J Hepatobiliary Pancreat Sci (2018) 25:3–16
DOI: 10.1002/jhbp.518

GUIDELINE

Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis

Harumi Gomi · Joseph S. Solomkin · David Schlossberg · Kohji Okamoto · Tadahiro Takada · Steven M. Strasberg · Tomohiko Ukai · Itaru Endo · Yukio Iwashita · Taizo Hibi · Henry A. Pitt · Naohisa Matsunaga · Yoriyuki Takamori · Akiko Umezawa · Koji Asai · Kenji Suzuki · Ho-Seong Han · Tsann-Long Hwang · Yasuhisa Mori · Yoo-Seok Yoon · Wayne Shih-Wei Huang · Giulio Belli · Christos Dervenis · Masamichi Yokoe · Seiki Kiriyama · Takao Itoi · Palepu Jagannath · O. James Garden · Fumihiko Miura · Eduardo de Santibañes · Satoru Shikata · Yoshinori Noguchi · Keita Wada · Goro Honda · Avinash Nivritti Supe · Masahiro Yoshida · Toshihiko Mayumi · Dirk J. Gouma · Daniel J. Deziel · Kui-Hin Liau · Miin-Fu Chen · Keng-Hao Liu · Cheng-Hsi Su · Angus C. W. Chan · Dong-Sup Yoon · In-Seok Choi · Eduard Jonas · Xiao-Ping Chen · Sheung Tat Fan · Chen-Guo Ker · Mariano Eduardo Giménez · Seigo Kitano · Masafumi Inomata · Shuntaro Mukai · Ryota Higuchi · Koichi Hirata · Kazuo Inui · Yoshinobu Sumiyama · Masakazu Yamamoto

Published online: 9 January 2018

The author's affiliations are listed in the Appendix.

Correspondence to: Tadahiro Takada, Department of Surgery, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
e-mail: t-takada@jshbps.jp

DOI: 10.1002/jhbp.518

Abstract Antimicrobial therapy is a mainstay of the management for patients with acute cholangitis and/or cholecystitis. The Tokyo Guidelines 2018 (TG18) provides recommendations for the appropriate use of antimicrobials for community-acquired and healthcare-associated infections. The listed agents are for empirical therapy provided before the infecting isolates are identified. Antimicrobial agents are listed by class-definitions and TG18 severity grade I, II, and III subcategorized by clinical settings. In the era of emerging and increasing antimicrobial resistance, monitoring and updating local antibiograms is underscored. Prudent antimicrobial usage and early de-escalation or termination of antimicrobial therapy are now important parts of decision-making. What is new in TG18 is that the duration of antimicrobial therapy for both acute cholangitis and cholecystitis is systematically reviewed. Prophylactic antimicrobial usage for elective endoscopic retrograde cholangiopancreatography is no longer recommended and the section was deleted in TG18. Free full articles and mobile app of TG18 are available at: http://www.jshbps.jp/modules/en/index.php?content_id=47. Related clinical questions and references are also included.

Keywords Acute cholangitis · Acute cholecystitis · Antimicrobial therapy · Biliary tract infection · Treatment guidelines

Introduction

The Tokyo Guidelines 2013 (TG13) antimicrobial therapy for acute cholangitis and cholecystitis, international practice guidelines for the management of patients with acute cholangitis and cholecystitis [1] have been reviewed and revised along with other parts of the therapy for the patients with acute cholangitis and cholecystitis [2–6]. This paper provides the Tokyo Guidelines 2018 (TG18) antimicrobial therapy for acute cholangitis and cholecystitis.

In the TG18 guidelines, empiric therapy is defined as antimicrobial therapy until the cultures and susceptibility testing results are available. Once causative microorganisms and the susceptibility testing results are available, antimicrobial therapy should be adjusted to specific antimicrobial agents targeting the organisms. This process is defined as de-escalation of antimicrobial therapy in the TG18 guidelines [7].

Role of antimicrobial therapy

Acute cholangitis and cholecystitis are still fatal diseases if not appropriately treated in a timely fashion. In previous guidelines (TG13), we defined a severity grading system. A recent large-scale study indicated the mortality rate (30-day all-cause mortality rate) of 2.4%, 4.7%, 8.4% by TG13 severity grade I, II, and III, respectively [8]. For patients with septic shock, appropriate antimicrobial therapy should be administered within an hour [7]. For other, less acutely ill patients, therapy should be administered within 6 h of diagnosis. The primary goal of antimicrobial therapy in acute cholangitis and cholecystitis is to limit both the systemic septic response and local inflammation, to prevent surgical site infections in the superficial wound, fascia, or organ space, and to prevent intrahepatic abscess formation [9].

While drainage of the obstructed biliary trees (termed source control) has been recognized as the mainstay of the therapy for patients with acute cholangitis [9], the roles of antimicrobial therapy for acute cholangitis is to allow patients to have elective drainage procedures other than emergency [10]. Boey and Way retrospectively reviewed 99 consecutive patients with acute cholangitis, and reported that 53% of their patients who responded well to antimicrobial therapy were therefore provided elective instead of emergency operation [9, 10].

For acute cholecystitis, the role of antimicrobial therapy varies depending on the severity and pathology. In early and non-severe cases (or patients with acute cholecystitis of TG18 severity grade I [11]), it is not obvious that bacteria play a significant role in the pathology encountered. In these patients, antimicrobial therapy is at best prophylactic, preventing progression to infection. In more progressed, moderately severe or severe cases, with clinical findings of a systemic inflammatory response, antimicrobial therapy is therapeutic, and antimicrobial therapy may be required until the gallbladder is removed [12].

Decision process

A systematic literature review was performed using PubMed and Cochrane Clinical Controlled Trials (CCT) and Cochrane Database of Systematic Reviews (CDSR) from 1 January 2010 to 16 December 2016. All references were searched with the keywords "Acute cholangitis" AND "Antibiotics OR Antimicrobial therapy," and "Acute cholecystitis" AND "Antibiotics OR Antimicrobial therapy" among human studies. These references were further narrowed using "Clinical trials" and "Randomized trials." Literature cited in the TG07 [13, 14] and TG13 [1] was also reviewed and integrated for revision. In making recommendations, a consensus process utilizing the GRADE systems [15, 16] was used by the members of the Tokyo Guidelines Revision Committee. GRADE stands for Grades of Recommendation Assessment, Development, and Evaluation. In the TG18 guidelines, the strength of the recommendation was graded as 1 (strong) or 2 (weak). The quality of the evidence was graded as high (level A), moderate (level B), low (level C), and very low (level D). Newly identified literatures cited in the TG18 were mentioned in the clinical question sections.

Microbiology of acute cholangitis and cholecystitis

The bacteria commonly found in biliary tract infections are well known, and are presented in Tables 1 and 2 [8, 13, 14, 17–29]. A large-scale multicenter international observational study was conducted and published in 2017 on epidemiology and microbiology among patients with acute cholangitis [8]. In this study, the most frequently isolated organisms were *Escherichia coli* across the severity grades of TG13 [30].

