ORIGINAL RESEARCH

Evidence-based clinical standard for the diagnosis and treatment of acute calculous cholecystitis in adults

Estándar clínico basado en la evidencia para el diagnóstico y tratamiento de adultos con colecistitis aguda calculosa

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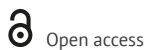[11] Universidad Nacional de Colombia - Bogotá Campus - Faculty of Medicine - Institute for Clinical Research - Bogotá D.C. - Colombia.
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Abstract

Introduction: Acute cholecystitis is the most common complication of cholelithiasis and is defined as inflammation of the gallbladder resulting from cystic duct obstruction. When such obstruction is caused by a gallstone, the condition is known as acute calculous cholecystitis (ACC), which accounts for 90–95% of cases. Comprehensive care for these patients involves professionals from various health areas, making it necessary to reduce variability in the care provided to these patients in institutions by means of guidelines that optimize the quality of care, diagnosis, and treatment.
Objective: To identify the clinical indications for the diagnosis and treatment of ACC in adults by developing an evidence-based clinical standard (EBCS) at a national referral university hospital in Bogotá, Colombia.
Materials and methods: After assembling the development group and defining the scope and objectives of the EBCS, systematic searches were conducted in December 2020 on MEDLINE, EMBASE, and LILACS, as well as in clinical practice guidelines (CPG) development and compiling agencies, to identify CPGs published in the last 10 years that met said objectives and scope. The quality of the selected CPGs was evaluated using the AGREE II instrument. A preliminary proposal of the EBCS (clinical algorithm and recommendations) was developed using the selected CPGs, which was subsequently validated through an interdisciplinary consensus (modified Delphi methodology).
Results: Two CPGs were selected. After reaching full agreement at the interdisciplinary consensus meeting, a four-section clinical algorithm was developed: "diagnostic approach to adult patients with ACC," "classification of ACC severity," "classification of choledocholithiasis risk and surgical treatment of patients with ACC," and "treatment of patients with ACC initially unsuitable for surgery." Key aspects were also defined for implementing the algorithm and clinical recommendations, as well as for evaluating and monitoring their implementation, referred to as checkpoints (section five).
Conclusion: The evidence-based clinical recommendations included in this EBCS contribute to standardizing practices and actions concerning the diagnosis and treatment of ACC in adults in Colombia and even the region.

Resumen

Introducción. La colecistitis aguda es la complicación más frecuente de la colelitiasis y se define como la inflamación de la vesícula como consecuencia de la obstrucción del conducto cístico. Cuando esta obstrucción es causada por un cálculo biliar, se conoce como colecistitis aguda calculosa (CAC), representando 90-95% de los casos. La atención integral de estos pacientes involucra a profesionales de varias áreas de la salud, por lo que es necesario reducir la variabilidad en la atención de estos pacientes en las instituciones mediante directrices que optimicen la calidad de la atención, el diagnóstico y el tratamiento.
Objetivo. Identificar las indicaciones clínicas para el diagnóstico y tratamiento de CAC en adultos mediante el desarrollo de un estándar clínico basado en la evidencia (ECBE) en un hospital universitario de referencia nacional de Bogotá, Colombia.
Materiales y métodos. Una vez conformado el grupo desarrollador y definidos el alcance y los objetivos del ECBE, en diciembre de 2020 se realizaron búsquedas sistemáticas en MEDLINE, EMBASE y LILACS y en organismos desarrolladores y compiladores de guías de práctica clínica (GPC) para identificar GPC publicadas en los últimos 10 años que respondieran a dichos objetivos y alcance. La calidad de las GPC seleccionadas fue evaluada con el instrumento AGREE II. Con base en las GPC seleccionadas se desarrolló una propuesta preliminar de EBCE (algoritmo clínico y recomendaciones) que fue validada mediante un consenso interdisciplinario (metodología Delphi modificada).
Resultados. Se seleccionaron 2 GPC. Luego de lograr un acuerdo total en el consenso interdisciplinario se consolidó un algoritmo clínico de cuatro secciones: "enfoque diagnóstico del paciente adulto con CAC", "clasificación de la severidad de la CAC", "clasificación del riesgo de coledocolitiasis y tratamiento quirúrgico del paciente con CAC" y "tratamiento del paciente con CAC inicialmente no apto para cirugía". Además, se definieron aspectos claves para la implementación del algoritmo y las recomendaciones clínicas y para la evaluación y seguimiento de su implementación, denominados como puntos de control (sección cinco).
Conclusión. Las recomendaciones clínicas basadas en la evidencia incluidas en este ECBE contribuyen a estandarizar las prácticas y acciones relacionadas con el diagnóstico y tratamiento de la CAC en adultos en Colombia e incluso la región.

Introduction

Acute cholecystitis is defined as the inflammation of the gallbladder following cystic duct obstruction, often caused by gallstones or bile sludge.[1] This condition may occur whether or not gallstones form. When the obstruction is caused by a gallstone, it is known as acute calculous cholecystitis (ACC),[1] accounting for approximately 90-95% of cases. The remaining 5-10% of cases correspond to acute non-calculous cholecystitis, defined as inflammation of the gallbladder when there are no gallstones, which is usually observed in the context of a serious critical illness,[2,3] with a higher incidence in the intensive care unit (ICU), particularly in patients admitted for burns and trauma.[4]

It should be noted that if a patient experiences pain as a result of a temporary obstruction of the cystic duct by a gallstone, this pain is referred to as biliary colic, but if the pain does not resolve within 6 hours, the diagnosis progresses to ACC.[1] This type of obstruction increases the pressure inside the gallbladder, causing it to dilate and leading to bile stasis, proliferation of bacteria (most commonly *Escherichia coli*, followed by *Klebsiella*, *Enterococcus*, and *Enterobacter*), and congestion of the lymphatic capillaries in the gallbladder wall, resulting in subserosal edema and thickening of the gallbladder wall.[2,5,6] This stage lasts between 2 and 4 days, and if acute cholecystitis is not detected and treated at this point, areas of bleeding and necrosis will begin to appear in the gallbladder wall due to vascular thrombosis. If left untreated, the wall becomes inflamed with neutrophil infiltration and areas of suppuration affecting the entire thickness of the gallbladder wall, with the formation of pericholecystic abscesses.[6]

Patients with acute cholecystitis typically exhibit persistent, severe, and prolonged (more than 6 hours) abdominal pain in the upper right quadrant accompanied by fever, nausea, and vomiting.[1-3,6,7] Moreover, the pain may radiate to the epigastrium, right scapula, or right shoulder area,[1,2] so symptoms are often mistaken for cardiac problems.[1] In this regard, finding a positive Murphy's sign (cessation of inspiration on palpation of the right upper quadrant) suggests the presence of this condition, with a specificity between 87% and 97%.[2] Acute cholecystitis is the most common complication of cholelithiasis,[2,8] occurring in about 10% of patients with symptomatic gallstones.[3,4] According to the BMJ best practice website, its distribution and incidence is similar to those of cholelithiasis due to their close relationship.[4]

Cholelithiasis occurs in about 15% of the adult population. Estimates suggest that between 20 and 25 million people in the United States have gallstones and that 750 000 cholecystectomies are performed there every year, while the prevalence of the condition is relatively low in Asia and Africa.[4] In addition, being female, being obese, having experienced rapid and substantial weight loss, being of Hispanic or Native American descent, using medications such as octreotide and ceftriaxone, being in the fifth decade of life, being pregnant, having diabetes, and history of gastrectomy have been identified as risk factors for gallstones.[1,2] Although most of these patients do not exhibit symptoms,[4,8] gallstones become symptomatic in 1-2% of cases each year.[4] As mentioned above, acute cholecystitis is a complication that occurs in approximately 10% of symptomatic patients, affecting women more frequently than men (three times more common in women than in men up to age 50 and 1.5 times more common after that age).[4]

Acute cholecystitis is a common cause of hospitalization (3-10% of patients who visit the emergency department due to abdominal pain) and mainly affects older adults, with a higher incidence in people over 50 years of age and a high morbidity rate. As for associated mortality, the overall mortality rate is approximately 3%, but it increases in older adults, especially those with comorbidities.[2]

In Colombia, Otálora-Esteban *et al.*[8] reported that 343 254 cases of acute cholecystitis were reported between 2018 and 2022, with an unadjusted prevalence of 681 cases per 100 000 inhabitants. Furthermore, according to these authors, this condition was more common in women (69.9%), with a male:female ratio of 2.3:1 (unadjusted prevalence in women of 942 cases per 100 000 inhabitants vs. 414 cases per 100 000 inhabitants in men).[8]

