The importance of early management of severe biliary infection: current concepts

Abstract:
Background. The incidence of biliary infections is rising worldwide and has become one of the main reasons for emergency admissions.
Methods. Narrative review of the literature emphasizing new concepts related to the early management of biliary diseases.
Results. The bacteriology is frequently polymicrobial, with a progressive increase of multidrug resistant bacteria. The form of presentation is variable, and the mortality rate may reach 20%. When cholecystitis or cholangitis is suspected, ultrasound is the gold standard imaging test. Depending on the severity of presentation, local resistances and risk factors for multi-resistant organisms, the most appropriate empirical antibiotic treatment must be initiated. In acute cholecystitis, cholecystectomy plays the main therapeutic role. In patients not suitable for surgery, percutaneous cholecystostomy is a valid alternative for source control. Treatment of severe cholangitis is based on the drainage of the bile duct and antibiotic therapy.
Conclusions. Biliary infections are serious conditions which can lead to sepsis and death. The introduction of new internationally accepted guidelines, based on clinical presentation, laboratory tests and imaging, provides a platform for their timely diagnosis and management. Early severity assessment, initiation of intravenous antibiotics and source control are fundamental to improving morbidity and mortality.
The importance of early management of severe biliary infection: current concepts.

Running title: Early management of severe biliary infection.

Authors:

1. Mireia Amillo-Zaragüeta, MD a mamillo@fphag.org
2. Esther Nve, MD a enve@fphag.org
3. Daniel Casanova, MD a danielcasanovaportoles@gmail.com
4. Pau Garro, MD b pgarro@fphag.org
5. Josep M Badia MD, PhD a,c imbadiaperez@gmail.com https://orcid.org/0000-0002-3614-9873

a Department of Surgery, Hospital General de Granollers, Barcelona, Spain
b Intensive Care Unit, Hospital General de Granollers, Barcelona, Spain
c Universitat Internacional de Catalunya, Barcelona, Spain

Correspondence:
Josep M Badia, Department of Surgery, Hospital General de Granollers
Av Francesc Ribas 1. 08402 Granollers, Barcelona, Spain
Phone +34 670702099. E-mail: imbadiaperez@gmail.com

Authors’ contributions:

Study conception and design: E Nve, M Amillo, JM Badia,

Acquisition of data: D Casanova, E Nve, M Amillo

Analysis and interpretation of data: JM Badia, E Nve, M Amillo

Drafting of manuscript: JM Badia, M Amillo

Critical revision of manuscript: M Amillo, E Nve, D Casanova, P Garro, JM Badia
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Conclusions. Biliary infections are serious conditions which can lead to sepsis and death. The introduction of new internationally accepted guidelines, based on clinical presentation, laboratory tests and imaging, provides a platform for their timely diagnosis and management. Early severity assessment, initiation of intravenous antibiotics and source control are fundamental to improving morbidity and mortality.

Keywords: biliary infection; acute cholecystitis; acute cholangitis; acalculous cholecystitis; antibiotic treatment; gallbladder, surgery; review
Introduction

Biliary infections are one of the main reasons for admission to the Emergency Department, especially in elderly patients with comorbidities\(^1\). In recent decades their prevalence has increased worldwide due to the increase in invasive diagnostic and therapeutic interventions on the bile duct (by percutaneous, endoscopic or surgical access) and the increase in hepatobiliary surgery, including liver transplantation\(^2\).

In 2007, the first edition of the Tokyo Clinical Guidelines (TG07)\(^3\) made progress in unifying definitions and proposing diagnostic and severity criteria for bile infections. Its three successive editions are based on an extensive review of the literature, the establishment of diagnostic and therapeutic criteria and the development of studies to validate them. Although they have been criticized in the Western world\(^4\),\(^5\), especially for some aspects of the treatment algorithms, their publication has helped, beyond doubt, to homogenize the management of these frequent and severe infections. The Tokyo guidelines (TG) establish the classification of bile infections into mild, moderate and severe, and take into account local and systemic signs of inflammation, imaging findings and an organ failure score to establish the level of severity and treatment options.

Several studies have analysed the impact of the application of TG on outcomes, with no substantial benefits described in the management of cholecystitis, for example\(^6\). These results have been incorporated into the editions of 2013 (TG13)\(^7\) and 2018 (TG18)\(^8\), with some changes in severity criteria and the recommendations for antibiotic treatment and source control.

The overall mortality rate of biliary infections is between 1% and 6%\(^9\). However, when bacteraemia is associated (10% of cholecystitis and 50% of acute cholangitis), mortality can reach 10%-20%\(^10\),\(^11\). Bacteraemia of biliary origin represents up to 20% of community bacteraemia in the elderly population\(^12\) and, is the second most common cause of sepsis in this age group\(^13\).

