Calculated Antibiosis of Acute Cholangitis and Cholecystitis

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Summary
Background: The aim of this article is to present the most recent suggestions for the therapy of acute cholangitis and cholecystitis based on a review of the current literature. Methods: We performed a systematic literature search in the Medline, PubMed, and Google Scholar databases using the keywords mentioned above. This article is strongly influenced by the publication of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07, TG13) in 2007 and 2013. These were the first practical guidelines targeting diagnosis and treatment of acute cholangitis and cholecystitis. These guidelines are based on the best published evidence and a consensus conference of international experts in the field. Results and Conclusion: Acute cholangitis and acute cholecystitis are common conditions that may result in progressively severe infection and death when not treated appropriately. Beside supportive therapy and antiobstructive measures, therapy with antimicrobial agents is an important component in the management of affected patients. Here, we discuss the use of antimicrobial agents that are suitable for the first-line management of these infections. Empirical therapy depends upon the knowledge of local microbial epidemiology and patient-specific factors affecting the selection of appropriate agents.
Introduction

Patients exhibiting one of the local signs of inflammation, such as Murphy’s sign, a mass, pain, jaundice, or tenderness in the right upper quadrant, and systemic inflammation are diagnosed as having acute cholangitis or cholecystitis. Patients with clinical findings that are confirmed by diagnostic imaging are also diagnosed with acute cholangitis or cholecystitis. In these patients, a therapy with appropriate antimicrobial agents is an important component of the management. The goal of antimicrobial therapy in acute cholangitis and cholecystitis is to limit the systemic septic response and local inflammation [1].

Acute cholangitis and cholecystitis are common conditions that may result in progressively severe infection, particularly in debilitated hosts. An appropriate treatment is required in the acute phase. Severe acute cholangitis or cholecystitis may result in early death if appropriate medical care is not provided [2–6]. An attempt to develop a clinical guidance was provided by the Tokyo Guidelines (TG) 2007 in which international standards for diagnostics and severity assessment criteria for acute cholecystitis and cholangitis were defined for the first time [2].

Here, we discuss antimicrobial agents that are suitable for the first-line management of these infections. We focus primarily on empirical therapy (presumptive therapy), which is provided before the infecting isolates are identified. Such therapy depends upon the knowledge of local microbial epidemiology and patient-specific factors affecting the selection of appropriate agents [3].

Etiology and Pathogenesis

Acute biliary infections are systemic infectious diseases requiring prompt treatment. Acute cholangitis and cholecystitis are conditions with acute inflammation and infection of the biliary system, which are often accompanied by chills, right upper quadrant pain, and jaundice (Charcot trias); sometimes, lethargy, confusion, and shock are additionally present. In many cases, biliary obstruction plays a leading role in the pathogenesis and is sometimes complicated by abscess formation [7]. Frequent causes of biliary obstruction are choledocholithiasis, benign biliary stenosis, strictures after biliary interventions as well as after ischemic (SSC) or sterile inflammation (PSC), and stenosis caused by malignant tumors. An overview of common underlying causes for biliary obstruction and inflammation is given in table 1 [8].

Quite often, acute cholangitis and cholecystitis are due to biliary obstruction and ascending infection of the bile. In the vast majority of cases, bacteria are the causative infective organisms for acute biliary infections. In some populations, immunosuppressed viral (cytomegalovirus) or parasitic agents (cryptosporidia, isospora) [9] may be found. This article focuses on the majority of cases, which are due to bacterial infections.

The bacteria commonly found in biliary tract infections are well known. Most of these bacteria originate from the upper and lower intestine (table 2, 3) [10, 11]. The bile of healthy subjects is generally aseptic. However, bile cultures are posi-

### Table 1. Etiology of acute cholangitis (modified according to [8])

| Organisms                      | Proportion, % |
|-------------------------------|---------------|
| Cholelithiasis                |               |
| Benign biliary stricture      |               |
| After surgical, endoscopic, or other invasive procedures, ERCP complications |               |
| Inflammatory factors (oriental cholangitis etc.) |               |
| Sclerosing cholangitis        |               |
| Malignancies                  |               |
| Bile duct tumor               |               |
| Gallbladder tumor             |               |
| Pancreatic tumor              |               |
| Duodenal tumor or diverticulum|               |
| Pancreatitis                  |               |
| Parasites in bile ducts       |               |
| External compression or adhesion |           |
| Fibrotic papilla              |               |
| Obstruction by blood clot     |               |

