Study Title: Optimal Care of Complicated Appendicitis

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Institution: University of Michigan

NCT: NCT03159754

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CLINICAL PROTOCOL

STUDY TITLE

Optimal Care of Complicated Appendicitis

Study Agents: None

HUM #: 00103791

Principal Investigator: Steven Bruch, MD, MSc

Institution: University of Michigan

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PROTOCOL SYNOPSIS

Sponsor: Steven Bruch, MD, MSc

Name of Product(s):

Study Title: Optimal Care of Complicated Appendicitis

Study Phase:

Objectives:

- To determine the best management strategy for complicated appendicitis

Outcomes

Primary:

- Cost

Secondary:

- Complications
- Time (days) away from activities/Parents lost work days
- Days of antibiotics
- Length of Stay
- Number of radiographic studies
- Number of percutaneous drainage procedures
- Quality of life
- Recurrent appendicitis

Hypotheses:

Primary:

- Non-operative management of perforated appendicitis without interval appendectomy will result in decreased overall cost
- There will be no significant difference in cost between early and interval appendectomy groups

Secondary:

- Patients who undergo non-operative management of perforated appendicitis without interval appendectomy will have fewer days away from activities and shorter lengths of stay
- Patients who undergo non-operative management of perforated appendicitis will require more radiographic studies and/or percutaneous drains

Study Design: Pilot study with N=40; Group placement will be determined by patient choice both for early appendectomy vs. non-operative management, and for interval appendectomy vs. no interval appendectomy for those initially managed non-operatively.

This is a single center, prospective study to compare early appendectomy vs. non-operative management of immunocompetent patients with complicated appendicitis, and then to compare interval appendectomy vs. no interval appendectomy in those managed with the initial non-operative approach. Patients who choose early appendectomy will have surgery within 24 hours of diagnosis and be discharged once they are afebrile for 24 hours, have a normal WBC count, and can tolerate a diet. They will be discharged with 5 days of oral ciprofloxacin and metronidazole and follow-up in clinic 2-4 weeks later. Patients who choose non-operative management will receive piperacillin-tazobactam with or without abscess drainage until they are afebrile 24 hours with a normal WBC count and are tolerating a diet, followed by 5 days of oral ciprofloxacin and metronidazole upon discharge. These patients will then be seen in clinic in 2-4 weeks, at which time they will be given the choice of whether or not to undergo interval appendectomy at least 8 weeks from initial presentation. Those in the interval appendectomy group will follow-up one month post-operatively. Patients in both groups will be contacted 3 months and 2 years following initial presentation.

Study Population: Patients ages 5-17 with the clinical diagnosis of complicated appendicitis.

Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Age 5-17 years
2. CT or MRI read with free intraperitoneal air, RLQ abscess, visible hole in the appendix, and/or extruded fecalith, OR
3. CT or MRI read with phlegmon or diffuse/extensive inflammation/free fluid plus 1 of 3 of the following (with CT) or 2 of 3 of the following (with MRI) *:
    a. WBC > 15
    b. Peritonitis (involuntary RLQ guarding, + Rosving sign, percussion tenderness, and/or rebound tenderness)
    c. Temperature > 38.0 C

*>90% specificity for complicated appendicitis based on unpublished institutional data

Exclusion Criteria

1. Immunocompromized
2. History of major abdominal operation
3. Previous appendicitis
4. Major comorbidities that preclude safe operation
5. Inability to follow-up or appropriately consent

Test Product; Dose; and Mode of Administration:
Reference or Placebo Therapy; Dose; and Mode of Administration:
Duration of Treatment:
Variables: • Duration of IV antibiotic therapy and length of stay in all groups will be determined by clinical features including duration of fever, leukocytosis, and ability to tolerate a diet • Need for percutaneous drainage will be based on imaging findings (ultrasound, CT, or MRI) and clinical status • Number of radiographic studies will be determined by clinical course • Management plan (early appendectomy, interval appendectomy, or no appendectomy) will be determined by patient/parent choice.
Statistical Methods: The direct cost is a continuous variable, which may be assessed by univariate analysis (independent t-test). The secondary endpoints of complications, time away from activities/parents from work, days of antibiotics, length of stay, and number of percutaneous drainages are continuous variables and will be analyzed in the same manner. Sample size determination: The study is powered to show a $7,000 reduction in cost. To do this, we will enroll at least 68 patients in each arm. We will begin with a pilot study of 40 total patients to better predict our sample size requirement.