Methods

A narrative review of the literature from January 1980 until June 2020 has been carried out through PubMed, Clinical Key and The Cochrane Library. MeSH terminology was used for the literature research under the topics: acute cholecystitis, acute cholangitis, gallstones, choledocholithiasis, bile duct stones, biliary tract infection, biliary sepsis, biliary surgery, antibiotic treatment, ECRP and cholecystostomy.

The inclusion criteria were: clinical practice guidelines, controlled clinical studies, cohort studies, meta-analyses, and systematic reviews. Only articles with full-text descriptions were
included. The literature search was conducted by two researchers. The final review of the selected papers and the inclusion decisions were jointly made by all the researchers.

**Results**

**Bacteriology.** Human bile is colonized in the presence of biliary calculi, obstruction, bile stents or biliary-enteric anastomosis. Eighty percent of bile infections are polymicrobial and are often associated with bacteraemia (tables 1 and 2). Enteric organisms represent the majority of the flora and are isolated from 70% of cultures. Gram-positives account for 20% of isolates. Among these, *Enterococcus* spp. is the second most common organism (up to 34%). Anaerobes can be found in up to 40% of cases of cholecystitis, 50% of cholangitis and 72% of gangrenous cholecystitis.

Distinctions must be made between the bacteriology of cholecystitis and cholangitis, and between community-acquired and healthcare-associated infections (HAI). In a study on bacteraemia of biliary origin, a progressive increase in *Enterococcus* spp and *Pseudomonas aeruginosa* in HAI was observed, with 22% of *E. coli* and *Klebsiella* spp being resistant to fluoroquinolones. The microbiology of patients with biliary stents is very characteristic, with a high incidence of enterococci and non-fermenting gram-negatives, especially *Enterococcus faecium* and *Pseudomonas aeruginosa*. The increasing isolations of *E. faecium* is of particular concern, given its intrinsic resistance to common antibiotics. Its incidence has been reported in 12% of patients with calculous cholecystitis, 17% with acalculous cholecystitis and 45% with cholangitis. The rate of extended-spectrum beta-lactamase-producing (ESBL) microorganisms is also increasing (Table 3). The increasing incidence of multidrug resistant (MDR) bacteria may be the reason for treatment failure, and antimicrobials such as amoxicillin/clavulanate, some cephalosporins and fluoroquinolones should not be used empirically.

**Early detection of severe biliary infection.** Sepsis can be identified by various signs and symptoms in a patient with suspected infection. The SIRS criteria have not been considered sufficient to identify this syndrome, with the serum lactate or the criteria for organ failure, especially those of the SOFA score (Sequential Organ Failure Assessment), being more reliable. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. This dysfunction can be represented by an increase in the SOFA score of ≥2 points. QuickSOFA (qSOFA) has been proposed as a new bedside score, including 3 variables: a Glasgow scale score of ≤13, a systolic pressure ≤100 mm Hg, and a respiratory rate of ≥22/minute. The presence of 2 of these 3 criteria has a predictive value similar to that of ≥2 criteria of the SOFA score (10% mortality). Furthermore, septic shock is defined as a subset of sepsis with profound circulatory and cellular metabolism abnormalities. It is a "state of acute circulatory failure" that results in sustained hypotension requiring vasopressors to maintain...
MAP ≥65mmHg and a serum lactate >2mmol/L (18mg/dL) despite resuscitation with adequate volume. 

Early detection of severe biliary infection using these definitions of sepsis and septic shock should optimize management and improve outcomes. However, several studies have questioned the use of qSOFA for early detection of sepsis, finding high specificity but low sensitivity for organ dysfunction (96.1% and 29.7%, respectively). In a Norwegian study, qSOFA could not detect two thirds of the cases of severe sepsis. Other studies confirm the low sensitivity of qSOFA in the out-of-hospital setting and in emergency triage, while the SIRS criteria behave slightly better. It would seem that the qSOFA score is not of great help for initial sepsis screening, when early treatment is most effective. In the meantime, the Surviving Sepsis Campaign considers that the SIRS criteria remain useful for the identification of infection.

**Early diagnosis.** The classic signs are not highly reliable. Murphy’s sign has a sensitivity of 20% and a specificity of 87% for the diagnosis of acute cholecystitis. The same is applicable for the Charcot triad in acute cholangitis, which maintains a high specificity, but with a sensitivity of around 21-26%. Routine tests for biliary infection (blood count, liver function, serum amylase, blood cultures, chest X-ray and abdominal ultrasound) are usually sufficient for diagnosis. In the presence of sepsis an early management protocol based on the revised “hour-1 bundle” of the Surviving Sepsis Campaign should be activated. This includes obtaining blood for measuring lactate and blood cultures, administration of fluids and empirical antibiotics, and in the case of life-threatening hypotension, initiation of vasopressor therapy.

