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## Use of Antibiotics in Therapeutic Endoscopy

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### Abstract

The gastrointestinal (GI) tract harbors about 10–100 trillion bacteria, which surpass the number of cells in a human being. The intestinal microflora is a complex ecosystem containing over 500 bacterial species. Most pathogenic bacteria are kept under control by the host immune system, the gut microenvironment and the help of non-pathogenic commensal microorganisms. In addition, entrance of pathogenic bacteria into the lymphatic and blood system is impeded by several types of mucosal and immunological barriers. Occasionally, the endoscopist partially or entirely destroys these barriers to perform a therapeutic intervention (e.g. skin incision for PEG tube placement, endoscopic resection of polyps or tumors, perforation). Under these circumstances, bacteria can cause infections such as cellulitis, abscess and peritonitis. Thus, antibiotics are helpful to decrease the risk of infection in such circumstances. However, the use of prophylaxis for bacterial endocarditis has been a matter of debate. Currently, the routine use of prophylactic antibiotics during GI procedures is no longer recommended by the American Heart Association. On other occasions the endoscopist needs to treat specific GI infections such as cholangitis and diverticulitis. The objective here is to provide the therapeutic endoscopist with a summary of conditions commonly encountered in therapeutic endoscopy which will require prophylactic or specific antibiotic use, describe the rationale and principles of antibiotic choice and provide a useful guide on appropriate antibiotic utilization.

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### Prophylactic Use of Antibiotics in Therapeutic Endoscopy

Currently there are very few situations in which prophylactic antibiotic use is indicated (table 1) [1–3]. As a rule antibiotic prophylaxis, or prompt antibiotic use, is indicated when the risk of infection as a result of an endoscopic intervention is very high.

#### *Prevention of Bacterial Endocarditis*

The use of antibiotics for the prevention of bacterial endocarditis has been a matter of debate for the last decades [4–6]. This resulted in complex and inconclusive guidelines over the years [2, 7]. However, recently the guidelines for endocarditis prophylaxis of the American Heart Association were updated and also endorsed by the Infectious Disease Society of America, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons [1, 3]. These guidelines take a significant departure from

**Table 1.** Conditions for which antibiotic prophylaxis is indicated

Condition	Microorganism	Choice of antibiotic	Alternative antibiotic
Bacterial endocarditis	Enterococci	Penicillin, ampicillin, amoxicillin	Piperacillin, vancomycin
Bacterial endocarditis <i>Enterococcus faecalis</i>	Resistant to vancomycin and streptomycin/GM (>500 µg/ml)	Penicillin G or Ampicillin (systemic infection)	Ampicillin and ceftriaxone (adequate for SBE, even if high level AG resistance), Linezolid (effective in 70%)
<i>Enterococcus faecium</i>	Resistant to vancomycin and streptomycin/gentamycin (>500 µg/ml)	Penicillin G, ampicillin (systemic infection)	Penicillin/ampicillin resistance >8 <64 MIC: high dose ampicillin (300 mg/kg/day) Penicillin G or ampicillin + FQ or cloramfenicol or rifampycin or doxycyclin Synercid (70%) <sup>1</sup> Linezolid <sup>2</sup> (58%) <sup>1</sup>
PEG	Staphylococci	Cefazolin, ceftazidime, cefotetan, cefuroxime or ceftizoxime	
Necrotizing pancreatitis	Enterobacteriaceae, streptococci, anaerobic bacteria	Imipenem, carbapenems	Treat based on culture results
Bleeding gastric or esophageal varices	Oral bacteria <sup>3</sup> (peptostreptococci, anaerobic streptococci, enterobacteria)	Ceftriaxone fluoroquinolones	
ERCP in the setting of obstructed biliary tree	Enterobacteriaceae (68%) (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> ) Enterococci, 14% Bacteroides spp, 10% Clostridium spp 7%	Ciprofloxacin, piperacillin-tazobactam, ceftizoxime	
Drainage of PFC	Same as above, also peptostreptococci	Ciprofloxacin, piperacillin-tazobactam	
EUS-guided FNA	Same as PFC and ERCP	Fluoroquinolones	Ceftriaxone

GM = Gentamycin; MIC = minimum inhibitory concentration; SBE = spontaneous bacterial endocarditis; ERCP = endoscopic retrograde cholangiopancreatography; PFC = pancreatic fluid collection. Data adapted from Gilbert et al. [3].

<sup>1</sup> Resistance can develop in monotherapy regimens.

<sup>2</sup> Useful for β-lactamase-positive vancomycin-resistant enterococci, faecalis strains.

<sup>3</sup> The oral bacteria of patients with cirrhosis, alcoholics, immunosuppressed and elderly patients may contain more gram negative bacteria.

previous ones as the indications for antibiotics have been significantly cut down, being recommended only for cardiac conditions with the greatest risks of complications and for dental procedures that involve perforation of oral mucosa, manipulation of gingival tissue or periapical region of the teeth [1, 3].

