| Sponsor                  | Amiens University Hospital  
|                         | Place Victor Pauchet  
|                         | 80 054 AMIENS Cedex 1  
|                         | France                  |
| **PROTOCOL** (ABCAL STUDY)                                      |
| **PRODUCT/MOLECULE**    | Amoxicillin + clavulanic acid |
| **TITLE**               | Place of postoperative antibiotics in acute  
|                         | calculous cholecystitis  
|                         | Postoperative antibiotic versus no postoperative antibiotics (in mild and moderate acute  
|                         | cholecystitis)  
|                         | III phase  
|                         | Acute calculous cholecystitis |
| **COORDINATOR INVESTIGATOR** | Professor Jean-Marc REGIMBEAU  
|                         | Digestive surgery department  
|                         | Amiens Hospital  
|                         | 80054 Amiens |
| **PROTOCOL VERSION**    | 18                      |
| **PROTOCOL DATE**       | 27th august 2012        |
| **CPP**                 | Approvued in 2009  
|                         | By the Comité de Protection des Personnes Nord  
|                         | Ouest II                |
| **AFSSAPS**             | Approvued in 2009    |
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**SUMMARY**

| TITLE | Place of postoperative antibiotics in acute calculous cholecystitis  
Postoperative antibiotic versus no postoperative antibiotics (in mild and moderate acute cholecystitis) |
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| PRINCIPAL INVESTIGATORS | Professor Jean-Marc Régimbeau  
Digestive surgery department  
Place Victor Pauchet  
80054 AMIENS Cedex 1 |
| PROTOCOL VERSION | 18 – 08/27/2012 |
| BACKGROUND | Acute Calculous cholecystitis is a common disease whose treatment involves antibiotics and cholecystectomy. Currently, there is no rational for extended antibiotic therapy in the postoperative period. |
| HYPOTHESIS | Postoperative complications after early cholecystectomy for mild or moderate acute cholecystitis are not more frequent in the absence of postoperative antibiotics. |
| AIM | To determine whether postoperative antibiotics after cholecystectomy for mild or moderate acute cholecystitis is effective and justified. |
| PRIMARY OBJECTIVE | To compare the occurrence of postoperative infections after early cholecystectomy for mild or moderate acute cholecystitis considering the use of postoperative antibiotics |
| SECONDARY OBJECTIVE | • complications rate depending on the duration of the preoperative antibiotics  
• Influence of postoperative surgical drainage on the occurrence of postoperative infections  
• Analysis of the nature of infectious complications (surgical site infections, distant infection)  
• Comparison of germs found in the bile and during the postoperative infections  
• Duration of hospitalization  
• readmission rates for surgical site infection (SSI)  
• Rate of reoperation for SSI  
• overall mortality rate at 30 days  
• specific mortality rate at 30 days |
| CONDITION | Mild or moderate acute calculous cholecystitis |
| STUDY DESIGN | Prospective, multicenter, open labeled, randomized, Intention-to-treat clinical trial. |
| INCLUSION CRITERIA | • Acute calculous cholecystitis (ACC) confirmed by morphological examination (echography, CT scan, MRI)  
• Mild or moderate  
• Complaints for less than 5 days  
• Written consent  
• Patient older than 18 |
| NON INCLUSION CRITERIA | • Grade III ACC |
| STUDY PROCEEDINGS | • Hospitalization  
|                   | • Selection after verification of the inclusion criteria  
|                   | • systematic preoperative antibiotic therapy for <5 days  
|                   | • peroperative antibiotics  
|                   | • Laparoscopic or laparotomy Cholecystectomy  
|                   | • systematic biliary Sampling  
|                   | • cholangiography by operator  
|                   | • Drainage according to local conditions  
|                   | • Randomization in the operating room after surgery  
|                   | • postoperative antibiotic therapy for less than  days versus no postoperative antibiotics  
|                   | • Monitoring during hospitalization  
|                   | • Consultation (4 weeks) after the surgery  

| PREOPERATIVE MANAGEMENT | The preoperative management systematically include a probabilistic curative preoperative antibiotics whose duration will depend on the time of surgical treatment (<5 days).  

| SURGERY | Intraoperative antibiotics include the same antibiotics that started preoperatively. Cholecystectomy should be completed within 5 days after onset of symptoms. The incision is preferably by laparoscopy but may be performed by laparotomy (median or subcostal right). Bile sampling will be carried out systematically for bacteriological analysis. An intraoperative cholangiography may be performed according to the habits. Abdominal drainage will be made based on intraoperative local conditions.  

| RANDOMIZATION | The randomization will be performed in the operating room immediately after cholecystectomy. Randomization will be made by lot at the time of the declaration of patient via the Web. It will be stratified by center and to ensure a better balance, blocks of equal size with patients randomized to each treatment will be used at each center.  

| POSTOPERATIVE MANAGEMENT | Patients randomized to receive Antibiotics have empirical antibiotic therapy (directed against Gram-negative bacilli, gram-positive cocci and anaerobic) for a period of 5 days. The type of antibiotic is amoxicillin + clavulanic acid 2gx3 / d. Per os relay will be made early based on the clinical and biological evolution. Antibiotic treatment will be tailored to the results of susceptibility testing.  

|   | • Biliary peritonitis  
|   | • Hepatic abscess  
|   | • Acute pancreatitis  
|   | • Septic shock  
|   | • Patient under guardianship  
|   | • ASA score IV or V  
|   | • Suspected gallbladder cancer  
|   | • Pregnancy  
|   | • Treatment with methotrexate  
|   | • Allergy to amoxicillin plus clavulanic acid
**PRIMARY ENDPOINT**  
The proportion of patients with a post-operative infection (surgical site and/or distant infections) recorded before or at a consultation four weeks after cholecystectomy. The diagnosis of a post-operative infection was based on clinical, biochemical and/or morphological features and was confirmed (if possible) by bacteriological data. A successful outcome was defined as the absence of surgical-site infection.  
Post-operative infections were defined as superficial or deep incisional infections or organ/space infections, according to the Centers for Disease Control and Prevention’s guidelines on the prevention of surgical site infections (SSIs). Superficial incisional SSIs had to meet the following criteria: (a) occurrence within 30 days of the surgical procedure, and (b) involvement of only skin or subcutaneous tissue around the incision but with at least one of the following: (i) purulent drainage from the superficial incision; (ii) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (iii) one or more of the following signs or symptoms (pain or tenderness; localized swelling; redness or heat and opening of the superficial incision by the surgeon unless culture of incision is negative); (iv) diagnosis of a superficial incisional SSI by the surgeon or attending physician (according to the CDC’s definition in the American Journal of Infection Control, 1992). Organ/space infections involved any organ or space (other than the incised body wall layer) that was opened or manipulated during the initial surgical procedure. Distant infections included pulmonary and urinary infections, bacteremia and lymphangitis.

**NUMBER OF PATIENTS TO ENROLL**  
- Postoperative infection after cholecystectomy: 18.5%.
- Non inferiority test
- Alpha risk: 5%
- Power: 80%
- Unilateral test
- Non inferiority margin 11%
- Overall effective to enroll: 414 (217 patients per arm)

**STUDY DURATION**  
Inclusion period: 24 months  
Follow up: 4 weeks  
Study duration: 25 months  
Centres: 21
2. SCIENTIFIC JUSTIFICATION AN GENERAL DESCRIPTION OF THE RESEARCH

2.1. EXPERIMENTAL TREATMENT

The drug used in this study is the association of amoxicillin and clavulanic acid (Augmentin® or Generic). The description of the drug is detailed in Chapter 6.

2.2. RESUME DES RESULTATS DES ESSAIS NON CLINIQUES ET DES ESSAIS CLINIQUES DISPONIBLES ET PERTINENTS AU REGARD DE LA RECHERCHE BIOMEDICALE CONCERNEE

It exists in the literature very few randomized controlled trials on antibiotics in the ACC. Although the majority of patients have simple postoperative course (no complications), postoperative antibiotics is widely prescribed.