In terms of economic burden, cholelithiasis and cholecystitis were the second most common gastrointestinal cause of hospitalization in the United States in 2018, with 316 200 hospitalizations per year and a consultation rate of 99.2 per 100 000 people, as well as the fifth leading cause of readmission to emergency departments.[8]

According to the Tokyo Guidelines 2018 (TG18) diagnostic criteria and severity grading for acute cholecystitis,[9] ACC is diagnosed based on clinical findings suggestive of local inflammation, signs of systemic inflammatory response, and imaging findings. The use of these diagnostic criteria, according to the guidelines, has a sensitivity of 91.2% and a specificity of 96.9% for acute cholecystitis.[9] It is worth noting that these sensitivity and specificity values apply to the criteria established in the Tokyo Guidelines 2013 (TG13), but they also apply to TG18, as the latter are an update of the TG13 criteria after their diagnostic accuracy was confirmed in several validation studies. Finally, they were adopted as TG18/TG13 diagnostic criteria without any changes.[9]

However, it has been reported that the diagnostic accuracy of the TG18/TG13 criteria varies between 60.3%[10] and 94.0%[11] when pathological samples are used as the gold standard, also showing marked differences between studies. For example, Yokoe *et al.*[11] report that the sensitivity and specificity of these diagnostic criteria for acute cholecystitis are 91.2% and 96.9%, respectively, while Naidu *et al.*[10] report values of 83.1% and 37.5%, respectively.

Once the diagnosis has been confirmed, defining the degree of severity according to the TG18/TG13 criteria is essential, as it is a predictor of mortality, longer hospital stays, and the need for open cholecystectomy during laparoscopic cholecystectomy.[9,12] Laparoscopic cholecystectomy is the treatment of choice for cholecystitis, including ACC,[1,12] showing low morbidity and mortality rates.[1] However, the treatment of these patients may vary depending on factors such as patient characteristics and resource availability, both technical and human, at the hospital.[12] For example, in individuals who are not candidates for a laparoscopic approach, cholecystectomy can be performed using an open technique, while in patients who are not candidates for surgery, temporary percutaneous drainage of the gallbladder may be used.[13] In patients with mild acute cholecystitis, treatment may also be conservative (parenteral fluid therapy, antibiotic therapy, and analgesia), but outcomes may vary.[13]

Furthermore, due to their involvement in the treatment of these patients, it is also necessary to determine the risk of choledocholithiasis (i.e., presence of gallstones in the common bile duct). For this purpose, the risk stratification system developed by the American Society of Gastrointestinal Endoscopy and the Society of American Gastrointestinal Endoscopic Surgeons can be used, which classifies risk as low (<10%), moderate (10-50%), and high (>50%) based on the patient's clinical characteristics and laboratory and imaging findings.[13]

Accordingly, patients with ACC and a low risk of choledocholithiasis must undergo surgery without additional testing. Patients with moderate risk must undergo preoperative endoscopic ultrasound or magnetic resonance cholangiopancreatography, or intraoperative laparoscopic ultrasound or cholangiography to determine the need for gallstone removal. Finally, patients at high risk must undergo diagnostic and therapeutic endoscopic retrograde cholangiopancreatography before cholecystectomy.[13]

Comprehensive care for these patients involves healthcare professionals from various fields, namely general medicine, general surgery, intensive care, gastroenterology, radiology and diagnostic imaging, infectious diseases, clinical laboratory, and nursing. Therefore, standardizing practices and actions related to the diagnosis and treatment of adult patients with ACC is essential to reduce treatment variability in general hospital wards and ICUs, thereby optimizing the use of resources and improving the quality of care provided to this population.

In light of the foregoing, the objective of this article is to identify the clinical indications for the diagnosis and treatment of ACC in adults by developing an evidence-based clinical standard (EBCS) at a national referral university hospital in Bogotá, Colombia.

Materials and methods

This EBCS was developed through a sequential seven-phase process proposed by the Hospital Universitario Nacional de Colombia, in collaboration with the Universidad Nacional de Colombia and the Instituto de Investigaciones Clínicas (Clinical Research Institute) of the Universidad Nacional de Colombia. The phases are described below:

Formation of the development group

The development group comprised experts in general surgery and clinical epidemiology (a methodological leader with experience in the development of clinical standards, two healthcare professionals trained in evidence-based medicine, a second-year general surgery resident, and a hepatobiliary surgeon with experience in the treatment of ACC), who participated in online meetings to establish the methodological, technical, and thematic guidelines for the formulation of the EBCS recommendations. Prior to agreeing to join the development group, all members completed a conflict-of-interest disclosure form.

EBCS scope definition and objectives

The EBCS scope was established based on the following elements: i) target population in which the recommendations will be used; ii) special populations on which the recommendations can be used, such as indigenous peoples, Afro-descendant communities, rural populations, etc., to ensure health equity; iii) aspect of the condition or disease to be addressed (treatment, diagnosis, prevention, follow-up, etc.); iv) aspects of the condition or disease that are beyond the scope of the recommendations; v) health care context (outpatient consultation, inpatient service, surgery service, intensive care, etc.); and vi) specialties, areas, or health services involved in the implementation and use of the recommendations.

This EBCS is intended to develop a clinical algorithm for the diagnosis and treatment of adult patients with ACC admitted to a national referral university hospital in Bogotá (general hospital ward or ICU) based on the best available evidence. It should be noted that the EBCS does not contain recommendations for pediatric population (<18 years of age) or pregnant women.

The recommendations included in the EBCS are aimed at healthcare workers involved in the care of adult patients with ACC (general practitioners, general surgeons, intensive care physicians, gastroenterologists, radiology and diagnostic imaging specialists, infectious disease specialists, nurses, and clinical laboratory and pharmacy specialists). Furthermore, it was established that the recommendations could also be used by health

sciences students (undergraduate and graduate) who are involved in the care of these patients during their clinical practice, their professors, and the healthcare or administrative staff of the healthcare institutions in charge of making decisions regarding the treatment and follow-up of this population.

The general and specific objectives of this EBCS were defined based on a literature review, an analysis of the care areas involved in the management of these patients, and an interdisciplinary consensus. The formulated objectives clearly and succinctly describe the purpose of the EBCS. Checkpoints and guidelines for the dissemination and implementation of the EBCS were also included in its preparation.

Systematic review of clinical practice guidelines

Systematic searches in MEDLINE, EMBASE and LILACS, as well as in clinical practice guideline (CPG) development and compiling agencies were conducted using controlled language and sensitive electronic search strategies to identify CPGs that met the stated objective and scope (Supplement 1). Searches were conducted between December 16 and 19, 2020. The CPG screening and selection process was carried out taking into account the following eligibility criteria established by the development group:

Inclusion criteria

- CPGs on the diagnosis and treatment of ACC in adults.
- CPGs published in English or Spanish with full-text access.
- CPGs published within the last 10 years at the time of performing the searches.

Exclusion criteria

- CPGs with an overall quality assessment <6 according to the AGREE II instrument[14] and a score <60% in the methodological rigor and editorial independence domains.
- CPGs on the diagnosis and treatment of ACC in pediatric patients and pregnant women.

Evidence was screened by reviewing titles and abstracts, as well as the full text of the papers identified in the systematic searches. This process was performed independently by the general surgery resident and a member of the methodological team. It was agreed that any discrepancies would be resolved by a third member (methodological leader). The quality of the selected CPGs was assessed using the AGREE II instrument;[14] this process was also carried out independently by two members of the development group: a clinical expert and a methodological expert.

Preliminary algorithm development

The development group used the selected CPGs to draft a preliminary proposal of the EBCS (clinical algorithm plus checkpoints [key recommendations for implementing the algorithm and clinical recommendations and for evaluating and monitoring their implementation]). To extract the evidence contained in the two selected CPGs, an information extraction table was created using a domain system. After reviewing the evidence gathered during several meetings, the development group elaborated the proposed clinical algorithm and recommendations for the diagnosis and treatment of adult patients with ACC. These recommendations included the level of evidence of each of the CPGs used to

formulate the recommendation. Importantly, the level of evidence is presented following the evidence grading system used in the CPG.

Developing an interdisciplinary agreement

After identifying the health areas/services involved in the comprehensive care process of adult patients with ACC, representatives of these services at the national reference university hospital where the EBCS was developed were appointed. They received the draft of the clinical algorithm for their assessment prior to attending a consensus meeting.

