EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS AND TREATMENT OF CHOLECYSTITIS

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It has been over a century since the first cholecystectomy was performed by Karl Langenbuch in 1882. Since that time, there have been an increasing number of advances in clinical research in the field of biliary surgery. Surgical evidence has progressed from anecdote and observations, case studies and reports of patient series, to sophisticated laboratory, clinical and epidemiologic research. Quite recently, the principles of evidence-based medicine have been increasingly integrated into the contemporary practice of biliary surgery. Despite this promulgation of clinical research however, no practice guidelines on the diagnosis and treatment of cholecystitis exists for surgeons to refer to during their day-to-day encounters of patients with gallstone disease.
These guidelines examine the evidence currently available and provide more specific recommendations for the diagnosis and management of patients with gallstone disease and cholecystitis. It aims to assist the surgeon optimize treatment by selecting the best course of action on the basis of the best-available evidence tempered by the opinion of experts. With regard to diagnosis, while medical history has traditionally been the cornerstone of the evaluation of the patient with gallstone disease, the available evidence will show the true significance and reliability of the diagnostic criteria for gallstone disease currently in use. For patients with asymptomatic gallstones, the guidelines will help the clinician determine whether he should proceed with an operative procedure or simply observe the patient. Since a significant proportion of patients present with symptomatic disease, the guidelines will likewise address the controversies concerning the preferred surgical approach for both acute and chronic cholecystitis in this era of minimally invasive surgery, the appropriate timing of surgical intervention, and make recommendations on the use of antimicrobials and drains.

With these evidence-based practice guidelines, the Philippine College of Surgeons looks forward to presenting data that not only will be of clinical use to the busy practitioner but likewise provide recommendations that will give the surgeon a rational choice between the available diagnostic and therapeutic options. The guidelines presented herein are not meant to be dogmatic decisions but rather merely presents the reader with practical tips that will assist in the evaluation and management of gallstone diseases. It is hoped that these guidelines will subsequently be incorporated into everyday practice and form the foundation for the management of gallstone disease and cholecystitis.

The following clinical questions were addressed by the guidelines:

1. What clinical findings are most helpful in diagnosing symptomatic cholecystitis?
2. What ancillary tests are helpful in the diagnosis of acute cholecystitis?
3. What ancillary test is most helpful in the diagnosis of chronic calculous cholecystitis?
4. Is cholecystectomy indicated for asymptomatic gallstones?
5. What is the recommended surgical approach in the management of acute cholecystitis?
6. What is the optimal timing of surgery for acute cholecystitis?
7. Is antibiotic therapy indicated in the management of acute cholecystitis? What antibiotic/s is/are recommended for the treatment of acute cholecystitis and what is the appropriate dose, route, and duration of administration?

8. What is the recommended surgical approach in the management of chronic cholecystitis?

9. Is antibiotic prophylaxis indicated in the management of chronic cholecystitis? What antibiotic/s is/are recommended for prophylaxis in chronic cholecystitis and what is the appropriate dose and route of administration?

10. Should an intra-peritoneal drain be routinely placed after cholecystectomy?

METHODS

The Technical Working Group (TWG) was composed of:
1. Domingo S. Bongala, Jr., MD, FPCS – Chairman
2. Antonio L. Anastacio, MD, FPCS
3. Michael Brillantes, MD, FPCS
4. Mario M. Panaligan, MD, FPSMID
5. Maita Theresa Rigor, MD, FPCS
6. Nilo C. de los Santos, MD, FPCS
7. Rey Melchor F. Santos, MD, FPCS – Regent-in-Charge

A search of publications was carried out using a sensitive search strategy combining MESH and free-text searches. This strategy included an extensive search of the following databases:
1. Medline (1966 to present)
3. Health Research and Development Network (Herdin)
4. Philippine Journal of Surgical Specialties CD-ROM (1979 to 1999) and hand searches from 2000 to present

From the search results, the TWG selected relevant articles for full-text retrieval using the Nominal Group Technique. Retrieved studies were then assessed for eligibility according to the criteria set by the guideline developers. The methodologic quality of the studies was appraised by two independent reviewers using a quality assessment instrument developed by the Philippine Cardiovascular Research Group.

The pertinent results of the selected articles as based on the clinical questions were summarized and compared. When appropriate and where relevant data were available, the sensitivities, specificities, accuracies, predictive values and likelihood ratios, including the 95 per cent confidence intervals were calculated for diagnostic articles; the relative risks and risk differences were computed and compared for articles on therapy.

Each guideline is rated using a two-part rating system. Roman numerals I through III are used to indicate the “quality of evidence” while the letters A through C are used to indicate the “strength of the recommendation.”

The clinical evidence was rated according to the assessment system of the Infectious Disease Society of America:

Level I – Evidence from at least one properly designed randomized controlled trial or meta-analysis

Level II – Evidence from at least one well-designed clinical trial without proper randomization, from cohort or case-controlled analytic studies (preferably from one center), from multiple time-series, or from dramatic results in uncontrolled experiments

Level III – Evidence from opinions of respected authorities on the basis of clinical

The members of the Technical Working Group prepared the evidence-based report based on the articles retrieved and appraised. After evaluation and validity appraisal, 50 articles were chosen and used to answer the clinical questions. The TWG then held several meetings to discuss each clinical question and the corresponding evidence, formulate the initial recommendations and thereafter reach a consensus utilizing the Nominal Group technique. A consensus was reached after having attained 70 per cent agreement among the members of the Technical Working Group.

The TWG together with the panel of experts reviewed the interim report during the Surgical Infection Forum held at the EDSA Shangri-la Hotel, Mandaluyong City on
November 22, 2003. Each clinical question, the evidence and the recommendations were analyzed and the participants given the opportunity to express their opinions and views. The modified Delphi Technique was then used to determine the degree of consensus regarding the recommendations.

The panel of experts included Drs. Isaac David Ampil II, Ma. Luisa Aquino, Francisco Y. Arcellana, Marvin Basco, Roman L. Belmonte Jr., Domingo S. Bongala, Jr., Michael Brillantes, Jose Bugayong, Edgardo Cabrera, Dominador M. Chiong, Edgardo R. Cortez, Arturo S. de la Pena, Nilo de los Santos, Ramon L. de Vera, Maximino Dy-R. Elgar, Alex A. Erasmo, Ramon S. Inso, Albert Ismael, Amado Lavalle, Fernando Lopez, Ray B. Malilay, Narciso S. Navarro, Jr., Maita Theresa Rigor Rey Melchor Santos, Stephen S. Siguan, Menandro Siozon, Jr., Kim Shi C. Tan, and Arturo Tolentino.

The strength of recommendations for the guidelines was categorized according to the level of agreement of the panel of experts after a votation of the participants:

Category A – Recommendations that were approved by consensus (at least 75 per cent of the multi-sectoral expert panel)

Category B – Recommendations that were somewhat controversial and did not meet consensus

Category C – Recommendations that caused real disagreements among the members of the panel

The letters A through C are used to indicate the “strength of recommendation” for or against the use of a particular option. Determination of the “strength of recommendation” was based on a consideration of several criteria, including the “quality of evidence” as determined by two independent appraisers of the studies used for the recommendation, potential for harm if an intervention did not take place, as well as the potential complications and costs associated with an intervention. Therefore an exact correlation does not exist between the “quality of evidence” and the “strength of a recommendation.”

These guidelines are designed to assist physicians and surgeons in the management of patients with gallbladder disease. It is important to recognize that in some instances the amount and quality of data available to inform the decision-making process were limited. In such cases, guidelines had to be developed from a review of studies incorporating small numbers of cases or from consensus expert opinion. It is also important to recognize that these guidelines should never be a substitute for clinical
judgment. Clinicians need to practice clinical discretion when applying a guideline to an individual patient since it is impossible to develop guidelines that apply to all situations.

The draft guidelines were then presented to the stakeholders during the Philippine College of Surgeons Annual Convention held at the EDSA Shangri-la Hotel, Mandaluyong City on December 3, 2003. The invited participants included practicing surgeons and representatives from the pharmaceutical companies and concerned government agencies.

The Evidence-Based Clinical Practice Guidelines on the Diagnosis and Treatment of Cholecystitis was then submitted to the 2004 PCS Board of Regents for final approval on March 2004.