### Table 2. Microorganisms isolated from bile cultures among patients with acute biliary infections (modified according to [10, 11])

| Organisms                      | Proportion, % |
|-------------------------------|---------------|
| Community-acquired            |               |
| Escherichia coli              | 31–44         |
| Klebsiella spp.               | 9–20          |
| Pseudomonas spp.              | 0.5–19        |
| Enterobacter spp.             | 5–9           |
| Acinetobacter spp.            | –             |
| Citrobacter spp.              | –             |
| Healthcare-associated         |               |
| Enterococcus spp.             | 3–34          |
| Streptococcus spp.            | 2–10          |
| Staphylococcus spp.           | –             |
| Anaerobes                     | 4–20          |

### Table 3. Common isolates from patients with bacteremic biliary tract infections (modified according to [10, 11])

| Organisms                      | Proportion, % |
|-------------------------------|---------------|
| Community-acquired            |               |
| Escherichia coli              | 35–62         |
| Klebsiella spp.               | 12–28         |
| Pseudomonas spp.              | 4–14          |
| Enterobacter spp.             | 2–7           |
| Acinetobacter spp.            | 3             |
| Citrobacter spp.              | 2–6           |
| Healthcare-associated         |               |
| Enterococcus spp.             | 10–23         |
| Streptococcus spp.            | 6–9           |
| Staphylococcus spp.           | 2             |
| Anaerobes                     | 1             |
| Others                        | 17            |
tive for microorganisms in 16% of the patients, in 72% of those with acute cholangitis, in 44% in chronic cholangitis patients, and in 50% of those with biliary obstruction [10–12].

Table 4. Diagnostic criteria for acute cholangitis (TG13) (modified according to [12])

| A. Systemic inflammation                  |
|------------------------------------------|
| Fever and/or chills                       |
| Laboratory evidence of inflammation      |

| B. Cholestasis                            |
|------------------------------------------|
| Jaundice                                  |
| Abnormal liver function tests             |

| C. Imaging                                |
|------------------------------------------|
| Biliary dilatation                       |
| Evidence of the etiology on imaging (obstruction, stricture, stone, stent, empyema etc.) |

*Suspected diagnosis: One item in A and one item in either B or C.

Table 5. Severity assessment criteria for acute cholangitis/cholecystitis (TG13) (modified according to [12])

| Grade I | Grade II (moderate) acute cholangitis/cholecystitis | Grade III (severe) acute cholangitis/cholecystitis |
|---------|-----------------------------------------------------|---------------------------------------------------|
| Grade I (mild) acute cholangitis/cholecystitis does not meet the criteria of Grade III (severe) or Grade II (moderate) acute cholangitis |
| Grade II (moderate) acute cholangitis/cholecystitis at initial diagnosis is associated with any two of the following conditions: |
| Abnormal WBC count (>12,000/mm³, <4,000/mm³) |
| High fever (>39.0 °C) |
| Age (>75 years) |
| Hyperbilirubinemia (total bilirubin >5 mg/dl) |
| Grade III (severe) acute cholangitis/cholecystitis is associated with cardiac, renal, neurological, respiratory, hepatic, and hematological dysfunction |

Table 6. Antimicrobial recommendations for acute biliary infections (TG13) (modified according to [1])

| Cholangitis and cholecystitis, severity | grade I | grade I | grade III | healthcare-associated |
|----------------------------------------|---------|---------|-----------|-----------------------|
| Anti-microbial agent | ampicillin/sulbactam is not recommended without an aminoglycoside; cefazolin, cefotiam, cefuroxime, ceftriaxone, cefotaxime | piperacillin/tacobactam; ceftriaxone, cefotaxim, cefepime, ceftazidime | piperacillin/tacobactam ± vancomycin, linezolid, daptomycin | piperacillin/tacobactam ± vancomycin, linezolid, daptomycin |
| | ciprofloxacin, levofloxacin ± metronidazole, oxefloxacin ± metronidazole; imipenem/cilastatin, meropenem ± vancomycin, linezolid, daptomycin | cefuroxime, cefuroxime | impinem/cilastatin, meropenem ± vancomycin, linezolid, daptomycin | cefepime, ceftazidime ± metronidazole ± vancomycin, linezolid, daptomycin |
| | cefotaxime, ceftriaxone, cefepime, ceftaxime, ceftriaxone, cefotaxim ± metronidazole | ± vancomycin, linezolid, daptomycin | impinem/cilastatin, meropenem ± vancomycin, linezolid, daptomycin | ± vancomycin, linezolid, daptomycin |
| | | ± vancomycin, linezolid, daptomycin | | ± vancomycin, linezolid, daptomycin |

