Initial non-operative treatment strategy versus appendectomy treatment strategy for simple appendicitis in children aged 7-17 years old. APAC study

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To generate high quality empirical evidence for the effectiveness in terms of proportion of patients experiencing complications, quality of life and costs of initial non-operative treatment strategy (reserving appendectomies for those not responding...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON54710

Source
ToetsingOnline

Brief title
Initial non-operative treatment for acute simple appendicitis in children

Condition

- Gastrointestinal therapeutic procedures

Synonym
Appendicitis, inflamed appendix

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw

Intervention

Keyword: Antibiotics, Appendectomy, Appendicitis, Children

Outcome measures

Primary outcome

Primary (patient level): The proportion of patients experiencing complications within one year-follow up. An adjudication committee will be installed to review the complications.

Complications are defined as:

• Allergic reaction to antibiotics administered. In case an allergic reaction is suspected, the child will be referred to the allergist for further evaluation.

• Re-admission for an indication other than recurrent appendicitis but related to appendicitis (such as readmission for observation of fever or abdominal pain)

• Complications associated with appendectomy:

- Superficial Site infection

- Intra-abdominal abscess

- Stump leakage/stump appendicitis

- Secondary / prolonged Bowel Obstruction

- Anesthesia Related complications (such us pneumonia)

- Hernia cicatricalis

- Need for other surgical or radiological intervention than appendectomy but related to appendicitis (such as percutaneous drainage of an abscess, surgical intervention for a superficial site infection)

Secondary outcome

Number of days absent from school, social or sport events (patient-level)

Number of days absent from work (parents-level)

Total number of extra visits (not the already scheduled ones) to the outpatient clinic, general practitioners office or emergency department for abdominal pain.

Total length of hospital stay during the follow-up period for strategy related treatment or complications (An adjudication committee will be installed to review the length of hospital stay)

Total days of analgesics medication use

Proportion of patients with missed diagnosis of complex appendicitis with risk of peritonitis

Proportion of patients not having to undergone appendectomy

Proportion of patients experiencing recurrent appendicitis within one-year follow-up.

Recurrent appendicitis is defined as those patients with a clinical and radiological high suspicion of recurrent appendicitis who undergo an appendectomy and histopathological examination confirms the diagnosis of recurrent appendicitis

Proportion of patients experiencing early failure of initial non-operative treatment.

Early failure is defined as all patients that undergo an appendectomy during the antibiotic course (iv or oral) due to persistent complaints, clinical deterioration or faecolith.

Proportion of patients that undergo interval appendectomy.

Interval appendectomy is defined as those patients that undergo an appendectomy with a clinical and radiological low suspicion of recurrent appendicitis.

Histopathological examination shows no signs of recurrent appendicitis.

Quality of life measured by the validated CHQ-CF87, EQ-5d-Youth and EQ-5d-Proxy questionnaire.

Medical, non-medical and indirect costs at one year follow up of the treatment strategy (iMCQ and iPCQ, adjusted to the situation of child and parents)

QALY*s

Patient satisfaction measured by the NET PROMOTOR SCORE en validated Patient Satisfaction Questionnaire (PSQ)18.

Factors associated with implementability

Study description

Background summary

Initial non-operative treatment of acute simple appendicitis has recently been investigated in both the adult as the paediatric population. In the adult population, six RCTs showed that an appendectomy could be avoided in 40-76% of the patients at the end of their follow-up period. Despite the fact that some patients need to undergo a delayed appendectomy, it has been demonstrated in systematic reviews that non-operative treatment strategy is associated with a significant reduction in complications, faster recovery and return to work, less pain duration and analgesic medication consumption. In children only pilot data is yet available. Short-term success rates of this strategy (including of our own pilot cohort study) are between the 83-92%. Long-term results (one-year

follow-up) are available from two studies; 62-75% did not require an appendectomy. No large RCT have yet been conducted in the paediatric population. It is therefore essential to generate high quality empirical evidence regarding this strategy in this subset of patients.

Study objective

To generate high quality empirical evidence for the effectiveness in terms of proportion of patients experiencing complications, quality of life and costs of initial non-operative treatment strategy (reserving appendectomies for those not responding or with recurrent disease), compared with appendectomy strategy in children, 7 and 17 years old, with acute simple appendicitis.

Study design

A national unblinded multi-centre non-inferiority randomized controlled trial with a 1:1 block randomization stratified by hospital will be performed. (academic en non-academic)

Intervention

Intervention group (Non-operative treatment strategy): Clinical observation for 48 hours with administration of Intravenous administration of amoxicillin/clavulanic acid 25/2.5mg 6-hourly (total 100/10 mg/kg daily; maximum 6000/600mg a day) and gentamicin 7mg/kg once daily for 48 hours. If after 48 hours the patient fulfils the predefined discharge criteria, the antibiotics will be switched to oral amoxicillin/clavulanic acid 50/12.5 mg/kg 8-hourly (max 1500/375mg a day) for in total 7 days and discharge. An appendectomy is reserved for those patients with clinical deterioration, non-improvement after 72 hours or recurrent appendicitis.