1 INTRODUCTION

1.1 Indication

A large prospective study is required to determine the optimal timing of appendectomy in complicated appendicitis, as well as the necessity of interval appendectomy in non-operative management.

1.2 Background and Rationale

Complicated appendicitis, defined as perforation with or without abscess, is currently treated one of two ways: Immediate operation, or IV antibiotics with or without drainage, followed by interval appendectomy 6-8 weeks later. Recent prospective studies have shown conflicting evidence as to which of these management strategies is preferred with respect to cost and length of hospital stay, and were influenced by lack of power or by earlier than anticipated failure of non-operative therapy [1,2]. Furthermore, in those patients initially managed non-operatively, the

majority of pediatric surgeons perform interval appendectomy 6-8 weeks following initial presentation despite a lack of clinical evidence [3]. In fact, retrospective studies in both adults and children have indicated that the risk of developing recurrent appendicitis in patients managed non-operatively for perforated appendicitis is low, calling into question the practice of interval appendectomy [4,5]. Therefore, a larger prospective study is required to determine the optimal timing of appendectomy in complicated appendicitis, as well as the necessity of interval appendectomy in non-operative management.

1.3 Hypothesis

Based on previous studies, our hypotheses are that 1) early appendectomy results in lower health care costs than non-operative management followed by interval appendectomy, and 2) interval appendectomy may be a non-essential procedure following non-operative management of complicated appendicitis resulting in higher costs.

1.4 Previous Human Experience

As mentioned above in 1.2, previous studies have shown conflicting data regarding cost-effectiveness of early versus interval appendectomy, and have been influenced by small sample size and earlier than anticipated failure of non-operative therapy. Previous studies have also suggested that interval appendectomy in both adults in children may not be necessary.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

- To quantify the cost of care and compare them between the three groups
- To assess complication rates between the three groups
- To assess the length of time until return to activity/parents return to work
- To assess the number of percutaneous drainage procedures and/or radiographic studies performed in all groups
- To monitor the length of stay and compare between the three groups
- To monitor the duration of antibiotic therapy and compare between the three groups
- To assess and compare quality of life between the three groups

2.2 Outcomes

2.2.1 Primary Outcome

- Overall cost of care

2.2.2 Secondary Outcomes

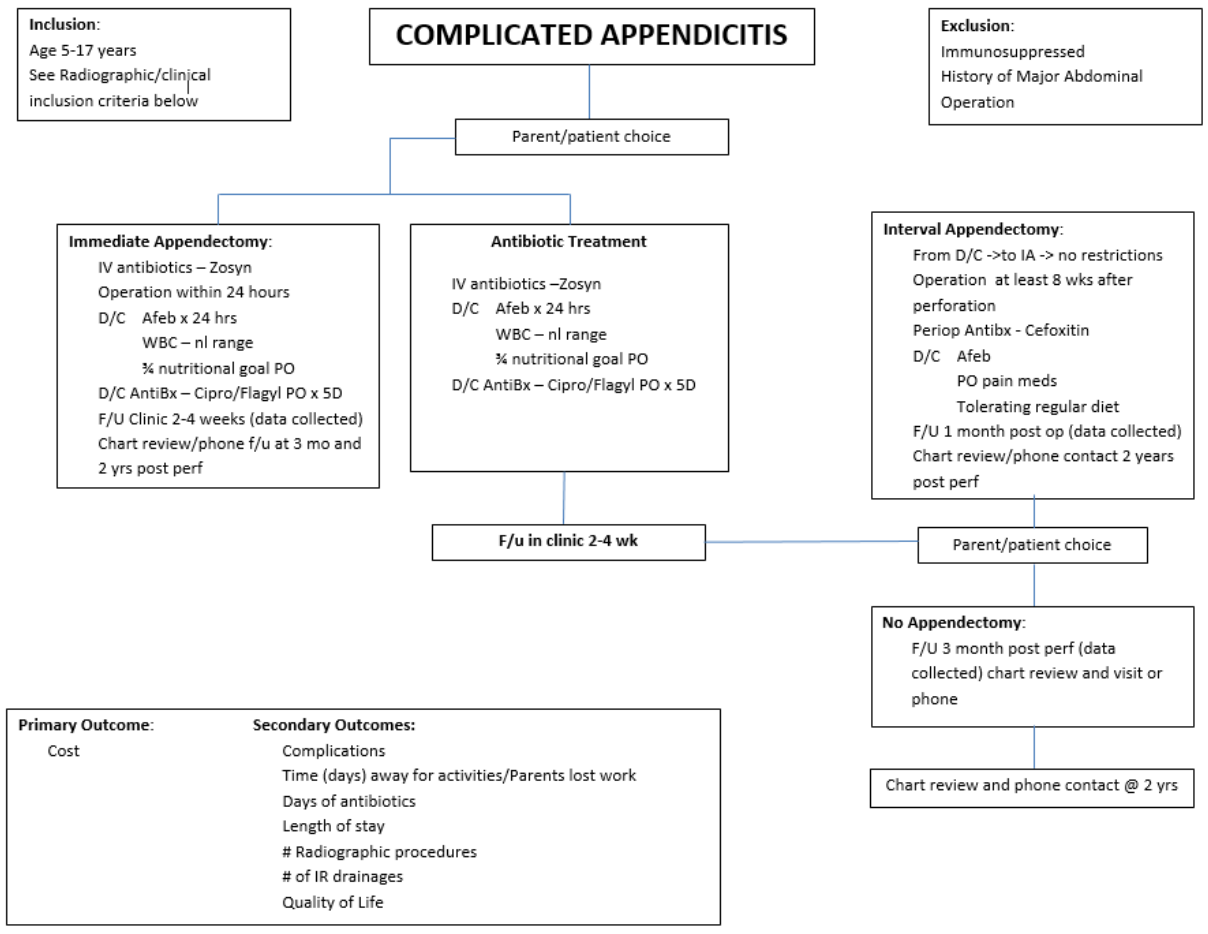
- Complications
- Time to return to activity/parents to return to work
- Duration of antibiotic therapy
- Length of stay