The consensus meeting took place in April 2022 and was attended by representatives of the following hospital care services: general surgery, critical care, gastroenterology, radiology and diagnostic imaging, infectious diseases, nursing, clinical laboratory, and pharmacy. Clinical leaders were responsible for the presentation of the preliminary algorithm (flowchart), and the meeting was moderated by a research methodologist. Four sections of the EBCS (algorithm), as well as an additional section on checkpoints, were presented at the meeting. Using the modified Delphi methodology and a 9-point Likert scale, it was possible to evaluate the level of agreement among the participants with the information presented in each section. The results of the five polls confirmed that all participants of the interdisciplinary consensus group fully endorsed the use of the recommendations for the diagnosis and treatment of patients with ACC contained in the flowcharts presented below. More detailed information on this step is available in the full text of this EBCS.[15]

Final algorithm development

Once the interdisciplinary consensus was achieved, the development team met and consolidated the suggestions made at the consensus meeting and based on them, modified the preliminary algorithm of the document.

EBCS review and editing

The final activity of the process involved the revision of the document's wording and layout, resulting in the final version of the EBCS.[15] As in the preliminary proposal, the recommendations include the level of evidence of each of the CPGs used to formulate the recommendation, and the level of evidence is presented in accordance with the evidence grading system used in each CPG.

Results

The preliminary searches retrieved 226 records. After removing duplicates (n=9), a total of 217 were identified, of which 210 were excluded at the title and abstract review stage. Then, out of the 7 that were fully read, 2 CPGs were selected for quality assessment using the AGREE II instrument.[14] Lastly, during the methodological quality assessment stage, no CPGs were excluded. The 2 CPGs that met the eligibility criteria and were finally included for evidence review are listed in Table 1. The evidence search, screening, and selection process is summarized in Figure 1.

Table 1. Clinical practice guidelines identified in the literature search that met the eligibility criteria for the development of the evidence-based clinical standard.

Id	CPG Title	Development group	Country or continent	Language	Year
CPG1	2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis[13]	World Society of Emergency Surgery	United States	English	2020
CPG2	Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos)[9]	Japanese Society of Hepato- Biliary- Pancreatic Surgery	Japan	English	2018

CPG: Clinical practice guidelines.
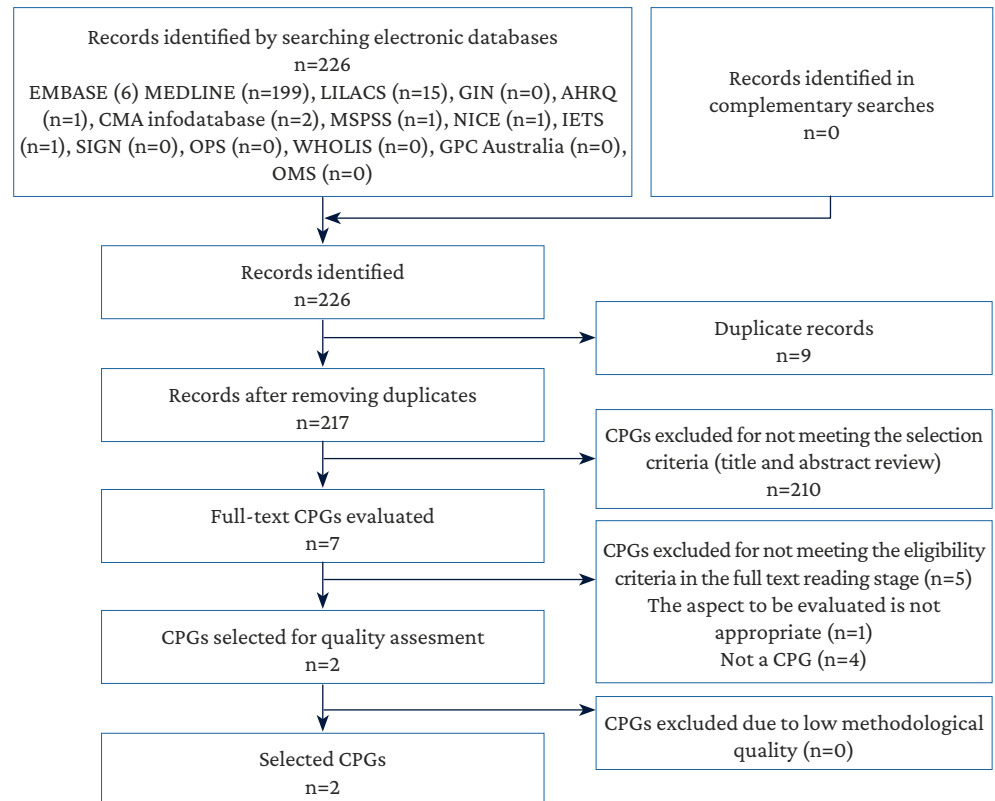
Figure 1. Systematic search for clinical practice guidelines.

Recommendations

The recommendations for diagnosing and treating patients with ACC are presented using the sections of the clinical algorithm formulated by the development group based on the evidence retrieved from the selected CPGs and the opinions of the expert members of the development group, as well as the experts involved in the interdisciplinary consensus (Figure 2). The results are described below:
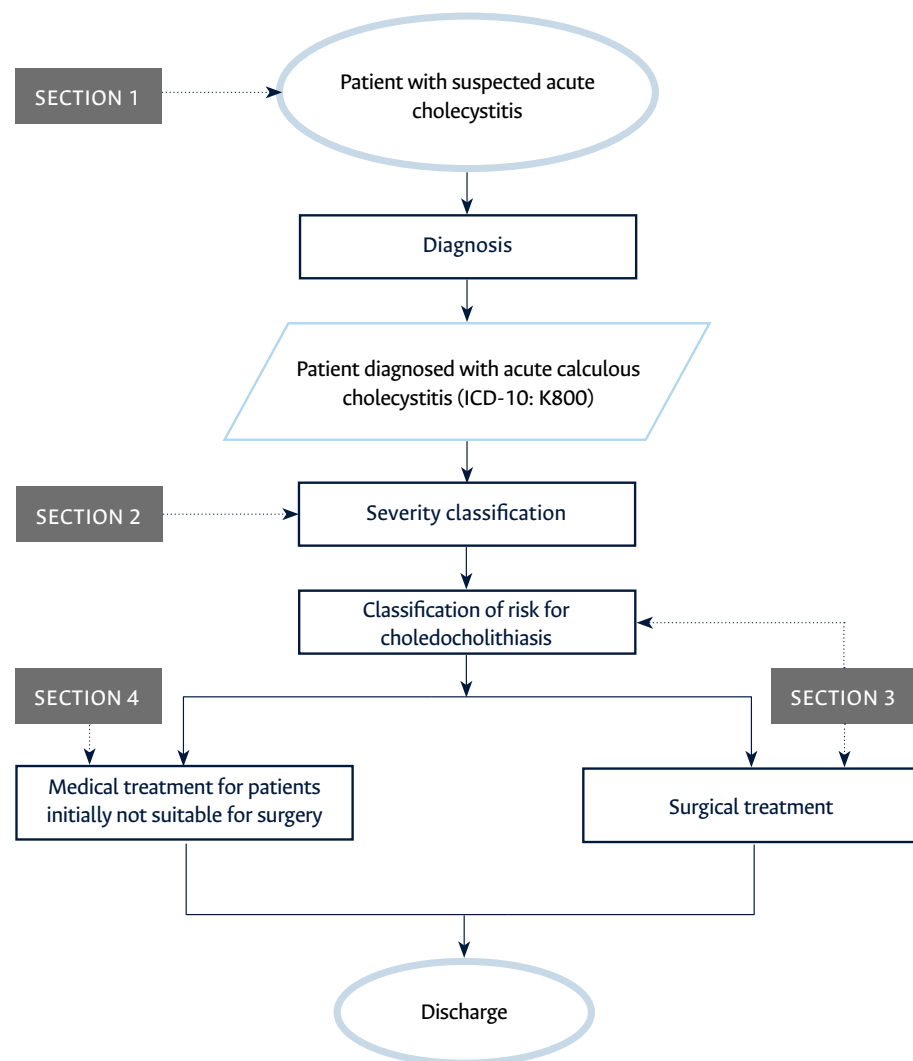
Figure 2. Flowchart for the diagnosis and treatment of adult patients with acute calculous cholecystitis (ICD-10: k80.0).
ICD-10: International Classification of Diseases and Related Health Problems, tenth Revision.

Section 1 - Recommendations for the diagnostic approach to adult patients with ACC

Context: ACC is a condition that affects the quality of life of those who suffer from it. It entails a high economic burden, particularly when it is not diagnosed in a timely manner. Therefore, patients with a suspected diagnosis of ACC must undergo a comprehensive initial assessment (medical history, semiology, and various diagnostic tests) for an early diagnosis. Figure 3 illustrates the flowchart for Section 1.

