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# Biliary Tract Infections
## A Guide to Drug Treatment

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## Contents



## Abstract

Initial therapy of acute cholecystitis and cholangitis is directed towards general support of the patient, including fluid and electrolyte replacement, correction of metabolic imbalances and antibacterial therapy.

Factors affecting the efficacy of antibacterial therapy include the activity of the agent against the common biliary tract pathogens and pharmacokinetic properties such as tissue distribution and the ratio of concentration in both bile and serum to the minimum inhibitory concentration for the expected micro-organism.

Antimicrobial therapy is usually empirical. Initial therapy should cover the Enterobacteriaceae, in particular *Escherichia coli*. Activity against enterococci is not required since their pathogenicity in biliary tract infections remains unclear. Coverage of anaerobes, in particular *Bacteroides* spp., is warranted in patients with previous bile duct–bowel anastomosis, in the elderly and in patients in serious clinical condition.

In patients with acute cholecystitis or cholangitis of moderate clinical severity, monotherapy with a ureidopenicillin – mezlocillin or piperacillin – is at least as effective as the combination of ampicillin plus aminoglycoside. In severely ill patients with septicaemia, an antibacterial combination is preferable. Therapy with aminoglycosides, mostly for *Pseudomonas aeruginosa*–related infections, should not exceed a few days because the risk of nephrotoxicity seems to be increased during cholestasis.

Relief of biliary obstruction is mandatory, even if there is clinical improvement with conservative therapy, because cholangitis is most likely to recur with continued obstruction. Emergency invasive therapy is reserved for patients who fail

to show a clinical response to antibacterial therapy within the first 36 to 48 hours or for those who deteriorate after an initial clinical improvement. Immediate surgery is indicated for gangrenous cholecystitis and perforation with peritonitis.

Long-term administration of antibacterials is required for recurrent cholangitis, as seen in bile duct–bowel anastomosis. Oral cotrimoxazole (trimethoprim/sulfamethoxazole) is the preferred agent.

Wound infection rates after biliary tract surgery can be significantly reduced by preoperative administration of prophylactic antibacterials. Newer generation β-lactams have not proven to be of greater benefit than older agents such as cefuroxime or cefazolin. Antibacterial prophylaxis before endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for patients with obstructive jaundice, since the risk of infectious complications seems to be strongly associated with this clinical condition. Failure to achieve full biliary drainage is the most important factor in predicting septicaemia, and prophylaxis should be prolonged until the bile duct is unobstructed. Piperacillin, cefazolin, cefuroxime, cefotaxime and ciprofloxacin are effective for this indication.

Biliary tract infections (BTIs) are common causes of intra-abdominal infections.[1] Normally, the biliary tract and its contents are free of bacteria unless inflammation, obstruction or foreign bodies are present.[2] Obstruction of biliary tract flow causes most cases of acute cholecystitis and cholangitis. As with other intra-abdominal infections, the appropriate management of BTIs involves a combination of antibacterial therapy and surgical (or endoscopic) intervention.

This article focuses on the factors governing the choice of antibacterials for the treatment of acute (i.e. clinically symptomatic) bacterial cholecystitis and cholangitis – the most frequently encountered clinical conditions – as well as for prophylaxis of the infectious complications following surgical or endoscopic interventions in the biliary tract. In accordance with the concept of evidence-based medicine,[3,4] attention is focused on the controlled clinical trials available in the literature in order to make substantiated recommendations where possible.

The establishment of a microbiological diagnosis in patients with acute biliary infection is limited by the difficulty of sampling bile for culture and by a low incidence of positive blood cultures. Thus, antimicrobial therapy is usually empirical. Selection of appropriate drugs depends on knowledge of the most common causative bacteria and of the reported therapeutic efficacy of antimicrobial agents in this kind of infection.

## 1. Pathogenesis and Microbiological Considerations

### 1.1 Acute Bacterial Cholecystitis and Cholangitis

Acute cholecystitis results in most cases from obstruction of the cystic duct by a gallstone that causes acute inflammation of the gallbladder. More than 90% of the cases of acute cholecystitis are associated with gallbladder stones.[5,6] The bile becomes infected as a secondary event. Thompson et al.[7] found positive bile or gallbladder wall cultures in 21 of 49 (43%) patients with pathologically proven acute cholecystitis.

Acute cholangitis is caused by infection in an obstructed biliary system, most commonly by gallstones in the common bile duct. It may also be the result of benign strictures resulting from prior surgery or endoscopy, congenital abnormalities, neoplasm of the pancreas or bile ducts, or sclerosing cholangitis.

Gallstones or benign strictures are associated with bile duct infection in about 50 to 75% and 80

to 100% of cases, respectively.[8-12] Infections are polymicrobial in 30 to 80% of the episodes.[13-15]

Gram-negative bacteria, mainly *Escherichia coli* and to a lesser extent *Klebsiella* spp., are the most common organisms causing acute cholecystitis or cholangitis (table I). Gram-positive organisms and anaerobes are also sometimes found. In some investigations of patients with biliary diseases, anaerobes have been detected in more than 15% of patients but rarely as the sole isolate. *Bacteroides* spp. and *Clostridium* spp. are the most frequently cultured anaerobes.[13-15] Anaerobic bacteria are commonly isolated from biliary tract specimens in patients who have a history of biliary surgery, especially those with a bile duct–bowel anastomosis, in patients with a chronic BTI and in the elderly. Anaerobes tend to be associated with more severe clinical illness than purely aerobic infections.[18-20]