**OPERATIONAL DEFINITIONS**

**Symptomatic Cholecystitis**  
- includes both acute and chronic cholecystitis

**Acute Cholecystitis**  
- acute upper abdominal pain with tenderness under the right costal margin  
  - accompanied by fever, laboratory markers of inflammation and scintigraphic or sonologic evidence

**Complicated Cholecystitis**  
- refers to emphysematous cholecystitis, cholecystitis with perforation and secondary peritonitis, pericholecystic abscess formation and generalized peritonitis

**Early Cholecystectomy**
- cholecystectomy performed within 72 hours of admission

**Delayed Cholecystectomy**
- initial conservative treatment with antimicrobials followed by cholecystectomy 8-12 weeks later

**Standard Open Cholecystectomy**
- transverse subcostal skin incision greater than 6 cm in length to provide comfortable exposure of the gallbladder

**Mini-incision/Minilaparotomy Cholecystectomy**
- transverse subcostal skin incision less than or equal to 6 cm in length

**Laparoscopic Cholecystectomy**
- use of 10 mm subxiphoid and 5 mm lateral trocars for cholecystectomy

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**EXECUTIVE SUMMARY**

1. **What clinical findings are most helpful in diagnosing symptomatic cholecystitis?**

   No single clinical finding or combination of findings is sufficient to establish or exclude the diagnosis of symptomatic cholecystitis. *(LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)*

2. **What ancillary tests are helpful in the diagnosis of acute cholecystitis?**

   The most accurate imaging test in suspected acute cholecystitis is hepatobiliary scintigraphy. *(LEVEL I EVIDENCE).* For practical purposes however, ultrasonography is the appropriate initial imaging procedure. *(LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)*
3. What ancillary test is most helpful in the diagnosis of chronic calculous cholecystitis?

   Ultrasound is the most helpful diagnostic test for chronic calculous cholecystitis.  
   (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

4. Is cholecystectomy indicated for asymptomatic gallstones?

   Routine cholecystectomy is not recommended for asymptomatic gallstones.  
   (LEVEL II EVIDENCE, CATEGORY A RECOMMENDATION) However, cholecystectomy may be considered in a selected group of patients.  
   (LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)

5. What is the recommended surgical approach in the management of acute cholecystitis?

   The recommended surgical approaches for acute cholecystitis are open cholecystectomy (standard or mini-cholecystectomy) or laparoscopic cholecystectomy.  
   (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

6. What is the optimal timing of surgery for acute cholecystitis?

   Patients with acute cholecystitis should undergo cholecystectomy within 72 hours of admission.  
   (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

7. Is antibiotic therapy indicated in the management of acute cholecystitis? What antibiotic/s is/are recommended for the treatment of acute cholecystitis and what is the appropriate dose, route, and duration of administration?

   Empiric antibiotic therapy is recommended for patients with acute cholecystitis. 
   (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION) 
   The following antibiotics are recommended for therapy in uncomplicated acute cholecystitis: 
   - Cefazolin 1 gram IV every 8 hours 
   - Cefuroxime 1.5 grams IV every 8 hours 
   - Cefoxitin 2 grams IV every 8 hours (if at risk for anaerobic infection)

   For patients with allergy to beta-lactam antibiotics: 
   Fluoroquinolone 400 mg IV every 12 hours +/- Metronidazole 500 mg IV every 6 hours 
   
   (LEVEL I EVIDENCE) 
   CATEGORY A RECOMMENDATION

   The following antibiotics are recommended for therapy in complicated acute cholecystitis: 
   - Cefoxitin 2 grams IV every 8 hours
Ertapenem 1 gram IV every 24 hours
Beta-lactam/Beta-lactamase inhibitors:
Ampicillin-sulbactam 1.5-3 grams IV every 6 hours (add Gentamicin 240 mg IV every 24 hours if with risk for enterococcal infection)

For patients with allergy to beta-lactam antibiotics:
Fluoroquinolone 400 mg IV every 12 hours plus Metronidazole 500 mg IV every 6 hours

**LEVEL I EVIDENCE**
**CATEGORY A RECOMMENDATION**

The duration of therapy may vary depending on the clinician’s assessment after the operation. Therapy may be maintained for 5 to 7 days for complicated cases. Sequential therapy to oral antibiotics may be considered when gastrointestinal function has returned. *(LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)*

The absence of fever for 24 hours (temperature < 38 C), the ability to tolerate oral intake and a normal WBC count with 3 per cent or less band forms are useful parameters for the discontinuation of antibiotic therapy. *(LEVEL II EVIDENCE, CATEGORY A RECOMMENDATION)*

**8. What is the recommended surgical approach in the management of chronic cholecystitis?**

Laparoscopic cholecystectomy is the recommended surgical approach in the management of chronic cholecystitis. *(LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)* Open cholecystectomy may be done on an individual basis. *(LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)*

**9. Is antibiotic prophylaxis indicated in the management of chronic cholecystitis? What antibiotic/s is/are recommended for prophylaxis in chronic cholecystitis and what is the appropriate dose and route of administration?**

Antibiotic prophylaxis is recommended for patients who will undergo open cholecystectomy for chronic cholecystitis. *(LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)* For patients who will undergo laparoscopic cholecystectomy, antibiotic prophylaxis is likewise recommended. *(LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)*

The following antibiotics are recommended for prophylaxis in chronic cholecystitis:
Cefazolin 1 gram IV single dose within 2 hours pre-operatively
Alternative agents:
Cefuroxime 1.5 grams IV single dose within 2 hours pre-operatively
Gentamicin 80 mg IV single dose within 2 hours pre-operatively

LEVEL I EVIDENCE
CATEGORY A RECOMMENDATION

10. Should an intra-peritoneal drain be routinely placed after cholecystectomy?

An intra-peritoneal drain need not be routinely placed after cholecystectomy. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

PRACTICE GUIDELINES

What clinical findings are most helpful in diagnosing symptomatic cholecystitis?

No single clinical finding or combination of findings is sufficient to establish or exclude the diagnosis of symptomatic cholecystitis. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

A meta-analysis (Trowbridge 2003) involving 3,460 patients in 17 studies was done to determine whether aspects of the history and physical examination could clearly identify patients who would require diagnostic imaging tests to rule in or rule out acute cholecystitis. Murphy’s sign had a sensitivity of 65 per cent (95% CI 58-71%), specificity of 87 per cent (95% CI 85-89%), positive LR of 2.8 (95% CI 0.8-8.6), and negative LR of
What ancillary tests are helpful in the diagnosis of acute cholecystitis?

The most accurate imaging test in suspected acute cholecystitis is hepatobiliary scintigraphy. (LEVEL I EVIDENCE) For practical purposes however, ultrasonography is the appropriate initial imaging procedure. (LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

A meta-analysis (Shea 1994) of 30 articles was done to estimate the sensitivity and specificity of diagnostic tests for gallstones and acute cholecystitis. Adjustments were made for estimates that were biased because the gold standard was applied preferentially to patients with positive test results. Radionuclide scanning had the best sensitivity of 97 per cent (95% CI 96-98%) and specificity of 90 per cent (95% CI 86-95%) for evaluating patients with acute cholecystitis. The use of ultrasound in the
evaluation of patients with suspected acute cholecystitis had an unadjusted sensitivity of 94 per cent (95% CI 92-96%), unadjusted specificity of 78 per cent (95% CI 61-96%), adjusted sensitivity of 88 per cent (95% CI 74-100%), and adjusted specificity of 80 per cent (95% CI 62-98%). The authors concluded that radionuclide scanning is the test of choice for acute cholecystitis. (LEVEL I EVIDENCE)

Although the results of the meta-analysis support the use of radionuclide scanning as the preferred diagnostic test for evaluating patients with suspected acute cholecystitis, this modality involves some radiation, its results are delayed for metabolism of the injected dye, is less widely available, and is more expensive compared to ultrasound. Furthermore, if the objective of the imaging test is to identify all patients with symptomatic gallbladder disease leading to acute right upper quadrant pain rather than only patients who meet the strict definition of acute cholecystitis- cystic duct obstruction with histologic evidence of gallbladder inflammation- then ultrasound has acceptable accuracy rates. (LEVEL III EVIDENCE)

A meta-analysis (Trowbridge 2003) involving 3,460 patients in 17 studies was done to determine whether basic laboratory testing alone could establish or exclude acute cholecystitis. A white blood cell count above 10,000/ml had a sensitivity of 63 per cent (95% CI 60-67%), specificity of 57 per cent (95% CI 54-59%), positive LR of 1.5 (95% CI 1.2-1.9), and negative LR of 0.6 (95% CI 0.5-1.8). An alkaline phosphatase level greater than 120 U/L had a sensitivity of 45 per cent (95% CI 41-49%), specificity of 52 per cent (95% CI 47-57%), positive LR of 0.8 (95% CI 0.4-1.6), and negative LR of 1.1 (95% CI 0.6-2.0). An alanine aminotransferase (ALT) level above 40 U/L or an aspartate aminotransferase (AST) level above 48 U/L had a sensitivity of 38 per cent (95% CI 35-42%), specificity of 62 per cent (95% CI 57-67%), positive LR of 1.0 (95% CI 0.5-2.0), and negative LR of 1.0 (95% CI 0.8-1.4). A total bilirubin level above 2 mg/dl had a sensitivity of 45 per cent (95% CI 41-49%), specificity of 63 per cent (95% CI 59-66%), positive LR of 1.3 (95% CI 0.7-2.3), and negative LR of 0.9 (95% CI 0.7-1.2). When the total bilirubin, aspartate aminotransferase and alkaline phosphatase were all elevated, the combination of the three tests had a sensitivity of 34 per cent (95% CI 30-36%), specificity of 80 per cent (95% CI 69-88%), positive LR of 1.6 (95% CI 1.0-2.8), and negative LR of 0.8 (95% CI 0.8-0.9). The authors concluded that no single laboratory finding had positive likelihood ratios sufficiently high to rule in or negative likelihood ratios sufficiently low to rule out the diagnosis of acute cholecystitis. (LEVEL I EVIDENCE)

What ancillary test is most helpful in the diagnosis of chronic calculous cholecystitis?