**Antibiotics in biliary infection.**

Therapeutic success in severe biliary infection is based on early drug treatment and timely source control. The choice of antibiotic will depend on the origin of the infection, its severity and the risk of MRD organisms (table 3). Table 4 shows the suggested empirical antibiotic treatment for bile infection.

For the coverage of gram-negative microorganisms, amoxicillin-clavulanate, aminoglycosides, piperacillin-tazobactam and carbapenems remain active. The last two are also the choice for anaerobes. The use of piperacillin-tazobactam, carbapenems or ceftriaxone, which reach high concentrations in bile, can induce colonization by vancomycin-resistant enterococci. Quinolones are not recommended because of their low activity for gram-negative (30-55% of resistant E. coli) and their low activity against streptococci and enterococci. Gram-positives maintain a high sensitivity to beta-lactams, except for E. faecium, which is sensitive to glycopeptides. In immunosuppressed patients, transplant patients, those previously treated
with antibiotics or in HAI bacteraemia, organisms such as ESBL-producing enterobacteriaceae or *Pseudomonas* spp can be isolated, and an empirical therapy with a carbapenem should be initiated\(^1\).

**Management of cholecystitis and cholangitis.**

**Acute calculous cholecystitis.** Clinical diagnosis is reached with the combination of three variables: continuous pain for more than 12 hours in the right upper quadrant, tenderness (with or without Murphy’s sign) and signs of acute inflammatory response\(^3\). Table 5 summarizes the TG18 diagnostic criteria. Mild jaundice (<3.5 mg/dL or 60 µmol/L) may be observed in 20% of patients, due to inflammation around the bile duct or direct compression by a distended gallbladder\(^4\).

Higher bilirubin values suggest choledocholithiasis, cholangitis or Mirizzi’s syndrome. The incidence of bile duct calculi in cholecystitis is 3-15\%\(^3\) similar to that found in elective cholecystectomy, so mild jaundice is not a reason to indicate a preoperative ERCP. Ultrasound is the preferred initial modality in the investigation of right upper quadrant pain, although its effectiveness in cholecystitis is controversial, according to a meta-analysis from 2012\(^3\). The most sensitive US finding in acute cholecystitis is the presence of gallstones in combination with the sonographic Murphy sign. Both gallbladder wall thickening (>3 mm) and pericholecystic fluid are secondary findings\(^4\).

**Antibiotic treatment.** According to the TG18, cholecystitis can be classified as severe (accompanied by organic dysfunction), moderate (with marked local or systemic inflammatory signs) and mild (without organic dysfunction and with minimal inflammatory signs)\(^3\) (Table 5). Mild-moderate cholecystitis can be treated with amoxicillin-clavulanate alone or associated with an aminoglycoside depending on local *E. coli* resistance, or with ertapenem monotherapy, which is the first choice if there is risk of ESBL-producing enterobacteriaceae. In patients with sepsis or risk factors for antibiotic failure, antibiotic combinations or monotherapy with piperacillin-tazobactam or carbapenem can be initially chosen\(^4\). Quinolone-based schemes would not be indicated given the rates of BGN resistance in many European countries.

In mild and moderate cholecystitis, antibiotic treatment can be discontinued 24 hours after cholecystectomy\(^4\). However, it should be maintained for 3-4 days if there is a pericholecystic abscess, biliary peritonitis or gallbladder necrosis.

**Early cholecystectomy.** Clinical results of early cholecystectomy are clearly superior to those of delayed surgery (antibiotic treatment and surgery in a second admission after 6 weeks). The appropriate time frame for early surgery has been extended to the first 7-10 days from the onset of symptoms\(^5\). Several meta-analyses comparing early and delayed surgery found no
difference in morbidity or mortality\textsuperscript{42-43}, nor in the rate of injury to the bile duct, both with open and laparoscopic techniques. Financial studies show lower healthcare costs and better quality of life for patients when a policy of early laparoscopic surgery for acute cholecystitis is applied\textsuperscript{44}.

The indication for early surgery is one of the points of discrepancy between Western practice and TG recommendations. The treatment algorithms of the latter, use the level of inflammation of the gallbladder and its classification of severity to operate\textsuperscript{45}. On the contrary, in the Western world the usual recommendation is to indicate surgery regardless of the degree of inflammation of the gallbladder, providing the baseline condition of the patient does not preclude it\textsuperscript{5,46,47}. Figure 1 summarizes the proposed treatment algorithm for acute cholecystitis.

