PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Extended Antibiotic Therapy after Laparoscopic Cholecystectomy for Acute Calculous Cholecystitis. Is it Necessary? (Cholecystectomy Antibiotic Randomized Trial - CHART)
AUTHORS	Pellegrini, Pablo; Campana, Juan; Dietrich, Agustin; Goransky, Jeremias; Glinka, Juan; Giunta, Diego; Barcan, Laura; Alvarez, Fernando; Mazza, Oscar; Sanchez Claria, Rodrigo; Palavacino, Martin; Arbues, Guillermo; Ardiles, Victoria; de Santibañes, Eduardo; Pekolj, Juan; de Santibañes, Martin

VERSION 1 - REVIEW

REVIEWER	Kurinchi Gurusamy University College London, UK
REVIEW RETURNED	16-Aug-2015

GENERAL COMMENTS	1. “Treatment according to randomization (Figure 1) must be carried out within 72 hours after randomisation”. The authors state that they will be providing antibiotics after laparoscopic cholecystectomy. The authors should state clearly whether they plan to administer antibiotics routinely until the time of surgery. Even if they do not plan to administer antibiotics routinely, they should also indicate whether they plan to administer antibiotics if any peritonism develops. How will patients who worsen during the waiting time treated? How will they be analysed? 2. Authors state “intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy”. They should clarify what they will do with these patients – will they give antibiotics to these patients? 3. Authors should include quality of life as one of the secondary outcomes. 4. The following two sentences are contradictory. “Exclusion criteria are: rejection to participate in the trial or the process of informed consent; hypersensitivity to AMC or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for more than 5 days; active oncological diseases; acquired immunodeficiency syndrome (AIDS); transplanted patients”. The results were analyzed on an intention-to-treat basis (there is also a typo in this sentence – the authors have not analysed the data yet). If some patients are excluded intra-operatively, how can an intention-to-treat analysis performed? Are the authors planning to perform any imputation? If so, how?

REVIEWER	Kirstine Moll Harboe Department of Clinical Pharmacology Bispebjerg Univerity Hospital Denmark
REVIEW RETURNED	28-Aug-2015

GENERAL COMMENTS	Important study question. Calculus or calculous? I am not a linguistic qualified person, but I think calculous is a more common way of spelling. In page 5 of 20 from line 22 to 31 the text is a copy+paste from a paper (Ünlü, BMC Surgery, 2010) The paper is not on the reference list. Please describe the adverse reactions of the trial medication more thoroughly. Nausea and diarrhea are also important adverse effects of antibiotics, especially in the first days after surgery. Methods: The study medication in this clinical trial is not fully described. Why is a quit high dose of 1000 mg of amoxicillin (and dose of clavulanic acid?) chosen? How is the placebo tablets prepared? The taste of amoxicillin is difficult to match. I will recommend that the patients after the treatment are asked what treatment they think they received to confirm the blinding. Damage and complications: how is leukocytosis defined? A clinical trial of medicines will in my country need approval by the medicines authorities in addition to the ethics approval. Please comment. It is not clear to me how cross-over is handled in the statistical analysis. That is, if the patient in the placebo group is given antibiotics, maybe by a doctor outside the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Kurinchi Gurusamy
Institution and Country
University College London, UK

Please state any competing interests or state 'None declared':
None declared
This was added in the section of competing interest (page 15)

1. "Treatment according to randomization (Figure 1) must be carried out within 72 hours after randomisation". The authors state that they will be providing antibiotics after laparoscopic cholecystectomy. The authors should state clearly whether they plan to administer antibiotics routinely until the time of surgery. Even if they do not plan to administer antibiotics routinely, they should also indicate whether they plan to administer antibiotics if any peritonism develops. How will patients who worsen during the waiting time treated? How will they be analysed?
All patients admitted with calculous acute cholecystitis will receive parenteral hydration, gastric protection with proton pump inhibitors, analgesics and intravenous treatment with AMC. This

treatment is continued until the operation. Surgery will be performed within the first 5 days after admission. Those patients who worsen during the waiting time will be explored as soon as possible. All this was added to the text (page 6). If we found bile peritonitis the patients will be excluded, as stated in the exclusion criteria (page 7).
2. Authors state “intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy”. They should clarify what they will do with these patients – will they give antibiotics to these patients?.
These are special situations. If any of these situations were not diagnosed preoperatively, the patients (as we state in the previous response) will receive antibiotics until the moment of surgery. If we find “liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy” the patient will be excluded from the trial and the use of postoperative antibiotics will depend on surgeon criteria.
3. Authors should include quality of life as one of the secondary outcomes.
We appreciate the advise of the referee for further studies in this cohort of patients for long term follow up. Remember that this trial had a maximum of 30 day follow up after surgery.
4. The following two sentences are contradictory.
“Exclusion criteria are: rejection to participate in the trial or the process of informed consent; hypersensitivity to AMC or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for more than 5 days; active oncological diseases; acquired immunodeficiency syndrome (AIDS); transplanted patients”.
The results were analyzed on an intention-to-treat basis (there is also a typo in this sentence – the authors have not analysed the data yet).
The results will be analyzed on an intention-to-treat basis

