Clinical trial results:
Antibiotic treatment alone for children with acute appendicitis; a prospective cohort study part of the Antibiotic versus Primary Appendectomy for Children with acute appendicitis; the APAC trial.

Summary

EudraCT number	2011-004495-12
Trial protocol	NL
Global end of trial date	10 January 2017

Results information

Result version number	v1 (current)
This version publication date	14 July 2021
First version publication date	14 July 2021
Summary attachment (see zip file)	Study rapport APAC pilot study (Clinical study report 2 Final.docx)

Trial information

Trial identification

Sponsor protocol code	KCA2011/APAC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01356641
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VU University medical center
Sponsor organisation address	de Boelelaan 1117, Amsterdam, Netherlands, 1081HV
Public contact	Ramon Gorter, VU University medical center, 0031 204442424, rr.gorter@vumc.nl
Scientific contact	Ramon Gorter, VU University medical center, 0031 204442424, rr.gorter@vumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2017
Global end of trial reached?	Yes
Global end of trial date	10 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To investigate the feasibility of a non inferiority multicenter randomized controlled trial, in order to evaluate the cost -effectiveness of initial antibiotic treatment strategy compared to appendectomy in The Netherlands?
2. To evaluate the safety and outcome (in terms of complications) of initial antibiotic treatment strategy for children aged 7-17 years with simple appendicitis.

Protection of trial subjects:

Multiple gastrointestinal infections including appendicitis (with the most severe types) can be treated with antibiotics. The medication used in this study (augmentin/gentamicin) are already registered for this indication. However for protection of the trial subjects several measurements were taken into account in the protocol:
1. Patients were admitted to the paediatric (surgical) ward for intensive (clinical and biochemical) monitoring in order to detect clinical deterioration at an early stage
2. After 48 hours an additional ultrasound was performed in order to make sure, no signs of complex appendicitis were missed
3. After reconsideration, it was decided to make small protocol modicifications such as an reduction of the restriction on oral intake and length of hospital stay in order to minimise discomfort with patients and parents

Background therapy:

All patients participating in this study and undergoing the initial antibiotic treatment strategy were administered besides the antibiotics the following medications:

Diet; during the first 12 hours, no oral intake was permitted.
Intravenous administration of fluids (Dextrose 3.75% with Sodium chloride 0,225% 0-10 kg 100 ml/kg
10-20 kg 50 ml/kg extra
>20 kg 20 ml/kg
For instance when a child weighs 20 kilogram the daily intake should be 10x100ml + 10x50 ml 1.5 litre

Own medication: patients were allowed to use their regular prescribed medication.

Pain medication (common practice): According to the local pain protocol of the Paediatric surgical centre, management of pain consisted of the following medication (doses adjusted to the www. kinderformularium.nl):
Acetaminophen (i.v.) Start dose: 20 mg/kg. Afterwards: 60 mg/kg/day (in 4 doses)
Acetaminophen (rectal) Start dose: 40 mg/kg. Afterwards: 90 mg/kg/day (in three doses)
Diclofenac 1-3 mg/kg/day (in 3 doses)
Morphine (rectal) 1.2-2.4 mg/kg/day (in 6 doses)
Morphine (I.v.) Start dose: 0.1 mg/kg (in 10 minutes. Afterwards continuous administration. Dose:0.25 mg/kg/day

In most cases, acetaminophen either intravenously or rectally, was administered. When this turned out to be inadequate (defined as a VAS score > 4), additional pain medication could be given following a step-up/step down principle, starting with diclofenac and in addition morphine. When the VAS score became < 4, attempts were made to remove additional pain medication.

Evidence for comparator:

All patients participating in this study underwent the initial antibiotic treatment strategy. It was decided (later on the study) that eligible patients not participating in this study will form a control group in the future.

Actual start date of recruitment	01 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	11
Adolescents (12-17 years)	39
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at the emergency departments of the participating hospitals. Information regarding this pilot study was provided to the child as well as their legal guardians (age specific information letters). Verbal explanation by treating physician. Informed consent after confirmation of diagnosis

Pre-assignment

Screening details:

Inclusion criteria:
- Age 7-17 years
- Radiologically confirmed simple appendicitis

Exclusion criteria
- Generalized peritonitis / severe sepsis / complex appendicitis
- Faecalith / associated conditions / allergy.

Screened:
N= 278
Excluded:
N= 228
a. Complex (138)
b. No ultrasound (33)
c. No IC (57)
Included:
N=50

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Initial Antibiotic Treatment strategy

Arm description:

1. Admission of patients under paediatric surgical responsibility and
2. Administration of intravenous antibiotics (amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (total 100/10mg/kg daily; maximum doses: 6000/600mg a day) and gentamicin 7mg/kg once daily) for the first 48 hours (Appendix 13.4 &13.5).
3. intravenous administration was continued.

If administration was changed to oral antibiotics, the patient was discharged (maximum doses: 1500/375mg a day) (for a total of seven days).