**Percutaneous cholecystostomy.** The insertion of a percutaneous drainage catheter into the gallbladder directed by ultrasound or CT scan is a good alternative in cases of severe inflammation, septic shock, or high risk for general anaesthesia patients. Its success rate in calculous cholecystitis is 90.77\textsuperscript{48}. The main issue regarding its indication is the definition of a high-risk patient. The TG18 define as high surgical risk Grade III cholecystitis (with associated organ dysfunction) or patients with ASA $\geq$ III or a Charlson comorbidity index $\geq$ 6. In these assumptions they contraindicate early cholecystectomy and recommend antibiotic treatment and cholecystostomy\textsuperscript{45}. These limits seem too strict in Western practice\textsuperscript{4}, where it is considered that, apart from septic shock, there are no validated risk criteria to identify patients as high surgical risk\textsuperscript{5}. There are also no studies comparing emergency cholecystectomy and cholecystostomy in elderly or high-risk patients. Even in critical patients, a systematic review of 53 studies and 1,918 patients\textsuperscript{48} did not find enough evidence to support the recommendation of TG in favour of percutaneous drainage instead of emergency surgery. The authors conclude that "it is possible that cholecystectomy is a better alternative for acute cholecystitis in the elderly and/or critically ill than cholecystostomy". In fact, reported mortality from emergency cholecystectomy for cholecystitis is between 0 and 1.5\% in studies with patients over 65\textsuperscript{49} or 70 years in the last decade\textsuperscript{50}.

Cholecystostomy is the definitive treatment for acalculous cholecystitis, but patients with gallstones should be assessed for cholecystectomy, as the risk of re-admission for biliary causes is 49\% in the first year\textsuperscript{51}. Patients who are definitely not suitable for surgery may be offered non-surgical treatments for gallstones or stone removal through the cholecystostomy route after six weeks of the acute process.

**Gangrenous cholecystitis.** Thirty percent of cholecystitis presents in an advanced stage in the form of gangrenous cholecystitis and requires an emergency operation. It can be suspected in males over 50 years of age, with cardiovascular disease and marked leucocytosis (> 17,000
leukocytes/mL). The ultrasound signs are: marked irregularity, multiple striations or asymmetric thickening of the vesicular wall and presence of intraluminal membranes. Murphy’s sign may be negative due to denervation of the gallbladder.52,53

**Emphysematous cholecystitis.** This condition is characterized by the presence of gas in the gallbladder or its wall and is caused by gas-producing bacteria, usually *Clostridium welchii* (45%) *Escherichia coli* (30%) and *Clostridium perfringens*. It is associated with cholelithiasis in 50% of patients and is more frequent in diabetics.54

Typical radiographic findings are a globular aerial image in the gallbladder area, submucosal or intramural gas or pericholecystic air.55

The incidence of perforation is 40-60%, and mortality is high. Emergency surgery should be indicated and treatment against gram-negative and anaerobic bacteria should be administered. A combination of 3rd or 4th generation cephalosporin with metronidazole, or with ertapenem or piperacillin-tazobactam monotherapy may be chosen.56

**Acute acalculous cholecystitis.** Acute acalculous cholecystitis (AAC) is observed with increasing frequency. Its mortality is high, with high incidence of gallbladder gangrene (50%) and perforation (10-15%). Two forms of presentation are distinguished: primary AAC complicating another serious disease and secondary infection of the gallbladder from a systemic infection. It has been described as a postoperative complication of aortic aneurysms, trauma, burns, heart transplantation and conventional heart surgery. Secondary AAC appears during systemic bacterial, fungal or viral infections, *Salmonella typhi*, brucellosis, disseminated candidiasis, systemic leptospirosis and Cytomegalovirus (CMV), hepatitis or Ebstein-Barr virus infections.57

The pathogenesis differs from calculous cholecystitis, and ischemia has been suggested as the main cause, which may explain the high percentage of mucosal necrosis, arteriolar thrombosis, gangrene and perforation. Other factors that may interact are increased intraluminal pressure, biliary stasis secondary to fasting and gastrointestinal hypomotility, compression of the cystic duct and spasm of the sphincter Oddi secondary to opioid analgesics. As in calculous AC, bacterial infection is a secondary phenomenon.58

Diagnosis can be difficult in critically ill patients with non-specific signs of SIRS or sepsis admitted to ICU and unable to express their symptoms.59 Ultrasonography is the best diagnostic test (sensitivity and specificity >80%). Diagnosis is based on the combination of hydrops, the finding of thick bile or bile mud and increased thickness of the vesicular wall (>3.5 mm), although critical patients may have wall oedema not attributable to AAC. CT may be superior in assessing pericholecystic inflammation and may show wall alterations, perforation, or fluid collections not visualized by ultrasound.
Cholecystectomy offers the best therapeutic results, but in unstable patient cholecystostomy is an excellent alternative in more than 85% of cases. If there is no rapid improvement in symptoms after cholecystostomy, surgery should be performed without delay. Open cholecystostomy allows limited vision to the right upper quadrant, while laparoscopic cholecystostomy allows evaluation of the rest of the abdomen. Both operations have the same limitations: the presence of a gangrenous or perforated vesicular wall, which forces a cholecystectomy.