Management

Patients suspected of having acute cholangitis or cholecystitis should be admitted to a hospital for further evaluation. An early assessment of disease severity is essential for all of these patients (table 4, 5) [1].

Patient Assessment

All patients with suspected or proven cholangitis or cholecystitis (table 6) should be evaluated and grouped according to the TG13 severity assessment criteria (table 7) [1, 2]. Early diagnosis, early biliary drainage or treatment for etiology, and antimicrobial administration are fundamental for the treatment for acute cholangitis/cholecystitis not only in severe and moderate but also in mild disease.

Therefore, it is recommended that patients with acute cholangitis/cholecystitis who do not respond to the initial medical treatment (general supportive care and antimicrobial therapy) undergo early biliary drainage or treatment for etiology, and, in the case of cholecystitis, surgical therapy.

Diagnostic Procedures

Identifying the causative organism is an essential step in the management of acute biliary infections. Blood cultures are not routinely recommended for non-severe acute cholecystitis. The Surgical Infection Society and the Infectious Diseases Society of America (SIS-NA/IDSA) guidelines from 2010 advise against routine blood cultures for community-acquired intra-abdominal infections, since the results do not change the management and outcomes [13, 14]. Positive rates of blood cultures among patients with acute cholangitis ranged from 21 to 71% [15]. However, we would recommend taking cultures as it is simple, easy to take, and might mandate changes in therapy.
Bile cultures should be obtained at the beginning of any surgical or endoscopic procedure. Cultures of bile and tissue should be performed when perforation, emphysematous changes, or necrosis of gallbladder are noted during cholecystectomy. Positive rates of bile cultures range from 59 to 93% for acute cholangitis and from 29 to 67% for acute cholecystitis. Table 2 shows common microbial isolates from bile cultures among patients with acute biliary infections [11–15].

In patients with confirmed cholangitis or cholecystitis, management consists of three cornerstones: i) supportive care, ii) empiric antibiotic coverage, and iii) biliary drainage in acute cholangitis and final surgical treatment for acute cholecystitis.

Supportive care consists of fluid reconstitution, pain management, and management of complications [1, 14, 16]. For biliary drainage in acute cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) is the treatment of choice. The optimal point of time depends on the severity of illness [17]. Early laparoscopic cholecystectomy is the standard definitive management for acute calculous cholecystitis [18].

### Antimicrobial Therapy for Cholangitis and Cholecystitis

The rationale for antimicrobial therapy is to prevent both a systemic septic response and a local inflammation. Furthermore, it should prevent infections after surgical procedures as well as intrahepatic abscess formation. The selection of antibiotics is essential since inadequate initial antibiotic therapy is an independent predictor of mortality [19].

Before choosing an antimicrobial therapy several points should be considered: suspected pathogens, local epidemiology and resistance patterns, pharmacodynamics and pharmacokinetics, the history of antimicrobial usage, severity of illness, nosocomial or community-acquired nature of infection, and allergies or adverse reactions [1].

The antimicrobial therapy should be initiated as soon as the diagnosis of cholangitis or cholecystitis is suspected. While antibiotics should be administered immediately for patients with suspected septic shock, up to 4 h could be spent for obtaining definitive diagnosis in other patients. In all patients, antimicrobial therapy should be started before any invasive procedure [1, 2, 10, 17, 19, 20].