Ultrasound is the most helpful diagnostic test for chronic calculous cholecystitis. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE
A meta-analysis (Shea 1994) of 30 articles was done to estimate the sensitivity and specificity of diagnostic tests for cholelithiasis. The use of ultrasound in the evaluation of patients with suspected gallstones had an unadjusted sensitivity of 97 per cent (95% CI 95-99 %), unadjusted specificity of 95 per cent (95% CI 88-100 %), adjusted sensitivity of 84 per cent (95% CI 76-92 %), and adjusted specificity of 99 per cent (95% CI 97-100 %). (LEVEL I EVIDENCE)

In the same meta-analysis, oral cholecystography had an unadjusted sensitivity of 90 per cent (95% CI 88-94 %), unadjusted specificity of 95 per cent (95% CI 84-100 %), adjusted sensitivity of 60 per cent (95% CI 41-79 %), and adjusted specificity of 97 per cent (95% CI 94-100 %). Computed tomography had an unadjusted sensitivity of 79 per cent and unadjusted specificity of 99 per cent. The authors concluded that the ultrasound is superior for diagnosing cholelithiasis compared to oral cholecystography and computed tomography. (LEVEL I EVIDENCE)

**Is cholecystectomy indicated for asymptomatic gallstones?**

Routine cholecystectomy is not recommended for asymptomatic gallstones. (LEVEL II EVIDENCE, CATEGORY A RECOMMENDATION). However, cholecystectomy may be considered in a selected group of patients. (LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)

**SUMMARY OF EVIDENCE**

A prospective study (Gracie and Ransohoff, 1982) involving 123 persons was done to determine the incidence of biliary pain and biliary complications such as acute cholecystitis, biliary obstruction, and pancreatitis with silent gallstone disease detected by cholecystographic screening of a healthy population of 4,300 individuals. Biliary pain was defined as an episode of upper abdominal pain that was not clearly due to another cause while symptoms of dyspepsia, such as abdominal discomfort after eating certain foods, were not regarded as biliary pain. Gallstone disease was considered to be present when the cholecystogram was reported to show gallstones or there was repeated non-visualization of the gallbladder. A person was followed up from the time silent gallstone disease was discovered until a specific end-point was reached: the onset of biliary pain or complications, prophylactic cholecystectomy, death or the pre-determined year of the end of the study. Biliary pain developed in 13 per cent (16 of 123 persons) and three of these 16 persons subsequently had biliary complications. Twenty nine per cent (35 of 123 persons) underwent prophylactic cholecystectomy but records revealed that their gallstone disease had remained silent during the 97 person-years from discovery to operation. Twenty-four per cent (30 of 123 persons) who died due to non-biliary causes had been at risk for biliary pain or complications for 552 person-years. The remaining 34 per cent (42 of 123 persons) reported in 1980 that their gallstones had remained silent for 11 to 24 years. The yearly risk of biliary pain appeared to decrease with the passage of time with the cumulative probability determined actuarially to be 10 ± 3 per cent at 5 years, 15 ± 4 per cent at 10 years and 18 ± 4 per cent at both 15 and 20 years. The authors
concluded that routine prophylactic operation for silent gallstone disease is neither necessary nor advisable. (LEVEL II EVIDENCE)

A prospective study (Ransohoff 1993) involving 139 patients with silent gallstones discovered coincidentally during ultrasonography for evaluation of other medical conditions showed that only 11 per cent (15 of 139 patients) developed symptoms suggestive of biliary colic over the next 5 years. Nine of the 15 patients underwent cholecystectomy, in 3 of whom it was incidental to other abdominal procedures. The authors concluded that ultrasound-detected coincidental gallstones are infrequently clinically significant. (LEVEL II EVIDENCE)

A retrospective study (McSherry, 1984) involving 135 patients with gallstones that were asymptomatic and 556 patients with symptoms attributable to biliary tract disease was done to define the natural history of gallstone disease. Among asymptomatic patients, 64.4 per cent (87 of 135 patients) had radiopaque stones on plain abdominal roengenograms performed as part of diagnostic studies for suspected non-biliary intra-abdominal diseases. Oral cholecystograms were then performed in 80 asymptomatic patients to confirm the location of the opaque calculi or as part of comprehensive diagnostic evaluations. Ultrasound was performed in 16 per cent (23 of 135 patients). The mean age of the asymptomatic patients was 73.6 + 13.9 years and 99 per cent of these asymptomatic patients had associated illnesses such as cardiovascular disease, malignancy, and diabetes. Only 10 per cent (14 of 135 patients) of asymptomatic individuals followed for 58 + 50.2 months (median of 46.3 months) developed symptoms of biliary calculi, four of whom progressed to biliary complications. While 7 per cent (10 of 135 patients) required operations, there were no deaths attributable to biliary tract disease among previously asymptomatic patients. The authors concluded that patients with silent stones do not need to be operated on prior to the development of symptoms. (LEVEL II EVIDENCE)

A retrospective study (Patino 1998) of 486 patients was done to identify reasonable evidence to support the policy of advising elective cholecystectomy in asymptomatic patients. Of the 27 totally asymptomatic patients who were operated on laparoscopically, the average hospital stay was 1.9 days and there was no morbidity or mortality. In contrast, of the 164 patients who were asymptomatic until a first clinical episode made emergency surgery necessary, 48 per cent (79 of 164 patients) underwent laparoscopy while 52 per cent (85 of 164 patients) had a conversion or underwent primary laparotomy. In this subset of patients, the hospital stay ranged from 5.5 days to 11.3 days, the morbidity rate was 55 per cent (90 of 164 patients) and the mortality rate was 3 per cent (5 of 164 patients). The authors concluded that expectant management of asymptomatic patients carries with it the risk of emergency surgery for serious complications of the cholelithiasis at a later date, when the patients are of more advanced age. In such a setting, the operation must frequently be done by laparotomy, with significantly higher morbidity and mortality. (LEVEL II EVIDENCE)

Based on the same study (Patino 1998), the authors stressed that not all patients with “silent” stones can be grouped under a single class of “asymptomatic cholelithiasis.”
They believe that patients with a functioning gallbladder whose calculi are greater than 3 mm but less than 2 cm in diameter and radiolucent and those who are free of concomitant serious disease can be managed with expectant follow-up. Those patients who have a life expectancy greater than 20 years, stones larger than 2 cm in diameter, those with multiple calculi (microlithiasis, stones less than 3 mm in diameter) and a patent cystic duct, radiopaque calculi, polyps in the gallbladder, nonfunctioning gallbladder, calcified “porcelain” gallbladder, biliary sludge, concomitant diabetes, women less than 60 years of age, and individuals in geographic regions with a high prevalence of gallbladder cancer were considered to be at high risk of evolving into the symptomatic state or of developing complications and the authors recommended elective laparoscopic cholecystectomy for this subgroup of patients. (LEVEL II EVIDENCE)

A review (Meshikhes, 2002) was done to evaluate the evidence for and against cholecystectomy in asymptomatic gallstones with special reference to the laparoscopic era. Gibney in 1990 and Friedman in 1993 showed that only 1-4 per cent with asymptomatic gallstones will develop symptoms or complications of gallstone disease. Other studies also suggest that almost all patients will experience symptoms for a period of time before they develop any complication. Capron in 1992 showed that none of the general factors such as age, sex, associated medical diseases such as diabetes, or local factors such as the number, size, nature, and alteration in wall thickness or gallbladder contractility were found to be predictive of symptoms or severe complications. The authors concluded that the natural history of asymptomatic gallstones is so benign that surgery is not generally recommended and watchful waiting is the best course of management. Early surgery for silent gallstones may however be recommended in high-risk patients while they are medically fit and in areas where the incidence of gallbladder cancer is high. (LEVEL III EVIDENCE)

What is the recommended surgical approach in the management of acute cholecystitis?