**Acute cholangitis.** Cholangitis is caused by a combination of bacterobilia and biliary obstruction. It has a wide spectrum of severity, from mild cases that respond easily to antibiotic treatment to more severe forms, which have been called toxic or suppurative cholangitis. Bacterial biliary infection is accompanied by shock and mortality rates of 15% and 9%, respectively.

Incomplete biliary obstruction by bile duct stones, accompanied by ascending infection, is the most frequent aetiology. The incidence of enterococcus is higher than in acute cholecystitis, representing up to 20% of isolates. Anaerobes are isolated in 50% of cases, cultures are polymicrobial in up to 80% of cholangitis and bacteraemia is detected in 25-75% of patients.

There is an increased frequency of other aetiologies, such as primary sclerosing cholangitis, hepatolithiasis, stent obstruction, endoscopic manipulations, biliary anastomosis stenosis and complications of liver transplantation. Another common cause is complication of percutaneous transhepatic cholangiography (PTC) or ERCP. These cases may be responsible for the change in the bacteriological profile of this disease observed in recent decades, with an increase in infection by *Enterobacter*, *enterococcus*, *Pseudomonas* spp and resistant enterobacteriaceae.

**Diagnosis.** The classic Charcot triad, with fever, right upper quadrant pain and jaundice is not very sensitive and it is only observed in 20-50% of the patients. The most severe cases are manifested by Reynolds' pentad, with the addition of shock and mental confusion. Acute cholangitis should be suspected in the septic patient with abdominal pain and rapid deterioration of general condition, particularly in the absence of a clear focus of infection.

The TG18 maintain the diagnostic criteria proposed in the TG13, given that they have shown a diagnostic capacity of 90% despite the fact that there are no studies on their specificity. According to TG18, diagnosis is based on a combination of signs of systemic inflammation, cholestasis and imaging criteria. Severity criteria TG18/TG13 appear to be good predictors of mortality and may identify patients requiring urgent biliary drainage.
Ultrasound is very specific for dilated ducts or bile duct calculi (96-100%, respectively), but not very sensitive (42%-63%)\textsuperscript{67}. CT is more effective in defining the cause and level of obstruction. Magnetic resonance cholangiography (MRCP) obtains high-resolution images of the biliary tract and pancreatic ducts, prevents contamination of the obstructed ducts by contrast material, allows visualization of the areas proximal and distal to the obstruction and provides intraluminal and extraluminal imaging of the ducts without the morbidity and mortality of invasive techniques. The sensitivity of MRCP for bile duct stones is greater than 90%, although calculi smaller than 6 mm may go undetected. Currently, MRCP has become the technique of choice for the study of jaundice following ultrasound and in the selection of patients for therapeutic ERCP or CPTH\textsuperscript{9}. Endoscopic ultrasound (EUS) show similar accuracy, sensitivity and specificity to MCCP and ERCP in diagnosing choledocolithiasis\textsuperscript{68}. Cholangiography (by ERCP or CPTH) obtains a detailed view of the biliary tree and can provide temporary or definitive drainage of the biliary system. However, it requires the injection of pressurized contrast in obstructed ducts, with risk of cholangitis and bacteraemia. Therefore, antibiotics must be administered until the correct drainage of the bile ducts is ensured.

**Early treatment.** According to the TG18, early diagnosis, antibiotic treatment and drainage of the bile duct are essential in acute cholangitis, regardless of its severity\textsuperscript{9}. It is important to identify high-risk patients (Table 7), in whom ICU admission and emergency bile duct drainage will be the key to treatment.

Antibiotic treatment should cover enterococci, gram-negative bacilli and anaerobes. General supportive measures and antibiotic treatment are initially effective in 74-85% of patients, in whom bile decompression can be delayed for 48-72 hours\textsuperscript{69}. For source control, minimally invasive techniques (ERCP or CTPH) are the first option. In unstable patients or patients in septic shock, bile decompression should be performed within 6 hours\textsuperscript{70,71}. A recent meta-analysis on the timing of ERCP found a 20% reduced mortality when ERCP is performed <24 hours compared with ≥24 hours\textsuperscript{72}.

Early ERCP with sphincterotomy and biliary drainage provides less morbidity and mortality than surgical or percutaneous decompression\textsuperscript{73}. In very severe patients, nasobiliary drainage or stenting may be the first step before definitive treatment. Emergency surgical intervention should be reserved for episodes of acute cholangitis that cannot be satisfactorily treated by less aggressive means. In the presence of risk factors (Table 7), the postoperative morbidity and mortality rates are 91% and 55%, respectively\textsuperscript{74}. Figure 2 summarizes the proposed treatment algorithm for acute cholangitis.