If some patients are excluded intra-operatively, how can an intention-to-treat analysis performed? Are the authors planning to perform any imputation? If so, how?
All patients admitted with acute calculous cholecystitis will receive parenteral hydration, gastric protection with proton pump inhibitors, analgesics and intravenous treatment with AMC. This treatment is continued until the operation. Surgery will be performed within the first 5 days after admission. Those patients who worsen during the waiting time will be explored as soon as possible. Potential complications (such as bile peritonitis, cholangitis, gallbladder perforation or abscesses) or evidence of greater severity of cholecystitis may occur and this can only be diagnosed during surgery. These patients will not be eligible for randomization and will be dismissed from the statistical analysis. Nevertheless, this group will be considered in the final flow chart.
After screening for eligibility and informed consent is obtained, the patient will undergo LC within 72 hours after admission., patients will be randomized in a 1:1 ratio into one of the following study groups (Figure 1) after LC:
• Antibiotic treatment
• Placebo
In summery, patients are recruited prior to surgery but are randomized only after surgery, once the investigators confirm that no exclusion criteria are present intraoperatively.

Reviewer: 2
Reviewer Name
Kirstine Moll Harboe
Institution and Country
Department of Clinical Pharmacology
Bispebjerg Univerity Hospital
Denmark

Please state any competing interests or state ‘None declared’:
None declared
This was corrected

Please leave your comments for the authors below
Important study question.

Calculus or calculous? I am not a linguistic qualified person, but I think calculous is a more common way of spelling.
According to Medical dictionary (world reference), the correct term is calculous as the reviewer suggested it. We changed it in the manuscript.

In page 5 of 20 from line 22 to 31 the text is a copy+paste from a paper (Ünlü, BMC Surgery, 2010) The paper is not on the reference list. Please describe the adverse reactions of the trial medication more thoroughly. Nausea and diarrhea are also important adverse effects of antibiotics, especially in the first days after surgery.
The whole paragraph was corrected according to the original reference. Final statement said: “Antibiotics are associated with common adverse effects such as allergic reactions and digestive intolerance (nausea, vomits and diarrhea). Nowadays, there is a clear tendency towards the rational use of antibiotics in order to prevent bacterial resistance. Amoxicilin has been associated with a 7-8% incidence of toxicodermia, 1% of allergy reactions and a very low incidence of anaphylactic shock (0.01-0.04% with the use of penicillin) [8]”.
Methods: The study medication in this clinical trial is not fully described. Why is a quit high dose of 1000 mg of amoxicillin (and dose of clavulanic acid?) chosen? How is the placebo tablets prepared? The taste of amoxicillin is difficult to match. I will recommend that the patients after the treatment are asked what treatment they think they received to confirm the blinding.
The dose of antibiotics is 1000 mg. divided in 875 mg. of amoxicillin and 125 mg. of clavulanic acid. They are based on recommendations to treat expected germs in gallbladder and bile ducts (Enterobacteriacea, Enteroccocus spp and anaerobes) that need higher concentrations than standard doses to treat Pneumococcal or streptococcal infections with the same drugs. (Tokyo Guidelines and Appendix 5. Antimicrobial therapy for biliary infections in no critically ill patient, in absence of risk factors for ESBL. WSES consensus conference: Guidelines for first-line management of intra-abdominal infections. doi: 10.1186/1749-7922-6-2)
Both placebo and antibiotic are provided and manufactured by Central Pharmacy of the Hospital Italiano de Buenos Aires (HIBA). The antibiotic and placebo capsules will be packaged and labelled identically. These capsules will be made of insipid gelatin material and will have the same colour.

Damage and complications: how is leukocytosis defined?
Leukocytosis was defined as a white blood cell count of 10,000/mm3 or more. This was added to the manuscript (page 12).

A clinical trial of medicines will in my country need approval by the medicines authorities in addition to the ethics approval. Please comment.
The CHART trial is conducted in line with the current national and international regulations: World Medical Association Declaration of Helsinki, Regulation 5330/07 ANMAT, the Standards of Good Practices ICH E6 and the laws and regulations of the country, providing the greatest protection of the patient. The trial protocol and informed consent sheets have been approved by the Research Projects Evaluating Committee (CEPI) of HIBA (protocol Nº 2111). The CHART trial has been registered at

Clinicaltrial.gov database (ClinicalTrials.gov, Identifier: NCT02057679).
The ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica / National Administration of Medicines, Food and Medical Technology) is the Argentine National agency that controls our protocol.

It is not clear to me how cross-over is handled in the statistical analysis. That is, if the patient in the placebo group is given antibiotics, maybe by a doctor outside the study.
Patients included are warned not to take medications from other doctors outside the study. In case a patient requires antibiotics for some reason, the blind will be revealed to ensure the proper treatment for this patient. This event will be registered and the patient will be considered in the statistical analysis.