In terms of intraoperative antibiotics, the term "antibiotic prophylaxis" cannot be used as part of the ACC because there is a potential infection of intra-gallbladder bile that is necessary to treat with antibiotics. Furthermore, obstruction of the cystic duct by the calculation does not allow obtaining concentrations of antibiotics adequate to eradicate germs. Several studies mixing cholecystectomy for uncomplicated cholelithiasis and ACC have evaluated the role of antibiotic prophylaxis. A prospective study showed that single injection of Cefazolin was comparable to placebo in 44 patients with ACC and / or symptomatic cholelithiasis for which cholecystectomy was performed. A study conducted in 175 hospitals in the Netherlands showed that antibiotic prophylaxis in biliary surgery was inappropriate, that is to say on inactive germs found in the bile collection in more than 23%.

However, other authors have highlighted the role of antibiotic prophylaxis in patients with a high risk of infection bilaire. In our study, preoperative antibiotics containing amoxicillin and clavulanic acid will be continued throughout the surgery. Several ancient randomized prospective trials sought to evaluate the efficacy of postoperative antibiotics in the CAL since the 1980s, any antibiotic treatment failed to show superiority in terms of efficacy compared to treatment with ampicillin and aminoglycosides.

Table 1 summarizes the different studies published on antibiotics in the ACC. Currently, the most commonly prescribed antibiotics in the ACC are penicillin associated with inhibitor of beta-lactamas, carbapenems and cephalosporins 3rd and 4th generation. The prospective study of Lau et al. compared a short postoperative antibiotics and prolonged postoperative antibiotics in patients who underwent surgery for a cholecystectomy for ACC. All patients had 2 grams of Cefamandole preoperatively. The patients were operated then randomized to receive either a short regimen of antibiotics (500mg feedback in the 6th and 12th hour) or a long pattern (cephalosporin for 7 days).

In this series, the duration of hospitalization was significantly longer in the long pattern and no significant difference in the occurrence of wound infection was observed between the arms. In an Indian study, 87% of surgeons who performed a cholecystectomy for ACC prolonged antibiotic therapy for more than 24 hours. Though all these series not only included patients with ACC, there not exist currently scientific argument in the literature to extend antibiotics in patients with ACC mild or moderate or prescribe oral antibiotics at the waning of hospitalization. Maintaining the antibiotics could unnecessarily prolong hospitalization and therefore the cost and promote the selection of multiresistant bacteria.

A consensus conference on the ACC was held in Tokyo in 2007. This consensus conference remained cautious in its recommendations about antibiotic advocating empirical antibiotic therapy tailored to the severity of ACC and the results of the sensitivity. This antibiotic must...
be effective on Gram-negative enterobacteria, streptococci (including enterococci) and
anaerobes (Bacteroides, Clostridium) and must take into account resistance usually
encountered. In conclusion, the prescription of postoperative antibiotics after
cholecystectomy for mild or moderate ACC is not based on reliable scientific criteria. In this
indication, early surgery could be sufficient to allow the removal of inflammatory or
infectious focus.

The choice of the combination of amoxicillin and clavulanic acid, in this study, is based on
several arguments. First, it is an antibiotic commonly used in digestive surgery, active on the
digestive and biliary germs. The combination of amoxicillin and clavulanic acid is
inexpensive, available, and having little side effects.

2.3. SUMMARY OF BENEFITS, IF ANY, AND ESTIMATED RISK AND KNOWN TO
THE PEOPLE TEND TO RESEARCH

2.3.a. benefits
2.3.a.1. individual benefit
This study will have no direct benefit to patients outside of a possible reduction in the
duration of hospitalization to the extent that, in the absence of this study, all patients have
received postoperative antibiotics. However, this study will propose to the future (s) patient
(s) the most appropriate treatment with the near certainty of efficiency.

2.3.a.2. collective benefits
This study will improve our knowledge of this common condition. The lack of need for
further antibiotics postoperatively after early cholecystectomy would optimize care
simplifying postoperative protocols (and therefore errors) in the visceral and gastrointestinal
surgery department. The medical and economic impact of ACC is important. This disease
accounts for approximately 10% of admissions to the emergency department for abdominal
pain. The rate of cholecystectomy is about 140 cholecystectomies per 10000 inhabitants and the
rate is constant over time (the second rank after appendectomy). Although no cost analysis
has been conducted specifically in this disease, decreased length of hospital stay would reduce
the overall cost of care for these patients. Finally, this work would suggest antibiotics only for
patients with documented postoperative infection and thus limit the emergence of resistant
bacterial strains.

2.3.b. Risks
2.3.b.1. Individual risks
2.3.b.1.a. Risks and physical constraints
Potential risks for patients participating in the study are directly related to the disease state
and consist of the appearance of a possible infectious postoperative complications
(pneumonia, bacteremia, catheter infection, urinary tract infection), including a surgical site
infection (wound infections and intra-abdominal abscess). Participation in this study does not
involve any particular risk compared to usual care. Indeed, the clinical information requested
as well as blood samples, imaging examinations and surgical strategy are those usually
collected and carried out in the usual care.

2.3.b.1.b. Risks and psychological constraints
Psychological stresses incurred by the person undergoing research are directly related to the disease state, and the possible re-hospitalization in connection with a postoperative complication. Clinical information requested as well as blood samples, imaging examinations and surgical management are those usually made in the usual care. No psychological consequences resulting from the research is incurred by the patient.

2.3.b.1.c. Risks and socio-economic constraints

No socio-economic constraint. The clinical informations requested and blood samples, imaging examinations and surgical treatment are those usually made in the usual care.

2.3.b.2. Collective risks

No late side effects are to be expected in connection with this study. Statistical analysis will be carried out by a team of qualified statistician for this kind of analysis. This study will not be commercial use since it is an antibiotic treatment for which there is a possible substitution by a generic.

2.3.b.3. Side effects and unexpected serious adverse events

In this study on the effect of antibiotic treatment after cholecystectomy for ACC mild or moderate, 2 types of serious adverse events (SAEs) may occur: SAEs related to the absence of antibiotics (death, systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, cholangitis) and SAEs related to antibiotics (anaphylaxis, angioedema, epilepsy, convulsions, acute renal failure, Stevens-Johnson syndrome, toxic epidermal necrolysis). Individual AEs and SAEs description expected will be specified in § 8.3.

2.3.c. Benefit / risk balance

The risks to patients participating in the study are the same as for patients not participating in this study namely the development of postoperative infectious complications including a surgical site infection. Expected benefits for the subjects participating in the study and for future patients are a reduction in the duration of hospitalization. The lack of need for further antibiotic therapy postoperatively after early cholecystectomy could help simplify postoperative protocols in visceral surgery departments. The decrease in length of hospitalization would reduce the overall cost of care for these patients. Finally, this work would suggest antibiotics only to patients with documented postoperative infection and thus limit the emergence of resistant bacterial strains.

In other words, this study expected benefits outweigh the risks for patients suitable for this search.

2.4. DESCRIPTION AND JUSTIFICATION OF THE ROUTE, OF THE POSOLOGY, OF THE SCHEME OF ADMINISTRATION AND THE DURATION OF TREATMENT

The prescription of preoperative antibiotics is systematic when the patient is included in the study. The preoperative antibiotics include the association of amoxicillin and clavulanic acid (Augmentin® 2gx3/day or with generic equivalent dosage). These preoperative antibiotics are continued in all patients during surgery. During this period, the antibiotic is delivered by intravenous route. During the intervention, randomization will distinguish patients who receive postoperative antibiotics. For these patients, the antibiotic will be issued for a period of 5 days. The oral route is preferred during the postoperative period. Throughout the study, the dose does not vary whatever the prescribed antibiotic. In total, the maximum duration of
antibiotic therapy is 5 days (5 postoperative days). The characteristics of the administration of antibiotic treatment will be detailed in Chapter 6.