**Conclusions.** Biliary infection is a frequent cause of sepsis with a high rate of bacteraemia and high morbidity-mortality. The acceptance of new international guidelines based on clinical
presentation, laboratory investigations and imaging, offers the basis for its timely diagnosis and treatment. The presence of rare organisms such as ESBL-producing enterobacteriaceae, Enterococcus faecium or Pseudomonas spp. should be ruled out in patients with risk factors. In case of sepsis or septic shock, antimicrobial treatment and prompt source control should be a priority. Early laparoscopic cholecystectomy is the treatment of choice for calculous cholecystitis, while for acute cholangitis, timely endoscopic drainage techniques are preferable. Percutaneous image-guided cholecystostomy is an excellent alternative for calculous or acalculous cholecystitis in patients at high surgical risk.

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Tables’ legends

**Table 1.** Microbiology of bile and blood cultures in patients with biliary infections. Modified from Tokyo Guidelines 201816.

**Table 2.** Microbiology of bacteremia of biliary origin in Spain. Comparison of microorganisms acquired in the community or associated with health care Taken from Ortega M, et al11.

**Table 3.** Risk factors for poor evolution in biliary infection.

**Table 4.** Summary of empirical antibiotic treatment of biliary infection.

**Table 5.** Diagnostic criteria and severity classification of acute cholecystitis of TG18/TG13. Modified from Yokoe et al16.

**Table 6.** Diagnostic criteria and severity classification for acute cholangitis from TG18/TG13. Modified from Kiriyama et al9.

**Table 7.** Factors associated with poor prognosis or high risk of therapeutic failure in acute cholangitis.

**Table 8.** Main novelties in the management of biliary infection over the last decade.
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Table 1. Microbiology of bile and blood cultures in patients with biliary infections. Modified from Tokyo Guidelines 2018^{16}.

| Microorganisms       | Proportion of isolates |          |          |
|----------------------|------------------------|----------|----------|
|                      | Bile (%)               |          |          |
| Gram negative        |                        | Community acquired | Nosocomial |
| *Escherichia coli*   | 31-44                  | 35-62    | 23       |
| *Klebsiella spp.*    | 9-20                   | 12-28    | 16       |
| *Pseudomonas spp.*   | 0.5-19                 | 4-14     | 17       |
| *Enterobacter spp.*  | 5-9                    | 2-7      | 7        |
| *Acinetobacter spp.* | -                      | 3        | 7        |
| *Citrobacter spp.*   | -                      | 2-6      | 5        |
| Gram positive        |                        |          |          |
| *Enterococcus spp.*  | 3-34                   | 10-23    | 20       |
| *Streptococcus spp.* | 2-10                   | 6-9      | 5        |
| *Staphylococcus spp.*| 0                      | 2        | 4        |
| Anaerobes            | 4-20                   | 1        | 2        |
| Others               | -                      | 17       | 11       |
**Table 2.** Microbiology of bacteremia of biliary origin in Spain. Comparison of microorganisms acquired in the community or associated with health care Taken from Ortega M, et al11.

| Microorganisms          | Bacteremia episodes (N=1373), n (%) | Community acquired (N=920), n (%) | Associated with health institutions (N=453), n (%) | P     |
|-------------------------|-------------------------------------|----------------------------------|-----------------------------------------------|-------|
| E. coli                 | 749 (55)                            | 568 (62)                         | 181 (40)                                      | 0.001 |
| CTX-R E. coli           | 38 (5)                              | 8 (1)a                           | 30 (17)a                                      | 0.001 |
| Klebsiella spp.         | 240 (17)                            | 172 (19)                         | 68 (15)                                       | 0.06  |
| K. pneumoniae           | 180 (13)                            | 119 (13)                         | 61 (13)                                       | NS    |
| K. oxytoca              | 60 (4)                              | 53 (6)                           | 7 (2)                                         | NS    |
| CTX-R Klebsiella spp.   | 9 (4)a                              | 0                                | 9 (13)a                                       | 0.001 |
| Enterococcus spp.       | 163 (12)                            | 72 (8)                           | 91 (20)                                       | 0.001 |
| E. faecalis             | 78 (6)                              | 37 (4)                           | 41 (9)                                        | 0.08  |
| E. faecium              | 54 (4)                              | 18 (2)                           | 36 (8)                                        | 0.06  |
| others Enterococcus spp.| 31 (2)                              | 17 (2)                           | 14 (3)                                        | NS    |
| P. aeruginosa           | 86 (6)                              | 26 (3)                           | 60 (13)                                       | 0.001 |
| Enterobacter spp.       | 63 (5)                              | 36 (4)                           | 27 (6)                                        | 0.07  |

CTX-R: resistant to cefotaxime
**Table 3.** Risk factors for poor evolution in biliary infection.