Bacteraemia in acute cholangitis is clearly related to the increased bile duct pressure favouring the reflux of bacteria into the blood and lymph.[21,22] Bacteraemia has been reported in 21 to 71% of patients with cholangitis.[23-25] The organisms isolated reflect a similar distribution to that of biliary cultures, except for anaerobes and enterococci which are infrequently found in blood cultures. [16,18]

## 1.2 Infectious Complications Following Endoscopic Intervention or Surgery on the Biliary Tract

### *1.2.1 Endoscopic Retrograde Cholangiopancreatography (ERCP)*

ERCP has become a standard technique currently applied in the management of patients with biliary tract diseases. The therapeutic potential of this procedure is well established: the sphincter of Oddi may be cut to facilitate removal of gallstones from the bile duct, and in patients with inoperable malignant biliary obstruction an endobiliary prosthesis (stent) may be placed to relieve jaundice.[26,27]

Endoscopic intervention may promote dissemination of organisms already present in the bile or may introduce enteric flora or nosocomial pathogens, mostly *Pseudomonas aeruginosa*, into the biliary system upon cannulation of the ampulla of Vater.

Biliary sepsis – postprocedure cholangitis and septicaemia – is among the most serious complications of ERCP.[28-31] The reported incidence of this complication ranges from <1 to 19%, depending on the patient population studied,[28,29] and the mortality rate may be as high as 10%.

**Table I.** Species of bacteria isolated from bile and blood in patients with cholangitis (after Leung et al.[16] and Hanau & Steigbigel[17])

| Organism isolated | Leung et al.[16] | | Hanau & Steigbigel[17] | |
|---|---|---|---|---|
| | bile (%) [n = 1236] | blood (%) [n = 128] | bile (%) [n = 578] | blood (%) [n = 145] |
| *Acinobacter* spp. | 1 | 0 | | |
| *Bacteroides* spp. | 1 | 1 | 1.5 | 0.5 |
| *Candida* spp. | 4 | 0 | 0.5 | 0.5 |
| *Citrobacter* spp. | 3 | 2 | 3 | 0.5 |
| *Clostridium* spp. | 2 | 0 | 2.5 | 1.5 |
| *Enterobacter* spp. | 8 | 5 | 5 | 4 |
| *Enterococcus* spp. | 17 | 0 | 8 | 5 |
| *Escherichia coli* | 27 | 71 | 38.5 | 51.5 |
| *Klebsiella* spp. | 17 | 14 | 16.5 | 16 |
| *Proteus* spp. | 3 | 0 | 4.5 | 3 |
| *Pseudomonas* spp. | 7 | 4 | 5 | 6 |
| *Staphylococcus* spp. | 2 | 3 | 0.5 | 3.5 |
| *Streptococcus* spp. | 8 | 0 | 2.5 | 2 |
| Others | 0 | 0 | 9 | 5.5 |

**n** = total number of isolates.

#### 1.2.2 Wound Infection After Biliary Tract Surgery

Wound infection after biliary tract surgery is correlated with the presence of bacteria in bile at operation.[32-34] Clinical risk factors significantly associated with infection in bile and characterising high risk patients include:[35,36]

- age >60 years
- presence of common duct gallstones
- previous biliary exploration or surgery
- jaundice at the time of surgery
- morbid obesity
- diabetes mellitus.

In a recent meta-analysis encompassing 42 randomised clinical studies,[36] the mean wound infection rate in patients not treated with prophylactic antibacterials was 15% (range 3 to 47%). The lower rates are encountered in simple cholecystectomy, while the higher rates are observed after common bile duct exploration.

#### 1.2.3 Recurrent Cholangitis

Extrahepatic biliary atresia is characterised by a total obliteration of the bile ducts outside the liver. In up to 80% of patients, bile drainage can be reconstituted by hepatic portoenterostomy. However, recurrent ascending cholangitis will develop in more than 50% of patients after successful restoration of bile flow.[37-39] Recurrent attacks of cholangitis are also one of the major long term complications[40] seen after resection of malignancy at the hepatic confluence.

Cholangitis occurring after biliary-enteric bypass is always assumed to be a result of obstruction of the anastomosis. However, it can also occur despite a widely patent anastomosis, whether it be a sphincteroplasty, a choledochoduodenostomy or a choledochojejunostomy.[41] Construction of a biliary-enteric anastomosis almost always results in biliary contamination (bacterobilia). Accordingly, clinically overt cholangitis would supervene as the bacterial inoculum in the bile increases to above some threshold value. As expected, the organisms most frequently responsible for ascending cholangitis are bacteria that constitute the usual colonic flora.[37,42]

## 2. Pharmacological Considerations

The efficacy of antibacterials in the treatment of biliary infection depends on more than the extent to which they are excreted in bile. The important factor is the antimicrobial activity of individual compounds against the most commonly encountered organisms in BTIs. Antibacterial monotherapy with mezlocillin[43] has proven to be more clinically effective than the standard combination of ampicillin plus aminoglycoside for the treatment of acute cholecystitis or cholangitis. The ratio of mezlocillin concentration in bile to the minimum inhibitory concentration (MIC) against *E. coli* was 127 and 195 times higher than that produced by ampicillin or gentamicin, respectively. In serum, the concentration : MIC ratio was 4.5 and 11 times higher, respectively.[44] As indicated by the authors of this study, it appears preferable to choose antibacterials providing high concentration : MIC ratios in both bile and serum against the usual causative pathogens for treating acute biliary infections.