The recommended surgical approaches for acute cholecystitis are open cholecystectomy (standard or mini-cholecystectomy) or laparoscopic cholecystectomy. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

A randomized study (Kiviluoto, 1998) involving 63 patients was done to compare the safety and outcome of laparoscopic cholecystectomy (LC) with open cholecystectomy (OC) in the treatment of acute and gangrenous cholecystitis. While there were no bile duct injuries or mortalities for both groups, the complication rate was significantly higher in the OC group with 23 per cent (7 patients) developing major complications such as
A prospective randomized study (Assalia, 1997) involving 60 patients was done to evaluate the efficacy of minicholecystectomy (MC) in cases of acute cholecystitis compared to conventional cholecystectomy (CC). Minicholecystectomy was defined as an initial 5-cm transverse incision that was increased by 1-cm increments if exposure was not adequate. The mean length of incision was 5.5 cm (range 4.5 - 9 cm) in the MC group compared to 13.5 cm (range 12-16 cm) in the CC group. There were no significant differences between MC and CC with regard to operating time (69.1 ± 17.0 and 68.1 ± 15.4 minutes, respectively, p=0.82), operative difficulty on a 1 to 10 scale (5.2 ± 1.5 vs. 4.6 ± 1.6 respectively; p=0.177) and complication rate (11 % and 17 %, respectively; p=0.19). Significantly lower analgesic requirements were noted in the MC group: 27.5 ± 14.6 mg of morphine sulfate compared to 44.5 ± 13.2 mg. in the CC group (p<0.001). The duration of hospital stay was significantly shorter for MC patients (3.1 ± 1.0 day) than in CC patients (4.7 ± 1.2 days, p<0.001). Twenty two patients (73.3 %) in the MC group were reported to return to normal daily activities 2 weeks after the operation compared to only 12 patients (40 %) in the CC group (p=0.0028). The authors concluded that minicholecystectomy is safe and applicable as an emergency procedure for acute cholecystitis and is superior to conventional cholecystectomy in terms of convalescence and cosmesis. (LEVEL I EVIDENCE)

A prospective randomized multicenter study (Ros, 2001) involving 724 patients was done to analyze the outcomes after minicholecystectomy (MC) and laparoscopic cholecystectomy (LC) for gallstone disease. Among randomized patients, 14.6 per cent (43 of 319 patients in the LC group and 63 of 299 patients in the MC group) underwent surgery within 7 days of the onset of persistent signs and symptoms of gallbladder disease. The median operating time of 108 ± 45 minutes for the LC group was longer compared to the 94 ± 45 minutes mean operating time for the MC group (p<.001). Although intraoperative complications occurred in 37 per cent in the LC group compared to 23 per cent in the MC group (p <.001), there was no significant difference in the postoperative complication rates between the two groups. There was no significant difference in the incidence of bile duct injuries which occurred in 6 of 362 (1.7%) LC patients compared to 7 of 362 (1.9%) MC patients. The LC group had a significantly
shorter mean hospital stay (2.6 ± 3.3 days vs. 3.2 ± 5.1 days respectively, p<0.04), return to normal activity at home (8.6 ± 7.7 days vs. 10.7 ± 7.2 days respectively, p<0.001), return to normal recreational activity (11.5 ± 8.1 days vs. 14.9 ± 8.9 days respectively, p<0.001), and mean sick leave days (12.7 ± 10.3 days vs. 16.0 ± 9.9 days respectively, p<0.001) compared to the MC group. One week after surgery, patients in the LC group had less pain compared to the MC group (p<.001) but after one month this difference was no longer evident. The authors concluded that laparoscopic cholecystectomy had a longer operating time but produced a slightly shorter post-operative hospital stay and a smoother convalescence compared with minicholecystectomy. (LEVEL I EVIDENCE)

A prospective nonrandomized study (Lujan, 1998) involving 224 patients was done to compare the results of laparoscopic cholecystectomy (LC) with open cholecystectomy (OC) in the treatment of acute cholecystitis. The patients underwent surgery within 72 hours of the onset of symptoms and patients were selected for LC or OC depending on the surgeon’s experience in laparoscopic surgery. Conversion from LC to OC was necessary in 15 per cent of the patients. There was no significant difference in complication rates (14 % vs. 23 %, p=0.06) between the LC and OC groups. The number of moderate and severe complications were similar in both groups but mild complications were more common in the OC group (p<.02). The mean operating time of 77 minutes in the OC group was significantly shorter compared to the 88 minutes for the LC group (p<.001). The average length of hospital stay however was significantly shorter for the LC group at 3.3 days compared to the 8.1 days for the OC group (p<.001). The authors concluded that laparoscopic cholecystectomy is a safe, valid alternative to open cholecystectomy for patients with acute cholecystitis. The technique has a low rate of complications, implies a shorter hospital stay, and offers the patient a more comfortable postoperative period than open cholecystectomy. (LEVEL II EVIDENCE)

What is the optimal timing of surgery for acute cholecystitis?

Patients with acute cholecystitis should undergo cholecystectomy within 72 hours of admission. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

A prospective randomized study (McArthur, 1975) involving 32 patients was done to compare immediate or early with interval cholecystectomy for acute cholecystitis. There was a misdiagnosis in 11.8 per cent (2 of 17 patients) managed conservatively and in 6.8 per cent (1 of 15 patients) treated by early cholecystectomy. Of the 15 patients with acute cholecystitis managed conservatively, 20 per cent (3 of 15 patients) required urgent operation due to a failure of medical treatment because of signs of spreading peritonitis, repeated severe attacks of pain or increasing or failure of jaundice to settle. Of the 14 patients treated by early cholecystectomy, surgery was
technically difficult in 2 patients but cholecystectomy was possible in all. There was no mortality in either group nor any complication directly attributable to biliary surgery. The incidence of minor postoperative complications was only slightly greater in those treated by early operation (20 %) compared to the conservative group (29.4 %). The length of postoperative stay was similar in both groups but those treated conservatively spent an average of 11 more days in the hospital. The authors concluded that those treated by early cholecystectomy spend less time in the hospital and avoided the complications of failed conservative treatment without the added risk of increased postoperative mortality and major complications. (LEVEL I EVIDENCE)

A prospective randomized study (Jarvinen, 1980) involving 165 patients was done to determine the applicability of early definitive cholecystectomy with delayed surgery for acute cholecystitis. Of the 82 patients in the delayed surgery group, the waiting period before the planned date of delayed operation was uneventful in 69 per cent (52 patients) but operative intervention proved necessary before the scheduled date in 13 per cent (10 patients) because of signs of spreading peritonitis, increasing jaundice and cholangitis or unresolving painful empyema. In addition 15 per cent (11 patients) undergoing delayed operation 2-4 months after the acute attack suffered from clear recurrent symptoms during the waiting period. There was no difference in the incidence of technical difficulty as measured by the operative complications and the duration of operation between the two groups and in post-operative morbidity (13.8 per cent in the early group and 17.3 per cent in the delayed group, p>0.1) and mortality rates. Early surgery significantly reduced both the total hospital stay by 7.5 days (p<0.001) and the period of the patient’s incapacity for work by 14.4 days. The authors concluded that in acute cholecystitis early surgery is preferable when performed by an experienced surgeon with adequate pre- and intra-operative aids because it lowers the costs and avoids recurrent attacks and emergency operations without increasing morbidity or mortality rates. (LEVEL I EVIDENCE)

A prospective randomized study (Lahtinen, 2000) involving 100 patients showed a significantly lower complication rate of 29.7% for the early group compared to the 47.7% for the delayed group. The mortality rate was also lower for the early group at 0% compared to 9% of the delayed group. (LEVEL I EVIDENCE)

A prospective randomized study (Lai, 1998) involving 104 patients was done to define the optimum management between early laparoscopic cholecystectomy within 24 hours of randomization and initial conservative treatment followed by delayed laparoscopic cholecystectomy 6-8 weeks later for patients with acute cholecystitis. There was no significant difference between the early and delayed approach with regard to conversion rate (21 % vs. 24 % respectively), postoperative analgesic requirements (1 vs. 2 doses respectively) and postoperative complications. However, the early group had a significantly longer operating time (122.8 mins vs. 106.6 mins, p=0.04) but shorter total hospital stay (7.6 vs. 11.6, p<0.001). The authors concluded that early laparoscopic cholecystectomy is safe and feasible for acute cholecystitis with the additional benefit of a shorter total hospital stay. (LEVEL I EVIDENCE)
A prospective randomized study (Lo, 1998) involving 86 patients was done to compare the safety and cost efficacy of early laparoscopic cholecystectomy within 72 hours of admission and delayed interval laparoscopic cholecystectomy for the treatment of acute cholecystitis. Nineteen per cent (8 of 41 patients) in the delayed group underwent urgent operation at a median of 63 hours (range 32 – 140 hours) after admission because of spreading peritonitis or persistent fever. Although the delayed group required less frequent modifications in operative technique and a shorter operative time, there was a tendency toward a higher conversion rate (23 % vs. 11 %, p = 0.174) and complication rate (29 % vs. 13 %, p = 0.07). Delayed laparoscopic surgery prolonged the total hospital stay (11 days vs. 6 days, p<0.001) and recuperation period (19 days vs. 10 days, p <0.001). The operating time was longest in patients who required urgent operation after failure of conservative treatment (median, 188 minutes; range 135-270 minutes) when compared to those of the early group (median, 135 minutes, range, 75 to 220 minutes; p = 0.008) and the delayed group undergoing interval elective surgery (median, 90 minutes, range 50 to 290 minutes, p <0.001). The authors concluded that the conversion rate and morbidity of laparoscopic cholecystectomy for patients with acute cholecystitis are not reduced by a period of initial conservative treatment. Early operation may be safer and has definite socioeconomic benefits so that for surgeons with adequate experience, the optimal timing of laparoscopic cholecystectomy for the treatment of acute cholecystitis is as soon after diagnosis as possible, within 72 hours of admission. (LEVEL I EVIDENCE)