- Number of percutaneous drainage procedures/radiographic imaging studies
- Quality of life
- Recurrent appendicitis

3 STUDY DESIGN

This is a single center, prospective study to compare early appendectomy vs. non-operative management of immunocompetent patients with complicated appendicitis, as well as interval appendectomy vs. no interval appendectomy in those managed with the initial non-operative approach. In our study we will identify patients between the ages of 5 and 17 with the diagnosis of complicated appendicitis who are not immunocompromised. We will present the two options to the patient and their parents using a prerecorded video that discusses the two treatments with their theoretical advantages and disadvantages. We will allow the patients and their parents to decide which option they would like. We then will treat each study participant using our present algorithm for complicated appendicitis (see diagram below). Study participants who select immediate operation will undergo an appendectomy within 24 hours and be treated using our present algorithm. They will follow up in our clinic in 2-4 weeks and complete a gastrointestinal quality of life survey at that time. Study participants who selected initial non-operative management will be treated using our present algorithm. They will follow up in clinic in 2-4 weeks after initial hospital discharge and also complete a gastrointestinal quality of life survey at this time. At this point in the treatment of complicated appendicitis, there are two options: Interval appendectomy, or no appendectomy or further treatment. We will again use a prerecorded video that discusses these two options and their theoretical advantages and disadvantages. The study participants and their parents will then decide whether or not to have an interval appendectomy which will be scheduled at least 8 weeks after initial hospital discharge. The interval appendectomy will be performed (admitted the day of the operation and most often discharged the following day), and patients will follow up in the clinic one month following the appendectomy and data will be collected. All participating subjects will be contacted by phone or email 3 months and again at 2 years after their initial admission and data will be collected. If the patient has not completed his/her clinical course by 3 months, treatment (antibiotics, percutaneous drainage, or operative intervention) and further follow-up will be determined by the discretion of the treating surgeon. A chart review and administration of a quality of life survey will also occur along with these follow up phone calls and emails. The primary outcome of our study will be cost. The secondary outcomes will be number and type of complications, time away from activities (school etc.) for patients and away from work for parents, number of days of antibiotic therapy required, length of stay, number of imaging tests, number of percutaneous drainage procedures required, quality of life, and recurrent appendicitis.

Figure 1:



4 SUBJECT SELECTION

4.1 Subject Recruitment

Informed consent will be obtained from the parents or legal guardian. The consent will be obtained in person. Consent will be obtained preoperatively if inclusion criteria are met.