Local prevalence of extended-spectrum beta-lactamase and carbapenemase producing Gram-negative bacilli

Antimicrobial therapy largely depends on local antimicrobial susceptibility data. The emergence of antimicrobial resistance among clinical isolates of *Enterobacteriaceae* from patients with community-acquired intra-abdominal infections has been widely reported [29, 31–37]. Especially, extended-spectrum beta-lactamases (ESBL) and carbapenemases (i.e. metallo-beta-lactamase and non-metallo-beta-lactamase) producing bacilli reported [38–42] have been significantly affecting the selection of empirical therapy for patients with intra-abdominal infections, including acute cholangitis and cholecystitis [43].

In selecting empirical antimicrobial therapy, special attention should be paid to the incidence of ESBL and carbapenemase-producing bacteria in non-urinary tract isolates. A prospective cohort study in patients with acute cholecystitis involving 116 institutions worldwide showed that among 96 isolated *E. coli*, 16 (16.7%) were

Table 1 Common microorganisms isolated from bile cultures among patients with acute biliary infections (endorsed from the Tokyo Guidelines 2013 [1], Table 1)

Isolated microorganisms from bile cultures	Proportions of isolated organisms (%)
Gram-negative organisms	
Escherichia coli	31–44
Klebsiella spp.	9–20
Pseudomonas spp.	0.5–19
Enterobacter spp.	5–9
Acinetobacter spp.	–
Citrobacter spp.	–
Gram-positive organisms	
Enterococcus spp.	3–34
Streptococcus spp.	2–10
Staphylococcus spp.	0[a]
Anaerobes	4–20
Others	–

Table 1 is cited from the Tokyo Guidelines 2013 (TG13) [1]. Data from Rhodes et al. [7] was integrated for the Tokyo Guidelines 2018 (TG18). The data are from references [8, 13, 14, 17–24, 27]

[a]A recent study by Salvador et al. [24] reported none from bile cultures, while a study by Sung et al. [29] reported 3.6% from blood cultures among community-acquired (2%) and healthcare-associated (4%) bacteremic acute biliary infections

Table 2 Common isolates from patients with bacteremic biliary tract infections (endorsed from the Tokyo Guidelines 2013 [1], Table 2)

Isolated microorganisms from blood cultures	Bacteremic biliary tract infections	
	Community-acquired infections[a] Proportions of isolates (%)	Healthcare-associated infections[b] Proportions of isolates (%)
Gram-negative organisms		
Escherichia coli	35–62	23
Klebsiella spp.	12–28	16
Pseudomonas spp.	4–14	17
Enterobacter spp.	2–7	7
Acinetobacter spp.	3	7
Citrobacter spp.	2–6	5
Gram-positive organisms		
Enterococcus spp.	10–23	20
Streptococcus spp.	6–9	5
Staphylococcus spp.	2	4
Anaerobes	1	2
Others	17	11

Table 2 is cited from the Tokyo Guidelines 2013 (TG13) [1]. Data from Gomi et al. [8] was integrated for the Tokyo Guidelines 2018 (TG18)

[a]Data are from references [8, 25–27, 29]

[b]Data are from reference [29]

producing ESBL [44]. However, the proportion of ESBL producing *E. coli* varies widely region to region: 31.2% in two German university hospitals [45], 70.0% in Korean university medical center [46] and 66% in Indian medical college hospital [47]. There are few reports about the prevalence of carbapenem resistant bacteria specifically among patients with acute cholangitis and cholecystitis. One from Korea reported 13 out of 376 (3.5%) isolates in bile were carbapenemase producing [48].

In TG18, the international practice guidelines for acute cholangitis and cholecystitis, agents appropriate for use are provided in Table 3 by antimicrobial class-based definitions. Table 3 has been re-evaluated with a systematic literature review and Tokyo Guidelines Revision Committee. There was no new significant evidence to modify the list of agents. Therefore, Table 3 has been endorsed from TG13, Table 3 [1]. Table 3 lists antimicrobial agents appropriate for use for the treatment of patients with both community-acquired and healthcare-associated cholangitis and cholecystitis.

Monitoring and updating local antibiograms are critical to provide effective therapy in a timely fashion in the clinical setting. We recommend that microbiology laboratories report resistance data by site of infection, and include biliary infections with other intra-abdominal infections. We also recommend empiric therapy for resistant isolates if they occur in more than 20% of patients [49].

In particular, ampicillin/sulbactam can be used as initial therapy if the susceptibility remains over 80% in the local area. However, in many places of the world, its susceptibility has been reported to be decreasing. Ampicillin/sulbactam can be used once its susceptibility is known as definitive or targeted therapy.

Clinical questions

Clinically relevant questions are provided with brief answers and explanations below.

Questions 1 and 2, and their answers and explanations have been endorsed from TG13 Q1 and Q2 [1].

Q1. What specimen should be sent for culture to identify the causative organisms in acute cholangitis and cholecystitis?

(Bile cultures)
Bile cultures should be obtained at the beginning of any procedure performed. Gallbladder bile should be sent for culture in all cases of acute cholecystitis except those with grade I severity. (Recommendation 1, level C)

Table 3 Antimicrobial recommendations for acute biliary infections

Severity	Community-acquired biliary infections			Healthcare-associated biliary infections[a]
	Grade I	Grade II	Grade III[a]	
Antimicrobial agents	Cholangitis and cholecystitis	Cholangitis and cholecystitis	Cholangitis and cholecystitis	Healthcare-associated cholangitis and cholecystitis
Penicillin-based therapy	Ampicillin/sulbactam[b] is not recommended if >20% resistance rate.	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam
Cephalosporin-based therapy	Cefazolin,[c] or Cefotiam,[c] or Cefuroxime,[c] or Ceftriaxone, or Cefotaxime ± Metronidazole[d] Cefmetazole,[c] Cefoxitin,[c] Flomoxef,[c] Cefoperazone/sulbactam	Ceftriaxone, or Cefotaxime, or Cefepime, or Cefozopran, or Ceftazidime ± Metronidazole[d] Cefoperazone/sulbactam	Cefepime, or Ceftazidime, or Cefozopran ± Metronidazole[d]	Cefepime, or Ceftazidime, or Cefozopran ± Metronidazole[d]
Carbapenem-based therapy	Ertapenem	Ertapenem	Imipenem/cilastatin, Meropenem, Doripenem, Ertapenem	Imipenem/cilastatin, Meropenem, Doripenem, Ertapenem
Monobactam-based therapy	–	–	Aztreonam ± Metronidazole[d]	Aztreonam ± Metronidazole[d]
Fluoroquinolone-based therapy[e]	Ciprofloxacin, Levofloxacin, Pazufloxacin ± Metronidazole[d] Moxifloxacin	Ciprofloxacin, Levofloxacin, Pazufloxacin ± Metronidazole[d] Moxifloxacin	–	–

Table 3 is modified and cited from the Tokyo Guidelines 2013 (TG13) [1]

[a]Vancomycin is recommended to cover *Enterococcus* spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant *Enterococcus* (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community

[b]Ampicillin/sulbactam has little activity left against *Escherichia coli*. It is removed from the North American guidelines [43, 49]

[c]Local antimicrobial susceptibility patterns (antibiogram) should be considered for use

[d]Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anaerobic activity for this situation

[e]Fluoroquinolones use is recommended if the susceptibility of cultured isolates is known or for patients with β-lactam allergies. Many extended-spectrum β-lactamase (ESBL)-producing Gram-negative isolates are fluoroquinolone resistant

We suggest cultures of bile and tissue when perforation, emphysematous changes, or necrosis of gallbladder are noted during cholecystectomy. (Recommendation 2, level D)

(Blood cultures)
Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis. (Recommendation 2, level D)

Identifying the causative organism(s) is an essential step for the management of acute biliary infections. Positive rates of bile cultures range from 28% to 93% for acute cholangitis [8, 13–24] and positive rates of either bile or gallbladder cultures range from 29% to 54% for acute cholecystitis [13–24]. In a recent study, which used the TG07 diagnostic classification, positive rates of bile cultures among patients with cholangitis were 67% (66 of 98 patients) and 33% (32 of 98) without [24]. Table 1 demonstrates common microbial isolates from bile cultures among patients with acute biliary infections [8, 13–24]. Common duct bile should be sent in all cases of suspected cholangitis.