SECTION 1

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┌─────────────────────────────┐
│ Patient with suspected acute │
│        cholecystitis         │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│ Assess probability of acute  │
│        cholecystitis.        │
│          Perform:            │
│    · Anamnesis[1A]           │
│    · Clinical examination[1B]│
│    · Laboratory tests[1C]    │
│    · Diagnostic imaging[1D]  │
└─────────────────────────────┘
              │
              ▼
        ◇ Does the p|atient
          meet the diagnostic
          criteria?[1E] ◇
     No ◄──────┴──────► Yes
      │                   │
      ▼                   ▼
┌──────────────┐   ╱────────────────────────╱
│  Consider    │  ╱ Patient diagnosed with  ╱
│ differential │ ╱ acute calculous          ╱
│  diagnoses   │╱ cholecystitis            ╱
└──────────────┘ (ICD-10: K800, K810) ────╱
                          │
                          ▼
               ┌────────────────────┐
               │ (Go to Section 2:  │
               │ severity           │
               │ classification)    │
               └────────────────────┘
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Figure 3. Flowchart for the diagnostic approach to patients with acute calculous cholecystitis. ICD-10: International Classification of Diseases and Related Health Problems, tenth Revision.

Summary of recommendations:

1.A Anamnesis: The diagnosis of acute cholecystitis is made based on a complete medical history obtained from a thorough interview, particularly emphasizing on pain characteristics. Anamnesis must focus on symptom onset; pain characteristics (constant, severe, consistent with biliary colic, located more frequently in the upper right quadrant or epigastrium, long-lasting [>4-6 hours]; and usually beginning after food intake); presence of other symptoms such as nausea, vomiting, fever, and jaundice; characteristics of urine output and bowel movements; and history of similar events (expert recommendation).[8]

1.B Clinical examination: A comprehensive physical examination must be performed, including: measurement and recording of vital signs; inspection and palpation of the abdomen, assessing the least painful site, emphasizing on the upper right quadrant and the presence of masses; Murphy's sign assessment (cessation of inspiration on deep palpation of the right subcostal area); and assessment of whether or not there are signs of peritoneal irritation, as these are essential aspects for diagnosing ACC. It is also important to check the sclera for jaundice, examine the mucous membranes to assess hydration status, and perform adequate pulmonary auscultation to rule out associated pleural effusion (level of evidence [LE]: very low; GRADE).[9]

1.C Laboratory tests: The following laboratory tests are recommended as diagnostic aids: complete blood count; C-reactive protein (CRP) test; liver profile: alkaline phosphatase (ALP), aspartate aminotransferase, alanine aminotransferase, total bilirubin,

direct bilirubin, and indirect bilirubin; amylase test; and renal function tests: blood urea nitrogen test and urine creatinine test (LE: low; GRADE).[13]

Based on the reference values reported by the laboratory, it is important to assess whether the patient has elevated ALP levels, as this could indicate a possible obstruction of the bile ducts, thus increasing the diagnostic suspicion of ACC. Furthermore, although it is beyond the scope of this standard, it is worth noting that elevated ALP levels can be observed in pregnant women and children, but they may be secondary to other causes (pregnancy or bone disease). It must also be considered whether bilirubin values are elevated or transaminase and amylase levels are altered, although the latter is not included in the liver profile, as these findings may be useful in the differential diagnosis of pancreatitis (LE: very low; GRADE).[9]

1.D Diagnostic imaging: An upper abdominal ultrasound or hepatobiliary ultrasound is recommended as the initial diagnostic imaging test of choice due to its cost-effectiveness, availability, minimally invasive nature, and high accuracy for the diagnosis of ACC, with a reported sensitivity of 82% and specificity of 81%[16] (LE: C; GRADE),[13] (LE: high; GRADE).[9]

Imaging findings suggestive of ACC include evidence of gallstones (particularly impacted in the neck of the gallbladder), positive Murphy's sign on ultrasound, gallbladder distension, presence of pericholecystic fluid, and thickened gallbladder walls >3mm (expert recommendation). Additional diagnostic imaging tests are recommended to confirm the diagnosis in selected patients based on local experience and availability.

Hepatobiliary iminodiacetic acid (HIDA) scan has the highest sensitivity (94%) and specificity (90%)[16] for the diagnosis of ACC compared to other imaging studies (LE: D; GRADE).[13] However, this procedure is more expensive than abdominal ultrasound, and obtaining timely results is more difficult because it is not available at the institution. Therefore, if necessary, it is preferable to use biliopancreatic endoscopy (expert recommendation), which is preferred in the following specific cases: patients with decompensated congestive heart failure, liver disease, or chronic renal failure with signs of fluid overload and findings suggestive of cholecystitis on ultrasound with uncertain clinical signs (expert recommendation).

Furthermore, the diagnostic accuracy of contrast-enhanced abdominal computed tomography is poor, except in cases of emphysematous cholecystitis (LE: D; GRADE),[13] but it is useful in patients at risk, such as those with a palpable mass or unintentional weight loss (expert recommendation). Finally, contrast-enhanced magnetic resonance imaging of the abdomen has a diagnostic accuracy similar to that of abdominal ultrasound (LE: moderate; GRADE),[9] with a reported sensitivity of 86% and specificity of 82%.[16]

1.E Diagnostic criteria for ACC: The Tokyo 2018 diagnostic criteria for ACC have high sensitivity and specificity, as well as good diagnostic performance. Therefore, it is recommended that they be used as diagnostic criteria for this condition (LE: C; GRADE).[9] These criteria have a sensitivity of 91.2% and a specificity of 96.6% for acute cholecystitis, making them the gold standard for diagnosis.[9] The Tokyo diagnostic criteria are listed below:

A. Local signs of inflammation: Murphy's sign or mass/pain/tenderness in the right hypochondrium or upper right quadrant (expert recommendation).[9]
B. Systemic signs of inflammation: fever, elevated CRP levels, or elevated white blood cell count.
C. Imaging findings consistent with ACC. If there is no diagnostic imaging evidence upon the patient's admission to the institution, the diagnosis will be defined as follows:
- Suspected diagnosis: one item in A + one item in B.
- Final diagnosis: one item in A + one item in B + C.
  Ultrasound findings consistent with ACC are the following (expert recommendation):[9,17]
- Anteroposterior biliary dilatation >4cm in diameter.
- Gallbladder wall thickness >3mm.

- Presence of pericystic fluid.
- Positive Murphy's sign on ultrasound.
- Evidence of gallstones, particularly impacting the neck of the gallbladder.

Section 2 - Recommendations for classifying ACC severity

Context: Treatment of patients with ACC must focus on maintaining electrolyte balance, controlling pain, and meeting nutritional needs depending on the severity of the condition. Furthermore, if it is considered that the patient may benefit from antibiotic therapy, it must be implemented taking into account susceptibility patterns. Figure 4 illustrates the flowchart for Section 2.
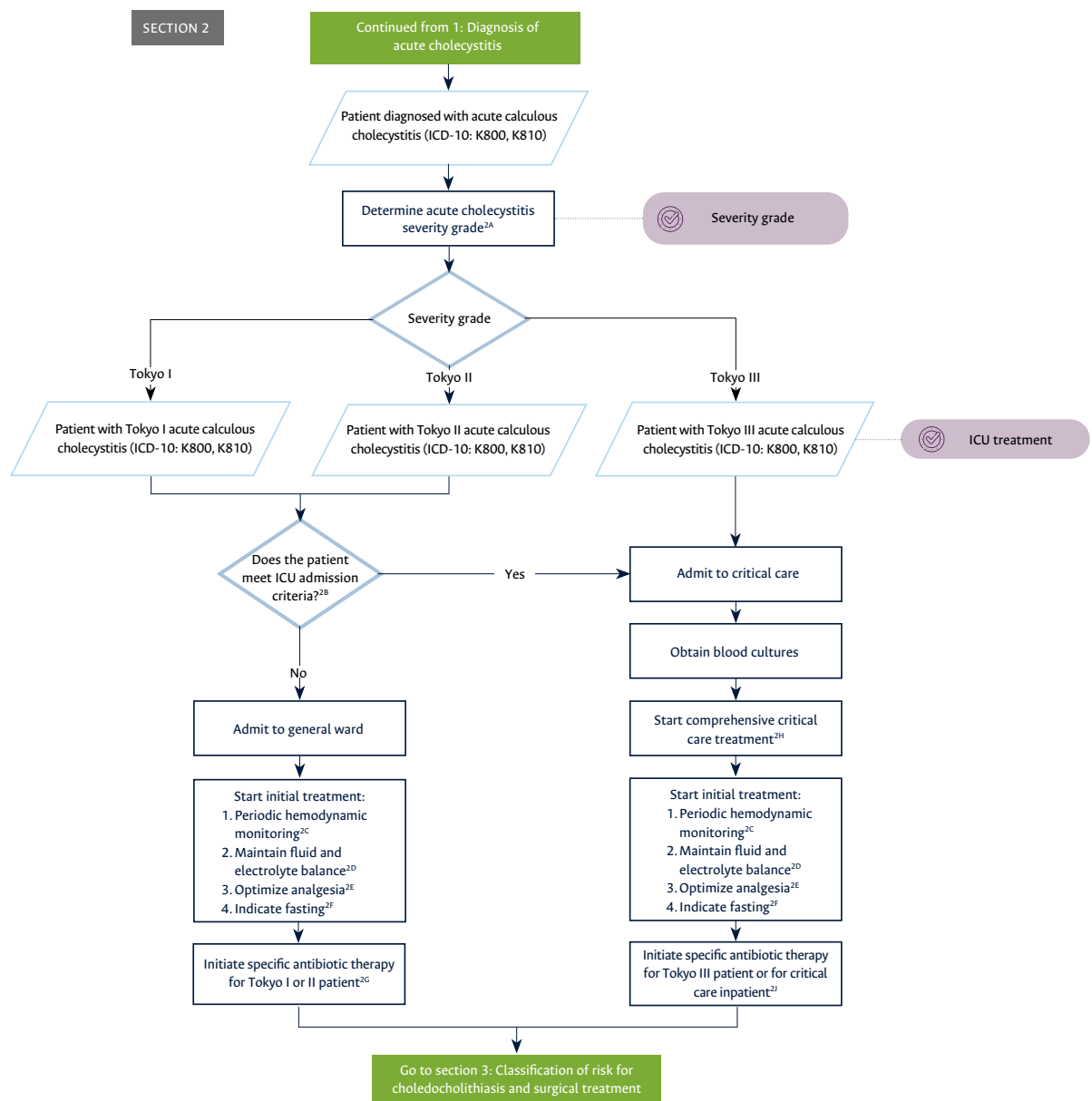

