PEANUTS 2 RESEARCH PROTOCOL

(March 2015)

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The use of PErioperative ANtibiotic prophylaxis in the treatment of acUte cholecysTitiS 2, a randomized, multicenter, open-label, non-inferiority trial

Protocol ID	PEANUTS 2
Short title	Perioperative antibiotic prophylaxis in the treatment of acute cholecystitis
EudraCT number	2015-001536-38
Version	2.0
Date	17-09-2015
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Laboratory sites <*if applicable*>	NA
Pharmacy <*if applicable*>	NA

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor or legal representative: ***<please include name and function>*** ***<For non-commercial research,>*** **Head of Department:** ***<include name and function>***	NA	
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale

It is current practice to administer a single prophylactic dose of intravenous antibiotics, 15-30 minutes prior the incision, in patients who undergo an *emergency* cholecystectomy. In current literature, high level evidence is available that in patients undergoing *elective* cholecystectomy for *uncomplicated* cholelithiasis, prophylactic antibiotics do not decrease the incidence of postoperative infections. Recent studies, as well as our own data, show that *extended* treatment with antibiotic prophylaxis doesn't benefit the outcome in terms of surgical site infections and does increase duration of hospital stay and costs. Furthermore the use of unnecessary antibiotics leads to an increased resistance to antibiotics. The remaining question is whether even a single dose antibiotic prophylaxis is beneficial in patient with acute cholecystitis who undergo laparoscopic cholecystectomy.

Objective

This study is designed to demonstrate whether or not patients who undergo cholecystectomy for acute calculous cholecystitis, benefit from preoperative antibiotic prophylaxis

Study design

A randomized controlled, multicenter, open-label non-inferiority trial

Study population

All patients with acute calculous cholecystitis undergoing emergency cholecystectomy over 18 years of age.

Intervention

A. No antibiotic treatment

B. A single dose of 2000 mg of cefazolin, 15-30 minutes prior to surgery

Main study parameters/endpoints

The primary outcome measure is the development of postoperative infections (surgical site and distant infections) within 30 days after surgery. Secondary endpoints are the individual infections, other postoperative complications, duration of hospital stay and total costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

If this study demonstrates that omitting antibiotic prophylaxis does not increase the infection rate, it's use for this indication can be dropped as a whole and the guidelines will be adapted. Then, the role of antibiotic prophylaxis in the entire upper gastrointestinal tract surgery becomes eminent. A decrease of use of antibiotics on such a scale may result in a large decrease of needless medical activities, costs and bacterial resistance.
If omitting antibiotic prophylaxis should be unjust, an infection that could have been prevented by antibiotic prophylaxis may occur. A distant infection requires antibiotic treatment, a surgical site infection may require opening of the wound or percutaneous drainage of an intra-abdominal abscess. All procedures in this study are part of the normal medical treatment for acute cholecystitis, no extra (invasive) procedures or laboratory tests will be performed. Patient will be seen at the outpatient clinic one week postoperative and will be called to answer questions, four weeks after surgery.

1. INTRODUCTION AND RATIONALE

Introduction

Acute calculous cholecystitis is the third most frequent cause of emergency admissions to surgical wards (ref.1). The standard treatment is cholecystectomy. In the United States, approximately 750.000 cholecystectomies are performed each year and 150.000 of these operations are due to acute calculous cholecystitis (ref.2). In the Netherlands, approximately 21.000 cholecystectomies are performed each year (ref.3). Surgical site infections are the most common complications after laparoscopic cholecystectomy (ref.4).

It is current practice to administer a single prophylactic dose of intravenous antibiotics, 15-30 minutes prior the incision, and often to continue antibiotic treatment postoperatively for several days. The rationale for the administration of antibiotic agents perioperatively is the probable decrease of postoperative infectious complications. The Dutch Working group on Antibiotic Policy (SWAB, Stichting Werkgroep Antibiotica Beleid. www.swab.nl) recommends antibiotic prophylaxis for surgical procedures with an intermediate (5-10%) or high risk of postoperative infections, based on the wound classification by Mayhall (ref.5,6). Surgery of the biliary tract (elective and emergency) is classified as intermediate risk and subsequently antibiotic prophylaxis is advised (ref.7). The Dutch guidelines for Gallstone Disease (ref.3) do not offer an opinion regarding the use of perioperative antibiotic prophylaxis in (elective or emergency) gallbladder surgery. Still, in current literature high level evidence is available that in patients undergoing *elective* cholecystectomy for *uncomplicated* cholelithiasis, prophylactic antibiotics do not decrease the incidence of postoperative infections (ref.8,9). The use of antibiotic prophylaxis in *elective* cholecystectomy is therefore discouraged and not general practice.