On the other hand, previous studies indicated that positive rates of blood cultures among patients with acute cholangitis ranged from 21% to 71% [13]. A recent multicenter study of patients with acute cholangitis showed the proportions of positive blood cultures were 15.2%, 21%, and 25.7% by TG13 severity grade I, II, and III, respectively [7]. For acute cholecystitis, the prevalence of positive blood cultures is less than acute cholangitis, and in the last two decades it has been reported to range from 7.7% to 15.8% [25, 28]. Table 2 demonstrates the most recently reported microbial isolates from patients with bacteremic biliary tract infections [8, 25–27, 29].

There is a lack of clinical trials examining the benefit of blood cultures in patients with acute biliary tract infections. On the other hand, there is an argument that every opportunity should be used to identify microorganisms and susceptibility testing in the era of antimicrobial resistance [45].

Most of the bacteremic isolates reported (Table 2) are organisms that do not form vegetations on normal cardiac valves or military abscesses [8]. Their intravascular presence does not lead to an extension of therapy or selection of multidrug regimens. We therefore recommend such cultures be taken only in high severity infections when such results might mandate changes in therapy [3, 4, 7]. Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis.

The SIS-NA/IDSA 2010 guidelines recommended against routine blood cultures for community-acquired intra-abdominal infections since the results do not change the management and outcomes [49]. This recommendation is carried forward in recent guidelines [43]. This is in part driven by a study of the clinical impact of blood cultures taken in the emergency department [51]. In this retrospective study, 1,062 blood cultures were obtained during the study period. Among them, 92 (9%) were positive. Of the positive blood cultures, 52 (5%) were true positive, and only 18 (1.6%) resulted in altered management.

Q2. What considerations should be taken when selecting antimicrobial agents for the treatment of acute cholangitis and cholecystitis?

When selecting antimicrobial agents, targeted organisms, pharmacokinetics and pharmacodynamics, local antibiogram, a history of antimicrobial usage, renal and hepatic function, and a history of allergies and other adverse events should be considered. (Recommendation 1, level D).
We suggest anaerobic therapy if a biliary-enteric anastomosis is present. (Recommendation 2, level C)

There are multiple factors to consider in selecting empiric antimicrobial agents. These include targeted organisms, local epidemiology and susceptibility data (antibiogram), alignment of *in vitro* activity (or spectrum) of the agents with these local data, characteristics of the agents such as pharmacokinetics and pharmacodynamics, and toxicities, renal and hepatic function, and any history of allergies and other adverse events with antimicrobial agents [13, 14, 17–24]. A history of antimicrobial usage is important because recent (<6 months) antimicrobial therapy greatly increases the risk of resistance among isolated organisms.

Renal function should be estimated before dosing antimicrobial agents with the commonly used equation: Serum creatinine = (140-age) (optimum body weight (kg))/72 × serum creatinine (mg/dl) [13, 14, 52]. Individual dosage adjustments for altered renal and hepatic function is available in several recent publications [53, 54]. Consultation with a clinical pharmacist is recommended if there are concerns.

Regarding the timing of therapy, therapy should be initiated as soon as the diagnosis of biliary infection is suspected. For patients in septic shock, antimicrobials should be administered within 1 h of recognition [7]. For other patients, as long as 6 h may be spent obtaining definitive diagnostic studies prior to beginning antimicrobial

therapy. Antimicrobial therapy should definitely be started before any procedure, either percutaneous, endoscopic, or operative, is performed. In addition, anaerobic therapy is appropriate if a biliary-enteric anastomosis is present [49].

Antimicrobial agents appropriate for use in the management of community-acquired acute cholangitis and cholecystitis

Table 3 summarizes antimicrobial recommendations [1]. It should be kept in mind that in the treatment of cholangitis, source control (i.e. drainage) is an essential part of management. The indications and timing for drainage are provided in the severity and flowchart of the management sections regarding acute cholangitis [2–6]. There have been multiple reports on clinical isolates with multiple drug resistance from intra-abdominal infections worldwide, and biliary infections in particular [29, 31–37, 55].

Recommendations for antimicrobial therapy are based primarily upon extrapolations of microbiologic efficacy and behavior of these agents against the more susceptible isolates treated in the cited clinical trials [56–66]. Some concerns about this approach to defining efficacy against resistant isolates has been raised [41].

The use of severity of illness as a guide to antimicrobial agent selection has been questioned in the face of the increasing numbers of ESBL-producing *E. coli* and *Klebsiella* in the community. These organisms are not reliably susceptible to cephalosporins, penicillin derivatives, or fluoroquinolones. Previous guidelines have recommended that if more than 10–20% of community isolates of *E. coli* are so resistant, then empiric coverage should be provided for these organisms until susceptibility data demonstrates sensitivity to narrower spectrum agents [49]. Carbapenems, piperacillin/tazobactam, tigecycline, amikacin, and other newer agents such as ceftazidime/avibactum and ceftolozane/tazobactam may also be used to treat these isolates.

For grade III community-acquired acute cholangitis and cholecystitis, as initial therapy (empirical therapy), agents with anti-pseudomonal activities are recommended until causative organisms are identified. *Pseudomonas aeruginosa* is present in approximately 20% of previous series [24, 29]. However, recent large-scale data showed very few ranging from 1.1% to 3.1% among isolates from blood cultures and 2.5% to 3.6% from bile cultures obtained from patients with acute cholangitis, respectively [8]. *P. aeruginosa* is a known virulent pathogen and failure to empirically cover this organism in critically ill patients may result in excess mortality.

Enterococcus spp. is another important pathogen for consideration in patients with grade III community-acquired acute cholangitis and cholecystitis. Vancomycin is recommended to cover *Enterococcus* spp. for patients with grade III community-acquired acute cholangitis and/or cholecystitis, until the results of cultures are available. Ampicillin can be used if isolated strains of *Enterococcus* spp. are susceptible to ampicillin. Ampicillin covers most of the strains of *Enterococcus faecalis* from community-acquired infections in general. For *Enterococcus faecium*, vancomycin is the drug of choice for empirical therapy. However, in many hospitals, vancomycin-resistant *Enterococcus* spp., both *E. faecium* and *E. faecalis*, have emerged as important causes of infection. Treatment for these organisms requires either linezolid or daptomycin. Surgeons and other physicians making treatment decisions for patients with healthcare-associated infections should be aware of the frequency of these isolates in their hospital and unit. Then regarding infrequently isolated anaerobes such as *Bacteroides fragilis* group, we suggest to cover these organisms empirically when a biliary-enteric anastomosis is present [49].