Figure 4. Flowchart for classifying acute calculous cholecystitis severity.
ICD-10: International Classification of Diseases and Related Health Problems, Tenth revision;
ICU: intensive care unit.

Summary of recommendations:

2.A ACC severity grade: The Tokyo 2018 Guidelines for acute cholecystitis severity classification is recommended as a prognostic indicator of hospital stay and requirement for open cholecystectomy during laparoscopic cholecystectomy (LE: C; GRADE).[13] This classification has the following severity grades:

- Tokyo I: Acute cholecystitis not meeting criteria for grade II or III.
- Tokyo II: Cases meeting any of the following criteria:
  - White blood cell count >18 000.
  - Palpable mass in upper right quadrant.
  - Duration of symptoms >72 hours.
  - Marked local inflammation (gangrenous cholecystitis, emphysematous cholecystitis, pericholecystic abscess, liver abscess, biliary peritonitis).
- Tokyo III: Acute cholecystitis associated with dysfunction of any of the following organs/systems:
  - Cardiovascular: low blood pressure requiring dopamine ≥5mcg (kg/min) or norepinephrine at any dose.
  - Neurological: decreased level of consciousness.
  - Respiratory: PaO2/FiO2 ratio <300.
  - Renal: oliguria, creatinine in urine >2mg/dL.
  - Hepatic: PT/INR >1.5
  - Hematological: platelet count <100 000.

2.B Criteria for admission to critical care: A patient with ACC is considered a candidate for admission to the ICU or intermediate care unit provided that their advance healthcare directives are not violated, the intensivist on duty approves them, or at least one of the following criteria is met (expert recommendation):

- Requirement for invasive/non-invasive mechanical ventilation.
- Hemodynamic instability due to mean arterial pressure (MAP) <60mmHg, septic shock, uncontrolled fever, uncontrolled infection, etc.
- Altered state of consciousness (marked decrease below 9/15 on the Glasgow Coma Scale).
- Electrocardiographic abnormalities.
- Clinical progression with signs of marked local inflammation (Tokyo II).

Other general considerations regarding admission to the ICU are available in the Criteria for Admission, Classification, and Discharge from the Intensive Care Unit - V6 medical protocol (available in the Daruma repository under code AC-PT-10) and include:

- Need for intensive and complex medical care.
- Need for intensive and complex nursing care.
- Invasive and/or intensive monitoring after major or complicated surgery.
- Neurological dysfunction requiring hourly neurological monitoring.
- Other respiratory, cardiovascular, gastrointestinal, hematological and oncological, endocrine and metabolic, genitourinary, and renal disorders.

2.C Hemodynamic monitoring: Hemodynamic monitoring refers to the periodic monitoring of vital signs and reporting of changes when they occur (expert recommendation).[18]

2.D Fluid and electrolyte balance support: Fluid and electrolyte support involves the intravenous administration of fluids to prevent dehydration and replenish electrolytes in cases of electrolyte loss, limited fluid intake, or fasting (expert recommendation).[19]

It is recommended to use crystalloids such as Ringer's lactate or normal saline solution, with dosage adjusted for patient weight (dosage calculated using the Holliday-Segar

formula: 1 500mL + 20L/kg for each kg >20 up to a maximum of 2 400mL per day), and consider the presence of comorbidities that lead to fluid overload (heart, liver, or kidney failure) (expert recommendation).[19]

2.E Analgesia: Controversy still exists regarding appropriate pain management in these patients. Several studies have demonstrated the usefulness of nonsteroidal anti-inflammatory drugs for early pain control. Opioids, antispasmodics, and paracetamol can also be used, the latter intravenously (expert recommendation).[20]

2.F Fasting: Fasting must be used as a measure of intestinal rest, since food intake, especially high fat meals, is associated with increased abdominal pain (expert recommendation).[20] If there are no contraindications to starting oral feeding, a clear liquid diet may be prescribed (expert recommendation).

2.G Antibiotic therapy in patients with Tokyo I or II acute cholecystitis: The main objectives of antibiotic therapy in patients with acute cholecystitis are limiting systemic response and local inflammation; preventing infections at the surgical site in superficial wounds, fascia, or organ spaces; and preventing the formation of abscesses in the liver. In cases of Tokyo I and II acute cholecystitis, antibiotic therapy must be started within the first six hours after diagnosis, but it must be started within the first hour for Tokyo III (LE: D; GRADE).[13]

The antibiotics to be used are selected based on target organisms, pharmacokinetics, pharmacodynamics, local microbiological characteristics, antibiogram results, history of antibiotic use, renal and hepatic function, and history of allergies and other adverse events (LE: D; GRADE).[13] Antibiotic therapy against anaerobic bacteria is recommended in cases of end-to-end anastomosis (LE: C; GRADE).[13]

In patients with Tokyo I and II acute cholecystitis, it is recommended to use cefuroxime 1.5g intravenously every 8 hours + metronidazole 500mg intravenously every 8 hours as the therapy of choice, or ampicillin sulbactam 3g intravenously every 6 hours as the second option for antibiotic therapy. In case of complications such as gangrenous cholecystitis, emphysematous cholecystitis, pericholecystic abscess, liver abscess, or biliary peritonitis, it is recommended to administer piperacillin tazobactam at a dose of 4.5g intravenously every 6 hours (expert recommendation).

Oral antibiotics may be used in patients with acute cholangitis and acute cholecystitis who can tolerate oral food intake. Depending on the antibiotic susceptibility patterns of the identified organisms, antimicrobial agents such as fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), amoxicillin/clavulanic acid, or cephalosporins may also be used (expert recommendation).

It is essential to note that ampicillin sulbactam is contraindicated in patients with known allergies to penicillin, cephalosporins, and imipenem, as well as in those with a history of atopy, such as asthma, eczema, and hay fever. Moreover, relative contraindications for the use of this antibiotic include viral infections or lymphatic leukemia, as these patients are prone to hypersensitivity reactions with rash. In these cases, the treatment of choice is ciprofloxacin 400mg intravenously every 12 hours plus metronidazole 50mg intravenously every 8 hours (expert recommendation).[21]

In patients with Tokyo I and II acute cholecystitis, it is recommended to start antibiotic therapy upon admission to the hospital (whether in a general ward, intermediate care, or ICU) and discontinue it up to 24 hours after cholecystectomy. However, in special circumstances such as bile duct perforation, emphysematous changes, or gallbladder wall necrosis, treatment must be extended from 4 to 7 days; also, in the presence of such intraoperative findings, a sample must be taken for bile culture (LE: B; GRADE).[13]

2.H Comprehensive treatment in the ICU: Once the patient is admitted to the ICU, they must be assessed by the critical care, nursing, and physical therapy services/ care areas. Each of these services will define the most relevant care objectives for the patient based on their condition and clinical progress. The objectives of comprehensive treatment in this clinical scenario will be adequate control of vital signs, implementation of organ support therapy, as necessary, and comprehensive rehabilitation of the patient. Additionally, in cases of Tokyo III acute cholecystitis, blood cultures must be taken upon admission (expert recommendation).