A prospective study (Eldar, 1997) involving 130 patients was done to determine the indications for and the optimal timing of laparoscopic cholecystectomy following the onset of acute cholecystitis and to evaluate preoperative and operative factors associated with conversion to open cholecystectomy in the presence of acute cholecystitis. The study showed that the conversion rate of 23 per cent for patients undergoing laparoscopic cholecystectomy within 96 hours was significantly lower compared to the 47 per cent conversion rate for those undergoing surgery after 96 hours (p = 0.022). The complication rate was 8.5 per cent in the laparoscopic group compared to 27 per cent in the converted group (p=0.013). Patients over 65 years of age, with a history of biliary disease, a nonpalpable gallbladder, WBC count over 13,000/cc, and acute gangrenous cholecystitis were independently associated with a high LC conversion rate. Male patients, finding large bile stones, serum bilirubin over 0.8 mg/dl and WBC count over 13,000/cc were independently associated with a high complication rate after laparoscopic cholecystectomy. The authors concluded that laparoscopic cholecystectomy can generally be performed safely for acute cholecystitis with acceptably low conversion and complication rates in selected cases especially when performed within 96 hours of the onset of disease. (LEVEL II EVIDENCE)

Is antibiotic therapy indicated in the management of acute cholecystitis? What antibiotic/s is/are recommended for the treatment of acute cholecystitis and what is the appropriate dose, route, and duration of administration?

Empiric antibiotic therapy is recommended for patients with acute cholecystitis.
The following antibiotics are recommended for therapy in uncomplicated acute cholecystitis:

- Cefazolin 1 gram IV every 8 hours
- Cefuroxime 1.5 grams IV every 8 hours
- Cefoxitin 2 grams IV every 8 hours (if at risk for anaerobic infection)

For patients with allergy to beta-lactam antibiotics:

- Fluoroquinolone 400 mg IV every 12 hours +/- Metronidazole 500 mg IV every 6 hours

The following antibiotics are recommended for therapy in complicated acute cholecystitis:

- Cefoxitin 2 grams IV every 8 hours
- Ertapenem 1 gram IV every 24 hours
- Beta-lactam/Beta-lactamase inhibitors:
  - Ampicillin-sulbactam 1.5-3 grams IV every 6 hours (add Gentamicin 240 mg IV once a day if with risk for enterococcal infection)

For patients with allergy to beta-lactam antibiotics:

- Fluoroquinolone 400 mg IV every 12 hours plus Metronidazole 500 mg IV every 6 hours

The duration of therapy may vary depending on the clinician’s assessment after the operation. Therapy may be maintained for 5 to 7 days for complicated cases. Sequential therapy to oral antibiotics may be considered when gastrointestinal function has returned. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)

The absence of fever for 24 hours (temperature < 38 C), the ability to tolerate oral intake and a normal WBC count with 3 per cent or less band forms are useful parameters for the discontinuation of antibiotic therapy. (LEVEL II EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

In biliary tract infections, the source of the infecting flora is the bowel particularly the duodenum and infection occurs through the ascending route. Although the duodenum has a sparse flora, substantial counts of aerobic and anaerobic organisms are found in patients with diseases such as peptic ulcer and bowel obstruction and following certain
types of gastrointestinal surgery. (Finegold 1979) The most common organisms include the aerobic gram-negative enteric bacteria, mainly *E. coli* (27-66 %) and *Klebsiella* spp. (4-21 %). These are followed by the gram-positive organisms such as *Streptococcus* spp., *Staphylococcus* spp. and *Enterococcus* spp. (Farnell 1981, Muller 1987, Wilson 1987, Berne 1990, Lau 1990, Thompson 1993)

Bactibilia frequently occurs among patients with biliary tract infections, including acute cholecystitis (21-79%), with an increased frequency noted among the elderly and those with acute emphysematous cholecystitis, choledocholithiasis, cholangitis and after multiple previous biliary tract surgeries. (Ram 1974, Mentzer 1975, England 1977, Morrow 1978, Lau 1990) An aerobic polymicrobial etiology has been reported in biliary tract infections with the frequency ranging from 17 to 50 per cent. (Gagic 1975, Bourgault 1979) Obligately anaerobic organisms, mainly *Clostridium* spp. and *Bacteroides* spp., are occasionally isolated either as a pure culture or as part of a mixed infection. (Muller 1987, Wilson 1987, Berne 1990, Lau 1990, Thompson 1993)

In a 2-year retrospective study involving 1, 892 patients who underwent biliary tract surgery, anaerobic organisms were isolated in 100 of 371 patients (41 %) with aerobic and anaerobic bile cultures, mainly as part of a mixed aerobic-anaerobic flora. Obstruction of the biliary tree was present in 66 per cent of these cases. (England 1977, Bourgalt 1979) The 100 patients from whom anaerobes were isolated were more likely to have had previous multiple and complicated biliary tract surgical procedures and severe symptoms. (Bourgalt 1979)

Anaerobic bactibilia has also been reported to occur frequently among elderly patients with acute cholecystitis. In one study (Bourgalt,1979), the mean age of patients with anaerobic biliary tract infections was 62.9 years compared to 56.9 years among those with pure aerobic infections. In another retrospective study (Morrow, 1978) of 88 male patients older than 60 years of age who underwent cholecystectomy 44 per cent of whom had acute cholecystitis and 15 per cent who had common bile duct stones, obligate anaerobes were isolated in 25 per cent of the 41 patients who had bile specimens obtained for culture. A local study (Samson, 1983) which examined the biliary bacteriology among 119 patients (18 of whom had acute cholecystitis) showed that *E. coli*, *Enterococcus faecalis* and *Klebsiella* were the most commonly isolated organisms. Anaerobic organisms were only occasionally isolated in 5 patients who had either a partially or completely obstructed bile duct. (LEVEL II EVIDENCE)

Although enterococci are isolated as part of a polymicrobial intra-abdominal infection, their role as pathogens is still unclear. A review (Gorbach, 1993) showed that the rate of isolation of *Enterococcus* in initial cultures performed for patients with intra-abdominal infections ranges from 14 per cent to 33 per cent in clinical trials. While none of the drugs used in these trials were active against this organism, the review and analysis failed to reveal any case that could be considered as a treatment failure due to infection by *Enterococcus*. (LEVEL III EVIDENCE)
A randomized trial (Burnett, 1995) which compared ciprofloxacin plus metronidazole with imipenem-cilastatin and examined the role of enterococci in intra-abdominal infections reported that enterococcal isolates are associated with treatment failure. In this study, enterococcal isolates were obtained from 22 per cent of the patients and failure rates were twice as high (28 % vs. 14 %) in the patients from whom enterococci were isolated. Higher APACHE II scores and enterococcal isolation were found to be independently associated with treatment failure by stepwise logistic regression. Identified factors that increased the likelihood of isolating enterococci at the time of initial drainage included age, colonic or small bowel source, APACHE II score, pre-infection length of hospital stay and postoperative infections. (LEVEL II EVIDENCE)

Enterococci are unlikely pathogens in healthy patients with infections that are diagnosed rapidly and treated definitively but they may be selected as pathogens in patients who are elderly, debilitated, immunocompromised, severely ill, hospitalized for prolonged periods, or who are undergoing reoperation for surgical complications or intractable disease. (Barie PS, 1993) Coverage against Enterococcus may be considered when a patient had been previously treated with antibiotics without improvement or response and when the organism is persistently isolated in repeat cultures. Recently, the Infectious Disease Society of America, the Surgical Infection Society, the American Society for Microbiology and the Society of Infectious Disease Pharmacists recommended anti-enterococcal coverage when the organism is recovered from patients with health-care associated (nosocomial) infections. (Solomkin 2003) (LEVEL III EVIDENCE)

Due to the frequency of bactibilia in acute cholecystitis, antibiotics given perioperatively as adjunctive therapy to surgery appear to be helpful in preventing infectious complications. This is particularly true among severely ill or elderly patients, those with complicated cholecystitis such as emphysematous cholecystitis which is commonly found among diabetics, those with perforation and secondary peritonitis, and those with pericholecystic abscess formation. (Mentzer 1975, Morrow 1978, Finegold 1979, Pitt 1979)

The literature is replete with randomized controlled trials that have dealt exclusively with acute cholecystitis without common bile duct involvement. Trials that evaluated the role of antibiotic therapy in biliary tract infections involved small populations and did not have sufficient power to differentiate the efficacy of one antibiotic over another. Larger trials which compared different antibiotics in the treatment of complicated intra-abdominal infections included biliary tract infections but this type of infection comprised only a small subset of the study population.

