Non-inferiority multicentre randomized controlled trial comparing short versus standard course postoperative antibiotic treatment for complex acute appendicitis

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON45262

Source
ToetsingOnline

Brief title
APPIC trial (Antibiotics following aPPendectomy In Complex appendicitis)

Condition

- Gastrointestinal inflammatory conditions
- Gastrointestinal therapeutic procedures

Synonym
Complex acute appendicitis; complicated inflammation of the appendix

Research involving
Human

Sponsors and support

Primary sponsor: Heelkunde
Source(s) of monetary or material Support: Subsidie ZonMw (in opdracht van het Ministerie van Volksgezondheid;Welzijn en Sport (VWS) en de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)

Intervention

Keyword: antibiotics, appendicitis, complex, postoperative

Outcome measures

Primary outcome

The primary outcome of this study is a composite endpoint of mortality and infectious complications related to appendectomy including intra-abdominal abscess and surigical site infection. You will find a more detailed definition of the primary endpoint in Chapter 8 (Methods) of the studyprotocol, on page 29.

Secondary outcome

Secundary outcomes are amongst others: intra-abdominal abscess, superficial and/or deep surgical site infections, restart of antibiotics, hospital stay in hours, readmission rate and cost-effectiveness.

Study variables are: age at time of diagnosis, location of operation, medical history (including diabetes mellitus, corticosteroid use), ASA score, gender, BMI, body temperature and laboratory results at time of presentation (CRP, WBC, eGFR), diagnostic radiological imaging, duration and severity of abdominal pain (VAS scale), antibiotic use prior to clinical diagnosis of acute appendicitis (type and dosage), prophylactic antibiotic use (type and dosage), laparoscopic

or open appendectomy, duration of operation (skin-to-skin time), type of appendicitis (phlegmonous, gangrenous or perforated, with or without abscess), degree of peritonitis, level of expertise of surgeon, peritoneal irrigation and/or suction, wound management, use of (endo)loops or (endo)stapler, intraperitoneal drain placement, cultures of intra-abdominal fluid collections, histological type of appendicitis, (time to reach) discharge criteria, postoperative imaging for suspected complications, intra-abdominal abscess (IAA), deep and/or superficial surgical site infection (SSI), treatment of IAAs and SSIs, any other postoperative complication including severity, duration and doses of antibiotics received, restart of antibiotics and type, adverse events on antibiotics, type and resistance profile of cultured micro-organisms postoperatively, length of hospital stay, post-operative outpatient visit, readmission, re-interventions for complications (all within 90 days after appendectomy).

Study description

Background summary

Acute appendicitis is an inflammation of the appendix. In the Netherlands, approximately 16.000 patients undergo appendectomy annually. After appendectomy for uncomplicated appendicitis most patients can be discharged within 24-48 hours. However, in 25%-30% of the patients, a complex appendicitis is diagnosed for which guidelines dictate postoperative intravenous antibiotics to reduce the rate of infectious complications. There is currently no consensus on the duration of postoperative antibiotics and randomized clinical studies are lacking. Cohort studies suggest there is no difference in infectious complications when comparing three to five days of postoperative antibiotics. To minimize hospital stay, costs and the risk of bacterial resistance, it is important to define a safe and effective antibiotic regimen. There is an urgent need for a high-quality study assessing the appropriate duration of

postoperative antimicrobial therapy for complex appendicitis in both children and adults.

Study objective

The goal of this study is to evaluate efficacy and safety of stopping postoperative antibiotic treatment after 48 hours of intravenous therapy versus continuing for three more days (to complete a total of five days which is common practice), following appendectomy in patients suffering from complex appendicitis. The primary endpoint is a composite endpoint of mortality and infectious complications related to appendectomy, including intra-abdominal abscess and surgical site infections, within 90 days after appendectomy. Secondary objectives are cost-effectiveness, intra-abdominal abscess, superficial and/or deep surgical site infections, mortality, duration of postoperative antibiotic treatment, re-start of antibiotics, hospital stay in hours from the operation, time to reach discharge criteria in hours from the operation, emergency room visits, readmission rate and adverse events on antibiotics (all within 90 days after appendectomy).

Study design

Non-inferiority, multicentre, randomized clinical trial comparing two postoperative treatment strategies of antibiotics for complex acute appendicitis.

Intervention

Patients will be randomized to either A) stopping antbiotic treatment after 48 hours of intravenous antibiotics (intervention group), or B) continuing antibiotic treatment for three more days (control group). Antibiotics given intravenously are cefuroxime and metronidazole. Alternatively, the combination of ceftriaxone and metronidazole is allowed, if preferred due to local bacterial resistance patterns. In children < 40kg the doses will be adjusted according to their weight.

Study burden and risks

Treatment of complex acute appendicitis with the proposed antibiotics is common practice in the Netherlands. These antibiotic regimens have been widely used for a long time already and toxicity and possible side effects are well documented. Therefore no extra risks are associated with the medicinal products. The risk of reducing antibiotic treatment in the intervention group in terms of a possibly higher rate of infectious complications is considered low. To closely monitor clinically important adverse events, an independent safety committee (DSMB) is established. Personal benefit for patients in the intervention group in terms of patient comfort may be shorter hospital stay. No

extra burden is associated with trial-participation in the context of blood samples taken, number of site visits and other physical examination or tests. The only difference compared to standard practice is one extra follow-up by phone and a productivity cost questionnaire.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- age minimum 8 years old (no upper limit)
- patients with suspected acute appendicitis, awaiting appendectomy
- written informed consent

- intraoperative diagnosis of a complex appendicitis*;*A complex appendicitis includes a gangrenous and/or perforated appendicitis, as well as appendicitis with an abscess. For more information and details regarding severity of appendicitis, see 4.1 Population in the studyprotocol (page 19).

Exclusion criteria

- not able to give informed consent
- appendectomy à froid
- severe sepsis, defined as sepsis-induced tissue hypoperfusion or organ dysfunction
- conservative treatment of acute appendicitis
- ASA score IV or not able to undergo surgery
- known allergy or any other contraindication for the use of the study medication
- immunocompromised patients
- pregnancy
- use of other antibiotics
- intraoperative diagnosis of a simple appendicitis
- intraoperative appendicular infiltration not amendable for appendectomy
- inadequate source control after appendectomy*;*the definition of adequate source control is given in the studyprotocol

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2017
Enrollment:	1066

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Flagyl
Generic name:	Metronidazole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rocephin
Generic name:	Ceftriaxone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zinacef
Generic name:	Cefuroxime
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2017

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24288
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-003428-21-NL
CCMO	NL59492.078.16

Register	ID
Other	NTR-6128
OMON	NL-OMON24288