However, BTIs are nearly always associated with some degree of cholestasis induced by mechanical obstruction of the bile duct, with subsequent impairment of antibacterial biliary excretion.[45-48] In cases of complete obstruction of the common bile duct, in general no significant biliary excretion of antibacterial occurs, so that biliary bactericidal concentrations cannot be achieved.[47,48] This fact emphasises the need for prompt treatment of the biliary tract obstruction after initiation of antibacterial therapy.

In addition to the blood, the anatomical sites where it is important to achieve bactericidal drug concentrations include the gallbladder wall, the peritoneal cavity, the liver and the wound, since the presence of the antibacterial in these tissues prevents the risk of bacterial seeding during surgery. The extent of diffusion of the antibacterial into the tissue depends primarily on the area under the serum concentration–time curve of the drug.[49,50] This applies also to antibacterial prophylaxis in the setting of surgical intervention in the biliary tract. In this situation, achieving high antibacterial con-

centrations in bile has proven to be of little relevance.[51]

Conversely, in the particular condition of bile duct–bowel anastomosis where bacterial contamination of the bile is always present, the goal of maintenance antibacterial therapy is to keep the bacterial count in the bile below some threshold value and thereby to prevent the reoccurrence of acute cholangitis. The only way to achieve this is to administer oral antibacterials that provide high and sustained concentration : MIC ratios in the bile against the Enterobacteriaceae.

Pharmacological parameters relevant to therapy or prophylaxis of biliary tract infections are summarised in table II.

## 3. Choice of Antibacterials

### 3.1 Treatment of Acute Cholecystitis or Cholangitis

Despite the fact that BTIs are a common clinical problem associated with high morbidity and mortality, there is no standardised approach to the therapy of these infections. This is most probably because of the very limited number of prospective randomised clinical trials comparing the efficacy of antibacterials in the treatment of these infections. Selection of the antibacterial(s) is based on the severity of the disease process, the suspected biliary pathogens and the *in vitro* activity of potentially effective antibacterial agents against the usual infecting organisms. The type and local resistance pattern should also be taken into account. Blood cultures should be obtained before beginning antibacterial therapy.

A broad-spectrum therapeutic regimen active against both Gram-negative and Gram-positive organisms is the preferred treatment. Until very recently, acute cholangitis was most frequently treated with a combination of a penicillin (usually ampicillin) and an aminoglycoside[23,24,52] to achieve activity against facultative Gram-negative bacilli and enterococci. However, the pathogenicity of *Enterococcus* spp. in BTIs is still unclear, as this species is nearly always part of a mixed infection. The elimination of other micro-organisms in bile may result in elimination of enterococci as well. In a recent analysis of the factors responsible for treatment failures in acute cholangitis, isolation of *Enterococcus* spp. was not identified as a predictor of treatment failure.[53] The combination of ampicillin and gentamicin has the disadvantages of limited anaerobic coverage, frequent resistance of Gram-negative bacilli to ampicillin and the risk of aminoglycoside-related nephrotoxicity, which appears to be significantly increased in patients with cholestasis.[44,54]

The ureidopenicillins exhibit a broad spectrum of activity that includes many anaerobes, the Gram-positive streptococci (including enterococci) and Gram-negative bacilli (including *P. aeruginosa*).[55] In a comparative randomised clinical study,[44] mezlocillin alone proved to be more effective than the combination ampicillin plus gentamicin for the anti-

**Table II.** Pharmacological parameters relevant to antibiotic therapy or prophylaxis of biliary sepsis

| Parameter | Therapeutic class | | | | Clinical relevance of the parameters for | | |
|---|---|---|---|---|---|---|---|
| | aminoglycosides | quinolones | penicillins | cephalosporins | treatment of acute infections | prophylaxis | maintenance therapy |
| Oral bioavailability | No | ++ | +/++ | +/++ | No | Yes | Yes |
| Distribution in tissues | + | +++ | ++ | ++ | Yes | Yes | More or less |
| Ratio of concentration to MIC for *Escherichia coli* | | | | | | | |
| in blood | +++ | +++ | ++ | +++ | Yes | Yes | More or less |
| in bile | + | +++ | ++[a] | +/+++[b] | Yes | No | Yes |

a Ureidopenicillins.

b Anionic cephalosporins with molecular weight >500 such as cefpiramide, cefoperazone, ceftriaxone, cefotetan or cefixime.

**MIC** = minimum inhibitory concentration; + = moderate; ++ = substantial; +++ = great.

bacterial treatment of acute cholangitis. In 2 additional prospective randomised trials including patients with, respectively, acute cholecystitis[56] and acute cholangitis,[57] equal clinical efficacy was observed with piperacillin alone compared with ampicillin plus tobramycin.

It still seems justifiable to combine an aminoglycoside with the ureidopenicillin when there is substantial risk that *P. aeruginosa* or *Enterobacter* spp. are involved as, for example, in patients who have undergone nonsurgical procedures on the biliary tract or who have recently received a broad spectrum antibacterial.[58,59] The combination of piperacillin plus tazobactam (substantially eliminated in bile[60]) might be another alternative when the local resistance pattern shows a relatively high incidence of ureidopenicillin-resistant *E. coli* or *Klebsiella* spp., as reported recently.[61]

Cephalosporin antibacterials have not been properly assessed in the management of BTIs. The only randomised clinical study available[62] shows that cefoperazone is more effective than the combination of ampicillin plus tobramycin for severe BTIs. One limitation in the use of cephalosporins is their poor activity against anaerobes.

