

Study Title: Appendicitis in the United States: a prospective observational study of the demographics, presentation, and outcomes of acute, perforated, and gangrenous appendicitis

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Background & Significance

Outline the burden of the problem:

Appendectomy is the most common emergency general surgical operation performed in the United States and is most commonly performed for acute appendicitis (AA), perforated appendicitis (PA), or gangrenous appendicitis (GA). The traditional teaching has been that AA, PA, and GA represent different time points along untreated disease (*natural history*) as well as different degrees of severity along a continuum represented by a single disease entity (*spectrum of illness*). Yet, it has long been recognized that these three phenotypes of appendicitis result in different expectations of clinical outcomes such as surgical site infection (SSI), organ-space infection, hospital length of stay (LOS), and mortality. It is plausible that AA, PA, and GA represent three distinct diseases with differing at-risk populations, clinical presentation, recommended treatment, and expected outcomes. Accurately defining these distinctions are an important first step towards benchmarking quality and planning treatment intervention trials. For example, recent randomized controlled trials (RCT) from Europe have reported equivalence of appendectomy and antibiotics alone (1). However, the surgical method was overwhelmingly open (vs. laparoscopic) and the average hospital length of stay was several days and this does not accurately reflect contemporary American practice. Comparative trials comparing laparoscopic appendectomy (with 1 to 2 days of post-operative hospital stay) to antibiotic therapy are needed in order to appropriately inform clinical practice. Additionally, for PA without a drainable abscess, it is unclear whether early appendectomy is superior to antibiotic therapy with possible interval appendectomy in terms of hospital LOS, secondary interventions, and overall morbidity.

Recently, the AAST described a grading scale to describe the anatomic severity of appendicitis (2). The next step is to externally validate this severity scoring system to confirm content validity and consequential validity. Ideally, this should occur in a prospective, multicenter fashion.

Primary aim:

To prospectively confirm/refute the concept that AA, PA, and GA lie along the same continuum of *natural history* and *spectrum of illness*. We hypothesize that AA, PA,

and GA are three distinct disease entities with clinically distinct at-risk populations, clinical presentations, and treatment recommendations, and outcomes expectations.

Secondary aims:

- 1) To validate the EGS disease severity scoring system as described by the AAST.
- 2) To prospectively evaluate outcomes of perforated appendicitis after differing treatments and to generate hypothesis for future randomized trials.
- 3) To estimate outcome events for acute appendicitis to adequately plan sample size calculations for future randomized trials.

Experimental Design/Methods

Inclusion Criteria:

Adult (age \geq 18)
Clinical suspicion of appendicitis

Exclusion Criteria:

None

Therapeutic Interventions:

Antibiotics alone
Appendectomy +/- antibiotics
Antibiotics plus percutaneous drainage

Outcomes Measures

Primary Outcome:

Appendectomy – successful completion of appendectomy
Antibiotics alone – discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up period
Antibiotics plus percutaneous drainage – discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up period

Secondary Outcomes:

Surgical site infection (SSI)
Secondary intervention rate
Hospital re-admission (30 day, 6 month, 1 year)
Hospital length of stay (LOS), index and cumulative
Pathologic diagnosis (acute, perforated, gangrenous, other)
Cost

Variables:

Demographics: age, sex, weight, BMI, co-morbid medical conditions, Charlson Comorbidity scale, prior operations, immunosuppressive medications

History of present illness: duration of symptoms (by 6 hour blocks), nausea, vomiting, anorexia, diarrhea, migration, prior episodes

Admission physical exam: temperature (C), heart rate (HR), systolic blood pressure, right lower quadrant tenderness, right lower quadrant rebound tenderness, diffuse abdominal tenderness, diffuse abdominal rebound tenderness, Rovsing's sign, Obturator sign, Psoas sign

Admission laboratory test: WBC, %polys, C-reactive peptide (if available), erythrocyte sedimentation rate (ESR, if available)

Antibiotics: drug class, drug dose, duration of treatment

Surgical variables: time from hospital admission to operation, initial laparoscopic or open, conversion to open, duration of operation

Pathologic variables: final pathologic diagnosis (normal, acute, perforated, gangrenous, neoplastic, other)

Outcomes: index hospital LOS, 1 year cumulative hospital LOS (includes subsequent hospital readmissions), hospital readmission rate (repeated measures), surgical site infection (SSI), secondary interventions, duration of antibiotic treatment, Clavien-Dindo complications, intra-operative adverse events (iAE)

Data Collection Statistical Analysis

Standardized data will be collected for each patient (see data sheet, Appendix A).

Continuous variables will be compared using Student's t-test and the Mann Whitney U test. The Chi-squared tests or Fisher's exact test will be used to compare categorical variables. All variables with a p value <0.2 on univariate analysis will be entered into a multivariable logistic regression analysis to identify independent risk factors for failure of initial chosen treatment strategy. Data will be reported as adjusted odds ratios with 95% confidence intervals. Statistical significance will be set at a $p < 0.05$

Consent Procedures:

This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers.

Risk/Benefit Analysis:

If the optimal timing for and type of intervention for acute appendicitis, perforated appendicitis, and gangrenous appendicitis can be identified to optimize outcomes in these patients, then significant benefit will result.

References:

1. Salminen P, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA*. 2015 Jun 16;313(23):2340-8.
2. Tominaga GT, Staudenmayer KL, Shafi S, Schuster KM, Savage SA, Ross S, et al. The American Association for the Surgery of Trauma grading scale for 16 emergency general surgery conditions: Disease-specific criteria characterizing anatomic severity grading. *J Trauma Acute Care Surg*. 2016 Sep;81(3):593-602.