2.5. DECLARATION THAT THE RESEARCH WILL CONDUCT IN ACCORDANCE WITH PROTOCOL AND THE GOOD CLINICAL PRACTICE AND LAWS AND REGULATIONS IN FORCE

The sponsor and the investigator also agree that this research will be conducted:
• according to the protocol
• in accordance with good clinical practice and international current,
• in accordance with the laws and regulations currently in force in France and internationally

2.6. DESCRIPTION OF THE POPULATION

This study will focus on patients with mild or moderate acute cholecystitis. The selection procedures are described in Chapter 5.

2.7. RELEVANT DATA FROM THE SCIENTIFIC LITERATURE

Acute Calculous cholecystitis (CAL) is a parietal inflammation of the gallbladder related to a long cystic duct obstruction by gallstones. ACC is a complication of cholelithiasis, responsible for abdominal pain requiring hospitalization and surgery. ACC represents between 3 and 10% of all abdominal pain to the emergency department\textsuperscript{18-20}. Through a national database established by the surgical research associations, it was possible to collect prospectively over a period of 2 years, data from 7000 patients hospitalized in gastrointestinal surgery departments suffering from persistent abdominal pain for less than 8 days.

Although it is difficult to know the exact number of acute abdominal pain treated at home, this study showed that the ACC was the third cause of abdominal pain requiring hospitalization with a prevalence of 9.7%, after the nonspecific abdominal pain (34%) and acute appendicitis (28.1%)\textsuperscript{21}. The incidence of ACC seems correlated with age: it was 6.3% in patients under age 50 and 20.9% in patients aged over 50 years\textsuperscript{20}.

The prolonged obstruction of the cystic duct will cause local inflammation of the gallbladder wall and parietal ischemia and necrosis\textsuperscript{22}. Because of this ischemia; gallbladder may take different evolutionary forms: Gangrenous ACC, suppurative ACC, gallbladder perforation and emphysematous ACC\textsuperscript{23}. The literature review found a rate of severe forms of acute cholecystitis which varies between 9 and 50% (average 30%) of cases according to series\textsuperscript{24-28}. The four major complications of ACC are: gallbladder perforation, biliary peritonitis, abscess of the gallbladder and biliary fistula. These complications occur between 7.2 and 26% of cases in the series\textsuperscript{29-30} published since 1990 but these figures are difficult to interpret because the diagnostic criteria and severity of ACC are highly variable from one series to another. In case of exclusive medical treatment of ACC, recurrence of symptoms occurs at an early stage in 2.5 to 22% of cases\textsuperscript{31-32} with a high risk of complications as cholangitis, of migration or acute pancreatitis, which makes that the only medical treatment is an inadequate treatment.

Overall mortality of patients with ACC is between 0 and 10%\textsuperscript{27, 30, 32-36}. This rate is 23-40% for severe ACC postoperatively\textsuperscript{37-38}. Mortality in patients older than 75 years is higher than that of younger patients\textsuperscript{50-51}. In the series of Ransohoff et al., Diabetes was found as a risk factor for mortality\textsuperscript{32}. Cholecystectomy that refers to complete removing the gallbladder is the standard treatment of the ACC. Although initially the ACC has been recognized as a contra-indication for laparoscopy because of the high incidence of intra and postoperative complications this incision is now widely accepted. Several ancient randomized controlled trials, conducted before the advent of laparoscopic cholecystectomy and evaluating open surgery (laparotomy) showed a benefit of early intervention in terms of blood loss, operative time, complication rate, length of hospitalization (and therefore cost), and resumption of
normal physical activity\textsuperscript{31, 41-43}. A recent meta-analysis of 44 randomized including 4 series\textsuperscript{45-48}, published between 1987 and 2006, compared early cholecystectomy and delayed cholecystectomy (2 months after the disappearance of symptoms) in the case of ACC whose symptoms had been present for less one week\textsuperscript{45-48}. All interventions were carried out by laparoscopy. A total of 375 patients were included in this meta-analysis and no difference was found in terms of conversion rate and postoperative complications.

Operative time and hospital stay were significantly decreased in the group of patients with delayed cholecystectomy. However, the total duration of hospitalization (2 hospitalizations for delayed group) and thus the cost was lower when cholecystectomy was performed early\textsuperscript{44}. The improvement of surgical techniques and increasing experience of surgeons in achieving laparoscopy for uncomplicated cholelithiasis led them to propose this way preferably for ACC\textsuperscript{49}. A prospective randomized study on a small number of patients (n = 63) compared with laparotomy cholecystectomy ("open") and laparoscopic cholecystectomy in terms of feasibility, morbidity and mortality. Forty-eight percent of patients had an open cholecystectomy. Fifty-nine percent of patients who underwent laparoscopic cholecystectomy were older than 60 years. In each group, 13 patients had one or gangrenous or emphysematous ACC and 1 patient in each group had bile peritonitis by gallbladder perforation. Sixteen percent of patients in the laparoscopic group required conversion due to inflammation of the hepatic pedicle. The overall mortality was zero and no wound bile duct was diagnosed during hospitalization. The postoperative complication rate was significantly higher (p = 0.0048) in the open cholecystectomy group: 23% versus 0% for major complications and 19% versus 3% for minor complications. The hospital stay was significantly shorter in the laparoscopic group (4 versus 6 days, p = 0.0063)\textsuperscript{49}. The authors conclude that laparoscopy is a safe and effective technique when performed by an experienced surgeon in laparoscopic surgery.

A conversion is necessary in 2-15% of cholecystectomies for ACC\textsuperscript{50}. The fact that "convert" an intervention led by laparoscopy should not be regarded as a failure but as a desire to avoid complications. It seems to be associated with increased morbidity and duration of hospitalization in some series\textsuperscript{28}.

Biliary stasis due to prolonged obstruction of the cystic duct will be responsible for a proliferation of bacteria from the digestive tract\textsuperscript{22}. The time to onset of bacterial contamination of the gallbladder bile in the ACC is debated (primary or secondary occurrence in the natural history of the ACC) although the presence of germs in the gall bladder is not systematically associated with the existence of ACC\textsuperscript{22, 51-54}. The bacteria most commonly found in bile in case of ACC are gastrointestinal bacteria and in particular E. coli, Klebsiella spp and Enterococcus spp and anaerobic bacteria. The incidence of bile contamination varies depending on the duration of disease progression: in a Finnish series that included 515 patients with ACC, the bile was infected in 63% of cases after 24 hours of symptom development while that after 11 days of evolution, the infection rate drops to 31% bile\textsuperscript{55}. Several risk factors for biliary contamination were highlighted in different series: diabetes, age over 60 years, a history of ACC, a preoperative temperature> 37.3 °C, serum bilirubin> 8.6 micromol / l, leukocytosis than 14000/mm\textsuperscript{3}\textsuperscript{56-57}. Bile contamination in the ACC is associated, according to some authors, with a higher rate of postoperative complications and a higher mortality rate, especially in severe forms\textsuperscript{53-54, 58-59}. The consensus conference in Tokyo recommends performing a bile sample with cultivation for patients with severe ACC.
3. RESEARCH OBJECTIVE

3.1. PRIMARY OBJECTIVE

The main objective is to compare the occurrence of postoperative infections including surgical site infections (SSI) and distant infections after early cholecystectomy (performed within 5 days after onset of symptoms) for mild or moderate acute calculous cholecystitis (ACC) (without organ dysfunction) with and without antibiotics.