Clinical experience with the quinolones in the treatment of BTIs is still limited.[63] Uncontrolled studies have shown that intravenous ciprofloxacin alone was successful in the treatment of BTIs, including cholecystitis and cholangitis,[64,65] with cure rates of >80%. The only randomised controlled clinical trial reported to date assessed intravenous ciprofloxacin 200mg twice daily versus a triple therapy comprising ceftazidime[66] 1g twice daily, intravenous ampicillin 500mg 4 times daily and intravenous metronidazole 500mg 3 times daily in 100 consecutive patients with acute suppurative cholangitis.[67] In this study, ciprofloxacin proved to be as effective as the triple therapy. Such a result seems to emphasise the fact that empirical therapy which provides coverage against all potential biliary pathogens is not essential. Quinolones should probably be used in combination with other antimicrobials in cases of severe or advanced sepsis, especially if *P. aeruginosa* is involved, since high bacterial inocula increase the risk of resistance developing.[68,69]

With respect to the possible involvement of anaerobes, it is warranted to ensure anaerobic coverage (with metronidazole, for example), including *Bacteroides fragilis*, in the initial management of those BTIs where a mixture of aerobic and anaerobic organisms is likely to be involved – namely in the elderly, in patients with previous bile duct–bowel anastomoses or in seriously ill patients. This is true for both β-lactam–based or quinolone-based antibacterial therapy.

Antibacterial therapy is usually continued for 7 to 10 days.[70]

It must again be emphasised that the cornerstone of treatment still relies on the prompt decompression and drainage of the biliary tract in patients with severe acute cholangitis. Endoscopic sphincterotomy is now an established technique for the removal of stones in the common bile duct. The aim of endoscopic treatment is rapid decompression of the biliary tract, especially in severely ill patients. In high risk patients in whom endoscopic extraction of a large stone has failed, an indwelling biliary stent can be inserted.[71] Alternatively, an elective biliary operation can be planned and emergency surgery avoided. In those patients with acute cholangitis who fail to improve within 48 hours under conservative treatment and appropriate antibacterial therapy, prompt endoscopic drainage with insertion of a nasobiliary catheter or an indwelling stent has been shown to reduce the overall mortality, especially in elderly patients.[72,73] In the particular condition where cholangitis complicates late stent blockage due to biliary sludge, replacement of the blocked stent is required after initiation of antibacterial therapy.[74]

### 3.2 Maintenance Antibacterial Therapy in Recurrent Cholangitis

A few case reports mention the use of maintenance antibacterial therapy for the prevention of recurrent cholangitis[41,75-77] in patients who had undergone a portoenterostomy for biliary atresia.

Maintenance therapy is defined as a prolonged course (usually >3 months) of antibacterial therapy administered with the aim of reducing the incidence of recurrent episodes of cholangitis.[40] Therefore, oral preparations of antibacterial agents should be available for long-term administration. Usually an attempt to stop the maintenance therapy is made after 3 months. Those patients who experience an immediate relapse of cholangitis should continue on maintenance therapy.

Present practice for the prolonged use of oral antibacterials as prophylaxis against recurrent ascending cholangitis indicates that cotrimoxazole (trimethoprim/sulfamethoxazole) is most commonly used.[40,41,75] Cotrimoxazole has a spectrum covering the common aerobic biliary pathogens. In anicteric patients, trimethoprim concentrations in bile are 2 to 3 times those in serum, whereas the bile : serum ratio for sulfamethoxazole is 0.1 to 1.0.[78] This antibacterial combination has previously been shown to be effective and have an acceptable tolerability profile in maintenance therapy for the prevention of recurrent urinary tract infections.[79]

A retrospective analysis of 14 patients who had undergone resection of a malignancy at the hepatic confluence and experienced recurrent episodes of cholangitis evaluated maintenance antibacterial therapy with oral cotrimoxazole (trimethoprim 800mg/sulfamethoxazole 160mg in twelve patients) or oral ciprofloxacin 500mg in 2 patients.[40] Treatment was started with a therapeutic dosage (twice daily) for 5 to 7 days and was continued as maintenance therapy with a single daily dose. Two patients were switched from cotrimoxazole to ciprofloxacin because of a lack of response to the initial antibacterial. 11 of 14 patients (80%) responded with either a major reduction in frequency or a complete disappearance of episodes of cholangitis. No adverse effects were observed. The median duration of maintenance therapy was 3 to 4 months.

In addition, a few case reports have pointed out the potential role of oral ciprofloxacin in the prevention of recurrent cholangitis.[76,77] However, clinical experience with this agent in such situations is rather too limited to advocate its use as first-line maintenance antibacterial therapy.

A persistent question in this field is the risk of the emergence of superinfections or recurrent cholangitis caused by resistant Enterobacteriaceae, *Pseudomonas* spp. or *Candida* spp. Indeed, there is a risk of colonisation of the gut with yeasts – as documented with β-lactam antibacterials[80] – or with Enterobacteriaceae resistant to the antibacterial therapy being administered – as shown with long term administration of quinolones in cancer patients.[81]

However, in view of the seriousness of the clinical condition represented by recurrent cholangitis in the compromised biliary tract, maintenance antibacterial therapy remains without valid alternative for the prevention of biliary sepsis. The choice of an antibacterial for maintenance therapy should be based on:

- its spectrum of activity
- pharmacokinetic considerations such as absolute bioavailability following oral administration and the ratio of biliary concentration to its MIC against enteric organisms
- its tolerability profile for long term use.

Cotrimoxazole seems to be an adequate choice, while ciprofloxacin might be an interesting alternative.