For grade I and II community-acquired cholangitis and cholecystitis, Table 3 provides the agents appropriate for use. Clindamycin resistance among *Bacteroides* spp. is significant and the use of clindamycin is no longer recommended in other intra-abdominal infections [49]. Cefoxitin, cefmetazole, flomoxef, and cefoperazone/sulbactam are the agents in cephalosporins that have activities against *Bacteroides* spp. Cefoxitin is no longer recommended by the SIS-NA/IDSA 2010 guidelines due to high prevalence of resistance among *Bacteroides* spp. [49]. Local availability of agents as well as local susceptibility results are emphasized when choosing empirical therapy.

Table 4 Antimicrobial agents with high prevalence of resistance among Enterobacteriaceae (endorsed from the Tokyo Guidelines 2013 [1], Table 4)

Antimicrobial class	Antimicrobial agents
Penicillin	Ampicillin/sulbactam
Cephalosporins	Cefazolin
	Cefuroxime
	Cefotiam
	Cefoxitin
	Cefmetazole
	Flomoxef
	Ceftriaxone[a] or Cefotaxime[a]
Fluoroquinolones	Ciprofloxacin
	Levofloxacin
	Moxifloxacin

Table 4 is cited from the Tokyo Guidelines 2013 (TG13) [1]

References [14, 31–35]

[a]This resistance indicates global spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

Table 4 summarizes antimicrobial agents with high prevalence of resistance among Enterobacteriaceae [29, 31–37]. Ampicillin/sulbactam is one of the most frequently used agents for intra-abdominal infections. Nonetheless, the activity of ampicillin/sulbactam against *E. coli*, with or without ESBLs, has fallen to levels that prevent a recommendation for its use.

In the TG18, ampicillin/sulbactam is not recommended as empirical therapy if the local susceptibility is <80%. It is reasonable to use ampicillin/sulbactam as definitive therapy when the susceptibility of this agent is proven. Ampicillin/sulbactam may be used if susceptibility testing results are available.

Fluoroquinolone use is only recommended if the susceptibility of cultured isolates is known since antimicrobial resistance has been increasing significantly [29, 31–37]. This agent can also be used as an alternative agent for patients with β-lactam allergies.

Antimicrobial agents appropriate for use in the management of healthcare-associated acute cholangitis and cholecystitis

Since 2010, there have been very few clinical studies on antimicrobial therapy for patients with healthcare-associated acute cholangitis and cholecystitis.

There is no evidence to support any agent as optimal treatment of healthcare-associated acute cholangitis and cholecystitis. The principles of empirical therapy of healthcare-associated infections include using agents with antipseudomonal activity until definitive causative organisms are found.

The local prevalence of ESBL and/or carbapenemase producing Enterobacteriacea is critical information in selecting empirical agents. Optimal agents vary from institution to institution. Therefore, it is underscored that local susceptibility should be monitored strictly and periodically.

A multi-disciplinary approach would be beneficial to provide and discuss appropriate antimicrobial agents in the institution, region, and country.

Table 3 provides empirical agents (presumptive therapy) for healthcare-associated acute cholangitis and cholecystitis. Vancomycin is recommended when patients are colonized with resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and/or *Enterococcus* spp. or these multidrug-resistant Gram-positives are of concern. *Staphylococcus aureus* is not a common isolate for acute biliary infections as *Enterococcus* spp. In recent study, *Staphylococcus aureus* was isolated less than 1% both from blood and bile for patients with acute cholangitis [8].

Vancomycin resistant *Enterococcus* (VRE) should be covered empirically with linezolid or daptomycin if this organism is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

Isolation of *Bacteroides fragilis* group was 1.1% from blood cultures, and 1.6% from bile cultures among patients with acute cholangitis [8]. For empirical therapy for anaerobes such as the *Bacteroides fragilis* group, we suggest to cover these organisms empirically in the presence of a biliary-enteric anastomosis [49].

Is it necessary for agents used in acute biliary infections to be concentrated in bile?

Historically, biliary penetration of agents has been considered in the selection of antimicrobial agents. However, there is considerable laboratory and clinical evidence that as obstruction occurs, secretion of antimicrobial agents into bile stops [10]. Recent international guidelines for acute calculous cholecystitis summarized the bile to serum concentration ratio and recommend to select agents with good infected sites penetration [50]. Well-designed randomized clinical trials comparing agents with or without good biliary penetration are needed to determine the clinical relevance and significance of biliary penetration in treating acute biliary infections.

How should highly resistant causative organisms be managed in treating acute cholangitis and cholecystitis?

Extended-spectrum beta-lactamases-producing *E. coli* is highly susceptible to carbapenems and to tigecycline. In multiple areas of the world, highly resistant *Klebsiella* spp. and *E. coli* with carbapenemases are seen [41, 67–69]. The widely accepted rule for empirical therapy is that resistant organisms occurring in more than 10–20% of patients should be treated. Colistin is the salvage agent for the above multidrug-resistant Gram-negative bacilli epidemic strains [55, 69]. This agent is toxic, dosing is uncertain, and its use should involve consultation with infectious disease specialists [55]. Newer agents such as ceftazidime/avibactam and ceftolozane/tazobactam has limited evidence for use among patients with acute cholangitis and cholecystitis.

In TG18, endorsed from TG13 [1], carbapenems, piperacillin/tazobactam, and ceftazidime or cefepime, each combined with metronidazole have been recommended when the prevalence of resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter* or other multidrug-resistant Gram-negative bacilli is less than 20% [49]. For ESBL-producing Enterobacteriaceae,

carbapenems, piperacillin/tazobactam, and aminoglycosides are recommended. For *Pseudomonas aeruginosa*, if the prevalence of resistance to ceftazidime is more than 20%, carbapenems, piperacillin/tazobactam, and aminoglycosides are empirically recommended until culture and susceptibility testing results are available.

Q3. What is the optimal duration and route of antimicrobial therapy for patients with acute cholangitis?

Once the source of infection is controlled, antimicrobial therapy for patients with acute cholangitis is recommended for the duration of 4 to 7 days. (Recommendation 1, level C)

Literature was searched using PubMed and Cochrane Library using the key words of (acute cholangitis* OR acute biliary tract infections*) AND (antimicrobial therapy* OR antibiotics*) AND duration of therapy.* MeSH was also used for each word. There was a total of 151 articles from PubMed, 16 from Cochrane Controlled Clinical Trials (CCT), and one from Cochrane Clinical Database of Systematic Reviews (CDSR). Among them, selection criteria were either randomized studies or observational studies. The articles that met the selection criteria were screened initially by title, then if it was difficult to judge, the abstract was also reviewed. As a result, there were four relevant articles found.