3.2. SECONDARY OBJECTIVE

The secondary objectives were:

• complications rate depending on the duration of the preoperative antibiotics
• Influence of postoperative surgical drainage on the occurrence of postoperative infections
• Analysis of the nature of infectious complications (surgical site infections, distant infection)
• Comparison of germs found in the bile and during the postoperative infections
• Duration of hospitalization
• readmission rates for surgical site infection (SSI)
• Rate of reoperation for SSI
• overall mortality rate at 30 days
• specific mortality rate at 30 days

4. RESEARCH DESIGN

4.1. STATEMENT OF PRIMARY AND SECONDARY CRITERIA

4.1.a. Primary endpoint

The primary endpoint was the proportion of patients with a post-operative infection (surgical site and/or distant infections) recorded before or at a consultation four weeks after cholecystectomy. The diagnosis of a post-operative infection was based on clinical, biochemical and/or morphological features and was confirmed (if possible) by bacteriological data. A successful outcome was defined as the absence of surgical-site infection.

Post-operative infections were defined as superficial or deep incisional infections or organ/space infections, according to the Centers for Disease Control and Prevention’s guidelines on the prevention of surgical site infections (SSIs).

4.1.a.1. Surgical site infection

Superficial incisional SSIs had to meet the following criteria: (a) occurrence within 30 days of the surgical procedure, and (b) involvement of only skin or subcutaneous tissue around the incision but with at least one of the following: (i) purulent drainage from the superficial incision; (ii) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (iii) one or more of the following signs or symptoms (pain or tenderness; localized swelling; redness or heat and opening of the superficial incision by the surgeon unless culture of incision is negative); (iv) diagnosis of a superficial incisional SSI by the surgeon or attending physician (according to the CDC’s definition in the American Journal of Infection Control, 1992).

Organ/space infections involved any organ or space (other than the incised body wall layer) that was opened or manipulated during the initial surgical procedure.

4.1.a.2. Distant infection

Distant infections included pulmonary and urinary infections, bacteremia and lymphangitis.
In case of doubt on the existence of a postoperative infection, the Monitoring Committee (see below) should be informed to distinguish postoperative infection and the adverse event. The existence of a fever, higher than 38.5 °C, in the postoperative period outside of first day postoperative should systematically carry out a biological assessment with blood cultures and possibly a morphological assessment. The existence of an inflammatory scar (laparotomy or trocars) without the presence of purulent discharge or a positive culture should not be considered a postoperative infection.

The duration of hospitalization and readmission rates for the SSI and the rate of reoperation for SSI will be analyzed. Similarly, mortality occurred during hospitalization or within 30 days will be analyzed (see case report form) distinguishing overall mortality and cause-specific mortality associated with postoperative infections. In case of occurrence of postoperative infection in the arm "Absence of postoperative antibiotics," the patient will be treated with appropriate antibiotics bacteriological samples and case report forms will be filled.

4.1.b. Secondary endpoints

The secondary endpoints are:
- complications rate depending on the duration of the preoperative antibiotics
- Influence of postoperative surgical drainage on the occurrence of postoperative infections
- Analysis of the nature of infectious complications (surgical site infections, distant infection)
- Comparison of germs found in the bile and during the postoperative infections
- Duration of hospitalization
- readmission rates for surgical site infection (SSI)
- Rate of reoperation for SSI
- overall mortality rate at 30 days
- specific mortality rate at 30 days

4.2. DESCRIPTION OF THE METHODOLOGY

4.2.a. experimental plan

It is a national multicenter, comparative, randomized in a ratio (1:1), non-controlled, non-inferiority, unblinded (open label) trial. Two groups of patients are compared (postoperative antibiotics versus no postoperative antibiotics).

4.2.b. Conduction of the study

4.2.b.1. Selection

In various medical and surgical series, the definition of ACC was very variable which resulted in some confusion in the comparison of different works. Recently, an international consensus conference held in Tokyo, has given a precise definition of the ACC and distinguishes several stages of severity. ACC is the association of local signs (Murphy sign, mass, pain, defense of the right hypochondrium), systemic symptoms (fever, leukocytosis, elevated C-reactive protein). When the diagnosis is suspected clinically, a morphological examination is necessary (ultrasound, a CT scan or MRI) to confirm the diagnosis. Morphological signs for diagnosis of ACC are: thickening of the gallbladder wall (> 4mm), a vesicular distension (>8 cm long axis and short axis 4cm), presence of gallstones or biliary debris (sludge), infiltration of pericholecystic fat, pericholecystic effusion. The echographic Murphy's sign is very supportive of the diagnosis of acute cholecystitis (Consensus Conference Tokyo). No studies have evaluated the sensitivity and specificity of these tests when these radiological signs are associated. Early ACC is defined in this work by disease duration of symptoms less than 5 days. This time is set by the start of appearance of abdominal pain and / or fever. These criteria will be collected in the case report form.
The patient will be informed of the existence of the protocol during the admission at the emergency department posing the indication of cholecystectomy for acute cholecystitis.

Medical examination as well as prior imaging exams in the study correspond to a routine practice (no extra cost):

- Clinical examination with collection of demographic data (gender, age, weight, height) should be noted. All co-morbidities as well as situations of potential risk of infection (diabetes mellitus, corticosteroid therapy, chronic renal failure, body mass index greater than 30, more than 65 years, recent surgery, albumin less than 35, COPD, tobacco or coronary insufficiency) should be recorded

- A review for imaging to confirm the diagnosis of acute cholecystitis which can be, depending on the habits ultrasound and / or CT and / or MRI. All patients selecting, verifying the criteria of inclusion and non-inclusion will be offered to participate in the study. They will be informed orally of the conduct of the study and the various examinations; an information form will be given (see Appendix).

The day of the surgery, after a period for reflection variable according to the date and the result of the surgery, the inclusion visit will be conducted and include:

- Verification of inclusion and non-inclusion criteria,

- A physical examination

- The organization of the planning of tests in the study.

After the inclusion of a patient, the investigator will inform the sponsor by faxing the completed Form Inclusion.

4.2.b.2. Patient’s follow up

4.2.b.2.1. preoperative management
The prescription of preoperative antibiotics is systematic when the patient is included in the study. The preoperative antibiotics include the association amoxicillin-clavulanic acid (Augmentin® 2gx3/day or generic). In case of allergy to beta-lactam antibiotics, the patient will be excluded from the study. Patients will be included in the study either through the Emergency department, or when the patient was hospitalized in a department (gastroenterology, geriatrics, internal medicine, etc.). A proportion of patients will have already started antibiotics (prescribed by the attending physician or the department in which the patient is hospitalized). The history of antibiotics received by the patient will be collected in the Case report form and analyzed. For these patients, after inclusion in the study and prior to cholecystectomy, antibiotics will be terminated and replaced by amoxicillin - clavulanic acid at a dose of 2gx3/day, in the absence of allergy for beta-lactam antibiotics. The total duration of preoperative antibiotic therapy will depend on the time of surgery and will in any case be less than 5 days (inclusion criteria). The total duration of antibiotic by amoxicillin - clavulanic acid is analyzed.

4.2.b.2.2. Peroperative management

Intraoperative antibiotic will be identical to antibiotics began preoperatively, namely amoxicillin and clavulanic acid.

A skin preparation before surgery (antiseptic shower) and at the operating room (cleansing and antisepsis of the surgical field) will be carried out. The procedure begins with a thorough exploration of the entire peritoneal cavity and of the gallbladder macroscopically to confirm the diagnosis of ACC. The treatment will consist of a complete cholecystectomy whose choice of incision will be at the convenience of the operator. The laparoscopic approach is preferred. The realization of a bile sample will be systematically performed to compare the germs found in the gallbladder bile and any germs found in postoperative complications. Performing intraoperative cholangiography will be left to the discretion of the surgical team. The need for surgical drainage (aspirative or not) will also be allowed in accordance with local conditions and the habits of the department. The operating time will be recorded and analyzed. These variables will be collected for statistical analysis. During the intervention may not be included in the study patients with biliary peritonitis and those with stones in the common bile duct discovered on intraoperative cholangiography.