2.I Organ support: A patient with ACC will be considered a candidate for organ support therapy (ventilatory support and/or hemodynamic support) provided that their health advance directives are not violated and they present at least one of the following conditions (LE: C; GRADE):[13]

- Reduced level of consciousness below 9/15 on the Glasgow Coma Scale.
- Decreased MAP below 65mmHg, with no response to intravenous fluid infusion.
- Low platelet count (<100 000).

2.J Antibiotic therapy for patients with Tokyo III acute cholecystitis or admitted to the ICU: In patients with Tokyo III acute cholecystitis, it is recommended to start piperacillin-tazobactam 4.5g intravenously every 6 hours or cefepime 2g intravenously every 8 hours plus metronidazole 500mg intravenously every 8 hours. Also, blood cultures and bile cultures must be taken, as mentioned above (expert recommendation).

In patients with Tokyo III acute cholecystitis, it is suggested to continue antibiotics for 4 to 7 days after the source of infection has been controlled. In cases of gram-positive cocci bacteremia, antibiotic therapy must last at least 2 weeks (LE: D; GRADE).[13]

In case of residual gallstones or bile duct obstruction, treatment must be continued until the clinical condition is resolved. Similarly, in patients with liver abscess associated with ACC, antibiotic therapy must be continued until there is clinical, biochemical, and radiological resolution of the disease (expert recommendation).

Section 3 - Recommendations for risk classification of choledocholithiasis and surgical treatment of patients with ACC

Context: Determining the probability of choledocholithiasis and classifying disease severity in a patient diagnosed with ACC is critical in order to adequately guide treatment. Different clinical parameters can also help identify whether clinical progress is satisfactory or whether the patient is experiencing postoperative deterioration. Figure 5 illustrates the flowchart for Section 3.
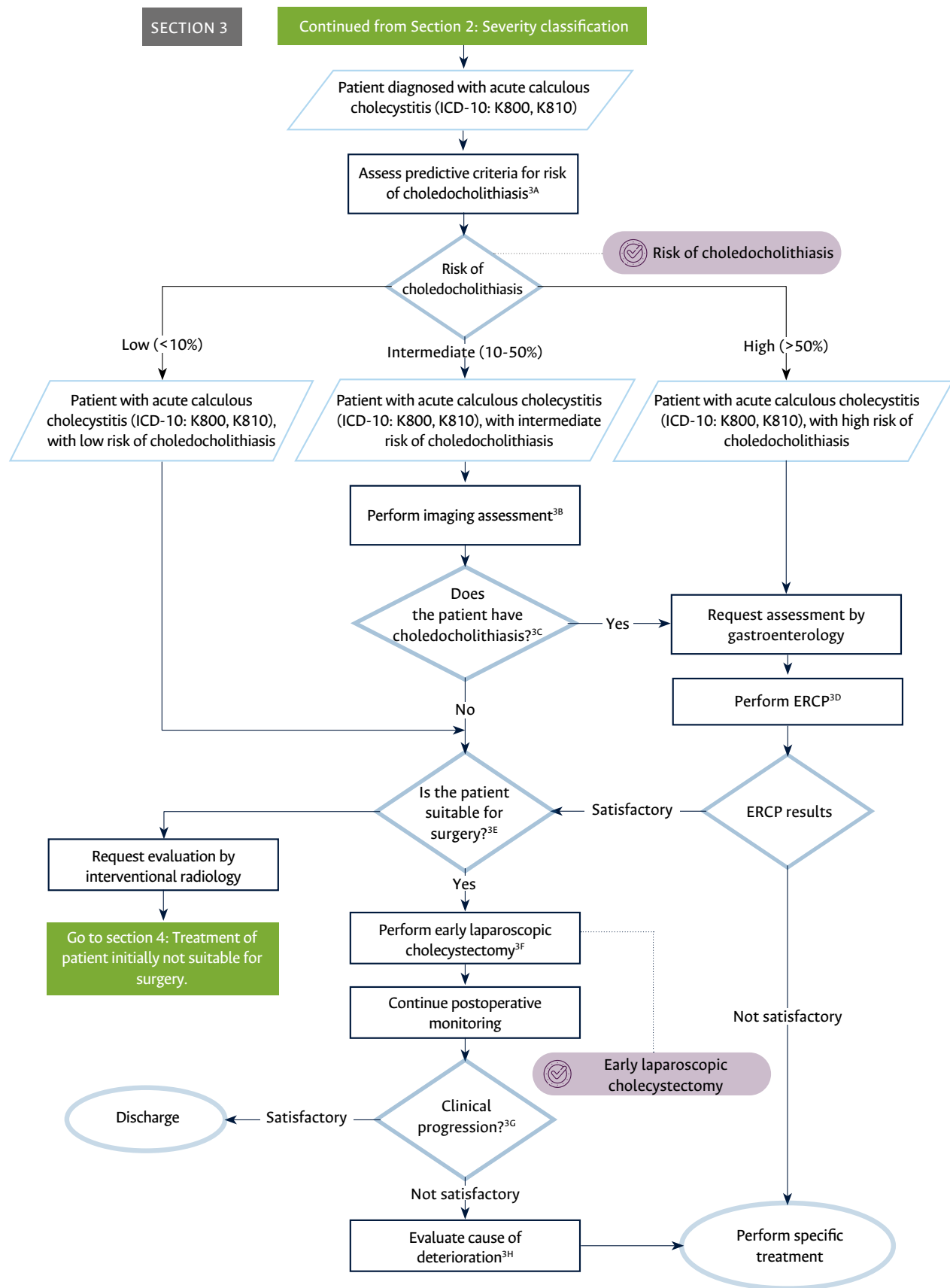
Figure 5. Flowchart for risk classification of choledocholithiasis and surgical treatment of patients with acute calculous cholecystitis.
ERCP: endoscopic retrograde cholangiopancreatography; ICD-10: International Classification of Diseases and Related Health Problems, Tenth revision.

Summary of recommendations:

3.A Determining the risk of choledocholithiasis: It is suggested to stratify the risk of choledocholithiasis according to the modified version of the classification proposed by the American Society for Gastrointestinal Endoscopy as follows (LE: very low; GRADE):[9,22,23]

- Low risk of choledocholithiasis (<10%): no predictive criteria for choledocholithiasis risk. These patients must undergo laparoscopic cholecystectomy, with or without intraoperative cholangiography.
- Intermediate risk of choledocholithiasis (10-50%): patients with abnormal liver function test results, age >55 years, or imaging findings of bile duct dilation >6mm. These patients must undergo magnetic resonance cholangiopancreatography, endoscopic ultrasonography, or laparoscopic cholecystectomy with intraoperative cholangiography.
- High risk of choledocholithiasis (>50%): presence of ascending cholangitis, evidence of gallstones in the bile duct on imaging studies, or bile duct dilation with total bilirubin >4mg/dL. These patients must undergo endoscopic retrograde cholangiopancreatography (ERCP).

3.B Imaging characterization of choledocholithiasis in patients with intermediate risk: In patients with intermediate risk of choledocholithiasis, it is recommended to perform any of the following imaging tests: i) magnetic resonance cholangiography, ii) endosonography (echoendoscopy), or iii) intraoperative cholangiography (LE: high; GRADE).[13]

Depending on availability at the institution, magnetic resonance cholangiography is recommended as the imaging study of choice and, if available, endoscopic ultrasound.

Magnetic resonance cholangiography is especially useful for evaluating the proximal segment of the common bile duct, as well as intrahepatic segments. It is the imaging test of choice in patients who have undergone surgery that resulted in distortion of the normal anatomy of the biliary tract (biliodigestive shunts), as endoscopic ultrasound uses vascular landmarks of the unaffected anatomy as a guide, with a reported sensitivity and specificity of 94% and 96%, respectively.[24] It is also recommended to perform this procedure in patients with high anesthesia risk based on preanesthetic assessment (expert recommendation).