Uno et al. [70] compared retrospectively the outcomes among patients with bacteremic acute cholangitis due to Gram-negative bacilli who received antimicrobial therapy over either 14 or 10 days. There were no differences between the two groups in 30-day mortality and recurrence rate within 3 months. There were statistically significant differences in the lengths of stay (17.5 days vs. 14 days, $P < 0.01$). van Lent et al. [71] reported that in their single institution, there were no differences in the recurrence rate for acute cholangitis between the patients who received less than 3-day therapy versus more than 5-day therapy once the source of infection was controlled among patients with acute cholangitis. Kogure et al. [72] conducted a prospective observational study to investigate how long antimicrobial therapy should be administered for patients with acute cholangitis after successful biliary drainage. In this study, 18 patients were analyzed for recurrent cholangitis within 3 days after discontinuing antimicrobial therapy. There were no recurrences noted. Park et al. [73] conducted a randomized study to compare the recurrence rate and 30-day mortality among patients with bacteremic cholangitis due to ciprofloxacin-susceptible *Enterobacteriacae* who

Table 5 Recommended duration of antimicrobial therapy

	Community-acquired biliary infections			Healthcare-associated biliary infections
Severity and diagnosis	Grade I and II cholecystitis	Grade I and II cholangitis	Grade III cholangitis and cholecystitis	Grade I, II, III healthcare-associated cholangitis and cholecystitis
Duration of therapy	Antimicrobial therapy can be discontinued within 24 h after cholecystectomy is performed.	Once source of infection is controlled, duration of 4–7 days is recommended. If bacteremia with Gram-positive cocci such as *Enterococcus* spp., *Streptococcus* spp. is present, duration of minimum 2 weeks is recommended.		If bacteremia with Gram-positive cocci such as *Enterococcus* spp., *Streptococcus* spp. is present, duration of minimum 2 weeks is recommended.
Specific conditions for extended therapy	Perforation, emphysematous changes, and necrosis of gallbladder are noted during cholecystectomy, duration of 4–7 days is recommended.	Residual stones or obstruction of the bile tract are present, treatment should be continued until these anatomic problems are resolved. If liver abscess is present, treatment should be continued until clinical, biochemical and radiological follow-up demonstrates complete resolution of the abscess.		

underwent successful biliary drainage and received either conventional intravenous therapy or 6-day intravenous antimicrobial therapy followed by oral therapy. In this study, there were no differences between the two groups in the recurrence of cholangitis and 30-day mortality. In the TG18, the duration of therapy for patients with acute cholangitis is for 4 to 7 days once the source of infection is controlled by integrating the above studies and expert opinion (Table 5). When bacteremia with Gram-positive bacteria such as *Enterococcus* spp. and *Streptococcus* spp. is present, it is prudent to offer antimicrobial therapy for 2 weeks since these organisms are well-known to cause infective endocarditis. The incidence of endocarditis among patients with acute cholangitis has been reported 17 (0.3%) out of 6,147 patients with acute cholangitis [8].

In June 2017, the 6th Asian Pacific Hepatobiliary Pancreatic Surgery Conference was held and a clinical question was asked among the expert panel, with successful biliary drainage, how long would you administer antimicrobial therapy for patients with bacteremic acute cholangitis due to Gram-positive cocci? Five answers were provided, such as A: 14 days, B: 10 days, C: 7 days, D: 4–5 days, and E: 3 days or less. The answers were as follows. A 9%, B 3.8%, C 26.9%, D 32.1%, and E 26.9%.

Q4. What is the optimal duration of antimicrobial therapy for patients with acute cholecystitis?

Antimicrobial therapy for patients with Grade I and II acute cholecystitis is recommended only before and at the time of surgery. (Recommendation 1, level B)

Once the source of infection is controlled, antimicrobial therapy for patients with Grade III acute cholecystitis is recommended for the duration of 4 to 7 days. (Recommendation 2, level D)

Literature was searched using PubMed and Cochrane Library using the key words of (acute cholecystitis* OR acute biliary tract infections*) AND (antimicrobial therapy* OR antibiotics*) AND duration of therapy.* MeSH was also used for each word.

There was a total of 51 articles from PubMed, 21 from CCT, and one from CDSR. Among them, selection criteria were either randomized studies or observational studies. The articles that met the selection criteria were screened initially by title, then if it was difficult to judge, the abstract was also reviewed. As a result, there were four relevant articles found: three randomized controlled trials (RCTs) [74–76] and one observational study [77].

TG13 [1] and SIS-IDSA 2010 [49] recommended postoperative antimicrobial therapy for different durations, ranging from 24 h to 7 days depending on the severity of cholecystitis given the lack of high-quality evidence. Recently, two RCTs assessing the non-inferiority of no postoperative antimicrobial therapy with postoperative antimicrobial therapy for patients with mild or moderate acute cholecystitis who underwent early cholecystectomy were conducted [74, 75]. Although non-inferiority was not proven in either RCT, there was no clinically significant difference. The results of the two RCTs were integrated and the risk difference for postoperative infection was 0.01 (95% CI −0.04–0.06) (Fig. 1). Considering the disadvantages of extended antimicrobial therapy, including increased medical costs, prolonged hospital stay, and increased bacterial resistance, the antimicrobial therapy should be limited to before and at the time of surgery for Grade I and II acute cholecystitis. Some patients would need extended postoperative antibiotics depending on their condition.

For Grade III acute cholecystitis, there are scarce data available. Hence, we suggest the expert opinion of continuing antimicrobial therapy for 4–7 days after the source of infection is controlled (Table 5). When bacteremia with Gram-positive bacteria is present, administering antimicrobial therapy for 2 weeks is prudent and recommended to decrease the risk of infective endocarditis.

In the consensus meeting, there was a statement by the member that there were no sufficient data to support this duration of therapy for patients with Grade III acute cholecystitis, and that it would be difficult to recommend this.

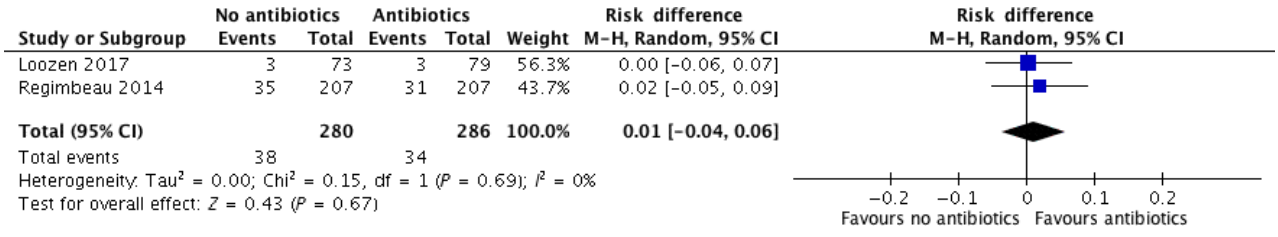

Fig. 1 This meta-analysis was performed by integrating two randomized studies, references [74] and [75]

(Antimicrobial therapy for special conditions)
In patients with pericholecystic abscesses or perforation of the gallbladder, treatment with an antimicrobial regimen as listed in Table 3 is recommended. Therapy should be continued until the patient is afebrile, with a normalized white count, and without abdominal findings. (Recommendation 1, level D)

In most cases, cholecystectomy removes the infection, and little if any infected tissue remains. Under these circumstances, there is no benefit to antimicrobial therapy extending beyond 24 h [74, 75].

Randomized clinical trials for antimicrobial therapy of acute cholecystitis are limited [60, 62–65]. In these randomized studies, comparisons were made such as ampicillin plus tobramycin versus piperacillin or cefoperazone, pefloxacin versus ampicillin and gentamicin, cefepime versus mezlocillin plus gentamicin [14, 60, 63, 65]. There were no significant differences between the agents compared. In the TG18, the agents considered as appropriate therapy, and listed in Table 3, have all been used in RCTs of intra-abdominal infections. These studies included patients with pathologically advanced cholecystitis (abscess or perforation). Table 3 is provided for both community-acquired and healthcare-associated acute cholecystitis.