4.2.b.2.3. Randomization

The randomization will be performed in the operating room immediately after surgery below). The randomization will be made by lot at the time of the declaration of patient via the Web. It will be stratified by center and to ensure a better balance, blocks of equal size with patients randomized to each treatment will be used at each center.

4.2.b.2.4. Postoperative management

- Choice of postoperative antibiotics:
The prescription or not of postoperative antibiotics will be determined by randomization. Before the administration of the antibiotic, the included patient was questioned about the existence of a possible allergy to beta-lactam antibiotics. Postoperative antibiotics will be identical to preoperative antibiotics and include the following antibiotics: amoxicillin - clavulanic acid (Augmentin® 2gx3/day or Generic).

The antibiotic treatment will be issued by pharmacies investigators centers. The association with a nitroimidazole will not be allowed in this study. The route of administration (intravenous or oral) and the date of per os relay depend on the postoperative clinical and
biological evolution of the patient and will be collected in the case report form. The introduction of the antibiotic will be carried out in hospital with monitoring of drug tolerance. The duration of postoperative antibiotic treatment is 5 days.

- **Postoperative management during the hospitalization:**

  Patients will be followed clinically every day by the surgical team. All patients have a blood test with a blood count on the day after the intervention. Other blood tests may be performed depending on the clinical and biological evolution of the patient. Patients may be discharged, when the surgeon deems necessary, from the second postoperative day. The antibiotic treatment with Augmentin® or Generic is issued by each investigator center. Antibiotics will be stored and dispensed by pharmacies of each center. For a practical matter, antibiotics will be purchased by pharmacies and reimbursed by the investigator center. Antibiotics will be delivered to the patient (1 gram sachets or tablets of 500 mg) at its output for the total duration of 5 days.

  * **For the antibiotic group**

    If no infection occurs during hospitalization, the patient can be discharged, when the surgeon deems appropriate, from the second postoperative day; antibiotics will be continued for a total duration of 5 days. The susceptibility of the bile will not be consulted. In other words, if it is found resistant bacteria to antibiotics in progress and the patient has no symptoms, there will be no change in antibiotic therapy.

    If the patient has fever > 38.5 °C outside of first postoperative day, it will be necessary to perform additional tests (laboratory tests with blood cultures, ultrasound scanner according to habits or department) to detect a postoperative infection (bacteriological evidence). In case of postoperative infection requiring a change of antibiotics (unlike amoxicillin - clavulanic acid or ciprofloxacin), this antibiotics should be adapted to the results of susceptibility testing. If infection occurred before bacteriological results, antibiotic therapy would first be probabilistic then adapted to the antibiogram.

  * **For the non antibiotic group**

    If no infection occurs during hospitalization, the patient can be discharged, when the surgeon deems necessary, from the second postoperative day. The susceptibility of the bile will not be consulted. In other words, if it is found resistant bacteria and the patient has no symptoms, there will be no change in management.

    If the patient has fever > 38.5 °C outside of first postoperative day, it will be necessary to perform additional tests (laboratory tests with blood cultures, ultrasound scanner according to habits or department) to detect a postoperative infection (bacteriological evidence). In case of postoperative infection requiring an antibiotic treatment, it should be adapted to the results of susceptibility testing. If infection occurred before bacteriological results, antibiotic therapy would first be probabilistic then adapted to the antibiogram. Analysis will be performed by intention to treat and patients with postoperative infection despite postoperative antibiotics will be considered as failure of the arm. In total, in the case of postoperative infections, the patient will be supported appropriately: antibiotics, possibly endoscopic treatment, radiological drainage and / or surgical drainage.

- **Postoperative management after the hospitalization:**

  At the discharge of the patient, the case report form will be controlled by a Clinical Research Associate (CRA) of the investigator center to check the quality of filling the CRF. The patient will be informed by his surgeon as well as through the information sheet of the need to
monitor the temperature at home. At the onset of fever (temperature > 38.5 °C) and/or abdominal pain, the patient should call the surgeon on call (telephone number given to the patient) from the department in which he has been managed and go to the emergency department for completion of a clinical examination, laboratory tests and possibly a morphological assessment according to the warning signs. In the absence of postoperative complications objectified the patient can return home with the same instructions. However, in case of postoperative infections, the case report form will be filled. The patient will be hospitalized depending on the severity of the complication. Similarly, the attending physician of the patients included in the study ABCAL will be notified in writing that the patient involved in the study ABCAL and it is necessary to carry out laboratory tests to emergencies in case of fever > 38.5 °C.

All patients will be reviewed in a follow up consultation four week after the surgery (routine visit) during which will be collected possible infections. The surgeon will complete the case report form (end of study visit).
4.2.b.3. Calendar of the study:

<table>
<thead>
<tr>
<th>Selection</th>
<th>Preoperative period</th>
<th>Postoperative period</th>
<th>Postoperative period</th>
<th>Week 4 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Demographic data</td>
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<tr>
<td>Clinical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Morphological examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
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<td>X</td>
<td>X (arm)</td>
<td>X (arm)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Letter to the attending physician</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

4.4. DESCRIPTION OF THE TREATMENT

4.4.a. Posology

The prescription of preoperative antibiotics will be systematically performed when the patient is included in the study. The preoperative antibiotics include the combination amoxicillin and clavulanic acid (Augmentin® 2gx3/day or with generic equivalent). This preoperative antibiotics will be continued in all patients during surgery. During this, the antibiotic will be delivered intravenously. During of the intervention, randomization will distinguish patients who receive postoperative antibiotics. For these patients, the antibiotic will be issued for a period of 5 days. The per os will be chosen during the postoperative period. Throughout the study, the dose does not vary whatever the prescribed antibiotic. In total, the maximum duration of antibiotics will be 5 days (5 postoperative days). The description of the dosage and administration procedures is detailed in Chapter 6.1.

4.4.b. Labelling

The description of the labelling is reported in chapter 6.

4.5. REQUIRED PERIOD FOR PARTICIPATION OF PERSONS AND DESCRIPTION OF THE CHRONOLOGY AND DURATION OF ALL PERIODS OF TESTING INCLUDING FOLLOW UP

From the first inclusion, the sponsor shall immediately inform the competent authority and the CPP II North West of the effective date of start of the study. The date of completion will be forwarded by the sponsor to AFSSaPS and CPP within 90 days. The ending date of the research corresponds to the end of the participation of the last person included in this research. The duration of the study is estimated to be 31 months. The total duration of study participation for the patient is 4 weeks.

4.6. DESCRIPTION OF RULES FOR PERMANENT OR TEMPORARY CESSION

4.6.a. Permanent cessation
Subjects may withdraw their consent and request to leave the study at any time and whatever the reason. In the event of early cessation, the investigator must document the reasons as fully as possible.

The investigator will permanently discontinue the participation of a subject in the study for any reason that would serve the best interests of the subject especially in cases of serious adverse events.

4.6.b. Cessation of the research

The study can be stopped early in case of unexpected adverse events, serious (requiring or not a review of the safety profile of the product). Similarly, unforeseen events or new product information, upon which the objectives of the study or clinical program are unlikely to be achieved, may lead the sponsor to stop the study prematurely. The Amiens University Hospital reserves the right to interrupt the study at any time, if it appears that the inclusion objectives are not reached.

In case of early termination of the study, the information will be sent by the sponsor within 15 days at AFSSaPS and the CPP.