Whether antibiotic prophylaxis is beneficial in case of *emergency* cholecystectomy for acute cholecystitis remains unclear. It is plausible that the inflammatory process could be a predisposing risk factor for the development of infectious complications (ref.10,11).Until now, the decision whether or not to use antibiotic prophylaxis and for how long (a single preoperative dose or also postoperative continuation), is largely dependent on the opinion of the individual surgeon and thus extremely variable, due to the lack of evidence (ref.12). In recent years, more evidence has become available on the subject. In a large retrospective nationwide Swedish study among 13.911 patients with acute cholecystitis undergoing cholecystectomy, the authors suggest that antibiotic prophylaxis provides no benefit in preventing postoperative infections (ref.13). Very recently, a large (and first) prospective randomized trial was conducted among 414 patients undergoing cholecystectomy for acute cholecystitis (ref.4). Patients were randomized between single preoperative antibiotic dose alone versus preoperative dose *and* postoperative continuation for five days. This

prospective evidence demonstrated that extended postoperative antibiotics after cholecystectomy for acute calculous cholecystitis, does not reduce the postoperative infection rate. During the same years we conducted a similar, multicenter, randomized controlled trial, comparing a single preoperative dose of antibiotic with a single preoperative dose *and* postoperative continuation for 3 days (PEANUTS trial, ref 14). Since the last patient of this trial was only randomized very recently, the results have not been published yet. However, the results are the same: postoperative prolonged antibiotic treatment does not lead to a decrease in infection rate and may therefore be omitted. The remaining question is whether even a single dose antibiotic prophylaxis is necessary in these patients. Unnecessary use of antibiotics leads to needless medical activity and costs and an increased resistance to antibiotics. According to the WHO, antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections (ref.15). It is an increasingly serious threat to global public health that requires action across all government sectors and society. Bacterial resistance is a serious and growing issue in contemporary medicine and has emerged as one of the eminent public health concerns nowadays. On the European Antibiotic Awareness Day (18 November 2014), the Dutch minister of Health, Edith Schippers, warned for antibiotic resistance as a global threat to the treatment of bacterial infectious diseases (ref.16).
Therefore, the benefit of antibiotic prophylaxis in acute cholecystectomy needs to be assessed. We aim to conduct a randomized controlled, multicenter, open-label, non-inferiority trial, comparing single dose antibiotic prophylaxis and no prophylaxis in patients who undergo cholecystectomy for acute cholecystitis.

Concrete revenues
High level evidence about the efficacy of perioperative antibiotic treatment in patients undergoing cholecystectomy is needed to formulate solid recommendations in national and international guidelines. If this study demonstrates that omitting antibiotic prophylaxis does not increase the infection rate, the use of perioperative antibiotic for this indication can be dropped as a whole and the guidelines will be adapted. Even the role of antibiotic prophylaxis in the entire upper gastrointestinal tract surgery becomes eminent. A decrease of use of antibiotics on such a scale may result in a large decrease of needless medical activities, costs and bacterial resistance. By reducing the use of antibiotics, future treatment of infections by first-line antibiotics will probably be more effective. This will reduce or prevent multiple admissions to the general practitioner or even to the hospital when first-line antibiotic treatment fails, thereby necessitating the use of second-line agents.

2. OBJECTIVES

To provide high level of evidence that omitting perioperative antibiotic prophylaxis does not increase the postoperative infection rate, in patients with acute calculous cholecystitis undergoing laparoscopic cholecystectomy. The primary outcome measure is the development of postoperative infections (surgical site and distant infections) within 30 days after surgery. Secondary endpoints are the individual infections, other postoperative complications, duration of hospital stay and total costs.

3. STUDY DESIGN

A randomized controlled, multicentre, open-label, non-inferiority trial.
Patients will be randomly allocated to:

- No antibiotic treatment
- A single dose of 2000 milligrams of first generation cephalosporin, 15-30 minutes prior to surgery.

Randomization will be done online with random permutated block sizes with ALEA randomization program. The study will be conducted in multiple high volume, non-university teaching hospitals. Expected inclusion will take 36 months.

4. STUDY POPULATION

4.1 Population (base)

All patients aged 18 years or older, with acute calculous cholecystitis, will be checked for eligibility. In order to be eligible to participate in this study, a subject must meet all of the criteria listed below.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Acute calculous cholecystitis, defined as mild or moderate according to Tokyo Guidelines (ref.17)
- Cholecystectomy
- Written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- < 18 years of age
- Acalculous cholecystitis
- Acute calculous cholecystitis, defined as severe according to Tokyo Guidelines (ref.17)
- Patients who received antibiotic treatment on admission
- Proven allergy to cefazoline
- Pregnancy
- Immune compromised patients
- Indication for endoscopic retrograde pancreaticocholangiography (ERCP) on admission

Definitions

Diagnostic criteria for cholecystitis (ref.17)

***A**. Local signs of inflammation etc.:*

(1) Murphy's sign,

(2) Right upper abdominal quadrant mass/pain/tenderness

***B**. Systemic signs of inflammation etc.:*

(1) Fever,

(2) elevated C-reactive protein

(3) elevated white blood cell count

***C**. Imaging findings:*

Imaging findings characteristic of acute cholecystitis

Definitive diagnosis of cholecystitis: *One item in A and one item + one item in B* + C

Suspected diagnosis of cholecystitis: *One item in A and one item + one item in B*

Severity grading for cholecystitis (ref.17)

- *Severe (Grade III) acute cholecystitis*

  Associated with dysfunction of any of the following organs/systems:

  1. Cardiovascular dysfunction (Hypotension requiring treatment with dopamine > 5µg/kg per min, or any dose of norepinephrine)
  2. Neurological dysfunction (Decreased level of consciousness)
  3. Respiratory dysfunction (PaO_2/FiO_2 ratio < 300)
  4. Renal dysfunction (Oliguria, creatinine > 2.0mg/dl)
  5. Hepatic dysfunction (PT-INR > 1.5)
  6. Hematological dysfunction (Platelet count < 100.000/mm^3)

- *Moderate (Grade II) acute cholecystitis*

  Associated with any one of the following conditions:

  1. Elevated white blood cell count (>18.000/mm^3)
  2. Palpable tender mass in the right upper abdominal quadrant
  3. Duration of complaints > 72 h
  4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

- *Mild (Grade I) acute cholecystitis*

  Does not meet the criteria of 'Severe' of 'Moderate' acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder.

4.4 Sample size calculation

Incidence of the primary endpoint

Sample size calculations are preferably made based on data from previous studies, especially randomized controlled trials, or at least prospective cohort studies. In the only published prospective study on the subject of perioperative antibiotics in patients undergoing cholecystectomy for acute cholecystitis, a postoperative infection rate of 17% was seen (ref.4).

Calculations

We assume a noninferiority margin of 10%. This margin is based on recommendations from the US Food and Drug Administration, who recommend 10% for anti-infective trials.

The clinical relevance of this margin is based on the Altemeier classification of cholecystectomy for which the expected postoperative infection rate is between 10% and 20% without antibiotics (ref.4). With a 1-sided risk of 2.5% and a power of 80%,a total of 454 (2x 227) patients in both groups are required.

Feasibility

An average of 30 patients with acute calculous cholecystitis are admitted to a large Dutch teaching hospital on a yearly basis. Assuming that 50% of patients will meet our inclusion criteria and give informed consent for randomization, approximately 15 patients per hospital remain for inclusion per year. With an expected loss to follow up of 15%, approximately 12 patient per hospital will be included in the trial each year. Fourteen hospitals (listed below) will participate in this study which results in an inclusion of 178 patients per year. The needed number of 454 patients will be reached within three years. The follow up duration is 30 days. Hereafter, the data-analysis and reporting will start and is planned to be finished 5 months later. The total duration of the study is 3.5 years.
To ascertain inclusion rates will be met, every six months the number of included patients will be analyzed and if necessary additional hospitals will be asked to join. Since this study does not implement new techniques or treatment, and perioperative antibiotic treatment is variably used in current surgical practice, no delay in study time is expected.

Participating hospitals

1. St. Antonius Ziekenhuis, Nieuwegein
2. Academisch Medisch Centrum, Amsterdam
3. Onze Lieve Vrouwe Gasthuis, Amsterdam
4. Gelre Ziekenhuizen, Apeldoorn
5. Tergooi Ziekenhuis, Hilversum
6. Ziekenhuis Rivierenland, Tiel
7. Zuwe Hofpoort Ziekenhuis, Woerden
8. Isala kliniek, Zwolle
9. Medisch Spectrum Twente, Enschede
10. TweeSteden ziekenhuis, Tilburg
11. Rijnstate Ziekenhuis, Arnhem
12. Catharina Ziekenhuis, Eindhoven
13. Ziekenhuis Gelderse Vallei, Ede
14. Albert Schweitzer ziekenhuis, Dordrecht

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will be allocated to:

A. No antibiotic prophylaxis, prior to surgery.

B. A single dose of 2000 milligrams of first generation cephalosporin intravenously administered, 15-30 minutes prior to surgery.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

All patients will be admitted postoperatively and will only receive intravenous fluids and/or analgesics if needed. Patients are allowed to use their own prescription drugs and pain medication. Antibiotic therapy is administered in case of a postoperative infection requiring antibiotic treatment according to the standard of care. Patients will be discharged, mostly after one day, based on their clinical condition. There are no dietary limitations.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Patients will be allocated to:

A. No antibiotic prophylaxis, prior to surgery.

B. A single dose of 2000 milligrams of first generation cephalosporin intravenously administered by a anesthesiologist, 15-30 minutes prior to surgery. The trade name of cefazolin is Kefzol.

6.2 Summary of findings from non-clinical studies

The Summary of Product Characteristics (SPC) of cefazolin is added as a supplement.

6.3 Summary of findings from clinical studies

The SPC of cefazolin is added as a supplement.

6.4 Summary of known and potential risks and benefits

The SPC of cefazolin is added as a supplement.

6.5 Description and justification of route of administration and dosage

2000 milligrams first generation cephalosporin (cefazolin) will be dissolved in 20mL water and will be administered intravenously.

6.6 Dosages, dosage modifications and method of administration

Cefazolin 2000 milligrams, powder for solution for injection

6.7 Preparation and labelling of Investigational Medicinal Product

Labelling of the IMP is unnecessary since cefazolin will be administered as a single dose, at the holding or operation room, by an anesthesiologist. Labelling of the IMP in the non-treatment arm is not applicable.

6.8 Drug accountability

Cefazolin is a registered product, and currently used as antibiotic prophylaxis in all hospitals involved in this study. Therefore, no Disciplinary Action Form (DAF) is required for this trial.