Antimicrobial therapy after susceptibility testing results are available

Once susceptibility testing results of causative microorganisms are available, specific therapy (or definitive therapy) should be offered. This process is called de-escalation [7]. Agents in Table 4 can be used safely once the susceptibility is proven.

Table 6 Representative oral antimicrobial agents for community-acquired and healthcare-associated acute cholangitis and cholecystitis with susceptible isolates (endorsed from the Tokyo Guidelines 2013 [1], Table 6)

Antimicrobial class	Antimicrobial agents
Penicillins	Amoxicillin/clavulanic acid
Cephalosporins	Cephalexin ± Metronidazole[a]
Fluoroquinolones	Ciprofloxacin or Levofloxacin ± Metronidazole[a]
	Moxifloxacin

[a]Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present

Conversion to oral antimicrobial agents

Patients with acute cholangitis and cholecystitis who can tolerate oral feeding may be treated with oral therapy [78]. Depending on the susceptibility patterns of the organisms identified, oral antimicrobial agents such as fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), amoxicillin/clavulanic acid, or cephalosporins may also be used. Table 6 lists commonly used oral antimicrobial agents with good bioavailabilities.

Use of antibiotic irrigation

There has been continuing interest in irrigation of surgical fields with antimicrobial agents, and the subject has recently been reviewed [79]. The authors concluded that topical antimicrobial agents are clearly effective in reducing wound infections and may be as effective as the use of systemic antimicrobial agents. The combined use of systemic and topical antimicrobial agents may have additive effects, but this is lessened if the same agent is used for both topical and systemic administration.

Conclusions

In TG18, antimicrobial agents appropriate for use as empirical therapy for community-acquired and healthcare-associated infections are provided. Globally increasing and spreading antimicrobial resistance, antimicrobial stewardship should be underscored and implemented for prudent antimicrobial usage in each institution. Local, national, and international continuous monitoring of antibiogram would provide safe and appropriate therapy for patients with acute cholangitis and cholecystitis in a timely fashion. More definitive studies to indicate the appropriate duration of antimicrobial therapy for patients with bacteremic cholangitis and cholecystitis are warranted.

Acknowledgments We express our deep gratitudes to the Japanese Society of Hepato-Biliary-Pancreatic Surgery, the Japanese Society of Abdominal Emergency Medicine, the Japanese Society of Surgical Infection, the Japan Biliary Association, for their substantial support and guidance in the preparation of the article. We would also like to express our deep gratitude to the Japanese Society of Hepato-Biliary-Pancreatic Surgery for the article processing managing office of Tokyo Guidelines 2018 to prepare the publication. We appreciate all secretariats of the Japanese Society of Hepato-Bilialy-Pancreatic Surgery for their technical support.

Conflict of interest Goro Honda has received honoraria from Johnson and Johnson and Medtronic.

Appendix: author's affiliations

Harumi Gomi, Center for Global Health, Mito Kyodo General Hospital, University of Tsukuba, Ibaraki, Japan; Joseph S. Solomkin, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA; David Schlossberg and Henry A. Pitt, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; Kohji Okamoto, Department of Surgery, Center for Gastroenterology and Liver Disease, Kitakyushu City Yahata Hospital, Fukuoka, Japan; Tadahiro Takada, Fumihiko Miura and Keita Wada, Department of Surgery, Teikyo University, School of Medicine, Tokyo, Japan; Steven M. Strasberg, Section of HPB Surgery, Washington University in St. Louis, St. Louis, MO, USA; Tomohiko Ukai, Department of Family Medicine, Mie Prefectural Ichishi Hospital, Mie, Japan; Itaru Endo, Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Kanagawa, Japan; Yukio Iwashita and Masafumi Inomata, Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine, Oita, Japan; Taizo Hibi, Department of Surgery, Keio University School of Medicine, Tokyo, Japan; Naohisa Matsunaga, Department of Infection Control and Prevention, Teikyo University, Tokyo, Japan; Yoriyuki Takamori, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; Akiko Umezawa, Minimally Invasive Surgery Center, Yotsuya Medical Cube, Tokyo, Japan; Koji Asai, Department of Surgery, Toho University Ohashi Medical Center, Tokyo, Japan; Kenji Suzuki, Department of Surgery, Fujinomiya City General Hospital, Shizuoka, Japan; Ho-Seong Han and Yoo-Seok Yoon, Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea; Tsann-Long Hwang, Miin-Fu Chen and Keng-Hao Liu, Division of General Surgery, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; Yasuhisa Mori, Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Wayne Shih-Wei Huang, Department of Surgery, Show Chwan Memorial Hospital, Changhua, Taiwan; Giulio Belli, Department of General and HPB Surgery, Loreto Nuovo Hospital, Naples, Italy; Christos Dervenis, First Department of Surgery, Agia Olga Hospital, Athens, Greece; Masamichi Yokoe and Yoshinori Noguchi, Department of General Internal Medicine, Japanese Red Cross Nagoya Daini Hospital, Aichi, Japan; Seiki Kiriyama, Department of Gastroenterology, Ogaki Municipal Hospital, Gifu, Japan; Takao Itoi and Shuntaro Mukai, Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital, Tokyo, Japan; Palepu Jagannath, Department of Surgical Oncology, Lilavati Hospital and Research Centre, Mumbai, India; O James Garden, Clinical Surgery, University of Edinburgh, Edinburgh, UK; Eduardo de Santibañes, Department of Surgery, Hospital Italiano, University of Buenos Aires, Buenos Aires, Argentina; Satoru Shikata, Director, Mie Prefectural Ichishi Hospital, Mie, Japan; Goro Honda, Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; Avinash Nivritti Supe, Department of Surgical Gastroenterology, Seth G S Medical College and K E M Hospital, Mumbai, India; Masahiro Yoshida, Department of Hemodialysis and Surgery, Ichikawa Hospital, International University of Health and Welfare, Chiba, Japan and Department of EBM and Guidelines, Japan Council for Quality Health Care, Tokyo, Japan; Toshihiko Mayumi, Department of Emergency Medicine, School of Medicine University of Occupational and Environmental Health, Fukuoka, Japan; Dirk J. Gouma, Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands; Daniel J. Deziel, Department of Surgery, Rush University Medical Center, Chicago, IL, USA; Kui-Hin Liau, Liau KH Consulting PL, Mt Elizabeth Novena Hospital, Singapore, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; Cheng-Hsi Su, Department of Surgery, Cheng Hsin General Hospital, Taipei, Taiwan; Angus C. W. Chan, Surgery Centre, Department of Surgery, Hong Kong Sanatorium and Hospital, Hong Kong, Hong Kong; Dong-Sup Yoon, Department of Surgery, Yonsei University Gangnam Severance Hospital, Seoul, Korea; In-Seok Choi, Department of Surgery, Konyang University Hospital, Daejeon, Korea; Eduard Jonas, Surgical Gastroenterology/Hepatopancreatobiliary Unit, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa; Xiao-Ping Chen, Hepatic Surgery Centre, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Sheung Tat Fan, Director, Liver Surgery Centre, Hong Kong Sanatorium and Hospital, Hong Kong, Hong Kong; Chen-Guo Ker, Department of Surgery, Yuan's General Hospital, Kaohsiung, Taiwan; Mariano Eduardo Giménez, Chair of General Surgery and Minimal Invasive Surgery "Taquini", University of Buenos Aires, DAICIM Foundation, Buenos Aires, Argentina; Seigo Kitano, President, Oita University, Oita, Japan; Ryota Higuchi and Masakazu Yamamoto, Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan; Koichi Hirata, Department of Surgery, JR Sapporo Hospital, Hokkaido, Japan; Kazuo Inui, Department of Gastroenterology, Second Teaching Hospital, Fujita Health University, Aichi, Japan; Yoshinobu Sumiyama, Director, Toho University, Tokyo, Japan.