5. PATIENTS’ SÉLECTION AND NON INCLUSION

5.1. PRE-INCLUSION CRITERIA
Not applicable.

5.2. INCLUSION CRITERIA
- Acute calculous cholecystitis (ACC) confirmed by morphological examination (echography, CT scan, MRI)
- Mild or moderate
- Complaints for less than 5 days
- Written consent
- Patient older than 18

5.3. NON INCLUSION CRITERIA
- Grade III ACC
- Biliary peritonitis
- Hepatic abcess
- Acute pancreatitis
- Septic shock
- Patient under guardianship
- ASA score IV or V
- Suspected gallbladder cancer
- Pregnancy
- Treatment with methotrexate
- Allergy to amoxicillin plus clavulanic acid

5.4. RECRUITMENT PROCEDURES

The target population is defined as ACC requiring surgical management by Laparoscopic or laparotomy cholecystectomy. The recruitment of these patients is achieved in 20 public hospitals (university hospitals).
5. PROCEDURE FOR EARLY CESSATION OF THE TESTED TREATMENT AND EXCLUSION FROM THIS RESEARCH

5.5.a. Criteria and procedures for premature discontinuation of treatment or exclusion of a patient

The output from the protocol will be made either by deliberate decision of the subject, either out of necessity, following a decision of the investigator, in the following cases:

- Non compliance with the conditions of the study (no postoperative antibiotic)
- Occurrence of a serious adverse event.

In case of the output of the protocol by deliberate decision of the subject, the patient will be followed in the same way as other patients (consultation to 4 weeks). In case of serious adverse event if the patient is readmitted, laboratory tests (blood count, C-reactive protein, Serum electrolytes, blood cultures) and morphological (CT scan) will be performed to detect postoperative complications.

The treatment will be adapted to the results of this assessment and may include antibiotics, radiological drainage and reoperation.

In case of adverse event, the patient will be followed until its full resolution (stabilization at a level considered acceptable by the investigator or return to the prior state) even if the patient was excluded from this study.

5.5.b. Modalities and timing for data collection

The criteria for early termination of the study will be collected daily during hospitalization (examination of the patient) and during the monitoring visit (end of study visit). In the case of a SAE, the surgeon will be informed by the patient (cf. annex).

5.5.c. Modalities for replacing these persons, if any

In case of a number of subjects excluded greater than or equal to 15% of the total number of patients to include (55 patients) the monitoring committee will be informed. The number of patients excluded patients will be replacing one for one.

5.5.d. Procedures for monitoring of these persons

The output of a patient study will not change his usual care from his illness. There will be no special exam in the study. In case of adverse events, serious or not, accurate monitoring can be considered depending on the gravity of the adverse event and its severity. The monitoring committee shall specify the procedures for monitoring on an individual basis. The scientific committee will be constituted by several investigators and will be chaired by the head of the coordinating center for the study (Prof. Jean-Marc Régimbeau). This committee will be responsible for validating the design of the study and verify the application. In particular, it will ensure that the investigators propose the study to all eligible patients, that the subject is included only if he has previously signed the consent form.

It will consider any changes to be made during the study, including potential problems of defining complications of cholecystectomy. It will centralize the results at the end of study, analyze it and take charge of their publication in a scientific journal after having submitted to
all investigators. The Monitoring Committee will be informed in case of SAEs requiring an output of the included patient and decide on the ethical character of continuing the study.

6. TREATMENTS ADMINISTERED TO PATIENTS

6.1. DESCRIPTION OF THE TREATMENT

6.1.a. Experimental drug

6.1.a.1. Identification of the treatment

AUGMENTIN 1 g/125 mg ADULT, powder (amoxicillin/clavulanic acid: 8/1)

The detailed composition is present in the summary of product characteristics.

AMM: Laboratoire GLAXO-SMITHKLINE

6.1.a.2. Storage

The experimental drug will be stored at the hospital pharmacy and will be delivered according to the randomization.

6.1.a.3. Administration

The antibiotic is given 3 times per day.

6.1.b. Non experimental drug

Not applicable

6.2. PERMITTED AND PROHIBITED DRUGS

6.2.a. Traitements autorisés

All treatment are allowed except methotrexate.

6.2.b. Traitements non autorisés

The methotrexate is not allowed

6.3. STORAGE

6.3.a. Description du stockage à la pharmacie

The treatment is stored as kit for 5 days in the pharmacy.

7. EVALUATION OF THE EFFECTIVENESS

7.1. DESCRIPTION OF PARAMETERS FOR EVALUATING THE EFFECTIVENESS

The parameters for evaluation of effectiveness will help diagnose the primary endpoint (postoperative infection) and the secondary endpoints. The parameters for assessing the effectiveness will be clinical (fever > 38.5 °C, heart rate, blood pressure, awareness, vigilance) and biological. Morphological examinations (CT or ultrasound) may be requested on a case by case to diagnose intra abdominal collections.
7.2. METHODS AND CALENDAR PROVIDED FOR MEASURING AND COLLECTING THE PARAMETERS FOR EVALUATING THE EFFECTIVENESS

During the hospitalization, a visit will be made twice a day by the medical staff who treated the patient. A blood sample and a morphological examination (CT scan with and without injection of contrast medium) will be made in case of suspicion of a surgical complication. At the follow-up visit, 4 weeks after the surgery the different occurred complications will be collected.

8. EVALUATION OF THE SAFETY

8.1. DESCRIPTION OF PARAMETERS FOR EVALUATING THE SAFETY

The parameters for safety assessment will be clinical (fever > 38.5 °C, heart rate, blood pressure, awareness, vigilance) and biological. The rate of reoperation, readmission and mortality will have to assess the safety of this protocol.

8.2. METHODS AND CALENDAR PROVIDED FOR MEASURING AND COLLECTING THE PARAMETERS FOR EVALUATING THE SAFETY

During the hospitalization, a visit will be made twice a day by the medical staff who treated the patient. A blood sample and a morphological examination (CT scan with and without injection of contrast medium) will be made in case of suspicion of a surgical complication.

8.3. PROCEDURES MISSES EN PLACE EN VUE DE L’ENREGISTREMENT ET DE LA NOTIFICATION DES EVENEMENTS INDESIRABLES

The definitions and the procedures implemented for the registration and notification of adverse events are reported in the International Conference of Harmonization (ICH).

8.3.b.1.5. specificity

The adverse events specific to this protocol are listed below:

- death
- Sepsis
- Severe Sepsis
- Septic shock

8.3.a. In utero exposition

If a woman becomes a pregnancy within the framework of the research or if her partner is involved in the research (drug up to the seminal line of man), the pregnancy must be reported to the sponsor within the time he has defined. The investigator informs the vigilance department of the sponsor with a standard sheet of "collection of initial data of the pregnancy". This form must include the estimated date of delivery, the coordinates of the obstetrician and the maternity if the pregnancy continues. The investigator should follow the patient until the end of the pregnancy or its termination and notify the outcome to the sponsor through a standard sheet collection of pregnancy outcome. If the outcome of pregnancy is part of the definition of serious adverse events (hospitalization with miscarriage, fetal death, birth defects, etc..) the investigator must follow the procedure.
for reporting SAEs. If it is a paternal exposure, the investigator must obtain the agreement of
the partner to collect information on pregnancy.

8.3.b. Monitoring Committee
The Independent Monitoring Committee is responsible for monitoring the clinical and
biological tolerance of the study. It is responsible to inform the Scientific Committee in its
decisions for the amendment or termination of the study. It is made in the initiation of the
study. The Monitoring Committee shall forward its recommendations to the Scientific
Committee which decides whether or not the study must be stopped. The decision to stop the
study can be taken earlier if it appears contrary to the rules to pursue it (occurrence of serious
adverse events, publication of trial results providing the answer to the question ...). The
Monitoring Committee will be informed in case of SAEs requiring an output of the patient
included. In case of output of the study of a proportion of patients significantly different
between the two treatment arms studied (use of fibrin glue vs. no glue), the monitoring
committee will decide on the ethical character of continuing the study.

The scientific committee will be constituted by several investigators of the two centers and
will be chaired by the head of the coordinating center for the study (Prof. Jean-Marc
Regimbeau). This committee will be responsible for validating the design of the study and
verify the application. It will consider any changes to be made during the study including
potential problems in defining complications of cholecystectomy. It will centralize the results
at the end of study, analyze it and take charge of their publication in a scientific journal after
having submitted to all investigators.