The anaesthesiologist prepares and administers the antibiotic prophylaxis at the holding or operation room, prior to surgery. The anaesthesiologist always writes down the type

and dosage of the administered antibiotic, and the way and time of administration in the electronic medical record. This is current standard of care. In this way, the exact information about the preoperative antibiotic prophylaxis (cefazoline), or no antibiotic prophylaxis, can be verified later by the coordinating investigator.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint is a composite endpoint consisting of all postoperative infectious complications, within 4 weeks postoperative. This endpoint is designed to prove that omitting antibiotic treatment does not lead to an increase in postoperative infections in comparison to a single prophylactic preoperative dose of antibiotics. The diagnosis of a postoperative infection is based on clinical, biochemical, or morphological features and is confirmed, if possible, by bacteriological data. The majority of surgical site infections become apparent within 30 days of an operative procedure and most often between the 5th and 10th postoperative days (ref.34). Therefore, the presence or absence of postoperative infections will be systematically checked by either a senior resident, fellow or attending surgeon at the outpatient clinic, one week postoperative, and four weeks postoperative by the study investigators by telephone. A successful outcome is defined as the absence of postoperative infections.

Definitions

Postoperative infections can be divided in two groups: surgical site infection and distant infections.

Surgical site infections

According to The Centers for Disease Control and Prevention (CDC), a surgical wound/site infection is defined by the following criteria (ref.39):

- Infection must occur within 30 days of the surgical operation.
- And at least one of the following is present:
    - Purulent discharge from the surgical site
    - Purulent discharge from wound or drain placed in wound
    - Organisms isolated from aseptically obtained wound culture
    - Must be at least one of the signs and symptoms of infection; pain or tenderness, localised swelling, or redness/heat.

Surgical site infections frequently only affect the superficial tissues, but some more serious infections affect the deeper tissues or other parts of the body manipulated during the procedure. The Centers for Disease Control and Prevention (CDC) describes three levels of surgical site infections (ref.39):

● *Superficial incisional*, affecting the skin and subcutaneous tissue. These infections may be indicated by localised signs such as redness, pain, heat or swelling at the site of the incision or by the drainage of pus.
● *Deep incisional*, affecting the fascial and muscle layers. These infections may be indicated by the presence of pus or an abscess, fever with tenderness of the wound, or a separation of the edges of the incision exposing the deeper tissues.
● *Organ or space infection*, which involves any part of the anatomy other than the incision that is opened or manipulated during the surgical procedure. These infections may be Indicated by the drainage of pus or the formation of an abscess detected by histopathological or radiological examination or during re-operation.

Distant infections
Distant infections includes pneumonia (defined as coughing or dyspnoea, radiography with infiltrative abnormalities, elevated infection parameters, confirmed by positive sputum culture), urinary infections (presence of clinical symptoms and biological inflammatory syndrome associated with a positive urinary cytology), bacteraemia (presence of ≥1 positive hemoccult to the same pathogen)

8.1.2 Secondary study parameters/endpoints (if applicable)
Secondary endpoints are the individual infections of the composite endpoint,all other postoperative complications, duration of hospital stay and total costs (a budget impact model will be used to estimate the financial consequences of the absence of antibiotic prophylaxis) within 30 days postoperatively. The definitions of the individual components are displayed in table 1.

8.1.3 Other study parameters (if applicable)
Not applicable

8.2 Randomisation, blinding and treatment allocation
Randomization will be done online (nl.tenalea.net/ALEA/amc) with random permutated block sizes. Neither the patient nor the surgeon will be blinded for the intervention. A non-blinded approach is chosen because most emergency cholecystectomies are performed by senior residents (supervised by an attending surgeon on duty) during evening-, night-, and weekend shifts, which means the patients will generally be seen at the outpatient clinic by any possible surgeon, who will determine the presence of postoperative infections based on subjective measurements.

8.3 Study procedures

Anonymous study number

Each patient will receive an anonymous study number.

Procedure

Preoperative

On admission at the emergency department, blood is collected for testing. The apache-II score (see appendix I) of each patient will be calculated and the grade of severity of the acute cholecystitis (mild, moderate, severe) will be assessed according to the Tokyo guidelines (ref.17). A potential subject who meets all of the inclusion criteria as mentioned before, will be asked to participate in this study. A potential subject who meets any of the exclusion criteria will be excluded. Prior to surgery, the patient will be randomized online with random permutated block sizes with ALEA randomization program. Patients will receive no antibiotic prophylaxis prior to surgery (A) or a single dose of 2000 milligrams of first generation cephalosporin, 15-30 minutes prior to surgery (B). The anaesthesiologist will prepare and administer the antibiotic prophylaxis at the holding or operation room according to the standard of care and will write down the type of antibiotic prophylaxis (cefazoline), the way of administration and the dosage, in the patient record. In this way, the administration of cefazolin, or no antibiotic prophylaxis, can be verified later by the coordinating investigator.