4.1.1 Inclusion Criteria

1. Patient age 5-17 years
2. At least 1 of the following CT or MRI findings:
    a. Peri-appendicular abscess
    b. Extruded appendicolith
    c. Visible hole in appendiceal wall
    d. Free peritoneal air

OR

3. CT or MRI read with phlegmon or diffuse/extensive inflammation/free fluid plus 1 of 3 of the following (with CT) or 2 of 3 of the following (with MRI) *:
    a. WBC > 15
    b. Peritonitis (involuntary RLQ guarding, + Rosving sign, percussion tenderness, and/or rebound tenderness)
    c. Temperature > 38.0 C

*>90% specificity for complicated appendicitis based on unpublished institutional data

4.1.2 Exclusion Criteria

1. Immunocompromized state
2. History of major abdominal operation
3. Previous appendicitis
4. Major comorbidities that preclude safe operation
5. Inability to follow-up or appropriately consent
6. Pregnant women
7. Allergy to penicillin plus any one of the following:
    a. Hypersensitivity to ciprofloxacin and/or metronidazole
    b. Pregnant/lactating women
    c. Patients taking theophylline
    d. Patient taking tizanidine

5 STUDY TREATMENTS

5.1 Allocation to Treatment

Treatment group will be determined by patient/parent choice. All patients and families will be shown a pre-recorded video describing the treatment options and their theoretic advantages and disadvantages prior to making their decision. This applies to the decisions of early appendectomy vs. non-operative therapy, as well as to interval appendectomy vs. no interval appendectomy.

6 STUDY PROCEDURES

At Baseline (Presentation to Emergency Department)

We will record the following:

- Demographic information including age, gender, duration of symptoms, medical history (including any immunosuppressive medications or medical diagnoses causing immunocompromised state), WBC count, and imaging findings.
- Pregnancy test if past menarche

If the patient undergoes appendectomy:

We will record the following:

- Operative approach (laparoscopic, open, or laparoscopic converted to open)
- Operative time
- Operative findings
- Intraoperative complications, if any

During admission (for both immediate appendectomy and non-operative groups):

- See Appendix A (complicated appendicitis clinical pathway) for patient management and procedures during initial hospitalization

At Discharge (for both immediate appendectomy and non-operative groups):

- Record length of stay, duration of IV antibiotics, and post-operative complications
- Administer PedsQL™ quality of life survey

Remainder of post-discharge procedures per schedule of activities below:

SCHEDULE OF ACTIVITIES

Table 1:

	Time Post-presentation				
Protocol Activity	**Presentation**	**2-4 weeks**	**8 weeks**	**3 months**	**2 years**
Informed Consent	X				
Demographic and Medical History	X				
Vitals	X				
Patient/Parent Choice	X	X (for non-op)			
Initial appendectomy	X (within 24 hours)				
Initiate complicated appendicitis clinical pathway (see Appendix A)	X				
Clinic follow-up		X		X (for interval operative)	
GI QOL survey administration		X			
Interval appendectomy			X		
PedsQL administration	X (discharge)			X	X
Phone/email follow-up				X	X
Chart Review				X	X

7 ASSESSMENTS

7.1 Primary Endpoint Assessments

Cost will be determined by data extraction the cost accounting section of the Health System Data Warehouse (HSDW).

7.2 Secondary Endpoint Assessments

Complications will be determined and documented during the initial hospitalization and at subsequent clinic appointments and phone follow-ups, as documented above.

Time to return to activity/parents to work will be determined and documented at subsequent clinic appointments and phone follow-ups, as documented above.

Days of antibiotics will be determined by our current algorithm (depicted in Figure 1), based on patient fever and WBC count.

Length of stay will be determined by our current algorithm, documented at the end of the initial hospitalization, and accrued at any subsequent readmissions.

Number of percutaneous drainage procedures and imaging procedures will be determined by clinical course.

Quality of life will be determined by the PedsQL and gastrointestinal QOL surveys.

Recurrent appendicitis will be determined by chart review and patient phone or email follow-up.

8 RISK AND RISK MITIGATION

Studies comparing early appendectomy to interval appendectomy for complicated appendicitis have demonstrated conflicting results, and therefore it is unclear if one strategy bears more risk than the other [1,2]. Both are considered acceptable in current practice. The same can be said of whether or not to perform interval appendectomy at all. Interval appendectomy has been shown in the literature to be a safe and effective operation [6].

ADVERSE EVENTS

Adverse events associated with complicated appendicitis include intra-abdominal abscess, small bowel obstruction, wound infection, unplanned readmission, and complications related to central line placement (if necessary) and percutaneous drain placement (if necessary). These risks pertain to patient who both do and do not undergo appendectomy. Recurrent appendicitis is also

a risk of non-operative management of complicated appendicitis, as is the need for additional treatment with antibiotics [2]. All patients in this study will receive antibiotics (piperacillin-tazobactam, ciprofloxacin, metronidazole), and will be subject to the risk of drug reaction or allergy. Metronidazole should be administered with caution to patients with central nervous system diseases. Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses, below those usually recommended should be administered cautiously

9 ADVERSE EVENT REPORTING

Adverse Event Definition
An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience
c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the Investigator's Brochure (current edition) or in the study informed consent document.