8.4 MODALITIES AND DURATION OF FOLLOW-UP FOR PEOPLE WITH ADVERSE
EVENTS
Each adverse event will be followed to its full resolution (stabilization at a level considered
acceptable by the investigator or return to the prior state) even if the patient was excluded
from this study

9. STATISTICS
The head of the analysis is Momar Diouf statistician. Direction de la Recherche Clinique –
CHU Sud Amiens — 80054 Amiens Cedex 1- FRANCE

9.1. DESCRIPTIOn OF STATISTICAL METHODS
No interim analysis is planned in this study.
The bilateral Student t test will be used to compare quantitative values between the two
groups. The bilateral Fisher exact test will be used to compare qualitative variables between
the two groups including the primary endpoint. The results are expressed as mean ± standard
deviation or median [interquartile range] (for quantitative variables) and percentages (for
qualitative variables).

9.2. NUMBER OF PATIENTS
This was a non-inferiority study based on the hypothesis that the absence of post-operative
AB treatment (amoxicillin plus clavulanic acid) would not be inferior to use of the treatment,
as judged by the post-operative infection rate (including surgical site and distant infections)
four weeks after cholecystectomy. Our calculation of the sample size was based on published
data \cite{16-21} and an expected post-operative infection rate in the AB group of 18.5%. Validation
of the starting hypothesis required a clinically significant non-inferiority margin of 11%. Our
choice of 11% was prompted by the discussion in D’Agostino et al (Stat in Med, 2003, page
177) on the physician’s point of view of non-inferiority margins in anti-infective trials. With a one-sided \( \alpha \) risk of 2.5% and a \( \beta \) risk of 20%, application of the equation developed by Piantadosi\(^{22} \) yielded a sample size of 196 patients per arm. Taking into account an expected drop-out/missing data rate of 5%, the final sample size was 414 patients. Non-inferiority would be established if the upper limit of two-sided 95% confidence interval of the difference of proportion of infections between the two arms was lower than the non-inferiority margin.

9.3. SIGNIFICATIVITY
With regard to the main variable, the threshold test of superiority is 5% in terms of the type I error. As the analysis by subgroup, as well as those on secondary variables were exploratory, no adjustment of p values are expected to account for inflation risk of Type I error.

9.4. STATISTICAL CRITERIA FOR STOPPING THE STUDY
As no intermediate statistical analysis is provided, the search will be stopped when all information will be collected and validated for all included patients.

9.5. MISSING OR NON–VALID DATA
To ensure that the evaluation of the primary objective concerns the size as complete as possible (full analysis set), patients for whom it is not possible to determine at 30 days if they had a postoperative complication will be considered as having had a complication. Thus, missing values should be observed for the main variable if the patient has requested a total cancellation of its stored information.

If such an imputation was necessary, the primary endpoint analysis would also be made for all patients for whom the information will be available (evaluable subjects sample) to determine the sensitivity of the method of imputation.

For the analysis by subgroup, as well as those on the secondary variables, it is assumed that missing data are achievements of a random process (missing completely at random).

9.6. MANAGEMENT OF CHANGES IN THE PLAN OF ANALYSIS OF THE INITIAL STRATEGY
In case of substantial changes to the plan of analysis, it will be approved by the sponsor. If necessary, the sponsor shall obtain prior to its implementation a favorable opinion of the CPP and an authorization from the at AFSSaPS within their respective jurisdictions.

9.7. PEOPLE TO BE INCLUDED IN THE ANALYSIS
The comparison of the complication rate within 30 postoperative days after the procedure will cover the size as complete as possible (full set analysis).

Analyses by subgroups as well as those on secondary variables included all patients for which the information is available (evaluable subjects sample).

10. SOURCE DOCUMENTS
10.1. ACCESS TO DATA
According to GCP:
- the sponsor is responsible for obtaining the agreement of all parties involved in the research to ensure the direct access to all places of conduct of research, source data, source documents and reporting for the purpose of quality control and audit by the sponsor.
• the investigators will make available to persons responsible for monitoring, quality control or audit of biomedical research, documents and personal data strictly necessary for this control, accordance with the laws and regulations in force (articles L.1121-3 et R.5121-13 du code de la santé publique).

10.2. SOURCE DOCUMENTS

Source documents are defined as any document or original thing to prove the existence or the accuracy of a fact recorded during the clinical study will be retained for 15 years by the investigator or by the hospital if it is a medical file.

10.3. CONFIDENTIAL DATA

According to the provisions concerning the confidentiality of data that are available to those responsible for quality control of biomedical research (Article L.1121-3 of the Code of Public Health), according to the provisions relating to confidentiality of information including nature of experimental drugs, studies (Article R. 5121-13 of the Code of public Health), people with direct access to data shall take all necessary precautions to ensure confidentiality of information relating to experimental drugs, studies and patients who are suitable in particular as regards their identity and the results achieved. These people, as well as the investigators themselves, are subject to professional secrecy (under the conditions laid down in Articles 226-13 and 226-14 of the Criminal Code).

During the biomedical research or its outcome, the data on people and sent to the sponsor by the investigator (or other specialized responders) will be made anonymous. It never should appear clearly the names of involved persons or their address.

Only the first three letters of the firstname's subject and the first two letters of his name will be recorded, along with a code number specific to the study indicating the order of inclusion of subjects.

The sponsor will ensure that every person included in this research has agreed in writing for the access to personal data relating to him and strictly necessary for checking the quality of research.

11. QUALITY CONTROL

A CRA mandated by the sponsor will ensure the successful completion of the study, the collection of data generated by writing, their documentation, recording and reporting in accordance with implemented standard operating procedures and in accordance with Good Clinical Practice as well as laws and regulations. The investigator and his team are willing to make themselves available during the visits of Quality Control performed regularly by the CRA.

During these visits, the following items will be reviewed:

• informed consent,
• Compliance with the study protocol and the procedures that are defined,
• Quality of data collected in case report forms: accuracy, missing data, data consistency with the source documents 'source' (medical records, appointment books, original laboratory results, etc..)
• Management of potential products.

In addition, the investigators agree to accept audits of quality assurance conducted by the sponsor as well as inspections by the competent authorities. All data, all documents and reports may be subject to audits and regulatory inspections without being opposed to medical confidentiality.
12. ETHICAL CONSIDERATIONS

12.1. COMITE DE PROTECTION DES PERSONNES

The protocol, information sheet and consent form of the study will be submitted for review to the Committee on the Protection of Persons (North West II).

Notification of the approval of the CPP will be sent to the study sponsor and the Competent Authority. A request for authorization shall be sent by the Sponsor to AFSSaPS before the start of the study.

12.2. SUBSTANTIAL MODIFICATIONS

In case of substantial modification to the protocol by the investigator, it will be approved by the sponsor. The sponsor must obtain prior to its implementation a favorable opinion of the CPP and an authorization from the AFSSaPS within their respective competencies. A new consent of patients involved in the research will be collected if necessary.

12.3. PATIENT INFORMATION AND CONSENT FORM

The patients will be informed fully and fairly, in understandable terms, about the objectives and the constraints of the study, the potential risks involved, the surveillance measures and the safety measures. They must be informed about their rights to refuse to participate in the study or the possibility to withdraw at any time.

All of this information is stipulated in the consent form given to the patient by the investigator. The written consent of the patient will be collected by the investigator, or a physician who represents him before the final inclusion in the study. A copy of the information letter and the consent form signed by both parties will be given to the patient; the investigator will retain the original of these two documents. A copy will be placed at the end of study in a sealed envelope containing all consent forms; it will be archived by the sponsor.

Women who are pregnant or breastfeeding, minors and persons unable to express their consent will be excluded from the study.