Perioperative

All patients included in this study will undergo a laparoscopic cholecystectomy. This surgical procedure will be performed by the four trocar technique, with transection of the duct and artery after reaching the critical view of safety as described in the Dutch Guidelines for Gallstone disease (ref.3). There is evidence in current literature that small-incision cholecystectomy and laparoscopic cholecystectomy are comparable in terms of complications, mortality and duration of recovery (ref.32). Therefore, small incision cholecystectomy may be performed instead of laparoscopic cholecystectomy, when this is according to local hospital protocol. Patients undergoing primary open cholecystectomy are not excluded from the trial, but we recommend not to use this strategy since it is currently not the gold standard in treatment.

The operation will be scored by the surgeon in terms of difficulty of the procedure and the severity of the cholecystitis (stone loss, empyema, gallbladder perforation. Bile cultures will be obtained during laparoscopic cholecystectomy to evaluate the incidence and specifics of bactobilia in acute calculous cholecystitis and their influence on the outcome.

The gall bladder will be examined by a pathologist to confirm the diagnosis of acute cholecystitis (current standard care).

Postoperative

All patients will be admitted postoperatively and will only receive intravenous fluids and/or analgesics if needed. Antibiotics will not be prescribed, unless they develop a documented infectious complication according to the afore mentioned criteria, requiring treatment. Patients will generally be discharged based on their clinical condition, mostly one day post-operatively.

All procedures in this study are part of the normal medical treatment for acute cholecystitis, except for omitting the single dose of antibiotic prior to surgery in the intervention group. No extra invasive procedures or laboratory tests will be performed. The presence or absence of a postoperative infection will be systematically checked by either a senior resident, fellow or attending surgeon at the outpatient clinic four weeks postoperative.

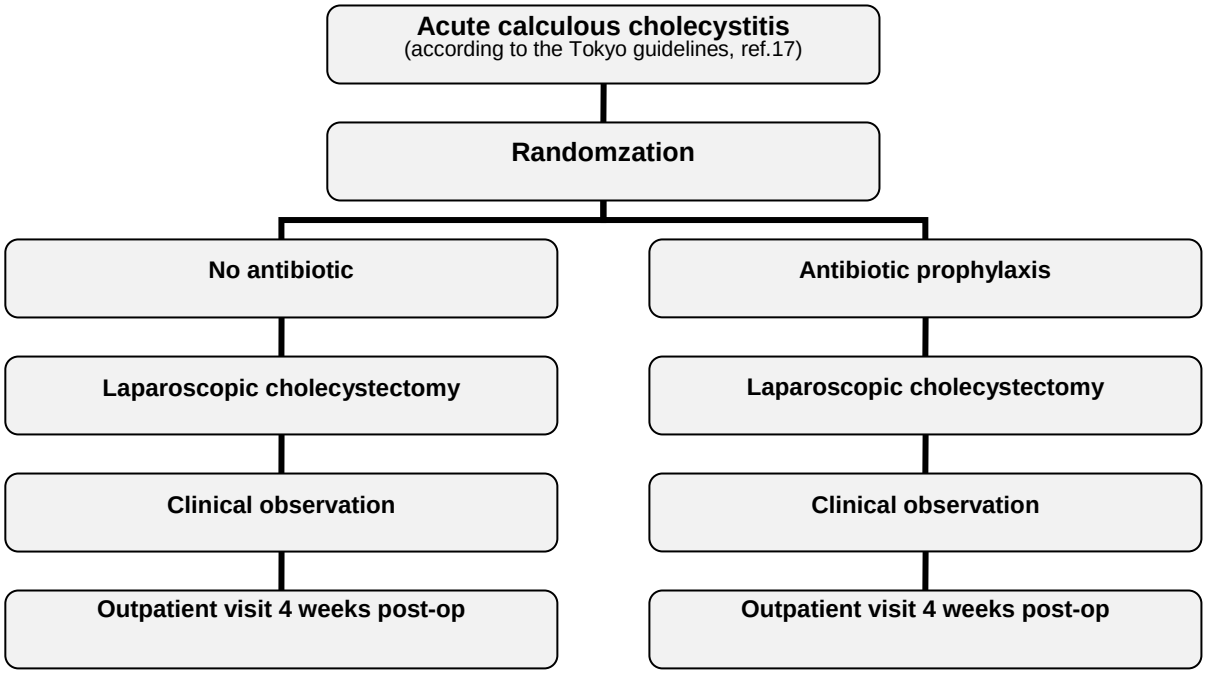

Figure. Flowchart of study outline for included patients

Data collection

After written informed consent is obtained, each patient will receive an anonymous study number which will be used for the study-record-forms and the database. Clinical data with regard to baseline characteristics (gender, date of birth, length, weight, admitting

physician, speciality and ward, date of onset of pain, date of admission, date of randomization) and outcomes will be collected during hospital admission using case record forms.
Whether or not antibiotic prophylaxis has been administered by the anesthesiologist (and the type and dosage) will later be verified by the investigator by checking the electronic patient records.
The case record forms will be checked with source data (unblinded admission and discharge letters, unblinded surgery report). Only the study coordinators will have access to the unblinded source data.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason and if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

There will be no replacement of individual subjects after withdrawal.