In patients undergoing endoscopic procedures, prophylaxis is no longer recommended, even in patients deemed at high risk, e.g. those with previous spontaneous bacterial peritonitis, prosthetic valve, valvulopathy following heart transplant, and congenital heart disease with one of the following: completely repaired cardiac defect using prosthetic material, partially corrected but with residual defect near prosthetic material, uncorrected cyanotic congenital heart disease, surgically constructed shunts and conduits [1, 3]. However, in patients who have an active infection with enterococci, it is important to treat before an elective procedure or, if the procedure is emergent, use an accepted enterococcal regimen [1, 3]. Also if a patient undergoes procedures involving infected skin or soft tissues, include coverage against staphylococci and  $\beta$ -hemolytic streptococci in the treatment regimen [1, 3].

#### *Percutaneous Endoscopic Gastrostomy or Percutaneous Endoscopic Jejunostomy Placement*

The rate of infection after percutaneous endoscopic gastrostomy or percutaneous endoscopic jejunostomy placement is significantly decreased with the use of prophylactic antibiotics [8, 9]. The recommended agents are those with activity against skin flora (staphylococci): first-generation cephalosporins (table 1). Most experts use only one dose of antibiotic 6 h before the procedure. However, others prefer to use 'prophylactic' antibiotics for 3 days [3, 6, 8].

#### *Endoscopic Manipulation of the Biliary Tract*

Conditions that increase of cholangitis in the setting of endoscopic retrograde cholangiopancreatography (ERCP) are: obstructed biliary tree due cholangiocellular carcinoma, pancreatic head cancer, and practically any common bile duct (CBD) or hilar lesion that impedes adequate bile flow (metastasis, lymph nodes, sclerosis, fibrosis). The incidence of cholangitis and sepsis after ERCP is as high as 3% [2, 10–12]. In addition, choledocolithiasis, acute cholecystitis, a non-functioning gallbladder, and increased age (>65 years) increase the risk of biliary sepsis [2, 3, 10–13]. However, if adequate bile flow is guaranteed after ERCP the risk of infection is minimal. Thus, most biliary tract interventions do not result in cholangitis. Nevertheless, one can never assume that all ERCPs performed in patients with obstructive cholestasis will result in adequate drainage, and thus antibiotic prophylaxis is recommended for the above-mentioned conditions [2, 3]. The antibiotics should have coverage against enterobacteriaceae and enterococci. Ciprofloxacin has the advantage of excellent absorption, and therefore can be administered orally [3, 10–12]. Piperacillin has additional coverage against many enterococci [3].

#### *Drainage of Pancreatic Fluid Collections*

Antibiotic prophylaxis should be administered before endoscopic, endosonographic or percutaneous drainage of any pancreatic fluid condition [3]. Generally, these fluid collections are sterile, but puncture and drainage will automatically results in contamination of this contained fluid collection. Commonly employed antibiotic prophylactic agents are fluorquinolones [2, 3].

#### *Endoscopic Ultrasound-Guided Fine Needle Aspiration*

No clear guidelines exist regarding the use of antibiotic prophylaxis during endoscopic ultrasound-guided fine needle aspiration. However, experts routinely use prophylaxis [14, 15]. The

most commonly used antibiotic in this situation is ciprofloxacin, 400 mg one dose before the procedure [14, 15].

#### *Bleeding Gastric or Esophageal Varices*

Bacteremia has been reported to occur in up to 50% of patients undergoing sclerotherapy and 25% of patients undergoing endoscopic variceal ligation [16–20]. Currently, endoscopic variceal ligation is the standard therapy to treat esophageal varices [18]. Whether antibiotics decrease the risk of spontaneous bacterial peritonitis is not known. However, the existing data clearly support the use of antibiotics to decrease infectious complications, rebleeding and mortality in cirrhotic patients presenting with gastrointestinal hemorrhage [2, 3]. Quinolones are the preferred prophylactic antibiotics in cirrhotic patients with gastrointestinal hemorrhage.

#### *Endoscopic Dilation of Esophageal Strictures*

Esophageal dilation is frequently associated with bacteremia [21–23]. However, no studies to date have demonstrated a clinically significant reduction in the incidence of infections by the use of prophylactic antibiotics in patients undergoing esophageal dilation. Nevertheless, the author prefers to use antibiotic prophylaxis in cirrhotic patients with ascites and those with primary or secondary immunosuppression (e.g. steroids, antineoplastic agents, azathioprine).