## 3.3 Prophylaxis

### *3.3.1 Antibacterial Prophylaxis Before Biliary Tract Surgery*

The results of many controlled clinical trials substantiate the value of antibacterial prophylaxis in biliary tract surgery. A definitive answer seems to have been given by Meijer et al.[36] in a meta-analysis of 42 randomised controlled trials (n = 4125) of antibacterial prophylaxis in biliary tract surgery; groups of patients treated with antibacterials were compared with untreated groups. Wound infection rates in the control groups ranged from 3 to 47%, and averaged 15%. The authors found a 9% difference in wound infection rates in favour of antibacterial treatment i.e. the expected infec-

tion rate with antibacterial prophylaxis is approximately 6%.

As well as demonstrating the effectiveness of antibacterial prophylaxis in biliary tract surgery, this meta-analysis provides 2 additional interesting points of information. First, no greater benefit could be detected for the newer generation cephalosporins over the compounds of the first generation. Secondly, a multiple-dose regimen provided no greater efficacy than a single-dose regimen given preoperatively. Hence, the choice of antimicrobial agent for prophylaxis can largely be made on the basis of cost, as suggested by the authors of the meta-analysis.

However, it should be noted that this meta-analysis does not include the fluoroquinolones, because these agents have only recently been evaluated for antibacterial prophylaxis in biliary tract surgery. A few comparative clinical trials have studied the potential of the quinolones in surgical prophylaxis of BTIs, in which these agents proved to be as effective as the commonly used β-lactam antibacterials such as cefuroxime,[82] piperacillin[60] and ceftriaxone.[83-86] However, given the relative paucity of data regarding the effectiveness of quinolones in this field, the use of earlier generation cephalosporins such as cefazolin or cefuroxime is still warranted.

#### 3.3.2 Antibacterial Prophylaxis Before ERCP

The role of antibacterial prophylaxis in the prevention of infection after ERCP remains controversial. This stems from the results of a number of prospective trials in unselected patients undergoing ERCP which have failed to demonstrate the usefulness of antibacterial prophylaxis. The drugs used in these studies were minocycline, cefotaxime, cefonicid and piperacillin.[87-90]

However, reviews of complications after ERCP have identified a number of factors associated with a higher risk of septicaemia and cholangitis. These include:[28,29,91-93]

- failure to achieve complete biliary tract drainage
- history of cholangitis
- cholestasis
- malignancy of the stricture
- elevated white blood cell count
- previous diagnostic ERCP.

In the randomised study by Niederau et al.,[94] prophylactic treatment with cefotaxime reduced the rate of both bacteraemia and cholangitis related to ERCP. The higher incidence of septic complications in the control group (i.e. those who did not receive cefotaxime) was ascribed to the fact that only patients who had an interventional ERCP – and therefore an underlying obstructive bile duct disease – were included.

The results of the study by Byl et al.[95] further support the use of antibacterial prophylaxis in selected groups of patients before ERCP. A total of 82 patients were enrolled, with various causes of biliary tract obstruction of which cancer accounted for more than 50%. All patients presented with cholestasis. Piperacillin 4g or placebo 3 times daily were administered, starting just before ERCP and continuing until biliary passage was completely unobstructed. Clinical success was recorded in 94 versus 71% ($p = 0.01$) in the piperacillin versus placebo groups, respectively. All bacteriological failures occurred in the placebo group. Antibacterial prophylaxis and completeness of biliary drainage proved to be the factors affecting the probability of infections following ERCP.

Therefore, and according to Motte et al.,[93] the following recommendations may be made for antibacterial prophylaxis before ERCP:

(a) Prophylaxis should be performed in all patients with suspected obstructive jaundice.

(b) Coverage of *P. aeruginosa* is warranted if a previous ERCP has been performed.

(c) If complete drainage is achieved, a single dose administered before the procedure should be sufficient. However, where there is still partial obstruction the antibacterial should be continued until complete biliary drainage is obtained.

It is more difficult to make recommendations regarding the choice of antibacterial for prophylaxis before ERCP. Unfortunately, very few direct comparisons have so far been performed between antimicrobial agents in this field. Two comparative

clinical trials have shown that oral ciprofloxacin 750mg was as effective as intravenous cefazolin 1g[96] or cefuroxime 1.5g.[97] In terms of cost, chemoprophylaxis with oral ciprofloxacin was more economical.

*In summary,* piperacillin, cefazolin, cefuroxime, cefotaxime and ciprofloxacin have been shown to be effective in the prophylaxis of BTIs after ERCP, and consequently, pending further data, should be considered the antibacterials of choice for this indication.

## 4. Conclusion

On the basis of data from randomised clinical trials, the ureidopenicillins mezlocillin and piperacillin (or tazocillin) may be recommended as first-choice antibacterials for the treatment of acute BTIs. Further data are needed to substantiate the usefulness of cephalosporins or quinolones in this field. Antibacterial combination therapy is justified for severely ill patients. De-obstruction of the biliary tract still remains the cornerstone of treatment.

Maintenance antibacterial therapy to prevent recurrent cholangitis has been poorly addressed by clinical trials to date. Cotrimoxazole or ciprofloxacin appear to be adequate for this purpose.

As for prophylaxis, earlier generation cephalosporins remain the standard choice in the field of biliary tract surgery, while a number of antibacterials have proven to be effective as prophylaxis against BTIs after ERCP. In the latter indication, prophylaxis should be restricted to patients considered to be at higher risk for septic complications, and should be continued until complete biliary drainage is achieved.