8.6 Follow-up of subjects withdrawn from treatment

All patients randomized will be analyzed, according to the intention to treat principle, until withdrawal from treatment.

8.7 Premature termination of the study

A formal interim analysis will be performed after the first 20 included patients and subsequently once per 50 included patients. The trial will not be stopped for futility, the reason being that this is the first randomized trial on this subject and treatment policy will be based on this trial. To guarantee the safety of patients throughout the study the DSMB follows the occurrence of all components of the composite endpoint between groups. The outcome of this analysis is only known to the DSMB. Whenever a significant difference occurs, the METC and the investigators will be informed and the study will be put on hold until the results of a formal interim-analysis are discussed. Also see the paragraph on DSMB.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental interventiont]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Local investigators will report mortality within 24 hours to the study coordinator. The study coordinator will report mortality to the accredited central-METC via the "Toetsingonline" website of the website of the Central Committee on Research inv. Human Subjects (CCMO, ccmo.nl) within 7 days after the study coordinator has been made aware of this. All other SAE's have to be reported within 72 hours to the study

coordinator. In all study meetings all participating physicians will be reminded to report mortality and other SAE's to the study coordinator as soon as possible.
Data on mortality and all other SAE's/AE's will be collected per 30 randomized patients and presented to the DSMB and will at that time be listed in "Toetsingonline" The DSMB will discuss the SAE's and give advice to the trial steering-committee and the METC.
If in one patient multiple similar endpoints (e.g. intra-abdominal abscess and pulmonary infection) occur only the initial endpoint will be reported as a SAE/AE. The rationale for this being that in the final table made for the DSMB only one such endpoint will count per patient as is current 'best practice' in reporting of RCTs.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

No annual safety report is drafted as during the study the DSMB will continuously be monitoring patient safety. The DSMB will be reporting directly to the METC.

9.4 Follow-up of adverse events

All AE's will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAE's need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will consist of three members: an epidemiologist/statistician, a surgeon and a microbiologist. All members are independent and constructively critical of the ongoing trial, not involved with the study and have enough expertise to carry out this task. The epidemiologist will be the chairperson and another member will produce written short transcripts of the meeting that should include: data, location, participants, patient numbers that were discussed and decisions made. These transcripts will be send to the study coordinator and the METC.

To guarantee the safety of patients throughout the study, the DSMB will come together after the first 20 included patients and follows the occurrence of all components of the composite endpoint between the groups. The trial statistician will perform the interim-analysis, using an unblinded database. The results of this analysis will be discussed in the private meeting with only the DSMB members present. Prior to this meeting the principal investigator and study coordinator may present additional data/studies/arguments that the DSMB should take into account. If a clear relation exists from the data that either treatment modality is associated with harm, the METC and the investigators will be informed and the study will be put on hold until the results of a formal interim-analysis are discussed. After the first meeting, the DSMB will perform an interim-analysis once per 50 included patients. The trial will not be stopped for futility, the reason being that this is the first randomized trial on this subject and treatment policy will be based on this trial.

The primary endpoint will be monitored for benefit or harm using a restricted procedure (Whitehead, 1997), designed according to the sample size characteristics as described before. Efficacy and safety monitoring will be performed using the PEST 4 software (PEST, 2000). Formal statistical methods are more generally used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.

When the DSMB performs the interim-analysis, the Peto approach will be followed, meaning that the study will only be stopped for beneficial effects in case of a $P<0.001$ (ref.33). For harm (higher incidence of the primary endpoint in either group) the Pocock approach will be followed, a P-value of 0.029 is required (ref.33).

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

In the group of patients who undergo laparoscopic cholecystectomy without antibiotic prophylaxis, either an increase or no effect on the infectious complication rate will be seen. The absence of antibiotic prophylaxis will obviously not lead to a decrease of the infectious complication rate or at least very improbable. However, the other benefits (reducing needless medical activity and costs and bacterial resistance) are of great importance. The main question to be answered is: does omitting antibiotic prophylaxis lead to an increase of postoperative infections?

Because only deviations in one direction is considered possible (let alone that superiority of omitting antibiotics is desirable), a non-inferiority design is best suited to provide the answer to this primary question. Non-inferiotiy will be established if the upper limit of the 2-sided 95% confidence interval of the difference of proportion of infections between the two groups is lower than the non-inferiority margin.

The primary endpoint is a composite endpoint consisting of all postoperative infectious complications, within 4 weeks postoperative. The main statistical analysis will be on intention-to-treat-basis. The measure of effect will be the absolute risk difference, the precision will be quantified by means of the 95% confidence interval. Formal statistical hypothesis testing regarding the non-inferiority will be performed by means of the Westlake-Schuirmann test, with the non-inferiority margin set at 10%. A one tailed p-value < 0.025 is considered statistically significant.

In general missing data will not be imputed; we do not expect missing data for the primary endpoint.

10.2 Secondary study parameter(s)

The secondary endpoints of the individual infections of the composite endpoint and all other postoperative complications will be analysed primarily in descriptive statistics; formal p-values for count data will be calculated, but the inference is largely as measure of precision rather than decision.

The secondary endpoint, duration of hospital stay, will be analysed as time to event (i.e. hospital discharge). Data will be shown graphically by means of Kaplan-Meier plots and formal statistical hypothesis testing with the log-rank test.