Echoendoscopy, on the other hand, is more useful for evaluating the pancreas and the distal section of the common bile duct. It is recommended for patients with claustrophobia, metal implants, or when there is doubt about interference between these elements and the resonator; patients with persistent symptoms despite negative cholangiography; and patients with suspected microlithiasis (stones <2mm), disease or alteration of the ampulla of Vater, and distal stenosis. Before undergoing echoendoscopy the patient must undergo a pre-anesthetic assessment, given the risks inherent to the procedure and the need for sedation. The sensitivity and specificity described for this procedure are 95% and 97%, respectively.[24]

Intraoperative cholangiography is recommended in patients who have not undergone cholangiography or endoscopic ultrasound and if one of the following conditions is present (expert recommendation):[25]

- Jaundice or history of jaundice.
- History of pancreatitis, particularly biliary pancreatitis.
- Abnormal liver function test results.
- Common bile duct with diameter >6mm on ultrasound.
- Cystic duct with a diameter >3mm on ultrasound.
- Presence of multiple small gallstones.
- Unclear anatomy in imaging studies.
- Suspected bile duct injury or bile leakage.
- Short cystic duct.

3.C Imaging findings of choledocholithiasis: The following imaging findings, depending on the diagnostic imaging test performed, confirm the diagnosis of choledocholithiasis (expert recommendation):[22,26-29]

- Magnetic resonance cholangiography: evidence of filling defect in the common bile duct secondary to the presence of a gallstone.
- Endosonography: hyperechoic defects in the bile duct that cast a posterior acoustic shadow.
- Intraoperative cholangiography: evidence of filling defect in the common bile duct, bile duct dilation, or no passage of contrast medium to the duodenum after its infusion into the bile duct.

3.D ERCP: It is recommended to perform ERCP in patients at high risk of choledocholithiasis (LE: high; GRADE).[9] ERCP is useful for diagnosing and treating choledocholithiasis, with a sensitivity of 99% and a specificity of 99%,[30] but it is an invasive procedure with potentially serious complications. Currently, it is preferred as a therapeutic method (expert recommendation). Morbidity associated with diagnostic ERCP includes pancreatitis, cholangitis, hemorrhage, duodenal perforation, and allergic reaction to contrast medium. These complications occur in 1% to 2% of cases, but the rate increases up to 10% in patients undergoing sphincterotomy (expert recommendation).[30] If choledocholithiasis cannot be solved through ERCP due to failure to cannulate the duodenal papilla (major or minor), the rendezvous technique must be considered as an option for accessing the bile duct during laparoscopic cholecystectomy (expert recommendation).[31]

3.E Surgical treatment:

- Tokyo I and II: Early laparoscopic cholecystectomy is the treatment of choice for cases of Tokyo I and II acute cholecystitis. However, in patients at high surgical risk (Charlson Comorbidity Index [CCI] ≥6 and American Society of Anesthesiologists Physical Status Classification System [ASA-PS] ≥3), medical treatment must be initiated and the gallbladder drained early or urgently (LE: D; GRADE).[9]
- Tokyo III: Early or urgent cholecystectomy is indicated in selected patients with Tokyo III acute cholecystitis (CCI <4 and ASA-PS <3) and in patients who show improvement but exhibit cardiovascular or renal dysfunction. On the other hand, this intervention is contraindicated in individuals with high anesthesia risk, neurological dysfunction, respiratory failure, and jaundice with bilirubin levels ≥2mg/dL; in these cases, early or urgent gallbladder drainage must be performed (LE: D; GRADE).[9]

It is recommended to take a bile sample during surgery to perform a bile culture in patients with Tokyo II or Tokyo III acute cholecystitis with complications such as gangrenous cholecystitis, emphysematous cholecystitis, pericholecystic abscess, liver abscess, or biliary peritonitis. Antibiotic therapy must be based on culture results (expert recommendation).[9]

3.F Early cholecystectomy: Early cholecystectomy is defined as a procedure performed within the first seven days after symptom onset. This procedure is associated with a lower incidence of surgical site infection, shorter hospital stays, and fewer days of work disability. Furthermore, early cholecystectomy does not increase mortality rates, bile duct injury, bile leakage, the need for open cholecystectomy, or general complications (expert recommendation).[13]

3.G Clinical course: A patient is considered to have a satisfactory clinical course when their postoperative recovery is adequate, they tolerate oral intake of liquids and food (with intake beginning 12 hours after the procedure), adequate pain modulation has been achieved, and they show signs of bowel movement. Conversely, a patient is considered to be progressing unsatisfactorily if there are alterations in their vital signs, they are unable to tolerate oral intake of food and liquids, they continue to suffer from abdominal pain, they have jaundice, and they show no signs of bowel movement. In such cases, further tests are necessary to determine the cause of the deterioration in their clinical status (expert recommendation).

3.H Deterioration of clinical condition: The clinical condition of the patient with ACC will be considered deteriorated when there is evidence of postoperative bleeding (which can be observed through external drains placed during the intervention), increased abdominal dilatation and abdominal pain intensity, and decreased hemoglobin levels. If there is no improvement in systemic inflammatory response despite the supportive measures implemented, the patient must be reoperated (expert recommendation).

In patients whose condition is deteriorating, bile duct injury must also be suspected when bile is observed in external drains placed during surgery. The injury must be confirmed by imaging studies and, depending on its severity and extent, will be treated endoscopically or surgically (expert recommendation). Finally, in these patients, visceral injuries may occur as unnoticed intestinal injuries and must be suspected in cases of progressive clinical deterioration, changes in vital signs, persistent intolerance to oral intake of food and fluids, increased abdominal pain, signs of peritoneal irritation, or characteristic findings of fluid collections on imaging studies. These patients will require reoperation (expert recommendation).

Section 4 - Recommendations for the treatment of patients with ACC initially unsuitable for surgery

Context: Surgical treatment for ACC may be contraindicated in some patients due to individual characteristics, and/or clinical instability, and/or the development of complications during the course of the disease, so different treatment options must be available. Figure 6 illustrates the flow chart for Section 4.
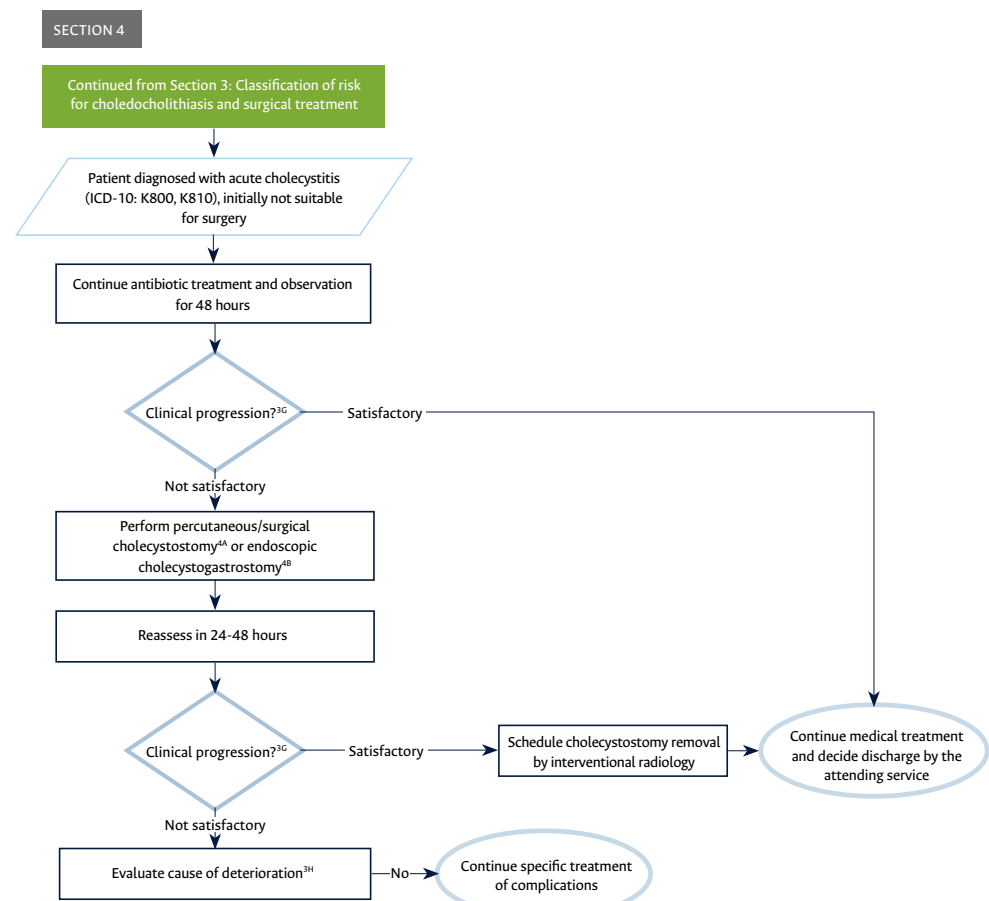

Figure 6. Flowchart for the treatment of patients with acute calculous cholecystitis initially unsuitable for surgery.
ICD-10: International Classification of Diseases and Related Health Problems, Tenth Revision.

