Trauma Research will access the data through the website and download to a secure, password-protected network drive at PCH for storage and analysis.

Identifiable patient information will be retained only for as long as the data can be cleaned, verified, and prepped for data analysis. De-identified data will be maintained for up to three months after acceptance of the first scholarly journal article or until study closure, whichever comes first. For data identified for disposal, appropriate measures will be taken; electronic data will be deleted from office computers and the primary location of storage in the network drive, and hard copies containing data will be shredded and disposed of in accordance with PCH policy.

E.2. Standard of Care, Confidentiality, and Privacy

This study includes all patients age 2-17 years old who, upon presentation to the emergency department, are treated for acute perforated appendicitis. Standard of care will apply to all patients in the study, and no change will be made to the standard of care. In accordance with PCH policy and GCP, study protocol will ensure the privacy of study participants and the confidentiality of patient data. All patients and their families will be consented and counseled in a private room.

E.3. Eligibility Determination, Incentives, and Consent

Patients will be randomly assigned to a study arm once eligibility determination is complete and patients are deemed eligible. Patients are eligible if they meet the eligibility criteria and are willing to participate. A random number generator will be used to assign eligible patients and fill study arms. All patient families will be fully consented in person by the pediatric surgeon in English or Spanish; other languages are excluded.

Study personnel, including the attending physician and designated research personnel, will participate in the consent/assent process. Patients and their families will be consented at multiple points throughout the study (at eligibility/randomization and at drainage). Patients old enough to assent (8 years of age or older) will be provided with an assent form, and families will be provided with a copy of the signed informed consent/assent form(s).

All families with patients age 2-17 years who are diagnosed with acute perforated appendicitis confirmed via laparoscopy will be approached at the time of laparoscopy and provided with a study information/recruitment sheet. The consent sheet will describe the study in detail, its risks and benefits, and the informed consent process. If the patient develops a post-appendectomy abscess, the family will be approached to participate in the study by the PI/research staff. The patient will be provided with an assent form, and the family will be provided with an informed consent form. The PI/research staff will consent the family by reviewing the consent form—and the assent form with the patient where age-appropriate—and requesting signatures as needed. The family will be informed that at any point in the study they may withdraw or decline further participation. All consent forms have been developed in accordance with PCH IRB protocol (informed consent/assent forms have been submitted in conjunction with this protocol). Informed consent/assent forms will be available in Spanish, and all forms will include the following required elements:

- The purpose of the informed consent;
- Identification of the investigator;
- Description of the study procedures;
- The voluntary nature of participation;
- The absence of any penalty for not choosing to participate;
- The benefits and risks involved in participation;
- The protection of data confidentiality and privacy;
- Additional information if the participant has questions;
- A place to give written consent to participate in a research study.

E.4. Data Security

All electronic health records will be kept in a secure folder on a password-protected drive on a HIPAA-compliant, secure, cloud-based server (REDCap). Access will be limited to study personnel. Confidentiality will be maintained within legal limits. Subject identifiers (e.g., name, medical record number, date of birth, and dates of service) will be retained in a research file. However, data retained for the study (listed above in "Data Collection") will be assigned an identification code for the database. A master list of study IDs will be kept in a separate file maintained by the study coordinator/staff under password protection.

Data will not be shared with individuals outside of those listed in the approved IRB application. Data will be maintained at all times by none other than the listed individuals on a password-secured drive and will only be reported or shared in de-identified form. Data will be maintained up to 3 months after the last published article or until study closure—whichever comes first—and then destroyed following PCH site policy.

F. Dissemination Plan

The data and analysis from this study will be compiled into a manuscript or several manuscripts for publication in peer-reviewed journals, and an abstract may be submitted for presentation at a national conference.

G. References

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