Control group (Operative treatment strategy): Clinical observation and semi-urgent appendectomy. Pre-, peri- and postoperative care according to local protocol. No routine postoperative antibiotics. Discharge if the patient fulfils the predefined discharge criteria.

Study burden and risks

1. Risks of participation:
- Specific non-operative treatment strategy: possible need for delayed operation (10-25%), recurrent appendicitis (10%).
- Both strategies: Allergic reaction to antibiotics (<1%), known appendectomy associated complications (5-10%).
2. Burden of participation:
- Specific non-operative treatment strategy: Extra admission day (in comparison with appendectomy), ultrasonography after 48 hours (extra non-invasive

procedure), Blood samples after 24 and 48 hours for determination of C-reactive protein / Leucocytes (2x extra a 1 cc). Blood samples will be obtained through the already placed IV access. In case this is not successful, an extra venapunction will be performed.
- Both strategies:
• Telephone interviews/Email (3x5minutes=15 minutes).
* Filling out questionnaires (1x only QOL, 4x QOL, iMCQ and iPCQ, adjusted to the situation of child and parents
, PSQ-18, net promotor scale). Duration of filling out questionnaires:
QOL: 10 minutes (5x10=50 minutes)
iMCQ and iPCQ: 10 minutes (3x10=30 minutes)
PSQ/Net premotor scale: 5 minutes (4x5=20 minutes)
Total time per participant in one year follow up: 100 minutes
3.Benefit of non-operative treatment strategy: Avoidance of surgery (75-90%) and its related early and late morbidity, potential better quality of life.

The risk and burden are minimised although in order to improve safety, some extra procedures are necessary.

External monitoring and a DMC will be installed in order to improve patient safety.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Eligible for inclusion are all children from 7 to 17 years old, inclusive, with a radiologically confirmed simple appendicitis. Definition of simple appendicitis is based upon predefined clinical, biochemical and radiological (ultrasound) criteria.
Clinical & biochemical criteria:
- Unwell but not generally ill
- Localized tenderness in the right iliac fossa region
- Normal/hyperactive bowel sounds
- No guarding or palpable mass
- Biochemical signs of infection (Elevated White Blood Cell count (WBC) and/or C-reactive protein (CRP)).
As recommended by the national guideline, all children with a clinical and/or biochemical suspicion should undergo ultrasound studies. Ultrasound criteria to confirm the diagnosis of acute simple appendicitis are:
- An incompressible, painful appendix with an outer diameter > 6 mm
- Secondary signs of inflammation such as surrounding fat infiltration, limited clear free fluid surrounding the appendix, hyperemia within the appendiceal wall.
- No fecolith, no signs of perforation, no signs of intra-abdominal abscess or phlegmone.
In case the ultrasound is inconclusive, additional imaging studies may be obtained. CT-scan is not recommended in the young children (due to its risk of radiation induced malignancy). MRI is recommended in those places with sufficient experience in the interpretation of the results. Only those in whom imaging studies confirm the diagnosis of simple appendicitis can be included.
In case there is no certain diagnosis and a *watchful waiting* strategy is chosen, the patient cannot be included.

Exclusion criteria

Exclusion criteria:
• Generalized peritonitis, complex appendicitis or sepsis (based upon predefined criteria and scoring system).
Scoring system: As scoring system was developed determining the risk of

complex appendicitis based upon five pre-operative variable. Points have been awarded to each variable. In case the total score is less than 4 points, the patient is likely to have a simple appendicitis. In case the score is 4 or more points, the chance of having complex appendicitis is significant and those children will be excluded from this study. Variables:
Diffuse abdominal guarding (3 points)
CRP level more than 38 mg/L (2 points)
Signs on ultrasound indicative of complex appendicitis (2 points)
More than one day abdominal pain (2 points)
Temperature: more than 37.5 degree Celsius (1 point)
• Fecolith (ultrasound)
• Serious co-morbidity
• Recurrent appendicitis
• Suspicion of an underlying malignancy or inflammatory bowel disease
• Documented type 1 allergy to the antibiotics used.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-01-2017
Enrollment:	302
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Amoxicillin/Clavulanic acid

Generic name:	Amoxicillin/Clavulanic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gentamicine
Generic name:	Gentamicine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
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Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	01-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003052-70-NL
ClinicalTrials.gov	NCT02848820
CCMO	NL56792.018.16