Since the susceptibility patterns of the commonly isolated organisms in acute cholecystitis are quite predictable, the appropriate choice of antibiotics for therapy can be based on their reported spectrum of activity and pharmacokinetic properties. The cephalosporins and the quinolones have been shown to achieve rapid tissue penetration in the biliary tract with persistent levels appropriate for treatment of biliary pathogens. (Wilson 1987, Dougherty 1988, Edmiston 1996)
In the Infectious Disease Society of America guidelines for the selection of anti-infective agents for complicated intraabdominal infections (Solomkin 2003), once acute cholecystitis is suspected on the basis of clinical and radiographic findings, urgent intervention is indicated and antimicrobial therapy should provide coverage against Enterobacteriaceae. (GRADE B RECOMMENDATION, LEVEL II EVIDENCE) Coverage against anaerobes is warranted for patients with previous bile-duct anastomosis. (GRADE C RECOMMENDATION, LEVEL III EVIDENCE)

A review of 79 randomized trials (Holzheimer 2001) evaluating antibiotic therapy of intra-abdominal infections showed comparable success rates among the different antibiotics evaluated, whether as monotherapy or combination therapy. Because of the variability in the study population, methodology, interventions and definition of outcome measures, an analysis of pooled data to estimate the overall effect of antibiotic treatment was not possible. The clinical failure rates of the antibiotics studied in large populations were 19.4 per cent ± 21.5 for gentamicin + clindamycin, 10.7 per cent ± 5.93 for meropenem, 15.32 per cent ± 12.37 for imipenem, 12.31 per cent ± 0.56 for cefoxitin, 8.4 per cent ± 2.8 for cefotetan, 13.25 per cent ± 11.32 for cefotaxime + metronidazole and 13 per cent ± 1.41 for ampicillin/subactam. (LEVEL III EVIDENCE)

An open-label trial (Polk, 1993) comparing piperacillin-tazobactam with gentamicin and clindamycin involving 331 patients with complicated intraabdominal infections (including a small subset of patients with acute cholecystitis of 12 %) showed favorable cured and improved response rates which were equivalent between the two groups (88 % vs. 81 %). (LEVEL II EVIDENCE)

A randomized double-blind trial (Walker, 1993) involving 385 patients with suspected bacterial intra-abdominal infections compared the efficacy of ampicillin-sulbactam with cefoxitin. In the efficacy analysis of 197 patients, clinical success rates for both groups are equivalent (86 % vs. 79 %). There was also no significant difference between the two groups with respect to bacterial eradication rates (88 % vs. 79 %). Because of the small number of included subjects with biliary tract infections (10 %), a subgroup analysis was not done. (LEVEL I EVIDENCE)

A randomized double-blind controlled trial (Solomkin, 2003) involving 615 evaluable adult patients was done to determine the efficacy and safety of ertapenem compared with tazobactam-piperacillin in the antimicrobial management of complicated intra-abdominal infections. Overall, the clinical cure rate for ertapenem of 79.3 per cent was comparable to that of piperacillin-tazobactam at 76.2 per cent with an ARR of 3.1 per cent (95% CI -3.6, 9.8). Among patients with biliary tract infections (cholecystitis and cholangitis, n =25), the 92 per cent efficacy rate for ertapenem was likewise comparable to 83 per cent efficacy rate for piperacillin-tazobactam. (LEVEL I EVIDENCE)

A prospective, randomized trial (Muller, 1987) involving 106 patients was done to compare ampicillin plus tobramycin, cefoperazone and piperacillin in the therapy of
patients with biliary tract infections. In 53 patients with acute cholecystitis, the clinical cure rates were 85 per cent for the ampicillin-tobramycin group, 95 per cent for the cefoperazone group and 95 per cent for the piperacillin group (p > 0.05). Similar overall cure rates were likewise observed. Thirteen per cent of the patients receiving cefoperazone however had an increased prothrombin time (with 3 of the 39 patients in this group having bleeding) compared with 6 per cent for the ampicillin-tobramycin group and 3 per cent for the piperacillin group. Nephrotoxity was noted in 6 per cent of the 33 patients in the ampicillin-tobramycin group compared with 3 per cent for the piperacillin group. Two patients, both in the piperacillin group, experienced allergic cutaneous reactions. (LEVEL I EVIDENCE)

A randomized trial (Lau, 1990) involving 211 patients was done to evaluate the use of short course (< 1 day) versus long course (7 days) cefamandole for acute cholecystitis treated by early cholecystectomy. The incidence of surgical site infection was similar for both groups (7 % vs. 5.8 %). There was a higher rate of thrombophlebitis (15.9 % vs. 6 %, p < 0.05) related to intravenous antibiotic injections seen in the group which received a long course of the antibiotic and a longer hospital stay (7.2 ± 5.5 vs 8.9 ± 6.1 days, p < 0.05). Aside from the non-blinded study design, the patients belonging to the long course group had a longer operative time and a larger volume of intra-operative blood loss which may have favored the short course group. (LEVEL II EVIDENCE)

Sequential therapy from intravenous to oral antibiotics may be considered among patients with complicated intra-abdominal infections who need prolonged antibiotic therapy but can tolerate oral intake. A randomized controlled trial (Cohn, 2000) involving 459 adult patients with complicated intra-abdominal infections showed that patients who have clinically improved after being treated with intravenous antibiotics for at least 48 hours can be safely switched to oral therapy once feasible. In this study, the IV antibiotics given were either monotherapy with tazobactam-piperacillin or combination therapy with ciprofloxacin and metronidazole. The combination of oral ciprofloxacin and metronidazole was used for sequential therapy. A total of 282 patients were evaluated for efficacy (151 CIP + MET, 131 PIP/TAZO), of which 64 per cent in the CIP + MET and 57 per cent in the PIP/TAZO group were considered candidates for oral therapy. Overall clinical resolution rates were significantly higher for CIP + MET (74 %) compared with PIP/TAZO (63 %). The corresponding rates in the subgroup suitable for oral therapy were 85 per cent for CIP + MET and 70 per cent for PIP/TAZO. Post-surgical wound infection rates were lower in the CIP + MET (11 %) versus PIP/TAZO group (19 %). The mean length of stay was 14 days for CIP + MET and 17 days for PIP/TAZO patients. In this study, sequential therapy after 48 hours among eligible patients was shown to generate cost savings. Initial therapy with IV ciprofloxacin plus metronidazole also allows switching to the oral preparation using the same drugs with equivalent bioavailability in adult patients with complicated intra-abdominal infections. (LEVEL I EVIDENCE)

Clinical and laboratory tools may be used in deciding when to say that the administered antibiotics are sufficient and the antimicrobials can be safely stopped. A review of 11 prospective clinical trials (Stone, 1985) involving 2,567 patients with
surgical peritonitis was conducted to identify reliable predictors of sepsis eradication and determine which among these predictors may be used as guides for the discontinuation of antibiotic therapy. Upon discontinuation of antibiotic therapy, sepsis recurred in 19 per cent of patients who had a normal rectal temperature, in 3 per cent of patients if the rectal temperature and WBC count were normal, but in none when both the temperature and the WBC count were normal and the differential blood smear contained less than 73 per cent granulocytes and less than 3 per cent immature forms. In this review, the rates for recurrent sepsis once antibiotic therapy was discontinued for more than 48 hours were 8 per cent, 2 per cent and 0 per cent, respectively, for the same criteria at hospital discharge. (LEVEL II EVIDENCE)

What is the recommended surgical approach in the management of chronic cholecystitis?