#### *Pancreatitis*

Antibiotics in acute pancreatitis are rarely indicated. Even in the presence of significant pancreatic necrosis or severe acute pancreatitis (SAP) there is controversy on the utility of prophylactic antibiotics [24–28]. Based on results of double-blind, randomized, placebo-controlled trials, antibiotic prophylaxis in SAP is ineffective for reducing the frequency of infected necrosis and to decrease hospital mortality [28]. In patients with SAP and multi-organ failure on admission and in those with hemodynamic shock, it is advisable to use antibiotic treatment with carbapenems and quinolones on demand [28]. In addition, patients with biliary sepsis (acute biliary pancreatitis and acute cholecystitis and/or cholangitis) also benefit from antibiotic treatment [2, 3, 28]. In addition, SAP patients with documented bacteremia, urinary tract positive or a positive bronchoalveolar lavage infection should also be treated with antibiotics [28]. In essence, the most important issue in patients with SAP is to follow them closely and start antibiotics once there are clinical and laboratory signs of infection. If there is suspicion of pancreatic infection, a CT-guided fine needle aspiration with gram stain and cultures are mandatory [29, 30]. The most commonly used antibiotics are listed in table 1.

### **Specific (Non-Prophylactic) Use of Antibiotics in Therapeutic Endoscopy**

#### *Biliary Tract Infections*

The most common biliary tract infections encountered by the therapeutic endoscopist are cholecystitis and cholangitis. Cholecystitis usually results from the obstruction of a stone at the level of the cystic duct. However, up to one third of cholecystitis are acalculous. Acalculous cholecystitis is seen more frequently in the elderly, immunosuppressed and diabetic patients [31]. Thus, patients with typical clinical presentation may still have acute cholecystitis, even in the absence of radiographically documented gallstones.

### *Acute Suppurative Cholangitis*

Acute suppurative cholangitis can develop when one or more types of organisms enter the CBD [3, 13]. Bile is usually sterile but it is a nice culture media for bacteria. In fact, most culture media are enriched with bile to promote the growth of bacteria. Thus, it is logical to infer that cholangitis can result when the biliary tract is manipulated either percutaneously or endoscopically or when stones remain trapped inside the CBD and get impacted in the ampulla of Vater. Occasionally, a stone gets impacted in Hartmann's pouch, which is small indentation at the junction of a cystic duct and CBD. This impaction results in obstruction of the proximal bile duct (i.e. common hepatic duct), while the distal bile duct (CBD) remains patent. This condition is known as Mirizzi's syndrome [32]. Albeit less common, cholangitis can also develop spontaneously in the setting of malignant CBD obstruction [3, 13].

### *Sclerosing Cholangitis*

The most common types of sclerosing cholangitis are primary sclerosing cholangitis, secondary sclerosing cholangitis and Caroli's disease or syndrome [13, 33]. Patients with these conditions are at risk of developing recurrent bacterial cholangitis because of diminished bile flow resulting from one or multiple strictures and bacterial super-infection [3]. Whereas in Caroli's disease resection of the affected segment can result in improvement of the condition, in patients with diffuse sclerosing biliary changes, recurrent bacterial cholangitis is common. In this scenario it is important to relieve the stenosis through endoscopic biliary dilation. However, a significant number of patients will have multiple strictures. Thus, chronic, intermittent use of antibiotics is recommended to prevent acute, recurrent cholangitis [33]. The most commonly employed antibiotic is ciprofloxacin.

### *Cholangitis Resulting from Parasites*

Parasites are probably one of the most common causes of cholangitis worldwide [3, 13, 34, 35]. The problem when parasites enter the biliary tract is threefold. First, the parasite itself can lead to an inflammatory reaction and fibrosis, resulting in acute and chronic cholangitis [34]. Second, the parasite transports organisms into the biliary tract, potentially resulting in acute suppurative cholangitis. And third, the parasite itself can result in acute mechanical obstruction, such as *Ascaris lumbricoides* [35]. The workup and therapy of this type of cholangitis depends on the infecting organism and the timing of diagnosis. In case of acute mechanical obstruction, endoscopic removal of the parasites is mandatory [35]. Specific antiparasitic therapy is also indicated, even in patients with chronic, sclerosing cholangitis [3, 34]. Infestation with *Clonorchis sinensis* organisms can cause such complications as intrahepatic stones, recurrent pyogenic cholangitis, cirrhosis, cholelithiasis, pancreatitis, and cholangiocarcinoma [34]. *Opisthorchis viverrini*, *Opisthorchis felineus*, and *Dicrocoelium dendriticum* are closely related to *C. sinensis* and can also lead to cholangitis. Fascioliasis, caused by *Fasciola hepatica* and *F. gigantica*, is a zoonotic helminthiasis that can result in significant liver fibrosis and lead to acute hepatic or chronic biliary tract infection [35].

