Two Different Antibiotics Versus One Antibiotic for Pediatric Perforated Appendicitis
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STUDY PROTOCOL

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Randomized Control Trial: Two Different Antibiotics versus One Antibiotic for Pediatric Perforated Appendicitis

Justin Lee, Erin Garvey, Raphael Parrado, Bethany Sussman, Jodie Greenberg , Lois Sayrs, Daniel Ostlie

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BACKGROUND AND SIGNIFICANCE

Appendicitis is the most common pediatric surgical emergency. Postoperative antibiotic therapy has evolved from a 3-drug regimen to 2-drug regimen to once daily dosing of the 2-drug regimen including ceftriaxone and metronidazole (CM).[1] A recent retrospective review compared the CM regimen to other available antibiotic regimens including single-drug regimen.[2] Although statistically not significant, the study found a two-fold greater risk of infectious complications in those receiving the CM regimen. No patients on piperacillin-tazobactam (P) single-drug regimen had postoperative intraabdominal abscess. Despite this potential benefit of decreasing postoperative abscess rate, the literature lacks comparative analysis of CM versus P regimen. In addition to lower infectious complication rate, the single-drug regimen (P) may have additional benefits of simplicity and compliance in comparison to the 2-drug regimen (CM).[3-5]

GOALS AND OBJECTIVES

This study is a multisite (Phoenix Children's Hospital and The Children's Mercy Hospital) prospective randomized trial comparing the two-drug regimen with CM versus single-drug regimen with P.

Primary:

30 day intraabdominal abscess rate

Secondary:

30 day all complications: see list in "Data Collection" table

MATERIALS AND METHODS

Participants:

Patients with perforated appendicitis treated at Phoenix Children's Hospital (PCH) and Children's Mercy Hospital (CMH) with perforated appendicitis will be included in the study. Inclusion criterion is applied using a strict definition of perforation: visible hole in the appendix or extraluminal stool contents. The visible hole or extraluminal stool contents must be photographed and stored in the medical records. Exclusion criteria include iatrogenic perforation of the appendix, documented allergy to antibiotics in the trial, nonoperative management of perforated appendicitis with radiographic evidence of abscess, and open appendectomies

Interventions:

After perforation is determined in the operating room, postoperative antibiotic regimen is randomized to either two-drug regimen (CM) or single-drug regimen (P).

Sample Size:

The power calculation was based on the postoperative intra-abdominal abscess rate of 8% with CM versus 4% with other antibiotic regimens.

Prior data indicated that the abscess rate among controls (CM) is 8% and 4% with "*other antibiotic*" regimens. Included in this *"other antibiotic regimens"* was single-drug regimen (P) with no postoperative abscess. If the true failure rate for experimental group (P) was set as 0.1%, a sample size of 121 control subjects (CM) and 121 experimental subjects (P) would yield alpha of 0.05 and a power of 0.80. The study will proceed until 121 cases are collected on each arm with an expected 5% retrition rate.

Each site will contribute 121 participants with approximately half of the subject at each site in each treatment group.

Assignment:

Perforation is clearly defined by the operating surgeon at the time of the operation. Postoperatively, consent is obtained from the parents. The randomization sequence is accessed to identify the next allotment. Each institution will have a randomization sequence. Randomization sequences will be generated by the lead site (PCH) and sent to non-lead sites (CMH).

Protocol:

Institutional staff surgeons will perform appendectomies based on the call schedule and practices at each institution. Computerized order sets are currently being used for postop operative orders. All patients will receive a course of antibiotics. Intravenous antibiotics will transition to oral antibiotics when tolerating regular diet. A white blood cell (WBC) count is drawn on the day of discharge if ready for discharge before postoperative day 5. Elevated WBC will lead to discharge home with oral antibiotics for a cumulative total of 7 day course of antibiotics including IV and PO. For all patients, discharge criteria include temperature less than 38.0 for 24 hours, tolerating regular diet, and pain controlled on oral medications.

2-drug regimen (CM) includes once a day dosing of ceftriaxone (50 mg/kg) and metronidazole (30 mg/kg). Single drug regimen (P) includes piperacillin-tazobactam (<40 kg: 100 mg/kg Q8HR, >40 kg: 3000mg Q6HR)

All patients are followed postoperatively for 30 days. CT scans are obtained if the patient's clinical conditions suggest an abdominal abscess at any time *after 7 days* post-op (PCH procedure is to wait 7 days to CT for suspected abscess). Postoperative abscess or wound infection are treated with drainage and antibiotics dictated by the individual treating surgeons

Data Collection:

See attached data collection forms.

Statistical Analysis:

Phoenix Children's Hospital is responsible for data storage and statistical analysis.

Continuous variables will be compared using t-testsand regression analyses. Discrete variables will be analyzed with Chi-square and Fisher's Exact tests with Yates correction where appropriate. Statistical significance was defined as P value $\leq$0.05. Descriptive statistics such as mean, median standard deviation, percentage, and interquartile range will be calculated. Statistical analyses will be designed to address the primary and secondary outcomes.

RISK ASSESSMENT

There are no additional or unnecessary risks associated with this study. All antibiotic therapy options are already utilized and FDA-approved antibiotics for perforated appendicitis.

Participating in this study poses no additional medical risk to subjects. Both antibiotic courses are standard of care. Since patients with known allergies are not included in this study, the rate of complications due to the assigned antibiotic are no higher than if a patient declined to participate.

The highest risks of this study are breaches of confidentiality and/or privacy. Care and appropriate measures will be taken to minimize this risk.

Subjects will be assigned a study ID that will be maintained and recorded in a key. This key will be password protected and stored on drive. Only authorized personnel will have access to the sever location and only authorized personnel will have password knowledge for the key.

Any paper data collection will be de-identified and stored securely in a locked office. Any electronically filled data collection forms will be de-identified and stored separately from the subject key. Data will be entered into a secure HIPAA-compliant REDCap project hosted by Phoenix Children's Hospital/University of Arizona. Only authorized study personnel will have access to study data.

Data will be collected and entered into a REDCap based application.
The data will be stored, maintained, and protected at Phoenix Children's Hospital/University of Arizona. Research Electronic Data Capture (REDCap) is a secure web-based application which provides an intuitive interface for collection of research data. This system offers access via secure authentication (user ID and password) by clinical site users through the Internet, has audit trails for data manipulation and user activity, and can easily export data into formats for use in major statistical packages. Data exported from REDCap will be stored on a server that is HIPAA compliant (Phoenix Children's Hospital K Drive). Any dataframes containing PHI will be password protected.
Phoenix Children's Hospital is responsible for creating, designing, and customizing the project in REDCap.

DISSEMINATION

This study will be submitted to both regional and national pediatric surgery meetings after completion and full analysis.

REFERENCE

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