| Related to the inadequacy of antibiotic treatment | Risk of infection by unusual organisms (Enterobacteria-ESBL, *Pseudomonas* spp.) |
|--------------------------------------------------|----------------------------------------------------------------------------------|
|                                                  | Hospitalization > 5 days                                                        |
|                                                  | Antibiotic treatment > 3-5 days in the last 6 weeks                               |
|                                                  | Biliary prosthesis holder                                                        |
|                                                  | Cholangitis after ERCP                                                          |

| Related to the severity of infection             | Sepsis, septic shock |
|--------------------------------------------------|----------------------|

| Related with comorbidities                       | Immunosuppression    |
|--------------------------------------------------|----------------------|
|                                                  | Malnutrition         |
|                                                  | Diabetes             |
|                                                  | Chronic renal failure |
|                                                  | COPD                 |
|                                                  | Liver Cirrhosis       |

| Age related                                      | > 70 years old        |
|--------------------------------------------------|-----------------------|

ERCP: Endoscopic Retrograde Cholangio-Pancreatography
Table 4. Summary of empirical antibiotic treatment of biliary infection.

| ORIGIN | Community acquired | Health care-associated infections |
|--------|-------------------|----------------------------------|
|        | Acute calculous cholecystitis | Acalculous cholecystitis in critical patient |
|        | Acute calculous cholecystitis | Acute Cholangitis (c) |
|        | Acute Cholangitis (c) | Cholangitis with biliary prosthesis |
|        | Acute Cholangitis (c) | Cholangitis after ERCP or PTHC |

| SEVERITY | MILD-MODERATE | SEVERE |
|----------|---------------|--------|
| WITHOUT  |               |        |
| Risk factors of poor evolution (a) | Amoxycillin-clavulanate ± gentamicin (b) or Ertapenem or Cephalosporin 2ª + metronidazole | Piperacillin-tazobactam or Meropenem, imipenem or doripenem (d) |
|          | Gentamicin or aztreonam + metronidazole* | Tigecycline* ± Aztreonam or Amikacin (d) |

| WITH     |               |        |
| Risk factors of poor evolution (a) | Ertapenem | Meropenem or imipenem(d) |
|          |               |        |
|          | Tigecycline* | Tigecycline + ceftazidime, cefepime or amikacin |
|          |               | Tigecyclin + Aztreonam or Amikacin* |

(a) According to the criteria in Table 3.

(b) In some hospitals, 15-25 % of *E. coli* strains are resistant to amoxycillin-clavulanate, and an aminoglycoside should be associated.

(c) Acute cholangitis is considered a potentially serious infection, requiring coverage of enterococci and anaerobes.

(d) In patients at risk of infection by Enterobacteria resistant to cefotaxime or *P. aeruginosa* (nosocomial infection with previous antibiotic treatment, neutropenia, history of ERCP/biliary tract drainage) or those presenting septic shock, initial therapy should be considered with a carbapenemic or a specific anti-pseudomonic drug such as amikacin, ceftacidime or cefepime. The administration of colistine should be considered in those patients previously treated with an antibiotic with anti-pseudomonic activity and who present persistence or recurrence of IIA.
(e) In patients at risk of biliary infection involving *Candida* spp. (acalculous cholecystitis in the critically ill patient) an antifungal (fluconazole or candina) should be added to the treatment. An echinocandine is indicated in patients with severe sepsis or septic shock and in those who have previously received fluconazole.

- In italics: alternative pattern in betalactam allergy

The ± sign indicates the possibility of additional treatment.

ERCP: Endoscopic Retrograde Cholangio-Pancreatography

PTHC: Percutaneous transhepatic cholangiography
### Table 5. Diagnostic criteria and severity classification of acute cholecystitis of TG18/TG13. Modified from Yokoe et al.\(^3\)

| DIAGNOSIS                        | SEVERITY | MODERATE (grade II) | MILD (grade I)                              |
|----------------------------------|----------|---------------------|---------------------------------------------|
| **Suspicion**: one criterion A + one criterion B | SEVERE (grade III) | It is associated with dysfunction of one of the following: | It has no criteria for severe or moderate cholecystitis. It can be defined as an acute cholecystitis in a healthy patient without organic dysfunction and with mild inflammatory changes in the gallbladder |
| **Definitive diagnosis**: one criterion A + one criterion B + one criterion C | | 1.- Cardiovascular: hypotension requiring dopamine >5µg/kg/min, or any dose of norepinephrine | |
|                                  | | 2.- Neurological: decrease in the level of consciousness | |
|                                  | | 3.- Respiratory: PaO2/FiO2 ratio <300 | |
|                                  | | 4.- Renal: oliguria, creatinine >2.0mg/dl | |
|                                  | | 5.- Liver: PT-INR >1.5 | |
|                                  | | 6.- Hematological: platelets < 100000mm\(^3\) | |
|                                  | | B-1 Fever | |
|                                  | | B-2 PCR Elevation | |
|                                  | | B-3 Leukocyte count alteration | |
Table 6. Diagnostic criteria and severity classification for acute cholangitis from TG18/TG13. Modified from Kiriyama et al.9