Unexpected adverse events are those that are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), A serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED /FDA.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

Event reporting: The study will comply with the IRB & FDA reporting requirements and guidelines.

10 DATA ANALYSIS/STATISTICAL METHODS

10.1 Sample Size Determination

The study is powered to show a $7,000 reduction in overall cost. To do this, we will need to enroll at least 68 patients in each arm. This study represents a pilot study of 40 total patients to better determine our sample size requirement.

10.2 Data Analysis

10.2.1 Analysis of Primary Endpoint

The primary outcome measure of this study is the cost of care. This is a continuous variable, which may be assessed by univariate analysis (independent t-test).

10.2.2 Analysis of Secondary Endpoints

The secondary endpoints of this study are complications, time away from activities/parents from work, days of antibiotics, length of stay, and number of percutaneous drainage and radiographic procedures. These are also continuous variables and will be analyzed by univariate analysis (independent t-test).

11 MONITORING

11.1 Data Safety and Monitoring Board (DSMB)

The first DSMB meeting will occur 6 months after study initiation and every 6 months going forward. In addition to reviewing Serious Adverse Events (SAEs), the first DSMB meeting will focus on over all safety of the trial and study agent and will make a determination as to whether or not the study should proceed. The DSMB will then meet quarterly throughout the remainder of the study and at any time during the study in which an unexpected and possibly related Serious Adverse Event occurs. Interim data will also be discussed at the quarterly Midwest Pediatric Surgery Consortium meetings.

12 ETHICS

12.1 Institutional Review Board (IRB)

Prior to study commencement, the protocol, the proposed informed consent form and other information to be provided to subjects, will be reviewed by a properly constituted Institutional Review Board (IRB) at the University of Michigan (IRBMED). Any amendments to the protocol will be reviewed and approved by IRBMED before implementation.

12.2 Subject Information and Consent

The study team member will explain to each subject (in this case the parent) or legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

12.3 STUDY DISCONTINUATION CRITERIA

12.3.1 Stopping Rules for Safety reasons

The Data Safety Monitoring Board (DSMB) will review all Serious Adverse Events (SAEs) and make recommendations regarding the continuation or discontinuation of the study, as appropriate.

12.3.2 Rules for Discontinuation of a Subject

In the event a patient drops out of the study or is discontinued due to protocol violations, he/she will continue to receive standard of care, and data collection prior to discontinuation will be used in intent to treat analysis.

13 REFERENCES

1. St Peter SD, Aguayo P, Fraser JD, et al. Initial laparoscopic appendectomy versus initial nonoperative management and interval appendectomy for perforated appendicitis with abscess: a prospective, randomized trial. Journal of pediatric surgery 2010;45:236-40.
2. Blakely ML, Williams R, Dassinger MS, et al. Early vs interval appendectomy for children with perforated appendicitis. Archives of surgery (Chicago, Ill : 1960) 2011;146:660-5.
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4. Kaminski A, Liu IL, Applebaum H, Lee SL, Haigh PI. Routine interval appendectomy is not justified after initial nonoperative treatment of acute appendicitis. Archives of surgery (Chicago, Ill : 1960) 2005;140:897-901.
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14 APPENDIX A: COMPLICATED APPENDICITIS CLINICAL PATHWAY

On Admission:

- NPO until nausea/vomiting/distention has resolved
    - Upon resolution start clear liquid diet and advance to regular diet as tolerated
- IV fluids
    - Saline lock when tolerating PO fluids
- IV antibiotics
    - Zosyn (ciprofloxacin and metronidazole if penicillin allergy)
- Pain relief
    - Tylenol
    - Ibuprofen or toradol if appropriately hydrated and no bleeding concerns
    - Oxycodone/morphine prn
- Have patient out of bed and ambulating

Once the patient is afebrile for 24 hours, tolerating ¾ nutritional goals PO (determined by calorie count with the aid of a registered dietitian), diarrhea (if originally present) has resolved, and appears clinically improved, check CBC the next morning

- If WBC is normal (decreased from admission), change to PO ciprofloxacin and metronidazole for 5 days
    - OK to discharge to home
- If WBC is elevated or fever/symptoms still present Post-op or hospital day 5-7, continue IV antibiotics and obtain abdominal ultrasound +/- CT scan
    - If abscess identified, consider IR drainage