Laparoscopic cholecystectomy is the recommended surgical approach in the management of chronic cholecystitis. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION) Open cholecystectomy may be done on an individual basis. (LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)

SUMMARY OF EVIDENCE

A prospective randomized study (Hendolin, 2000) involving 49 patients was done to compare open cholecystectomy (OC) with laparoscopic cholecystectomy (LC) in the elective setting. The conversion rate was 8 per cent. There was no significant difference in operating time between the two groups. The hospital stay was 2 days shorter after LC than OC (p < 0.01). The convalescence time was significantly shorter by 15 days after LC (p < 0.01). The LC group had less analgesic requirement (p < 0.01). Postoperative complications were rare. There was a substantial decrease in postoperative pulmonary function after OC than LC (p < 0.01). Stress response was equal in both groups. The authors concluded that laparoscopic cholecystectomy had significantly better postoperative results than the open method. (LEVEL I EVIDENCE)

A prospective randomized study (Berggren, 1994) involving 30 patients was done to compare elective laparoscopic cholecystectomy (LC) with open cholecystectomy (OC) with respect to the duration of post-operative hospital stay and sick leave, post-operative pain as measured by intravenous pethidine consumption, and the response of trauma markers in blood and urine before, during, and after surgery. The LC group had a significantly longer operating time (mean 87 vs. 69 minutes, p < 0.05) compared to the OC group but had a shorter hospital stay (mean 1.8 vs. 2.8 days, p < 0.05), shorter sick leave (mean 11.7 vs. 24 days, p < 0.01), shorter time in convalescence (8 vs. 49 days, p < 0.01) and less analgesic requirements at 13-24 hours after surgery (p = 0.04). Complications were rare, no postoperative deaths occurred and none of the preoperative and postoperative variables showed any significant difference between the two groups. The authors concluded that laparoscopic cholecystectomy is one of the major improvements in surgery and resulted in a significant decrease in hospital stay, sick leave and postoperative pain. (LEVEL II EVIDENCE)
A prospective non-randomized study (Vander Velpen, 1993) involving 160 patients was done to compare laparoscopic with open cholecystectomy. The LC group had an earlier return to work or full activity (p = 0.00001) than the OC group. There was no significant difference in overall improvement of symptoms postoperatively. Scar satisfaction was higher for the LC group than the OC group (p = 0.0017). The authors concluded that laparoscopic cholecystectomy was associated with a better postoperative recovery than the open approach. (LEVEL II EVIDENCE)

A prospective non-randomized study (Soper, 1992) involving 50 patients was done to compare the early postoperative results of laparoscopic (LC) versus open cholecystectomy (OC). The LC group had a significantly longer operating time (p < 0.05) than the OC group but had a shorter time to resumption of diet (p < 0.05), hospital stay (p < 0.05), return to work or full activity (p < 0.05), and less analgesic requirements during the first 24 hours post-surgery (p < 0.05). The authors concluded that laparoscopic cholecystectomy is the treatment of choice for symptomatic cholelithiasis requiring operative treatment. (LEVEL II EVIDENCE)

A prospective randomized study (Schmitz, 1997) involving 130 patients was done to compare two forms of open cholecystectomy, namely conventional (CC) and minicholecystectomy (MC). There were no significant differences in the duration of surgery, pain perception and oral analgesic intake during the first 2 days after surgery between the two groups. The MC group however had a significantly higher postoperative complication rate (29 % vs. 7.7 %) and incidence of wound hematoma (18% vs. 6.2 %) compared to the CC group. No bile duct injuries were noted. The authors concluded that a smaller incision length could not lessen pain and postoperative analgesic requirements after surgery and minicholecystectomy cannot be regarded as a conversion or alternative operation to laparoscopic cholecystectomy. (LEVEL I EVIDENCE)

Two randomized trials compared laparoscopic cholecystectomy (LC) with minilaparotomy cholecystectomy (MC). In a prospective randomized multicenter study (Ros, 2001) involving 724 patients, the LC group had significantly longer operating time (mean 108 ± 45 vs. 94 ± 45 mins, p < 0.001) but slightly shorter post-operative stay (mean 2.6 ± 3.3 days vs. 3.2 ± 5.1 days, p = 0.04) than the MC group. Furthermore, the LC group had a significantly shorter sick leave (mean 12.7 ± 10.3 days vs. 16 ± 9.9 days, p < 0.001), earlier return to normal activity at home (mean 8.6 ± 7.7 days vs. 10.7 ± 7.2 days, p < 0.001), and recreation (mean 11.5 ± 8.1 days vs. 14.9 ± 8.9 days, p < 0.001) than the MC group. During the first week after surgery, there was significantly lesser pain in the LC group (p < 0.001) but this difference with the MC group was no longer evident 1 month later. While fewer intra-operative complications were detected in the open technique (23 % vs. 37 %, p < 0.001), there was no significant difference in their post-operative morbidity rates. Bile duct injuries were minimal and neither group had deaths within 30 days of surgery. The conversion rate was lower for LC than MC (19 % vs. 28 %, p < 0.001). The authors concluded that although the laparoscopic approach took longer to perform, it had a better post-operative course than the open method. (LEVEL I EVIDENCE)
A prospective randomized study (Majeed, 1996) involving 200 patients in a single center was done to compare laparoscopic cholecystectomy (LC) with mini-cholecystectomy (MC). The LC group had a significantly longer operating time (mean 69 mins vs. 45 mins, p < 0.001) but there were no significant differences in overall median initial time to feed, post-operative stay, resumption of work, return to full activity and complications between the two groups. Bile duct injury was rare. Sub-group analysis of the successfully completed procedures demonstrated similar findings. The elective conversion rate was 12 per cent and overall was 20 per cent. Converted operations had significantly longer hospital stay (median 4 vs. 3 nights p=0.003) than those which were laparoscopically completed. The authors concluded that laparoscopic cholecystectomy was a longer procedure and did not offer significant advantages over mini-laparotomy cholecystectomy during the recovery period. (LEVEL I EVIDENCE)

A prospective randomized multi-center trial (McMahon, 1994) involving 299 patients was done to compare the outcomes following laparoscopic (LC) and mini-cholecystectomy (MC). Assessment of recovery after surgery showed that the LC group had shorter hospital stay (median 2 days vs. 4 days; p < 0.001) and less pain at 1 week after surgery (67 % vs. 44 %; p < 0.001). Moreover, LC patients had an earlier return to normal activities: leisure (median 7 days vs. 12 days; p < 0.01), work in the home (10 days vs. 15 days; p < 0.001) and social activities (14 days vs. 21 days; p < 0.001) than MC patients. There however was no difference in the time to return to sexual activity or employment. At 4 weeks post-surgery, LC patients still had better physical function (p < 0.05), and lesser depression (p < 0.05) than MC patients but by 12 weeks the differences were no longer evident. While the LC group had significantly lesser pain (median 40 vs. 59; p < 0.001) than the MC group during the first day after surgery, no significant difference was noted after 4 weeks. Significantly lower morphine consumption (p < 0.001) was also noted 24 hours post-operatively in the LC group. The LC group had a longer operating time (mean 71 ± 20 vs. 57 ± 24 min, p < .001). The post-operative complication rates were similar in both groups and bile duct injuries were minimal. The conversion rate was 10 per cent for both procedures. LC patients were more satisfied with their scar appearance at 4 and 12 weeks post-surgery (x² linear trend p < 0.05). The laparoscopic procedure involving the use of disposables was however significantly more expensive than the open method (p < 0.001). The authors concluded that the laparoscopic approach conferred more benefits during the convalescent period but was costly. (LEVEL II EVIDENCE)

A follow-up study (McMahon, 1995) done to assess the symptomatic outcome one year after laparoscopic and mini-cholecystectomy revealed that the laparoscopic method did not have any overall long-term symptomatic advantage over mini-laparotomy cholecystectomy. (LEVEL II EVIDENCE)

A randomized study (McGinn, 1995) involving 310 patients was done to establish whether there are treatment benefits from cholecystectomy performed laparoscopically and whether it is as safe as mini-cholecystectomy thru an 8 cm or smaller incision. The LC group had a significantly shorter hospital stay (median 2 days vs. 3 days, p< 0.001),
quicker return to normal activity (median 1.5 days vs. 6 days, p < 0.05), and earlier return to work (median 3 weeks vs. 6 weeks, p < 0.05) but a longer operating time (median 74 mins vs. 50 mins, p < 0.05) and higher complication rate (10 % vs. 3 %, p < 0.02) than the MC group. Bile leaks occurred in 0.7 per cent of the LC group and 1.3 per cent of the MC group but no duct injuries were identified. Although lower doses of morphine was required by the LC group (p < 0.05), there was no significant difference in oral analgesic use between the two groups. The conversion rate was significantly more common for the LC group than the MC group (13 % vs. 4 %, p < 0.001) and complications were significantly more frequent with laparoscopic cholecystectomy (9 % vs. 3 %, p<0.02). The authors concluded that at present no clear-cut advantage for either operation could be demonstrated. (LEVEL II EVIDENCE)

A randomized study (Golder, 1998) involving 53 patients was done to compare the 10 mm (standard LC) and 5 mm (5-mm LC) epigastric ports in laparoscopic cholecystectomy. The study showed that there were no significant differences in operating time, pain perception, analgesic requirements, hospital stay and return to normal activity between the two groups. Standard LC had a lower complication rate than 5-mm LC (0 % vs. 19 %) and the conversion rate of the 5 mm LC to LC was high at 15 per cent. The authors concluded that a reduction in port size did not have any significant clinical benefit. (LEVEL I EVIDENCE)