12.4. DEFINITION OF THE PERIOD OF EXCLUSION

The exclusion period specified in this study is 1 month, during which the patient can not participate in another clinical research protocol after the end of the study or after its early termination.

12.5. MANAGEMENT SPECIFIC TO THE RESEARCH

The management of patients included in this study was modeled on the management usually recommended.

12.6. SUBJECT INDEMNITY

No compensation in compensation for constraints suffered will be paid to the patient.

12.7. REGISTRATION TO THE NATIONAL FILE

No registration is planned as part of the research because people present affection and the object of the research is relevant to their condition.

13. DATA TREATMENT AND SOURCE DOCUMENTS STORAGE

13.1. ELECTRONIC CASE REPORT FORM

Internet based support for data collection will be used in this study. This electronic case report form will be established in each center. It only requires Internet access and a browser. A help document for the use of this tool will be provided to investigators.
Control testing data consistency will be integrated into electronic format. An audit function (Audit Trail) is integrated into the electronic notebook to monitor any changes in the study data. This function also allows to clearly identifying the person who made the change and the date. Justification can be optionally integrated as comment.

All access will require the combination of a user and a password ("electronic signature") and health data name will be entered in encrypted 128 bit SSL mode. All information required by the protocol must be recorded in the CRFs. Data should be collected progressively and recorded in these CRFs explicitly. Each missing data should be coded.

The investigator is responsible for the accuracy, quality and relevance of all entries.

13.2. DATA ANALYSIS

The responsible of the analysis is Professor Pierre Duhaut, Internal medicine department – Amiens North Hospital – Place Victor Pauchet – 80054 Amiens Cedex 1 (duhaut.pierre@chu-amiens.fr).

The statistical analysis should focus on the primary endpoint, but also on secondary endpoints after prior verification on the quality and completeness of data. Intention-to-treat analysis will be performed.

A descriptive analysis of the entire population will be done to check whether there are deviations from the protocol. Be mentioned the percentage of subjects / patients wrongly included and the percentage of subjects / patients lost to follow. A descriptive analysis by treatment group will be conducted to verify the result of randomization. No interim analysis should be performed.

The Student t test will be used for bilateral comparison of quantitative variables between the two groups. The chi square test or Fisher exact test will be used to compare qualitative variables between the two groups. The results will be expressed as mean ± standard deviation (for quantitative variables) or median (minimum - maximum) or percentage (for qualitative variables). Results will be analyzed by integrating the duration of preoperative antibiotics and the severity of ACC.

13.3. CNIL

This study is part of the "Methodology Reference" (MR-001) pursuant to Article 54 paragraph 5 of the Law No. 78-17 of 6 January 1978 relating to data, files and freedoms. This change was approved by decision of 5 January 2006. Hospital of Amiens, sponsor of the study, signed a commitment to comply with the "Methodology of Reference."

13.4. FILING

The following documents will be archived by the name of the study in the local of Visceral and digestive Surgery department of the University Hospital of Amiens until the end of the period of practical utility.

These documents are:

- Protocol and Annexes, any amendments,
- Forms for information and original signed consents
- Individual data (authenticated copies of raw data)
- Follow-up documents
- Statistical Analysis
- Final Study Report

At the end of the period of practical utility, all documents to archive, as defined in the procedure of "filing and archiving documents related to biomedical research" of the
University Hospital of Amiens will be transferred to the site of archiving (Central Archives Department - Amiens Hospital) and will be under the responsibility of the Sponsor for 15 years after the end of the study in accordance with institutional practices. No displacement or destruction shall be made without the consent of the Sponsor. After 15 years, the sponsor will be consulted for destruction. All data, all documents and reports could be subject for audit or inspection.

14. FUNDING AND INSURANCE
14.1. FUNDING
The budget of the study is 154,850€.
14.2. INSURANCE
The Sponsor shall subscribe for the duration of the study an insurance guaranteeing its own liability and that of any doctor involved in the conduct of the study. It will also ensure full compensation for injuries for the person enrolled in the study.

15. FEASIBILITY
ACC is a common disease (prevalence of 9.7% among patients hospitalized for abdominal pain lasting for less than 8 days) has been clearly defined in an international consensus conference in 2007. Although approximately 30% of patients who have a severe form will be excluded, the number of predictable subject necessary seems consistent with the achievement of a national multicenter. Federation Research Surgery gave a very favorable review in the realization of this trial. Investigators are qualified clinicians in medicine and especially surgery. They justify a research experience.

The rate of postoperative infections during a cholecystectomy for acute cholecystitis is about 18% (8-29%)\(^6\). Proposing a study power of 80% and an alpha error of 5%, the number of subjects required is 207 patients in each arm (test for non-inferiority).

We propose a randomized trial including 414 patients in total (207 / arms). The number of subjects required seems consistent with the impact of disease on the national level. At Amiens Hospital, it is performed about 60 acute cholecystitis (all stages of severity combined) per year. A multicenter study with centers located throughout France could afford to get a number of patients included 414 over a period of 24 months. Among patients with ACC, approximately 30% will be excluded due to severe ACC. Among patients with mild or moderate ACC, some patients will be excluded due to the discovery of peroperative biliary peritonitis or stones in the common bile duct. Other centers could help bring a number of patients to answer the main question. Indeed, whatever the size of the center, the average number of patients to be included will be 10 per year. This realistic figure will be largely achieved whatever investigation centers.

16. PUBLICATION
Communications and scientific reports for this study will be carried out under the responsibility of the principal investigator of the study with the agreement of the responsible investigators. The co-authors of the report and publications will be investigators and clinicians involved in proportion to their contribution to the study and the biostatistician and research associates. The results of this work will be a major publication whose first author is Jean-Marc Régimbeau. The association FRENCH appear in the list of authors as well as the RECIF Network.

Rules publications will follow international recommendations (N Engl J Med 1997; 336 :309
The study will be recorded on a website with free access (Clinical trial) before the inclusion of the first patient in this study.

Any report, written or oral communication caused by this study should be sent to the developer and published in accordance with the charter of publication of HUS.
**Table 1: published studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Study design</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al.</td>
<td>1984</td>
<td>44</td>
<td>Randomisée</td>
<td>Cafazoline vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Havig et al.</td>
<td>1973</td>
<td>77</td>
<td>Randomisée</td>
<td>Ampicilline vs. Chloramphenicol vs. penicilline + streptomycine</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Kune et al.</td>
<td>1975</td>
<td>189</td>
<td>Rétrospective</td>
<td>Antibiothérapie pré-opératoire vs. absence d’antibiotiques</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Groezinger et al.</td>
<td>1987</td>
<td>80</td>
<td>Comparative</td>
<td>Mezlocilline schéma court vs. schéma long</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Muller et al.</td>
<td>1987</td>
<td>53</td>
<td>Randomisée</td>
<td>Ampicilline + tobramycine vs. Cefoperazone + piperacilline</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Friedler et al.</td>
<td>1988</td>
<td>40</td>
<td>Randomisée</td>
<td>Ceftriaxone vs. Cefoperazone</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Lau et al.</td>
<td>1990</td>
<td>203</td>
<td>Randomisée</td>
<td>Cefamandole schéma court vs. schéma long</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Grant et al.</td>
<td>1992</td>
<td>292</td>
<td>Randomisée</td>
<td>Cefamandole vs. Cefotaxime</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Krajden et al.</td>
<td>1993</td>
<td>47</td>
<td>Randomisée</td>
<td>Piperacilline vs. Cefazoline</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Chacon et al.</td>
<td>1990</td>
<td>97</td>
<td>Randomisée</td>
<td>Pefloxacine vs. Ampicilline + gentamycine</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>1993</td>
<td>120</td>
<td>Randomisée</td>
<td>Cefépime vs. Mezlocilline + gentamycine</td>
<td>Equivalence</td>
</tr>
</tbody>
</table>
17. RÉFÉRENCES