## References


1. Lea AS, Feliciano DV, Gentry LO. Intra-abdominal infections – an update. J Antimicrob Chemother 1982; 9 Suppl. A: 107-13
2. Csendes A, Fernandez M, Uribe P. Bacteriology of the gallbladder bile in normal subjects. Am J Surg 1975; 129: 629-31
3. Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992; 268: 2420-5
4. Davidoff F, Haynes B, Sackett D, et al. Evidence-based medicine. BMJ 1995; 310: 1085-6
5. Herman RE. The spectrum of biliary stone disease. Am J Surg 1989; 158: 171-3
6. Sievert W, Vakil NB. Emergencies of the biliary tree. Gastroenterol Clin North Am 1988; 17: 245-64
7. Thompson JE, Bennion RS, Doty JE, et al. Predictive factors for bactibilia in acute cholecystitis. Arch Surg 1990; 125: 261-4
8. Kosowski K, Karczewska E, Kasprowicz A, et al. Bacteria in bile of patients with bile duct inflammation. Eur J Clin Microbiol 1987; 6: 575-8
9. Jackaman FR, Hilson GR, Marlow LS. Bile bacteria in patients with benign bile duct stricture. Br J Surg 1980; 67: 329-32
10. Maddocks AC, Hilson GR, Taylor R. The bacteriology of the obstructed biliary tree. Ann R Coll Surg Engl 1973; 52: 316-9
11. Lygidakis NJ. Incidence of bile infection in patients with choledocholithiasis. Am J Gastroenterol 1982; 77: 12-7
12. Maluenda F, Csendes A, Burdiles P, et al. Bacteriological study of choledochal bile in patients with common bile duct stones, with or without acute suppurative cholangitis. Hepatogastroenterol 1989; 36: 132-5
13. Brook I. Aerobic and anaerobic microbiology of biliary tract disease. J Clin Microbiol 1989; 27: 2373-5
14. Lykkegaard-Nielsen M, Justesen T. Anaerobic and aerobic bacteriological studies in biliary tract disease. Scand J Gastroenterol 1976; 11: 437-46
15. England DM, Rosenblatt JE. Anaerobes in human biliary tracts. J Clin Microbiol 1977; 6: 494-8
16. Leung JW, Ling TK, Chan RC, et al. Antibiotics, biliary sepsis and bile duct stones. Gastrointest Endosc 1994; 40: 716-21
17. Hanau LH, Steigbigel NH. Cholangitis: pathogenesis, diagnosis, and treatment. Curr Clin Top Infect Dis 1995; 15: 153-78
18. Bourgault AM, England DM, Rosenblatt JE, et al. Clinical characteristics of anaerobic bactibilia. Arch Intern Med 1979; 139: 1346-9
19. Shimada K, Noro T, Inamatsu T, et al. Bacteriology of acute obstructive suppurative cholangitis of the aged. J Clin Microbiol 1981; 14: 522-6
20. Csendes A, Mitru N, Maluenda F, et al. Counts of bacteria and pyocites of choledocal bile in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology 1996; 43: 800-6
21. Raper SE, Barker ME, Jones AL, et al. Anatomic correlates of bacterial cholangiovenous reflux. Surgery 1989; 105: 352-9
22. Csendes A, Hurdiles P, Diaz JC, et al. Bacteriological studies of liver parenchyma in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology 1995; 42: 821-6
23. Boey JH, Way LW. Acute cholangitis. Ann Surg 1980; 191: 264-70
24. Thompson JE, Tomkins RK, Longmire WP. Factors in management of acute cholangitis. Ann Surg 1982; 195: 137-45
25. Lau WY, Chu KW, Yuen WK, et al. Operative choledochoscopy in patients with acute cholangitis: a prospective randomised study. Br J Surg 1991; 78: 1226-9
26. Classen M, Safrany L. Endoscopic papillotomy and removal of gallstones. BMJ 1975; 4: 371-4
27. Shepherd HA, Royle G, Ross AP, et al. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomised trial. Br J Surg 1988; 75: 1166-8
28. Bilbao MK, Dotter CT, Lee TG, et al. Complications of endoscopic retrograde cholangiopancreatography (ERCP): a study of 10 000 cases. Gastroenterology 1976; 70: 314-20