References

1. Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:60–70.
2. Kiriyama S, Kozaka K, Takada T, Strasberg SM, Pitt HA, Gabata T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:17–30.
3. Miura F, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. J Hepatobiliary Pancreat Sci. 2018;25:31–40.
4. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:55–72.
5. Mukai S, Itoi T, Baron TH, Takada T, Strasberg SM, Pitt HA, et al. Indications and techniques of biliary drainage for acute cholangitis in updated Tokyo Guidelines 2018. J Hepatobiliary Pancreat Sci. 2017;24:537–49.
6. Mori Y, Itoi T, Baron TH, Takada T, Strasberg SM, Pitt HA, et al. Tokyo Guidelines 2018: management strategies for gallbladder drainage in patients with acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:87–95.
7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43:304–77.
8. Gomi H, Takada T, Hwang TL, Akazawa K, Mori R, Endo I, et al. Updated comprehensive epidemiology, microbiology, and outcomes among patients with acute cholangitis. J Hepatobiliary Pancreat Sci. 2017;24:310–8.
9. van den Hazel SJ, Speelman P, Tytgat GNJ, Dankert J, van Leeuwen DJ. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. Clin Infect Dis. 1994;19:279–86.
10. Beoy JH, Way LW. Acute cholangitis. Ann Surg. 1980;191:264–70.
11. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:41–54.
12. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372:1996–2005.
13. Tanaka A, Takada T, Kawarada Y, Nimura Y, Yoshida M, Miura F, et al. Antimicrobial therapy for acute cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:59–67.
14. Yoshida M, Takada T, Kawarada Y, Tanaka A, Nimura Y, Gomi H, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:83–90.
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
16. US GRADE Network. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology. [Cited 12 Oct 2017]. Available from URL: http://www.gradeworkinggroup.org/
17. Kune G, Schutz E. Bacteria in the biliary tract. A study of their frequency and type. Med J Aust. 1974;1:255–8.
18. Csendes A, Fernandez M, Uribe P. Bacteriology of the gallbladder bile in normal subjects. Am J Surg. 1975;129:629–31.
19. Csendes A, Becerra M, Burdiles P, Demian I, Bancalari K, Csendes P. Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. Eur J Surg. 1994;160:363–7.
20. Csendes A, Burdiles P, Maluenda F, Diaz J, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. Arch Surg. 1996;131:389–94.
21. Csendes A, Mitru N, Maluenda F, Diaz J, Burdiles P, Csendes P, et al. Counts of bacteria and pyocites of choledochal bile in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology. 1996;43:800–6.
22. Maluenda F, Csendes A, Burdiles P, Diaz J. Bacteriological study of choledochal bile in patients with common bile duct stones, with or without acute suppurative cholangitis. Hepatogastroenterology. 1989;36:132–5.
23. Chang W, Lee K, Wang S, Chuang S, Kuo K, Chen J, et al. Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-year's experience. Kaohsiung J Med Sci. 2002;18:221–8.
24. Salvador V, Lozada M, Consunji R. Microbiology and antibiotic susceptibility of organisms in bile cultures from patients with and without cholangitis at an Asian Academic Medical Center. Surg Infect. 2011;12:105–11.
25. Kuo CHCC, Chen JJ, Tai DI, Chiou SS, Lee CM. Septic acute cholecystitis. Scand J Gastroenterol. 1995;30:272–5.
26. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteremia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J. 2007;83:773–6.
27. Lee C-C, Chang IJ, Lai Y-C, Chen S-Y, Chen S-C. Epidemiology and prognostic determinants of patients with bacteremic cholecystitis or cholangitis. Am J Gastroenterol. 2007;102:563–9.
28. Baitello AL, Colleoni Neto R, Herani Filho B, Cordeiro JA, Machado AMO, Godoy MF, et al. Prevalência e fatores associados à bacteremia nos portadores de colecistite aguda litiásica. Rev Assoc Med Bras (1992). 2004;50:373–9.
29. Sung YK, Lee JK, Lee KH, Lee KT, Kang C-I. The Clinical epidemiology and outcomes of bacteremic biliary tract infections caused by antimicrobial-resistant pathogens. Am J Gastroenterol. 2012;107:473–83.
30. Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci. 2013;20:24–34.
31. Paterson DL, Rossi F, Baquero F, Hsueh P-R, Woods GL, Satishchandran V, et al. *In vitro* susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). J Antimicrob Chemother. 2005;55:965–73.
32. Rossi F, Baquero F, Hsueh P-R, Paterson DL, Bochicchio GV, Snyder TA, et al. *In vitro* susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). J Antimicrob Chemother. 2006;58:205–10.
33. Yang Q, Wang H, Chen M, Ni Y, Yu Y, Hu B, et al. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002-2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents. 2010;36:507–12.