A randomized trial (Huang, 2003) involving 90 patients was done to compare the three types of laparoscopic cholecystectomy namely: standard (LC), 5 mm (5 mm LC), and minilaparoscopic (MLC). Converted operations were excluded from outcome analysis after randomization. Although the conversion rates to standard LC were 16.6 per cent for MLC and 3.3 per cent for the 5-mm LC, there were no conversions to the open method. The LC group had a significantly shorter operating time than the other groups (p = 0.03). There were no significant differences in terms of hospital stay, blood loss, resumption of diet and complications among the groups. There were no bile duct injuries. The LC group had a significantly lower analgesic requirement post-operatively than the other procedures (p= 0.02) and less pain at the umbilical port at 24 hours (p= 0.02) and 48 hours (p= 0.04) after surgery. Aesthetically, there were no significant differences among the groups. The authors concluded that mini-laparoscopic cholecystectomy did not provide any notable clinical benefit compared to standard laparoscopic cholecystectomy so that minilaparoscopic cholecystectomy cannot replace standard laparoscopic cholecystectomy as the universally accepted mode of treatment for symptomatic gallstones. (LEVEL II EVIDENCE)

A randomized trial (Alponat, 2002) involving 44 patients was done to compare laparoscopic cholecystectomy (LC) with mini-laparoscopic cholecystectomy (MLC). The conversion rate from MLC to LC was 23 per cent but there were no conversions to open cholecystectomy in either groups. There were no significant differences in operating time, pain perception, analgesic requirement, pulmonary function, and metabolic and hormonal levels postoperatively. MLC had less scar tissue than LC (p = 0.0045). The authors concluded that MLC is a feasible alternative in patients seeking better cosmesis. (LEVEL II EVIDENCE)
Is antibiotic prophylaxis indicated in the management of chronic cholecystitis? What antibiotic/s is/are recommended for prophylaxis in chronic cholecystitis and what is the appropriate dose and route of administration?

Antibiotic prophylaxis is recommended for patients who will undergo open cholecystectomy for chronic cholecystitis. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION) For patients who will undergo laparoscopic cholecystectomy, antibiotic prophylaxis is likewise recommended. (LEVEL III EVIDENCE, CATEGORY A RECOMMENDATION)

The following antibiotics are recommended for prophylaxis in chronic cholecystitis:
- Cefazolin 1 gram IV single dose within 2 hours pre-operatively

Alternative agents:
- Cefuroxime 1.5 grams IV single dose within 2 hours pre-operatively
- Gentamicin 80 mg IV single dose within 2 hours pre-operatively

**LEVEL I EVIDENCE
CATEGORY A RECOMMENDATION**

**SUMMARY OF EVIDENCE**

The use of antibiotics for prophylaxis in chronic cholecystitis is beneficial for patients who will undergo biliary tract surgery. A meta-analysis (Meijer, 1990) of 42 randomized trials involving 4,129 patients showed a lower overall surgical site infection rate in the treatment group (15 % vs. 6 %) compared to the placebo group. A post hoc analysis performed by the authors demonstrated an even greater beneficial effect for prophylaxis in the high-risk group (up to 25 % difference in surgical site infection rates). The authors classified patients as high-risk when they had one or more of the following criteria: (1) acute cholecystitis within 4 weeks of surgery (2) emergency cholecystectomy (3) common duct stone or ductal exploration (4) jaundice at the time of surgery (5) age over 60 years (6) previous biliary tract surgery (7) morbid obesity (8) non-visualization of the gallbladder on oral cholecystography (9) diabetes mellitus; and (10) concomitant alimentary procedures. (LEVEL I EVIDENCE)

A section of the meta-analysis (Meijer, 1990) of 15 trials involving 1,226 patients evaluated whether a single dose was as effective as multiple doses for antibiotic prophylaxis. The results showed that there was no significant difference in the frequency of surgical site infections (Odds Ratio = 0.8, 95% CI 0.41- 1.57). The authors noted however that almost all the trials compared a multiple dose, short-acting, first generation cephalosporin with a single dose, long-acting third generation cephalosporin. (LEVEL I EVIDENCE)
A randomized controlled double-blind study (Meijer, 1993) involving 1,004 patients was done to compare a single pre-operative dose versus multiple doses of cefuroxime for prophylaxis in biliary tract surgery among high-risk patients. The study showed that there was no difference in the incidence rates of major surgical site infections (3.8 % vs. 4.6 %, ARR of 0.8, 95% CI –1.7%– 3.3%) between the two strategies. (LEVEL I EVIDENCE)

A multicenter study (Fabian, 1988) involving 260 patients was done to compare cefotetan with cefoxitin in elective biliary surgery for both low-risk and high-risk patients. An analysis of the failure rates showed no significant difference in the two treatment groups (2 % vs. 3 %). Subgroup analysis was not performed for either low or high-risk patients due to the small sample size. (LEVEL II EVIDENCE)

A randomized double blind study (Dougherty, 1988) involving 150 patients with recent attacks of cholecystitis within a month was done to compare 2 g and 1 g cefamandole with 2 g cefoxitin for prophylaxis. There was only 1 surgical site infection which occurred in the group which received 1 g cefamandole. (LEVEL II EVIDENCE)

A randomized double-blind study (Jewesson, 1996) involving 150 patients was done to compare the use of cefazolin and ceftizoxime for prophylaxis in elective cholecystectomy. Majority of the included patients underwent laparoscopic cholecystectomy (82 % for cefazolin, 85 % for ceftizoxime). The 2 treatment groups had equivalent failure rates (7 % vs. 8 %) with most infections occurring late or 5 days after surgery. (LEVEL II EVIDENCE)

A randomized placebo-controlled study (Illig, 1997) was done to evaluate the use of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy. In this study, the computed sample size for each treatment arm was 419 patients for an 80 per cent chance of detecting a 4 per cent absolute difference in infection rates between the prophylaxis and the placebo or control group. The study was terminated after 250 patients (128 test, 122 control) were enrolled due to the very low incidence of surgical site infection which was the primary endpoint. The infection rate in the placebo group was 0.8 per cent while there were no infections in the prophylaxis group. The very low overall infection rate of 0.4 per cent precluded any analysis between the two groups. (LEVEL I EVIDENCE)

A randomized double-blind placebo-controlled trial (Higgins, 1999) involving 450 patients was done to compare Cefazolin, Cefotetan and placebo. The infection rates were 2.2 per cent in the placebo group, 2.9 per cent in the Cefazolin group and 2.2 per cent in the Cefotetan group. There was no statistically significant difference in infection rates between the three groups. (LEVEL II EVIDENCE)

Should an intra-peritoneal drain be routinely placed after cholecystectomy?

An intra-peritoneal drain need not be routinely placed after cholecystectomy. (LEVEL I EVIDENCE, CATEGORY A RECOMMENDATION)
SUMMARY OF EVIDENCE

A randomized prospective study (Maull, 1978) involving 200 patients showed that there was a significant difference in the incidence of surgical site infections and other complications between those with drains and those without drains (10.4% vs. 0.6%). Patients in the group with drains had a mean peak fever of 101.4°F compared to 100.7°F in the group without drains (p<0.001). Patients who had drains also had a longer period of temperature over 100°F at 2.71 days compared to 1.71 days in those without drains (p<0.001). Patients who had no drains were able to resume oral feedings sooner than the patients with drains (2.15 vs. 1.92 days) but the difference was not significant (p = 0.07). Patients who had no drains also were discharged earlier than those who had drains (4.52 vs. 5.02 days). The difference was significant (p <.05). The authors concluded that elective cholecystectomy without drainage can be done safely and that less post-operative fever and a shorter hospitalization can be expected. (LEVEL I EVIDENCE)

A prospective randomized study (Trowbridge, 1982) involving 100 patients showed that patients without drainage had a mean temperature lower than those in the group with drains. Patients without drains also tended to progress to a solid diet one day sooner and able to have fluids given intravenously discontinued although there was no significant difference in this regard. The need for dressing changes was significantly different between the drainage and no drainage groups. Patients without drainage were discharged earlier at 6.2 days compared to those without drainage who were discharged at 7.3 days. The difference however was not significant. There was no discernible difference between the groups with regard parenteral analgesic requirements. Three out of 50 patients (6%) in the no drainage group developed complications while 8 out of 50 patients (16%) who had drainage had complications. The authors concluded that there are subtle yet tangible benefits to the patient, the healthcare team, and the hospital when drainage is safely avoided after cholecystectomy. (LEVEL II EVIDENCE)

A prospective randomized study (Farha, 1981) involving 122 patients showed that pulmonary complications occurred more often in the penrose group compared to the closed-drainage or the undrained group. This was statistically significant (p<0.05). The authors concluded that subhepatic drainage was unnecessary after a simple and uncomplicated cholecystectomy. (LEVEL II EVIDENCE)
REFERENCES