29. Deviere J, Motte S, Dumonceau JM, et al. Septicemia after endoscopic retrograde cholangiopancreatography. Endoscopy 1990; 22: 72-5
30. Dutta SK, Cox M, Williams RB, et al. Prospective evaluation of the risk of bacteremia and the role of antibiotics in ERCP. J Clin Gastroenterol 1989; 5: 325-9
31. Cotton PB. Progress report – ERCP. Gut 1977; 18: 316-41
32. Keighley MR, Lister DM, Jacobs SI, et al. Hazards of surgical treatment due to microorganisms in the bile. Surgery 1974; 75: 578-83
33. Strachan CJ, Black J, Powis SJ, et al. Prophylactic use of cephazolin against wound sepsis after cholecystectomy. BMJ 1977; 1: 1254-6
34. Lykkegaard-Nielsen M, Moesgaard F, Justesen T, et al. Wound sepsis after elective cholecystectomy. Scand J Gastroenterol 1981; 16: 937-40
35. Keighley MR, Flinn R, Alexander-Williams J. Multivariate analysis of clinical and operative finding associated with biliary sepsis. Br J Surg 1976; 63: 528-31
36. Meijer WS, Schmitz PI, Jeekel J. Meta-analysis of randomized controlled clinical trials of antibiotic prophylaxis in biliary tract surgery. Br J Surg 1990; 77: 283-90
37. Kobayashi A, Utsunomiya T, Ohbe Y, et al. Ascending cholangitis after successful surgical repair of biliary atresia. Arch Dis Child 1973; 48: 697-701
38. Ohi R, Hanamatsu M, Mochizuki J, et al. Progress in the treatment of biliary atresia. World J Surg 1985; 9: 285-93
39. Rothenberg SS, Schroter GP, Karrer FM, et al. Cholangitis after the Kasai operation for biliary atresia. J Pediatr Surg 1989; 24: 729-32
40. Van den Hazel SJ, Speelman P, Tytgat GN, et al. Successful treatment of recurrent cholangitis with antibiotic maintenance therapy. Eur J Clin Microbiol Infect Dis 1994; 13: 662-5
41. Goldman LD, Steer ML, Silen W. Recurrent cholangitis after biliary surgery. Am J Surg 1983; 145: 450-4
42. Leblanc A, Lambert-Zechowsky N, Binge E, et al. Bacteriological analysis of jejunostomy fluid after surgery for extrahepatic biliary atresia. J Pediatr Gastroenterol Nutr 1983; 2: 307-10
43. Brogard JM, Kopferschmitt J, Arnaud JP, et al. Biliary elimination of mezlocillin: an experimental and clinical study. Antimicrob Agents Chemother 1980; 18: 69-76
44. Gerecht WB, Henry NK, Hoffman WW, 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
45. Van Delden OM, Jan Leeuwn DJ, Jansen PL, et al. Biliary excretion of ceftriaxone into non stagnant and stagnant bile. J Antimicrob Chemother 1994; 33: 193-4
46. Stewart JS, Roy A, Shrivastava RK, et al. Norfloxacin levels in human bile, serum, and tissues. Rev Infect Dis 1988; 10 Suppl. 1: S125-6
47. Leung JW, Chan RC, Cheung SW, et al. The effect of obstruction on the biliary excretion of cefoperazone and ceftazidime. J Antimicrob Chemother 1990; 25: 399-406
48. Van den Hazel SJ, De Vries XH, Speelman P, et al. Biliary excretion of ciprofloxacin and piperacillin in the obstructed biliary tract. Antimicrob Agents Chemother 1996; 40: 2658-60
49. Thomas M. Antibiotics in bile. J Antimicrob Chemother 1983; 12: 419-22
50. Bergan T. Pharmacokinetic parameters and characteristics relevant to antimicrobial surgical prophylaxis. Scand J Infect Dis Suppl 1990; 70: 31-5
51. Keighley MR, Drysdale RB, Quoraishi AH, et al. Antibiotics in biliary disease: the relative importance of antibiotic concentrations in the bile and serum. Gut 1976; 17: 495-500
52. Munro R, Sorrell TC. Biliary sepsis: reviewing treatment options. Pract Ther 1986; 31: 449-54
53. Thompson J, Bennion RS, Pitt HA. An analysis of infectious failures in acute cholangitis. HPB Surg 1994; 8: 139-45
54. Desai TK, Tsan TK. Aminoglycoside nephrotoxicity in obstructive jaundice. Am J Med 1988; 85: 47-50
55. Eliopoulos GM, Moellering RC. Azlocillin, mezlocillin, and piperacillin: new broad spectrum penicillins. Ann Intern Med 1982; 97: 755-60
56. Muller LE, Pitt HA, Thompson JE, et al. Antibiotics in infections of the biliary tract. Surg Gynecol Obstet 1987; 165: 285-92
57. Thompson JE, Pitt HA, Doty JE, et al. Broad spectrum penicillin as an adequate therapy for acute cholangitis. Surg Gynecol Obstet 1990; 171: 275-82
58. Demediuk B, Speer AG, Hellyar A. Induced antibiotic resistant bacteria in cholangitis with biliary sepsis. Aust NZ J Surg 1996; 66: 778-80
59. Wiedeman B. Selection of betalactamase producers during cephalosporin or penicillin therapy. Scand J Infect Dis 1986; 49 Suppl.: 100
60. Westphal JF, Brogard JM, Caro-Sampara F, et al. Assessment of the biliary excretion of piperacillin-tazobactam in humans. Antimicrob Agents Chemother 1997; 41: 1636-40
61. Chamberland S, Lécuyer J, Lessard C, et al. Antibiotic susceptibility profiles of 941 gram-negative bacteria isolated from septicemic patients throughout Canada. Clin Infect Dis 1992; 15: 615-28
62. Bergeron MG, Mendelson J, Harding GK, et al. Cefoperazone compared with ampicillin plus tobramycin for severe biliary tract infections. Antimicrob Agents Chemother 1988; 32: 1231-6
63. Westphal JF, Blicklé JF, Brogard JM. Management of biliary tract infections: potential role of the quinolones. J Antimicrob Chemother 1991; 28: 486-90
64. Chrysanthopoulos CJ, Skoutelis AT, Starakis JC, et al. Use of ciprofloxacin in biliary sepsis. Infection 1988; 16: 249
65. Karachalios GN, Zografos G, Patrikakos V, et al. Biliary tract infections treated with ciprofloxacin. Infection 1993; 21: 262-4
66. Brogard JM, Jehl F, Paris-Bockel D, et al. Biliary elimination of ceftazidime. J Antimicrob Agents Chemother 1987; 19: 671-8
67. Sung JJ, Lyon DJ, Suen R, et al. Intravenous ciprofloxacin as treatment for patients with acute suppurative cholangitis: a randomized, controlled clinical trial. J Antimicrob Chemother 1995; 35: 855-64
68. Neu HC. Bacterial resistance to fluoroquinolones. Rev Infect Dis 1988; 10 Suppl. 1: S57-63
69. Neu HC. Synergy of fluoroquinolones with other antimicrobial agents. Rev Infect Dis 1989; 11 Suppl. 5: S1025-35
70. Dooley JS, Hamilton-Miller JM, Brumfitt W, et al. Antibiotics in the treatment of biliary infection. Gut 1984; 25: 988-98
71. Leung JW, Cotton PB. Endoscopic nasobiliary catheter drainage in biliary and pancreatic disease. Am J Gastroenterol 1991; 86: 389-94
72. Leung JW, Chung SC, Sung JY, et al. Urgent endoscopic drainage of acute suppurative cholangitis. Lancet 1989; I: 307-9
73. Leese T, Neoptolemos JP, Baker AR, et al. Management of acute cholangitis and the impact of endoscopic sphincterotomy. Br J Surg 1986; 73: 988-92