| DIAGNOSIS | SEVERITY | MODERATE (grade II) | SEVERE (grade III) |
|-----------|----------|---------------------|---------------------|
| **Suspicion:** | SEVERE (grade III) | Two of the following conditions: |
| one criterion A + one criterion B or C | Dysfunction of one of the following organs/systems: |
| **Definitive diagnosis:** | | 1. abnormal WBC count (>12,000/mm3 or <4,000/mm3) |
| one criterion A + one criterion B + one criterion C | 1. Cardiovascular dysfunction: hypotension requiring dopamine ≥5 µg/kg per min, or any dose of norepinephrine |
| | 2. Neurological dysfunction: disturbance of consciousness |
| | 3. Respiratory dysfunction: PaO2/FiO2 ratio <300 |
| | 4. Renal dysfunction: oliguria, serum creatinine >2.0 mg/dl |
| | 5. Hepatic dysfunction: PT-INR >1.5 |
| | 6. Hematological dysfunction: platelet count <100,000/mm3 |
| | Two of the following conditions: |
| | 1. abnormal WBC count (>12,000/mm3 or <4,000/mm3) |
| | 2. High fever ≥ 39ºC |
| | 3. Age ≥ 75 years |
| | 4. Hyperbilirubinemia (total bilirubin ≥ 5mg/dL) |
| | 5. Hypoalbuminemia |
| **Severity** | SEVERE (grade III) | Two of the following conditions: |
| | Moderate (grade II) | "Grade II" acute cholangitis does not meet the criteria of "Grade III" or "Grade II" acute cholangitis. |
| | Mild (grade I) | |

C. Image
- C-1 Bile duct dilation
- C-2 Evidence of etiology (stenosis, lithiasis, choledochal prosthesis)
**Table 7.** Factors associated with poor prognosis or high risk of therapeutic failure in acute cholangitis.

| Factor                                                                 |
|------------------------------------------------------------------------|
| Acute renal failure                                                    |
| Old age                                                                |
| Liver cirrhosis                                                        |
| Malignant etiology of the obstruction                                  |
| Cholangitis after ERCP or TPH                                          |
| Bilirubin > 2.2 mg/dl (40 µmol/L),                                     |
| Albumin < 30 g/L                                                       |
| Platelet count < 150,000 / L                                           |
| Positive blood cultures                                                |
| More than 2 organisms in the bile culture                              |
| Isolation of *Candida spp*                                             |
| Isolation of multi-resistant organisms                                 |
Table 8. Main novelties in the management of biliary infection over the last decade.

| **Increasing isolation** of *Enterococcus* spp, *Enterococcus faecium* and *Pseudomonas* in acute cholangitis. |
| --- |

| **Increasing resistance** of *E. coli* and *Klebsiella* spp to fluoroquinolones. |
| --- |

| **QuickSOFA** (qSOFA) proposed as a new bedside score to identify sepsis (2016). |
| --- |

| **“Hour-1 bundle” of the Surviving Sepsis Campaign** revised (2018): |
| --- |
| • Measure lactate level; |
| • Obtain blood cultures prior to administration of antibiotics; |
| • Administer broad-spectrum antibiotics; |
| • Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L; |
| • Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm. |

| **Changes in Tokyo guidelines 2007, 2013 and 2018 (TG07, TG13, TG18)** |
| --- |
| • **Diagnostic criteria of acute cholecystitis** in TG13 provide better specificity and higher diagnostic accuracy than first Edition (TG07). |
| • **Severity grading of acute cholecystitis** is recommended unchanged in TG13 and TG18. |
| • **TG13 diagnostic criteria of acute cholangitis** are recommended to be used as the TG18 criteria. |
| • The **TG13 severity grading criteria of acute cholangitis** are recommended to be used as the TG18 criteria, and may be useful as an indicator for biliary drainage in Grade II patients. |
| • **MRI/MRCP** are recommended for the diagnosis of acute cholangitis in TG18, as they are useful when diagnosing the cause and evaluating inflammation. |

| **Role of Endoscopic ultrasound (EUS)** in the diagnosis of choledocholithiasis. |
| --- |

| **Early laparoscopic cholecystectomy** is recommended in acute cholecystitis. |
| --- |

| **Cholecystostomy** is recommended in unstable patients with acute cholecystitis. |
| --- |

| **Early biliary drainage** is recommended of in acute cholangitis. |
| --- |