To this day, only few randomized controlled trials have evaluated the effect of antimicrobial therapy on acute cholangitis and/or cholecystitis [1]. All these studies, except one from 2012, are outdated and were conducted in part with antibiotics no longer used in clinical practice. Comparisons of these trials are quite complex as they differ in tested antibiotics, study design, and tested population. However, all of them demonstrated that the chosen antibiotics had a comparable effectiveness and usefulness with ampicillin and an aminoglycoside, which was considered to be the standard regime for acute cholecystitis in the 1980s [21]. The nowadays widely used penicillin and β-lactamase inhibitors, the carbapenems, and the third- and fourth-generation cephalosporins were mainly not tested in these randomized controlled trials. In spite of this, the TG for antimicrobial therapy for acute cholangitis and cholecystitis (TG13) updated in 2013 and the SIS/IDSA 2010 define recommendations for antimicrobial treatment depending on severity of illness and the community-acquired and healthcare-associated nature of biliary infections [1, 14]. Tables 6 and 7 summarize antimicrobial recommendations of TG13 and SIS/IDSA for acute community-acquired cholangitis.

Several antibiotic regimes based on different antimicrobial classes seem to be reasonable. For cholecystitis and cholangitis with mild-to-moderate severity, the TG13 guidelines include penicillin-, cephalosporin-, carbapenem-, monobactam-, and, with limitations, fluorochinolone-based therapy regimes. In contrast, the SIS/IDSA guidelines for mild-to-moderate cholangitis/cholecystitis recommend only cephalosporin-

| Infection                                                                 | Regimen                                                                                     |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Community-acquired acute cholecystitis of mild-to-moderate severity       | cefazolin, cefuroxime, or ceftriaxone                                                       |
| Community-acquired acute cholecystitis of severe physiologic disturbance,  | imipenem-clistatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole |
| advanced age, or immunocompromised state                                 |                                                                                             |
| Acute cholangitis following bilio-enteric anastomosis of any severity     | imipenem-clistatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, evofloxacin, or cefepime, each in combination with metronidazole |
| Health care-associated biliary infection of any severity                 | imipenem-clistatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole |
based regimes. The use of ampicillin/sulbactam as a mono-
therapy is no longer recommended because of high rates of
resistance to this agent among community-acquired Escheri-
chia coli [14]. In face of the increasing number of multidrug-
resistant Gram-negative bacteria (MDRGN bacteria) and
Klebsiella in the community, it should be noted that these or-
ganisms are not sufficiently covered by cephalosporins, peni-
cillin derivatives, or fluorochinolones [21, 22]. If more than 10–
20% of isolates in the community are resistant, empiric ther-
apy should cover these resistant organisms until susceptibility
data are available [14].

One randomized prospective trial from 2012 evaluated the
effect of preoperative antibiotic treatment in 84 patients who
underwent delayed cholecystectomy. In this study, there were
no statistically significant differences regarding duration of
hospitalization and rate of readmission between patients who
received antibiotic treatment with amoxicillin/clavulanic acid
until discharge and those who received no antibiotic treat-
ment [23]. However, it should be noted that the chosen antibi-
otics are no longer recommended as monotherapy, and both
the TG from 2013 and the guidelines by the SIS/IDSA still
recommend the initiation of antimicrobial therapy when in-
fecation is suspected. The data of one recently published paper
justify the use of broad-spectrum antimicrobial regimens for
the empirical treatment of acute cholangitis in patients under-
going stent therapy to minimize the risk of a therapy failure
because of insufficient coverage of multidrug-resistant Gram-
negative organisms until susceptibility testing is available [24].

Summary and Recommendations

Current guidelines for the management of acute cholangi-
tis and cholecystitis recommend the following procedures.
Due to a lack of evidence from well-designed studies all cur-
rent recommendations dealing with antimicrobial therapy are
mainly based on expert opinion.

-- Patients suspected of having acute cholangitis or cholecys-
titis should be admitted to a hospital. A clinical assessment
should be performed for severity grading.
-- Blood culture should be taken before initiating empiric an-
tibiotic therapy and, whenever feasible, bile cultures should be
taken.
-- Empiric, antibiotic therapy tailored according to clinical
and epidemiological findings must get initiated early (<4 h).
-- Adjunctive therapy (fluid management, pain management,
antipyretics) should be administered.
-- Drainage therapy must get offered early in the course of
illness, preferably by means of ERCP. For choledocholithiasis, de-
finitive surgical therapy must be evaluated from the begin-
ing.
-- In mild cholecystitis, antibiotic therapy may be stopped
24 h after surgery.
-- Empirical antibiotics should be tailored after the results of
susceptibility testing become available.
-- Antimicrobial therapy should be given for 4–7 days.

Disclosure Statement

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