74. Leung JW, Venezuela RR. Cholangiosepsis: endoscopic drainage and antibiotic therapy. Endoscopy 1991; 23: 220-3
75. Chaudhary S, Turner RB. Trimethoprim-sulfamethoxazole for cholangitis following portoenterostomy for biliary atresia. J Pediatr 1981; 99: 656-8
76. Lonka L, Pedersen RS. Ciprofloxacin for cholangitis [letter]. Lancet 1987: II: 212
77. Houwen RH, Bijleveld CM, de Vries-Hospers HG. Ciprofloxacin for cholangitis after hepatic portoenterostomy [letter]. Lancet 1987; I: 1367
78. Rieder J. Excretion of sulfamethoxazole and trimethoprim into human bile. J Infect Dig 1973; 128 Suppl.: S574
79. Harding GK, Buckwold FJ, Marrie TJ, et al. Prophylaxis of recurrent urinary tract infection in female patients: efficacy of low-dose, thrice weekly therapy with trimethoprim-sulfamethoxazole. JAMA 1979; 242: 1975-7
80. Samonis G, Gikas A, Tolandis P, et al. Prospective study of the impact of broad-spectrum antibiotics on the yeast flora of the human gut. Eur J Clin Microbiol Infect Dis 1994; 13: 665-7
81. Carratala J, Fernandez-Sevilla A, Tubau F, et al. Emergence of fluoroquinolone-resistant *E. coli* in fecal flora of cancer patients receiving norfloxacin prophylaxis. Antimicrob Agents Chemother 1996; 40: 503-5
82. Brogard JM, Pinget M, Arnaud JP, et al. Biliary excretion of cefuroxime: experimental and human study. Chemotherapy 1981; 27: 18-28
83. Brogard JM, Jehl F, Paris-Bockel D, et al. La ceftriaxone, céphalosporine à forte élimination hépatique. Schweiz Med Wochenschr 1987; 117: 1549-59
84. De Lalla F, Peruzzo L, Ferraris P, et al. Chemoprophylaxis in elective biliary tract surgery: oral norfloxacin *vs* intravenous piperacillin. Rev Infect Dis 1988; 10 Suppl. 1: S126-7
85. Kujath P. Brief report: antibiotic prophylaxis in biliary tract surgery. Am J Med 1989; 87 Suppl. 5A: 255S-7S
86. McArdle CS, Morran CT, Pettit L, et al. The value of oral antibiotic prophylaxis in biliary tract surgery. J Hosp Infect 1991; 19 Suppl. C: 59-64
87. Brandes JW, Scheffer B, Lorenz-Meyer H, et al. ERCP: complications and prophylaxis. A controlled study. Endoscopy 1981; 13: 27-30
88. Sauter G, Grabein B, Huber G, et al. Antibiotic prophylaxis of infectious complications with endoscopic retrograde cholangiopancreatography: a randomized controlled study. Endoscopy 1990; 22: 164-7
89. Finkelstein R, Yassin K, Suissa A, et al. Failure of cefonicid prophylaxis for infectious complications related to endoscopic retrograde cholangiopancreatography. Clin Infect Dis 1996; 23: 378-9
90. Van den Hazel SJ, Speelman P, Dankert J, et al. Piperacillin to prevent cholangitis after endoscopic retrograde cholangiopancreatography: a randomized controlled trial. Ann Intern Med 1996; 125: 442-7
91. Lai EC, Lo CM, Choi TK, et al. Urgent biliary decompression after endoscopic retrograde cholangiopancreatography. Am J Surg 1989; 157: 121-5
92. Khardori N, Wong E, Carrasco CH, et al. Infections associated with biliary drainage procedures in patients with cancer. Rev Infect Dis 1991; 13: 587-91
93. Motte S, Deviere J, Dumonceau JM, et al. Risk factors for septicemia following endoscopic biliary stenting. Gastroenterology 1991; 101: 1374-81
94. Niederau C, Pohlman U, Lubke H, et al. Prophylactic antibiotic treatment in therapeutic or complicated diagnostic ERCP: results of a randomized controlled clinical study. Gastrointest Endosc 1994; 40: 533-7
95. Byl B, Deviere J, Struelens MJ, et al. Antibiotic prophylaxis for infectious complications after therapeutic endoscopic retrograde cholangiopancreatography: a randomized, double-blind, placebo-controlled study. Clin Infect Dis 1995; 20: 1236-40
96. Alveyn CG, Robertson DA, Whright R, et al. Prevention of sepsis following endoscopic retrograde cholangiopancreatography. J Hosp Infect 1991; 19 Suppl. C: 65-70
97. Mehal WZ, Culshaw KD, Tillotson GS, et al. Antibiotic prophylaxis for ERCP: a randomized clinical trial comparing ciprofloxacin and cefuroxime in 200 patients at risk of cholangitis. Eur J Gastroenterol Hepatol 1995; 7: 841-5

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