The absence of antibiotic prophylaxis will be economically evaluated from a societal perspective with a budget impact analysis. The budget impact model will be used to estimate the financial consequences of the absence of antibiotic prophylaxis in patients undergoing cholecystectomy for the provider, the insurer and government. All costs will be estimated based on the actual input in terms of resource use and personnel. For all cost-items such as intensive care unit or regular hospital admission, operation, medication, diagnostic tests, rehabilitation, unit costs will be derived from the Dutch costing manual or with hospital administration. The use of medical resources outside hospital (e.g. general practitioner consultation, physiotherapy) will be recorded. The costs pertaining to the actual sick leave will be calculated by means of the friction cost method. Thirty days post-discharge the definite outcome can be determined regardless of the approach used. Using bootstrap techniques we will estimate the range of costs for both treatment modalities as well as the point estimates and will project these data on the Dutch health care situation. Sensitivity analyses will be performed to assess factors of major influence on the total costs.

10.3 Other study parameters

All other analyses (per protocol, multivariate) will be considered post-hoc and explicitly tagged as such in publications.

10.4 Interim analysis (if applicable)

A formal safety analysis will be performed after the first 20 included patients and subsequently once per 50 patients. To guarantee the safety of patients throughout the study the DSMB follows the occurrence of all components of the composite endpoint between groups. The outcome of this analysis is only known to the DSMB. Whenever a significant difference occurs, the METC and the investigators will be informed and the study will be put on hold until the results of a formal interim-analysis are discussed. Final analysis will be done after follow-up of the final patient is completed. A blinded adjudication committee will assess all primary endpoints according to the definitions listed in this protocol. Also see the paragraph on DSMB.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The PEANUTS trial will be conducted according to the principles of the Declaration of Helsinki (version October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

All patients presenting at the emergency department meeting the inclusion criteria, will be informed about the PEANUTS trial by the surgical doctor in charge (this can be either a resident, a fellow or attending surgeon). Since there is no place for a wait-and-see approach in acute cholecystitis, patients will be asked to decide if they want to participate within 24 hours. The patient information letter and informed consent form are attached as a separate document.

11.3 Objection by minors or incapacitated subjects (if applicable)

Patients who are permanently unable to provide informed consent (already prior to this episode of acute pancreatitis) will not be included.

11.4 Benefits and risks assessment, group relatedness

Antibiotics are currently administered to theoretically avoid surgical site infections.
If this study demonstrates that the absence of antibiotic prophylaxis does not increase the infection rate, the use of perioperative antibiotic for this indication can be dropped as a whole and the guidelines will be adapted. When the use of antibiotics appears unnecessary in these patients, the role of antibiotic prophylaxis in the entire upper gastrointestinal tract surgery becomes eminent. A decrease of use of antibiotics on such a scale may result in a large decrease of needless medical activities, costs and bacterial resistance.
If omitting antibiotic prophylaxis should be unjust, an infection that could have been prevented by antibiotic prophylaxis may occur. A distant infection requires antibiotic treatment which is almost always effective. A surgical site infection may require drainage; opening of the wound or percutaneous drainage of an intra-abdominal abscess. Bleeding is another surgical complications that may occur. Nonsurgical complications that may occur include urinary tract infections, pneumonia, cardiac complications and deep venous thrombosis.

All procedures in this study are part of the normal medical treatment for acute cholecystitis, except for omitting the single dose of antibiotic prior to surgery in the intervention group. No extra invasive procedures or laboratory tests will be performed. Patient will be seen at the outpatient clinic one week postoperative and there will be a telephone follow-up four weeks after surgery.

11.5 Compensation for injury

The investigator of each participating hospital has a liability insurance which is in accordance with article 7 of the WMO. The investigator of the St Antonius Hospital has an insurance for all patients randomized in the different centers, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

- € 650.000,- for death or injury for each subject who participates in the Research
- € 5.000.000,- for death or injury for all subjects who participate in the Research
- € 7.500.000,- for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

There will be no financial or other form of compensation for study participants.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Patients will be coded by a numeric randomization code (anonymous) and the principal investigators will be the only ones to have access to this code. The main investigator/project coordinator will monitor all participating centers and guide the location coordinators in entering the data into the database. On inclusion of the first patients per center, the main investigator will be present to make sure data collection and entry is done accurately. The main investigator will perform a final check on all entries comparing source data with data entered into the database. The source data will be kept by the project leader for 15 years.

12.2 Monitoring and Quality Assurance

See chapter 8 and 12.1

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last follow-up telephone call.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final

study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

No arrangements have been made concerning public disclosure. The trial will be registered by Controlled-trials.com. The trials' results will be submitted to a peer-reviewed journal regardless of the outcome. Co-authorship will be based on the international guidelines. Clinicians that do not fulfill these criteria will be listed as 'collaborator' and the journal will be asked to present the names of all collaborators to be listed as well in Pubmed. The study coordinators will be first and second authors whereas the principal investigators will be the final authors. The further order of authors will be based primarily on scientific input and secondarily on the number of randomized patients to be judged by the principal investigators.