### *Choice of Antibiotics for Biliary Infections*

The choice of antibiotics depends on the etiologic microorganism. The most common microorganisms infecting the gallbladder and biliary tract are: Enterobacteriaceae (such as *Escherichia coli* and *Klebsiella pneumoniae*), 68%; enterococci, 14%, Bacteroides spp, 10% and Clostridium spp 7% [3]. First-line antibiotics include: piperacillin-tazobactam, ticarcillin-clavulanic acid, ampicillin-sulbactam and ertapenem [3]. Life-threatening infections should be treated with antibiotics such as imipenem or meronem [3] (table 2).

**Table 2.** Antibiotics used for specific gastrointestinal infections

Condition	Microorganism	Choice of antibiotic	Alternative antibiotic
Cholecystitis <sup>1</sup>	Enterobacteriaceae (68%) (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> )	Piperacillin-tazobactam, ticarcillin-clavulanic acid	Third-generation cephalosporin and metro or aztreonam and metro, or cipro and metro or moxifloxacin
Cholangitis <sup>1</sup>	Enterococci, 14% Bacteroides spp, 10% Clostridium spp 7%	Ampicillin-sulbactam ertapenem	
Pancreatic necrosis	Enterobacteriaceae, enterococci, <i>Staphylococcus</i> <i>aureus</i> , <i>S. epidermidis</i> , anaerobes, candida	Base antibiotic coverage on gram stain and culture	
Diverticulitis and perirectal abscess; small bowel/colon perforation	Enterobacteriaceae, Bacteroides, enterococci, occasionally <i>Pseudomonas</i> <i>aeruginosa</i>	Mild: (always drain perirectal abscess): TMP-SMX DS or cipro or levofloxacin + metro	Ampicillin clavulanate or moxifloxacin
		Moderate: pip-tazobactam, ampSB, tic-clavulanic acid, or moxifloxacin	Cipro or levofloxacin plus metro or moxifloxacin or tigecycline
		Severe: Imipenem or meronem	Amp + metro + cipro or levofloxacin oder amp + metron + aminoglycosides
Esophageal perforation	Oropharyngeal anaerobes, peptostreptococci, in elderly and immunosuppressed patients also gram-negative bacteria	pip-tazobactam, tic-clavulanic acid amp-sulbactam ERTA	
Liver abscess	Monobacterial and polybacterial (80%)	Depends on isolated microorganism(s) If culture results pending use coverage against enterobacteria, streptococci, enteococci and anaerobes (see cholangitis)	
Amebic liver abscess	<i>Entamoeba histolytica</i>	Metro or tinidazole, followed by paromomycin	
Parasites	<i>Ascaris lumbricoides</i> <i>Clonorchis sinensis</i> <i>Fasciola hepatica</i> <i>Opistorchis viverrini</i> Schistomiasis Intestinal tapeworms Echinococcosis	Mebendazole, albendazole Praziquantel or albendazole Praziquantel Praziquantel Praziquantel Praziquantel Albenadazole	Ivermectin, nitazoxanide

amp = Ampicillin; metro = metronidazole; cipro = ciprofloxacin; pip = piperacillin; tic = ticarcillin; TMP-SMX DS = trimetoprim-sulfamethoxazole double strength; ampSB = ampicillin sulbactam.

Data adapted from Gilbert et al. [3].

<sup>1</sup> Life-threatening infections should be treated with imipenem or meronem.

### *Diverticulitis and Perirectal Abscess*

The most common bacteria in diverticulitis and perirectal abscess are enterobacteriaceae and bacteroides. *Pseudomonas aeruginosa* and enterococci may also be present (table 2) [3, 36, 37]. Thus, the choice of antibiotics is dictated by these bacteria. Diverticulitis is categorized into mild, moderate and severe. Patients with mild diverticulitis can be treated on an ambulatory basis and receive trimetoprim sulfamethoxazole (double strength) twice a day for 7–10 days [3, 36, 37]. Patients with moderate to severe disease and patients with pelvic abscess should be treated initially in the hospital. Table 2 lists the antibiotic choices for these categories.

### *Hollow Viscus Perforation*

Albeit a rare event, perforation is a complication that every therapeutic endoscopist will eventually face [38, 39]. The choice of antibiotic will depend on the location of the perforation. In analogy to surgery, microbial infections are divided into those above the diaphragm and those below the diaphragm, where *Bacteroides fragilis* is a much more common occurrence. Thus, the antibiotic choice for any small bowel or colon perforation should cover against bacteroides [38]. The recommended antibiotics for perforations of the small bowel and colon are the same as for diverticulitis and pelvic abscess, with the exception that a perforation should always be considered a serious event (i.e. equivalent to severe diverticulitis), and thus, patients should be treated in the hospital. In contrast, antibiotics used for esophageal and stomach perforations should have spectrum against oral bacteria such as peptostreptococcus.

In case of suspected or frank perforation prompt initiation of antibiotics is mandatory. Thus, appropriate antibiotics should always be available in the endoscopic suite!

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