One Versus Five Days of Antibiotics Following Appendectomy for Straightforward Acute Appendicitis: Study Protocol for a Randomized Controlled Trial

Cover Page

Official Title: “One Versus Five Days of Antibiotics Following Appendectomy for Straightforward Acute Appendicitis: Study Protocol for a Randomized Controlled Trial”

NCT Number: [NCT number pending]

Document Type: Research Protocol

Document Date: 26/11/2025

Version Number: 1.0

Principal Investigator: Dr. Shahinda Kamal

Study Site: Fayoum General Hospital, Fayoum, Egypt

IRB Approval Number: 11-2025/23

One Versus Five Days of Antibiotics Following Appendectomy for Straightforward Acute Appendicitis: Study Protocol for a Randomized Controlled Trial

Research Protocol

Background

Antimicrobial resistance (AMR) has emerged as one of the most important threats to public health in the 21st century. World Health Organization (WHO) estimates suggest that AMR could cause 10 million deaths yearly by 2050, declaring it a top global priority (1). In surgical practice, antibiotics greatly reduced the burden of postoperative infections. However, their rampant abuse paradoxically led to the selective pressure of increasingly resistant bacteria (2). AMR not only addressed the issue of resistance, but demonstrated significant savings with reduced spending on drugs, shorter hospital stays, and lesser complications (3).

Acute appendicitis remains a leading indication for emergency surgery (4). Straightforward acute appendicitis — defined as non-gangrenous, non-perforated appendix without abscess or peritonitis — typically has low rates of postoperative infectious complications. While perioperative prophylactic antibiotics are universally recommended (5), the optimal duration post-surgery remains controversial. Extended antibiotic courses may not be necessary and could promote antimicrobial resistance. Shorter antibiotic regimens may be equally effective while minimizing risks of antimicrobial resistance (1). Research indicated for appendectomy, simplistic uncomplicated cases do not need to be overtreated, so longer antibiotic courses do not provide added value compared to the shorter ones (6). Yet, clinical practice surveyed still adhered to traditional longer courses dictated by history instead of clinical reasoning (5). This divergence of evidence and practice demonstrates the necessity of well-designed studies to guide antibiotic prescribing throughout surgical care.

Critical gaps in evidence concerning AMR went unexplored, particularly determining the optimal duration of postoperative antibiotics for uncomplicated acute appendicitis. The economic repercussions of excessive antibiotic usage were notable, highlighting that optimizing the duration of therapy could decrease healthcare expenditures by upwards of 30% in surgical patients (7). Guidelines used to differ significantly, reflecting a period of low-quality randomized

controlled trials (4), with some stipulating no antibiotics and others recommending 5-day courses. Most prior studies either concentrated on complicated cases or focused on the use of antibiotics versus placebo, leaving uncomplicated cases unattended (8). Additionally, many of the studies suffered from retrospective design, small sample size, or consisting of heterogeneous outcome measures, which made resulting conclusions inconclusive (9).

In addition, the clinical and economic repercussions of excessive antibiotic use in appendectomy patients have not been thoroughly studied. Adverse drug events, Clostridioides difficile infections, and increased duration of hospitalization were all outcomes correlated with extended antibiotic use, but rarely quantified specifically for appendectomy patients (10). The absence of robust cost-effectiveness analyses paired with inconsistent standard measures to define outcomes hindered the formulation of evidence-based guidelines, which resulted in erratic clinical practice (11).

Objectives

The primary objective is to prove that 1-day postoperative antibiotic therapy is non-inferior to a 5-day regimen in preventing infectious complications and mortality after appendectomy for straightforward appendicitis. This trial addresses an important clinical question regarding the necessity of prolonged antibiotic therapy after appendectomy for straightforward appendicitis. If 1-day therapy is proven non-inferior, it will have major implications for clinical practice, antibiotic stewardship (1), and patient care (2).

Methods

This randomized controlled non-blinded non-inferiority trial will be conducted at Fayoum General Hospital. The study sample will be patients aged ≥10 years who are admitted to the General Surgery Department to undergo appendectomy for straightforward acute appendicitis. A total of 200 patients will be randomized (100 per arm) using computer-based randomization 1:1 to receive either a single day (24 hours) or five days of postoperative intravenous antibiotics. The primary

outcome is a composite of infectious complications (surgical site infections [SSI] and intra-abdominal abscesses [IAA]) or mortality within 30 days post-surgery. Secondary outcomes include readmission rates, antibiotic-related adverse events, and cost-effectiveness. The non-inferiority margin is set at 5%. Analyses will be performed both per-protocol and intention-to-treat.

Trial Design: A prospective, randomized controlled, non-blinded, non-inferiority trial.

Trial Setting: The General Surgery Department, Fayoum General Hospital, Fayoum, Egypt.

Eligibility Criteria:

Inclusion criteria Patients aged ≥10 years.

Undergoing appendectomy with intraoperative diagnosis of straightforward acute appendicitis (non-phlegmonous, non-gangrenous, non-perforated, no abscess).

Exclusion criteria Complex appendicitis (gangrenous, perforated, abscess).

Severe sepsis at presentation.

Immunocompromised state (including diabetic patients).

Pregnancy.

Allergy to study antibiotics.

Concurrent infections requiring antibiotics.

Interventions

Antibiotics regimen short course (experimental arm): 24 hours of postoperative IV antibiotics (ampicillin/sulbactam)

One Versus Five Days of Antibiotics Following Appendectomy for Straightforward Acute Appendicitis: Study Protocol for a Randomized Controlled Trial

Standard course (active comparator arm): 1 day of postoperative IV antibiotics (the same regimen) followed by 4 days of oral antibiotic (amoxicillin/clavulanic acid)

Oral antibiotics are permitted after 24 hours of intravenous antibiotic.

Outcome Measures

Primary endpoint Composite of infectious complications or mortality: The proportion of participants experiencing any of the following within 30 days post-appendectomy:

Surgical site infection (SSI)

Intra-abdominal abscess (IAA)

All-cause mortality

Secondary endpoints: Rate of hospital readmission within 30 days

Incremental cost-effectiveness ratio (ICER)

Randomization and Allocation: Randomization (1:1) using computer-based randomization using R.

Blinding: The trial is non-blinded (open-label) due to practical and clinical reasons.

Data Collection and Management Data will be collected manually via clinical pharmacist and stored securely. Outcome assessors will not be blinded. Missing data will be minimized by standardized telephone follow-up at 30 days.

Sample Size Calculation: Assuming a baseline infectious complication rate of 5%, a 5% non-inferiority margin, and 90% power, we estimate 200 patients are needed (100 per arm). Allowing for 10% dropout, the target enrollment is 220 patients.

One Versus Five Days of Antibiotics Following Appendectomy for Straightforward Acute Appendicitis: Study Protocol for a Randomized Controlled Trial

Statistical Analysis

Primary analysis will calculate the one-sided 97.5% confidence interval for the difference in the primary outcome rate. Non-inferiority is established if the upper limit is <5%. Logistic regression will adjust for age, sex, surgical approach, and ASA score.

Secondary outcomes will be compared using appropriate statistical tests (t-test, chi-square, logistic regression).