13. STRUCTURED RISK ANALYSIS

Postoperative antibiotic prophylaxis for acute cholecystitis is commonly used in surgical practice. The rationale for the administration of antibiotic agents perioperatively is the probable decrease of postoperative infectious complications (see chapter 1). However, there is no real consensus regarding the use of antibiotic prophylaxis for acute cholecystitis and therefor it's use is extremely variable, mainly dependent on the surgeon's preference, and differs per hospital. A retrospective study that we conducted in our hospital among 284 patients undergoing emergency cholecystectomy showed that 50% of the patients received extended antibiotic prophylaxis; 38% a single prophylactic dose and 12% did not receive antibiotic treatment.

In current literature high level evidence is available that in patients undergoing *elective* cholecystectomy for *uncomplicated* cholelithiasis, prophylactic antibiotics do not decrease the incidence of postoperative infections (ref.8,9). The use of antibiotic prophylaxis in these cases is therefore discouraged and not general practice. In recent years, more evidence has become available on the effects of antibiotic prophylaxis in case of *emergency* cholecystectomy for acute cholecystitis. Both Regimbeau et al. (ref.4). and Jafaar et al. (ref.13) demonstrate that perioperative antibiotic prophylaxis in patients undergoing emergency cholecystectomy for acute calculous cholecystitis, does not reduce the postoperative infection rate. Recently, we conducted a similar, multicenter, randomized controlled trial, comparing a single preoperative dose of antibiotic with a single preoperative dose *and* postoperative continuation for 3 days (PEANUTS trial, ref 14). Since the last patient of this trial was only randomized very recently, the results have not been published yet. However, the results are the same: postoperative prolonged antibiotic treatment does not lead to a decrease in infection rate and may therefore be omitted.
We strongly presume that the use of antibiotic prophylaxis in patients undergoing emergency cholecystectomy is unnecessary and even the role of antibiotic prophylaxis in the entire upper gastrointestinal tract surgery becomes questionable.

If omitting antibiotic prophylaxis should be unjust, an infection that could have been prevented by antibiotic prophylaxis may occur. A distant infection requires antibiotic treatment which is almost always effective. A surgical site infection may require drainage; opening of the wound or percutaneous drainage of an intra-abdominal abscess. Bleeding is another surgical complications that may occur. Nonsurgical complications that may occur include urinary tract infections, pneumonia, cardiac complications and deep venous thrombosis.

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APPENDIX I. APACHE-II score

The APACHE-II score (ref.40) is a severity-of-disease classification system and consists of three scoring tables, resulting in the addition of the three individual scores.
APACHE-II Score = Score 1 + Score 2 + Score 3

1. KLINIEK	**+4**	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Temperatuur	≥41	39,0-40,9		38,5-38,9	36-38,4	24-35,9	32-33,9	30-31,9	≤29,9
MAP, mm HG	≥160	130-159	110-129		70-109		50-69		≤49
Hart frequentie	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Ademfrequentie	≥50	35-49		25-34	12-24	10-11	6-9		≤5
pO^2 (mmHg/kPA)					>70mmHg/ >9.3kPa	61-70mmHg/ 8.1-9.3kPa		55-60mmHg/ 7.3-8.0kPa	<55mm Hg/<7.3 kPa
PH (arterieel)	≥7,7	7,6-7,69		7,5-7,59	7,33-7,49		7,25-7,32	7,15-7,24	≤7,14
Serum Na	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum K	≥7	6,0-6,9		5,5-5,9	3,5-5,4	3-3,4	2,5-2,9		≤2,4
Serum creat (umol/L, x2 bij acuut nierfalen)	≥302	169-301	125-168		53-124		≤52		
Haematocriet	≥60		50-59,9	46-49,9	30-45,9		20-29,9		≤19
Leucocyten	≥40		20-39,9	15-19,9	3-14,9		1-2,9		≤0.9
Glasgow coma scale					15 minus actuele score				

*Omcirkel welke van toepassing is

2. Leeftijd*	**Punten**
<44	0
45-54	2
55-64	3
65-74	5
>75	6

*Omcirkel welke van toepassing is

3. Comorbiditeit*	**Punten**
Geen relevante comorbiditeit[#]	0
Wel electieve chirurgie mogelijk	2
Geen electieve chirurgie mogelijk	5

*Omcirkel welke van toepassing is

Relevante comorbiditeit:

- *Liver insufficiency*
  - Biopsy proven cirrhosis
  - Documented portal hypertension
  - Episodes of past upper GI bleeding attributed to portal hypertension
  - Prior episodes of hepatic failure / encephalopathy / coma.
- *Cardiovascular*
  - New Heart Association Class IV Heart Failure
- *Respiratory*
  - Chronic restrictive, obstructive or vascular disease resulting in severe exercice restriction, i.e. unable to climb stairs or perform household duties.
  - Documented chronic hypoxia, hypercapnia, secondary polycythemia , severe pulmonary hypertension (> 40 mmHg), or respirator dependency.
- *Renal*
  - Receiving chronic dialysis
- *Immunosuppression*
  - The patient has received therapy that suppresses resistance to infection e.g. immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS.