Operative Versus Non-Operative Management for Appendicitis with Abscess or Phlegmon: An EAST Multicenter Trial

Short Title: Perforated Appendicitis Treatment (PAT) Trial

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Prospective multicenter randomized controlled trial.

Complicated appendicitis with abscess or phlegmon represents a challenging problem to emergency general surgeons, and the preferred treatment remains controversial. Appendiceal abscess or phlegmon is encountered in approximately 2-10% of cases of acute appendicitis.[1] A variety of therapies have been recommended including early operative intervention, delayed operative intervention, and non-operative management. Early operation has been associated with a higher rate of cecal resection in retrospective analysis.[2] These data, however, generally arise from the period when appendectomy transitioned from a primarily open operation to a laparoscopic one. Other retrospective evaluations have been performed, but results are mixed, and biased by combining adult and pediatric populations. [3, 4, 5] To further complicate the matter, some groups have advocated for prolonged surveillance or enhanced imaging after non-operative management to reduce the risk of missed malignancy.[6] According to a meta-analysis conducted in 2017, patients who underwent early appendectomy experienced a length of stay benefit and higher pediatric quality of life scores. Only two studies were appropriate for evaluation, however, the quality of evidence was low, and the risk of bias high. Further, both studies included children. [1]

Recently, a prospective randomized controlled trial from a single center was conducted in Finland comparing operative and non-operative management of appendiceal abscess. [7] Patients

managed in the operative arm were found to have a shorter length of stay, fewer re-admissions, and fewer additional interventions than those managed in the non-operative group.[7] These results seem consistent with our experience but there is no high-quality randomized controlled trial conducted in the United States to support this. Additionally, many US surgeons choose non-operative management for patients with significant phlegmon without abscess, a group not examined in the Finnish study. For this reason, we propose a multi-center, prospective, randomized controlled trial comparing operative and non-operative management of complicated appendicitis with abscess or phlegmon in adult patients.

Primary aim: We aim to determine if early operative intervention is superior to non-operative management for adult patients with complicated appendicitis with phlegmon or abscess. The primary endpoint is total hospital days.

Secondary aim: We aim to quantify complications, need for readmission and need for additional procedures. Additional outcomes will include mortality, failed attempted primary procedure, recurrent abscess, recurrent appendicitis, need to convert to an open operation in operated patients, need for bowel resection, surgical site infection and all other NSQIP captured complications.

Inclusion Criteria: Age greater than or equal to 16, CT or MRI proven appendicitis with presumed perforation evidenced by either phlegmon, or abscess greater than or equal to 2cm. Because phlegmon is a somewhat nebulous CT finding, patients will be eligible when the initial consult by an attending surgeon recommends non-operative management.

Exclusion criteria: Antibiotic therapy greater than 24 hours, attempted drainage before randomization, pregnancy, antibiotic allergy to cephalosporin or metronidazole, previous major intra-abdominal surgery by laparotomy, hospitalization within 2 weeks prior to presentation, severe acute illness requiring vasopressors, mechanical ventilation, oxygen therapy more than nasal cannula or acute renal failure requiring dialysis.

Therapeutic interventions: In the surgery arm, patients will undergo attempted laparoscopic appendectomy within 12 hours of randomization, including abscess drainage if necessary. Some cases may need to be converted to open appendectomy. Any additional surgery is at the discretion of the operating surgeon. Patients will receive antibiotic therapy upon diagnosis and continuing for 96 hours after source control. Any management decisions regarding complications or otherwise will be made by the attending surgeon.

In the non-operative arm, patients will undergo percutaneous drainage if possible, with antibiotic therapy for 96 hours after drainage. For patients in which percutaneous drainage is not possible, antibiotic therapy will be continued for at least seven days and will otherwise be at the discretion of the attending surgeon. Any additional imaging, intervention or surgery decisions will be made by the attending surgeon. Post-discharge treatment decisions, including the decision to proceed with interval appendectomy, will be made by the treating surgeon in conjunction with the patient.

Primary Outcome: Number of hospital days within 60 days from index admission until the patient is deemed ready for discharge. This includes hospital days during the initial stay and readmission.

Secondary Outcomes:

1. Need for additional intervention (percutaneous drainage, unplanned operative intervention),
2. Intra-abdominal abscess more than 7 days after presentation.
3. Failed attempted procedure (conversion to open, failed laparoscopic appendectomy, percutaneous drainage not possible)
4. Complications within 60 days of randomization, as defined by NSQIP
5. Number of interventions for abscess in 60 days
6. Need for bowel resection.
7. Occurrence of delayed appendectomy.
8. Recurrence over one year in both groups. An attempt will be made to follow patients for five years with telephone follow up.
9. Presence of malignancy in any resected specimen.
10. Days of disability in the first 60 days after randomization (days away from work or school)
11. GI quality of life measured at 30 days, 60 days and one year after randomization using the PROMIS GI symptoms scales.

Variables:

1. Presenting condition:
    a. Vital signs
    b. NSQIP comorbidity
    c. NSQIP laboratory values
    d. CT findings
        i. AAST EGS grading scale for Acute Appendicitis
        ii. size of abscess
        iii. size of phlegmon
        iv. presence of free fluid
        v. evidence of bowel obstruction or ileus
        vi. extra-luminal air
    e. Need for percutaneous drainage
        i. Timing of drainage
        ii. Duration of drain
2. Operative characteristics for operative group and failed non-operative management
    a. AAST EGS Grading Scale for acute appendicitis
    b. Blood loss
    c. Time of procedure
    d. Duration of procedure

3. Length of stay (total hospital days related to appendicitis within 60 days of randomization)
4. Readmission
5. Recurrent or residual abscess between day 7-60
6. Additional intervention
7. Unplanned operation
8. Repeated CT scan
9. Failed intervention (conversion to open, bowel resection, failed percutaneous drainage)
10. Duration of antibiotics
11. Any complications, as defined by NSQIP after randomization.

Data Collection and Statistical Analysis: Data will be entered into the Yale's RedCap web server. Once all of the data has been collected it will be transmitted in a de-identified state to the primary center for analysis. Statistical analysis will be performed using SAS. Continuous variables will be compared with 2-sample *t* test for normally distributed data and differences of means with 95% confidence interval. Non-normally distributed data will be compared with the Mann-Whitney *U* test. Categorical data will be analyzed using the Chi-square and/or Fischer's exact test where appropriate. *P* values of less than 0.05 are considered significant. Data will be analyzed using the intention to treat principle. A priori subgroups will be those patients over 70 years old, those who present with hypotension, and those with abscess more than five centimeters.

Assuming an improved length of stay in the surgical group of 1 day with a standard deviation of 2 days, with alpha = 0.05 and beta = 0.8 the approximate number of patients to be enrolled will be 180 patients divided equally into two groups with no expectation or limit on the number centers.

Consent Procedures: Patients admitted for non-operative management of acute complicated appendicitis with phlegmon or abscess will be identified by whatever local mechanism is appropriate. For example, at Yale New Haven Hospital this will be by daily morning screening of the emergency general surgery patient list. Informed consent for participation in the study will be obtained at the time of evaluation for study entry. After the patient is randomized, informed consent for any necessary procedures will be obtained in accordance with standard practices.

Risk/Benefit Analysis: The risks and benefits will depend on the arm of the study to which the patient is assigned. Under non-study circumstances these patients would all be treated based on surgeon preference with the risk/benefit based on the chosen approach due to clinical equipoise. Because it is unclear which approach carries the better risk/benefit ratio it is the goal of this study to identify that difference, if any. Informed consent will be obtained prior to carrying out any intervention. The principal investigator will monitor the results at quarterly intervals and the study will be terminated early if one arm proves superior to the other based on the pre-defined stopping points. Finally, there is a small risk of breach in patient information which is minimized by using de-identified patient information and storing it in RedCap.

From a patient and societal perspective, the benefit will be a minimized duration of illness with earlier return to full functional activities including work or school if one approach is significantly better. If a difference in illness duration is present this will likely translate into less pain and improved quality of life.

This study is currently under review by the Yale Human Investigations Committee.

References

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