Arm type	Experimental
Investigational medicinal product name	Amoxicillin/clavulanic acid
Investigational medicinal product code	
Other name	Augmentin
Pharmaceutical forms	Concentrate for solution for injection/infusion, Concentrate for oral suspension
Routes of administration	Intravenous use, Enteral use

Dosage and administration details:

Intravenous administration of amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (total 100/10 mg/kg daily; maximum doses 6000/600 mg a day) 48 hours

Gentamicin 7 mg/kg once daily iv 48 hours

Oral amoxicillin/clavulanic acid 50/12,5 mg/kg in three times (maximum doses: 1500/375mg a day) for a total of 5 days.

Total duration of antibiotic treatment: 7 days

Rationale for this treatment and doses were based upon the SPC from the antibiotics administered and in line with doses reported on www.kinderformularium.nl

Investigational medicinal product name	Gentamicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gentamicin 7 mg/kg once daily iv for 48 hours

Rationale for this treatment and doses were based upon the SPC from the antibiotics administered and in line with doses reported on www.kinderformularium.nl

Number of subjects in period 1	Initial Antibiotic Treatment strategy
Started	50
Completed	49
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age distribution is displayed as Median (Min-Max)			
Units: years			
median	13		
full range (min-max)	7 to 17	-	
Gender categorical			
As mentioned, 1 patients withdrawn their informed consent, therefore only 49 patients are displayed			
Units: Subjects			
Female	29	29	
Male	21	21	
Duration of pain (days)			
The number of days with abdominal pain before start of the initial antibiotic treatment strategy			
Units: Days			
median	1		
full range (min-max)	1 to 5	-	
Temperature			
Temperature in degree celsius at time of presentation at the ER/Ward			
Units: Degree Celsius			
median	37.3		
full range (min-max)	36.0 to 39.1	-	
Weight			
Weight in kilogram			
Units: Kilogram			
median	46.1		
full range (min-max)	26.0 to 95.0	-	
CRP			
Level of CRP at time of presentation			
Units: mg/L			

median	29.0		
full range (min-max)	1.0 to 168.0	-	
Leucocytes			
Level of leucocytes at time of presentation			
Units: x10^9/L			
median	12.7		
full range (min-max)	5.7 to 19.9	-	
Diameter appendix			
Estimated diameter of the appendix at the initial ultrasound			
Units: cm			
median	9.0		
full range (min-max)	6.0 to 22.0	-	

Subject analysis sets

Subject analysis set title	Initial non-operative treatment strategy
Subject analysis set type	Full analysis

Subject analysis set description:

A total of 49 children aged between 7-17 years old with radiological proven simple appendicitis, who have been treated with the initial antibiotic treatment strategy as part of the pilot study.

Reporting group values	Initial non-operative treatment strategy		
Number of subjects	49		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age distribution is displayed as Median (Min-Max)			
Units: years median full range (min-max)			
Gender categorical			
As mentioned, 1 patients withdrawn their informed consent, therefore only 49 patients are displayed			
Units: Subjects			
Female	29		
Male	20		
Duration of pain (days)			
The number of days with abdominal pain before start of the initial antibiotic treatment strategy			
Units: Days median full range (min-max)			
Temperature			

Temperature in degree celsius at time of presentation at the ER/Ward			
Units: Degree Celsius median full range (min-max)			
Weight			
Weight in kilogram			
Units: Kilogram median full range (min-max)			
CRP			
Level of CRP at time of presentation			
Units: mg/L median full range (min-max)			
Leucocytes			
Level of leucocytes at time of presentation			
Units: x10^9/L median full range (min-max)			
Diameter appendix			
Estimated diameter of the appendix at the initial ultrasound			
Units: cm median full range (min-max)			

End points

End points reporting groups

Reporting group title	Initial Antibiotic Treatment strategy

Reporting group description:

1. Admission of patients under paediatric surgical responsibility and
2. Administration of intravenous antibiotics (amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (total 100/10mg/kg daily; maximum doses: 6000/600mg a day) and gentamicin 7mg/kg once daily) for the first 48 hours (Appendix 13.4 &13.5).
3. intravenous administration was continued.
If administration was changed to oral antibiotics, the patient was discharged (maximum doses: 1500/375mg a day) (for a total of seven days).

Subject analysis set title	Initial non-operative treatment strategy
Subject analysis set type	Full analysis

Subject analysis set description:

A total of 49 children aged between 7-17 years old with radiological proven simple appendicitis, who have been treated with the initial antibiotic treatment strategy as part of the pilot study.