34. Hsueh P-R, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, Ni Y, et al. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Int J Antimicrob Agents. 2010;36:408–14.
35. Chen Y-H, Hsueh P-R, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, et al. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. J Infect. 2011;62:280–91.
36. Ishii Y, Tateda K, Yamaguchi K. Evaluation of antimicrobial susceptibility for β-lactams using the Etest method against clinical isolates from 100 medical centers in Japan (2006). Diagn Microbiol Infect Dis. 2008;60:177–83.
37. Ishii Y, Ueda C, Kouyama Y, Tateda K, Yamaguchi K. Evaluation of antimicrobial susceptibility for β-lactams against clinical isolates from 51 medical centers in Japan (2008). Diagn Microbiol Infect Dis. 2011;69:443–8.
38. Paterson DL. Resistance in Gram-negative bacteria: Enterobacteriaceae. Am J Infect Control. 2006;34(5 Supplement):S20–8.
39. Choi SH, Lee J, Park S, Kim MN, Choo E, Kwak Y, et al. Prevalence, microbiology, and clinical characteristics of extended-spectrum; beta-lactamase-producing Enterobacter spp., Serratia marcescens, Citrobacter freundii and & Morganella morganii in Korea. Eur J Clin Microb. Infect Dis. 2007;26:557–61.
40. Kang CI, Cheong H, Chung D, Peck K, Song JH, Oh MD, et al. Clinical features and outcome of community-onset bloodstream infections caused by extended-spectrum β-lactamase-producing Escherichia coli. Eur J Clin Microb Infect Dis. 2008;27:85–8.
41. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10:597–602.
42. Peirano G, van der Bij AK, Gregson DB, Pitout JDD. Molecular epidemiology over an 11-year Ppriod (2000 to 2010) of extended-Spectrum β-lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. J Clin Microbiol. 2012;50:294–9.
43. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surgical infections. 2017;18:1–76.
44. Coccolini F, Sartelli M, Catena F, Montori G, Di Saverio S, Sugrue M, et al. Antibiotic resistance pattern and clinical outcomes in acute cholecystitis: 567 consecutive worldwide patients in a prospective cohort study. Int J Surg. 2015;21:32–7.
45. Reuken PA, Torres D, Baier M, Löffler B, Lübbert C, Lippmann N, et al. Risk factors for multi-drug resistant pathogens and failure of empiric first-line therapy in acute cholangitis. PLoS One. 2017;12:1–12.
46. Kwon JS, Han J, Kim TW, Oh JH, Kwon HH, Jung JT, et al. Changes in causative pathogens of acute cholangitis and their antimicrobial susceptibility over a period of 6 years. Korean J. Gastroenterol. 2014;63:299–307.
47. Shenoy S, Shenoy S, Gopal S, Tantry B, Baliga S, Jain A. Clinicomicrobiological analysis of patients with cholangitis. Indian J Med Microbiol. 2014;32:157.
48. Goo JC, Seong MH, Shim YK, Lee HS, Han J-H, Shin KS, et al. Extended Spectrum-β-Lactamase or Carbapenemase Producing bacteria isolated from patients with acute cholangitis. Clin Endosc. 2012;45:155–60.
49. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated Intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133–64.
50. Ansaloni L, Pisano M, Coccolini F, Peitzmann AB, Fingerhut A, Catena F, et al. 2016 WSES guidelines on acute calculous cholecystitis. World J Emerg Surg. 2016;11:25.
51. Kelly AM. Clinical impact of blood cultures taken in the emergency department. J Accid Emerg Med. 1998;15:254–6.
52. Brunton LL, Chabner BA, Knollman BC, editors. Goodman and Gilman's the pharmacological basis of therapeutics, 12th edn. New York: The McGraw-Hill Companies; 2011.
53. Amsden G. Chapter 49, Tables of antimicrobial agent pharmacology. In: Mandell G, Bennett J, Dolin R, editors. Principles and practice of infectious diseases, Vol. 1, 7th edn. Philadelphia: Churchill Livingston, Elsevier; 2010. p. 705–61.
54. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011;66(Suppl 2):ii25–31.
55. Schultsz C, Geerlings S. Plasmid-Mediated Resistance in Enterobacteriaceae: changing Landscape and implications for therapy. Drugs. 2012;72:1–16.
56. Goldstein EJ, Solomkin JS, Citron DM, Alder JD. Clinical efficacy and correlation of clinical outcomes with *In Vitro* susceptibility for anaerobic bacteria in patients with complicated intra-abdominal infections treated with moxifloxacin. Clin Infect Dis. 2011;53:1074–80.
57. Solomkin J, Zhao YP, Ma EL, Chen MJ, Hampel B; DRAGON Study Team. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. Int J Antimicrob Agents. 2009;34:439–45.
58. Weiss G, Reimnitz P, Hampel B, Muehlhofer E. Lippert H; AIDA Study Group. Moxifloxacin for the treatment of patients with complicated intra-abdominal infections (the AIDA Study). J Chemother. 2009;21:170–80.
59. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. Ann Surg. 2006;244:204–11.
60. Muller E, Pitt HA, Thompson JE Jr, Doty J, Mann L, Manchester B. Antibiotics in infections of the biliary tract. Surg Gynecol Obstet. 1987;165:285–92.
61. Gerecht W, Henry N, Hoffman W, Muller S, LaRusso N, Rosenblatt J, et al. Prospective randomized comparison of mezlocillin therapy alone with combined ampicillin and gentamicin therapy for patients with cholangitis. Arch Intern Med. 1989;149:1279–84.
62. Thompson JE Jr, Pitt HA, Doty J, Coleman J, Irving C. Broad spectrum penicillin as an adequate therapy for acute cholangitis. Surg Gynecol Obstet. 1990;171:275–82.
63. Chacon J, Criscuolo P, Kobata C, Ferraro J, Saad S, Reis C. Prospective randomized comparison of pefloxacin and ampicillin plus gentamicin in the treatment of bacteriologically proven biliary tract infections. J Antimicrob Chemother. 1990;26(Suppl B):167–72.
64. Thompson JE Jr, Bennion R, Roettger R, Lally K, Hopkins J, Wilson SE. Cefepime for infections of the biliary tract. Surg Gynecol Obstet. 1993;177(Suppl):30–4.
65. Yellin AE, Berne TV, Appleman MD, Heseltine PN, Gill MA, Okamoto MP, et al. A randomized study of cefepime versus the combination of gentamicin and mezlocillin as an adjunct to surgical treatment in patients with acute cholecystitis. Surg Gynecol Obstet. 1993;177(Suppl):23–9.
66. Sung J, Lyon D, Suen R, Chung S, Co A, Cheng A, et al. Intravenous ciprofloxacin as treatment for patients with acute

suppurative cholangitis: a randomized, controlled clinical trial. J Antimicrob Chemother. 1995;35:855–64.
67. Won SY, Munoz-Price LS, Lolans K, Hota B, Weinstein RA, Hayden MK; Centers for Disease Control and Prevention Epicenter Program. Emergence and rapid regional spread of Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2011;53:532–40.
68. Di Carlo P, Pantuso G, Cusimano A, D'Arpa F, Giammanco A, Gulotta G, et al. Two cases of monomicrobial intraabdominal abscesses due to KPC–3 Klebsiella pneumoniae ST258 clone. BMC Gastroenterol. 2011;11:103.
69. Bogdanovich T, Adams-Haduch JM, Tian GB, Nguyen MH, Kwak EJ, Muto CA, et al. Colistin-resistant, Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae belonging to the international epidemic clone ST258. Clin Infect Dis. 2011;53:373–6.
70. Uno S, Hase R, Kobayashi M, Shiratori T, Nakaji S, Hirata N, et al. Short-course antimicrobial treatment for acute cholangitis with Gram-negative bacillary bacteremia. Int J Infect Dis. 2016;55:81–5.
71. van Lent AU, Bartelsman JF, Tytgat GN, Speelman P, Prins JM. Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract. Gastrointest Endosc. 2002;55:518–22.
72. Kogure H, Tsujino T, Yamamoto K, Mizuno S, Yashima Y, Yagioka H, et al. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. J Gastroenterol. 2011;46:1411–7.
73. Park TY, Choi JS, Song TJ, Do JH, Choi SH, Oh HC. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. Dig Dis Sci. 2014;59:2790–6.
74. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA. 2014;312:145–54.
75. Loozen CS, Kortram K, Kornmann VN, van Ramshorst B, Vlaminckx B, Knibbe CA, et al. Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis. Br J Surg. 2017;104:e151–7.
76. Mazeh H, Mizrahi I, Dior U, Simanovsky N, Shapiro M, Freund HR, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg. 2012;36:1750–9.
77. Rodríguez-Sanjuán JC, Casella G, Antolín F, Castillo F, Fernández-Santiago R, Riaño M, et al. How long is antibiotic therapy necessary after urgent cholecystectomy for acute cholecystitis? J Gastrointest Surg. 2013;17:1947–52.
78. Solomkin JS, Dellinger EP, Bohnen JM, Rostein OD. The role of oral antimicrobias for the management of intra-abdominal infections. New Horiz. 1998;6(Suppl 2):S46–52.
79. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. Ann Surg. 2011;253:1082–93.