Summary of recommendations:

4.A Percutaneous cholecystostomy: Gallbladder drainage is recommended in patients with ACC who are not suitable for surgery (LE: low; GRADE).[13]

There are several case series, both retrospective and observational, on the use of cholecystostomy in these patients. For example, Winbladh *et al.,*[32] in a systematic review that included 53 studies conducted in older adult patients with acute cholecystitis (1 918 patients in total), reported that this intervention has a high success rate (85.6%) and a low associated mortality rate (0.36%), although the 30-day mortality rate was high (15.4%). Notwithstanding the above, it should be pointed out that a significant limitation of this systematic review is the inclusion of patients with acalculous cholecystitis, which is not addressed in this EBCS (expert recommendation).[32]

Gallbladder drainage may be a therapeutic option in patients who do not respond to conservative treatment 24 to 48 hours after its initiation and for whom surgical intervention (cholecystectomy) is absolutely contraindicated. In this regard, Barak *et al.,*[33] in a study conducted in Israel on 103 patients with acute cholecystitis (median age: 60 years), found that age over 70 years, diabetes, tachycardia, and gallbladder dilatation are predictors of treatment failure upon admission, while white blood cell counts >15 000 cells/mm^3, fever, and age over 70 years were predictors of failure of conservative treatment at 24 and 48 hours of follow-up (expert recommendation).[33]

4.B Cholecystogastrostomy: Cholecystogastrostomy is as useful as cholecystostomy for treating these patients and is a therapeutic alternative that must be considered depending on its availability at the institution. This procedure involves gallbladder drainage via endoscopic ultrasound-guided, lumen-apposing metal stent. It is usually performed in patients at high surgical risk who cannot undergo another intervention (expert recommendation).[34]

4.C Open cholecystostomy: This surgical technique involves accessing the abdominal cavity through a minimal incision at the point of greatest sensitivity in the upper right quadrant, then reaching the bottom of the gallbladder, draining its contents, removing as many gallstones as possible, and inserting a tube or catheter to continue drainage. This procedure can be performed under local anesthesia (expert recommendation).

Section 5 - Checkpoints

The checkpoints for the EBCS, which were defined considering key moments in the comprehensive care of adult patients with ACC and were chosen jointly by the members of the development team considering the suggestions made at the interdisciplinary consensus meeting, are presented below:

1. Classification of ACC severity in all patients with a confirmed diagnosis.
2. Classification of risk of choledocholithiasis in all patients with a confirmed diagnosis of ACC.
3. Early laparoscopic cholecystectomy in patients with Tokyo I ACC and indication for surgical treatment.
4. Patients with Tokyo III ACC must be admitted to the ICU.

Implementation and updating

A multi-stage approach is proposed to implement the EBCS and evaluate adherence to these recommendations. First, an interdisciplinary team will be created, comprising members of the development group and representatives of the administrative and clinical areas of the referral university hospital who can support the implementation process;

priority will be given to information technology staff. This team will be key to identifying barriers and facilitators of the implementation process.

Subsequently, two approaches will be adopted to address possible EBCS implementation actions. The first will focus on the dissemination of the clinical algorithm and its checkpoints through educational activities, such as face-to-face and pre-recorded educational talks, and dissemination using social networks and institutional billboards. The second approach will focus on developing administrative strategies that utilize information technology and electronic health record software to generate interactive prompts and reminders that are incorporated into educational activities.

Finally, the assessment of adherence to the EBCS will include three components: i) assessment of EBCS knowledge; ii) assessment of adherence using administrative information sources; and iii) evaluation of impact (clinical, financial, and patient-reported) through additional studies in priority areas of the hospital. The implementation process will take place in stages other than those of the development process, thereby allowing the identification of the best implementation solutions for this EBCS.

The EBCS will be updated in accordance with the stipulated institutional processes. To this end, the development group has set a time limit of 3 to 5 years for updating the EBCS, taking into account various critical aspects: i) the volume of evidence currently available, ii) the availability of new evidence that may have an impact on the comprehensive care of patients with ACC, iii) the quality of the evidence available at the time of EBCS development, and iv) the availability of institutional resources for the implementation and updating of the standard.

Conclusions

The evidence-based clinical recommendations included in this EBCS are intended to standardize practices and actions related to the diagnosis and treatment of adult patients with ACC in Colombia, and even the region. In this sense, the algorithm and clinical recommendations presented here aim to optimize the use of resources and improve the quality of care provided to this population and, therefore, their health outcomes. Finally, it is worth noting that this document can also be used as an educational tool in undergraduate and postgraduate studies for health professionals involved in the care of patients with this condition.

Conflicts of interest

Funding

Acknowledgments

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Supplement 1. Search strategy reporting tables
Database: Medline

Search type	Clinical practice guidelines
Database	Medline
Platform	Pubmed
Date of search	16/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	(((("Therapeutics"[Mesh]) OR ("Diagnosis"[Mesh])) AND (cholecystitis OR colecystitis OR colecistitis* OR "Cholecystitis, Acute"[Mesh] OR "Cholecystitis"[Mesh])) AND ("Practice Guideline" [Publication Type])
References obtained	6
References without duplicates	6

Database: EMBASE

Search type	Clinical practice guidelines
Database	EMBASE
Platform	ELSEVIER
Date of search	16/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	#8 #7 AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) #7#2 AND #3 OR #4 AND #5 #6'practice guideline'/exp #5'practice guideline'/exp #4'therapy'/exp OR therapy:ab,ti OR therapies:ab,ti OR therapeutic:ab,ti OR treatment:ab,ti OR treatments:ab,ti #3'diagnosis'/exp OR diagnoses:ab,ti OR diagnose:ab,ti OR (diagnoses:ab,ti AND examinations:ab,ti) OR (examinations:ab,ti AND diagnoses:ab,ti) #2'cholecystitis'/exp OR 'gallbladder inflammation':ab,ti OR 'inflammation, gallbladder':ab,ti OR 'empyema, gallbladder':ab,ti OR 'gallbladder empyema':ab,ti OR 'empyema, gall bladder':ab,ti OR 'gall bladder empyema':ab,ti
References obtained	199
References without duplicates	195

Database: LILACS

Search type	Clinical practice guidelines
Database	LILACS
Platform	VHL Regional Portal
Date of search	16/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	((Diagnóstico) OR (Técnicas de Diagnóstico) OR (Tratamiento Farmacológico) OR (Tratamiento de Urgencia) OR (Terapia)) AND ((Colecistitis) OR (Colecistitis Aguda)) AND (Guía de Práctica Clínica)
References obtained	15
References without duplicates	15

Compiler: Guidelines International Network (GIN)

Search type	Clinical practice guidelines
Compiler	GIN
Platform	GIN
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: AHRQ

Search type	Clinical practice guidelines
Developer	AHRQ
Platform	AHRQ
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	1
References without duplicates	1

Compiler: CMA Infodatabase

Search type	Clinical practice guidelines
Compiler	CMA infodatabase
Platform	CMA infodatabase
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: Ministerio de Salud y Protección Social (MSPSS)

Search type	Clinical practice guidelines
Developer	MSPSS
Platform	MSPSS
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Colecistitis aguda, colecistitis, cálculos, vesícula biliar
References obtained	1
References without duplicates	1

Developer: National Institute for Health and Clinical Excellence (NICE)

Search type	Clinical practice guidelines
Developer	NICE
Platform	NICE
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	1
References without duplicates	1

Developer: Instituto de Evaluación Tecnológica en Salud (IETS)

Search type	Clinical practice guidelines
Developer	IETS
Platform	IETS
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	1
References without duplicates	1

Developer: Centro Nacional de Excelencia Tecnológica en Salud - México (CENETEC)

Search type	Clinical practice guidelines
Developer	CENETEC
Platform	CENETEC
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: Scottish Intercollegiate Guidelines Network (SIGN):

Search type	Clinical practice guidelines
Developer	SIGN
Platform	SIGN
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: Pan American Health Organization (PAHO)

Search type	Clinical practice guidelines
Developer	PAHO
Platform	PAHO
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	2
References without duplicates	2

Developer: WHOLIS

Search type	Clinical practice guidelines
Developer	WHOLIS
Platform	WHOLIS
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: Australian Clinical Practice Guidelines (GPC Australia)

Search type	Clinical practice guidelines
Developer	GPC Australia
Platform	GPC Australia
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0

Developer: World Health Organization (WHO)

Search type	Clinical practice guidelines
Developer	WHO
Platform	WHO
Date of search	19/12/2020
Search date range	Last 10 years
Language restrictions	None
Other restrictions	None
Search strategy	Acute Cholecystitis, Cholecystitis, Gallbladder disease.
References obtained	0
References without duplicates	0