Primary: Percentage of patients willing to participate

End point title	Percentage of patients willing to participate[1]

End point description:

In the result section, we are displaying the percentage of patients willen to participate including a 95% CI.
In total 49/108 patients were willing to participate: 45% 95%CI: 37-55%

End point type	Primary

End point timeframe:

Start of the study - till inclusion of the 50th patient

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50[2]	49		
Units: Percentage				
number (confidence interval 95%)	46 (37 to 55)	45 (37 to 55)		

Notes:

[2] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with an appendectomy

End point title	Number of patients with an appendectomy[3]

End point description:

Number of patients who underwent an appendectomy during the one year follow up after the initial start of the initial non-operative treatment strategy. .

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[4]			
Units: Number	10	10		

Notes:

[4] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patient who underwent an appendectomy for histological proven recurrent appendicitis

End point title	Number of patient who underwent an appendectomy for histological proven recurrent appendicitis[5]

End point description:

Number of patients who underwent an appendectomy for the recurrent appendicitis that was proven by histological examination

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[6]	49		
Units: Number of patients	5	5		

Notes:

[6] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patient with complications

End point title	Number of patient with complications[7]

End point description:

Number of patients that suffered from complications.

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[8]	49		
Units: Number of patients	15	15		

Notes:

[8] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients who underwent an appendectomy during initial treatment (early failure)

End point title	Number of patients who underwent an appendectomy during initial treatment (early failure)[9]

End point description:

Number of patients that underwent an appendectomy during the initial treatment with antibiotics due to clinical deterioration(early failure).

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[10]	49		
Units: Number	4	4		

Notes:

[10] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with post-appendectomy complications

End point title	Number of patients with post-appendectomy complications[11]

End point description:

Number of patients who suffered from a post-appendectomy complication.

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[12]	49		
Units: Number	3	3		

Notes:

[12] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients undergoing interval appendectomy

End point title	Number of patients undergoing interval appendectomy[13]

End point description:

Number of patients that underwent an interval appendectomy based upon request of parents

End point type	Primary

End point timeframe:

Inclusion - One year follow up

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are displayed

End point values	Initial Antibiotic Treatment strategy	Initial non-operative treatment strategy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49[14]	49		
Units: Numer	1	1		

Notes:

[14] - 1 withdrew consent

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for reporting adverse events was from inclusion - one year follow up.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Initial non-operative (antibiotic) treatment group

Reporting group description:

Children aged 7-17 years old with a radiological proven simple appendicitis.

Serious adverse events	Initial non-operative (antibiotic) treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 49 (24.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Delayed appendectomy	Additional description: Number of patients who underwent an appendectomy due to failure of the initial non-operative treatment strategy, recurrent appendicitis and/or interval appendectomy		
subjects affected / exposed	10 / 49 (20.41%)		
occurrences causally related to treatment / all	10 / 10		
deaths causally related to treatment / all	0 / 0		
Post appendectomy abscess			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Fever eci	Additional description: Number of patients that were readmitted for fever e.c.i. (after appendectomy for non improvement, recurrent appendicitis or interval appendectomy)		
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Number of patients who were readmitted to the hospital due to gastroenteritis		

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash due to allergic reaction	Additional description: Number of patients who developed rash after antibiotic administration		
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Initial non-operative (antibiotic) treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 49 (20.41%)		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Gastroenteritis without the need for readmission		
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Abdominal pain	Additional description: Number of patients with abdominal pain e.c.i. after the initial non-operative treatment strategy for which patients visited the ER or outpatient clinic		
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Obstipation	Additional description: Number of patients treated for obstipation after the initial non operative treatment strategy		
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary tract infection	Additional description: Number of patients with an UTI needing antibiotics after the initial nonoperative treatment strategy		
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Product issues			
Higher dose of augmentin			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	Increasing the number of participating centers AMC: 21-08-2012
03 September 2012	Increasing the number of participating centers RKZ: 03-09-2012
16 July 2013	Expanding age group: Based upon preliminary results it was decided to expand our inclusion group (starting with 12-17 year old children) to 7-17 year old children. This was decided to increase generalizability and due to the fact that based upon interim descriptive methods, it was shown that this strategy was safe in the 12-17 age group (N=10). Date: 16-07-2013
04 September 2013	Increasing the number of participating centers Flevoziekenhuis: 04-09-2013
13 October 2014	Reducing the duration of the clinical phase: Based upon results from our interim analyses (N=25) it was decided to discharge the patients if they fulfilled the discharge criteria after 48 hours instead of monitoring them for another 24 hours in-hospital. Date: 13-10-2014 Reducing the duration of the "no oral intake" period: Based upon results of our interim analysis (N=25) it was decided to reduce the " no oral intake" period from 24 hours to 12 hours. Date: 13-10-2014
13 October 2014	Proposal was made to use the eligible patients who did not wanted to undergo the initial non-operative treatment protocol as a control group in the future (also those eligible in the past). This protocol was implemented in February 2015 (last inclusion was on 24-11-20-15) Then 50th patient undergoing the initial nonoperative treatment strategy was included since the start of the study and inclusion was stopped as per protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1. Small patient group
2. Only patients who underwent the initial non-operative treatment strategy

Notes: