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ACUTE CHOLANGITIS

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1. ABSTRACT

Acute cholangitis is an infectious disease of the biliary tract with a wide spectrum of presentation ranging in severity from a mild form with fever and jaundice, to a severe form with septic shock. Supportive care with hydration, antibiotics, and biliary decompression remain the cornerstones of care. Broad-spectrum antibiotics should include coverage of *E.coli*, *Klebsiella* sp., *Enterococcus* sp., and in severely critically ill patients, coverage of additional pathogens such as *Bacteriodes* sp., *Pseudomonas,* and yeast should be considered. Biliary decompression should be performed early in the course of the illness when the patient has not improved or if they worsen with hydration and antibiotics. Stable patients should have biliary decompression usually within 72 hours when the fever has resolved. Urgent decompression with a percutaneous or endoscopic stent is preferred over an operative decompression in most institutions. Outcome is dependent on the etiology of the obstruction (benign versus malignant) and the ability to achieve biliary decompression.

2. INTRODUCTION

Acute cholangitis, an infection of the biliary tree, has a variable presentation. In its most severe form, it is a life-threatening infection. Originally described in 1877 by Charcot, its symptoms have been traditionally described as the triad of jaundice, fever and right upper quadrant pain (1). In his initial description, Charcot conceived that "stagnant bile" caused cholangitis. In a healthy person, the biliary tree is normally sterile, but biliary pathology is often associated with secondary bacterial colonization. The presence of both obstruction and colonization leads to cholangitis, but neither by itself is sufficient to cause disease.

The spectrum of disease in patients with acute cholangitis is wide, with some patients mildly ill and others (5%) with severe sepsis and shock. Reynolds and Dargan first described these severely ill patients with cholangitis as having Charcot's triad and, in addition, mental obtundation and hypotension (2), a constellation of symptoms now recognized as Reynold's Pentad. Many terms such as "suppurative," "toxic" or severe cholangitis have described this group of patients. Since the presence or degree of purulence in bile does not define the severity of disease, the descriptive term of "suppurative" is probably not helpful and "toxic" or severe cholangitis is preferable.

Currently, the treatment of acute cholangitis is primarily supportive with intravenous hydration and antibiotics being the mainstay of therapy. High-risk patients warranting early biliary decompression have been identified in recent studies. Today, standard indications that warrant biliary decompression include septic shock, clinical deterioration or failure to improve. This chapter will discuss the pathophysiology, etiology, clinical presentation, laboratory and radiologic evaluation of the spectrum of patients with acute cholangitis. Treatment

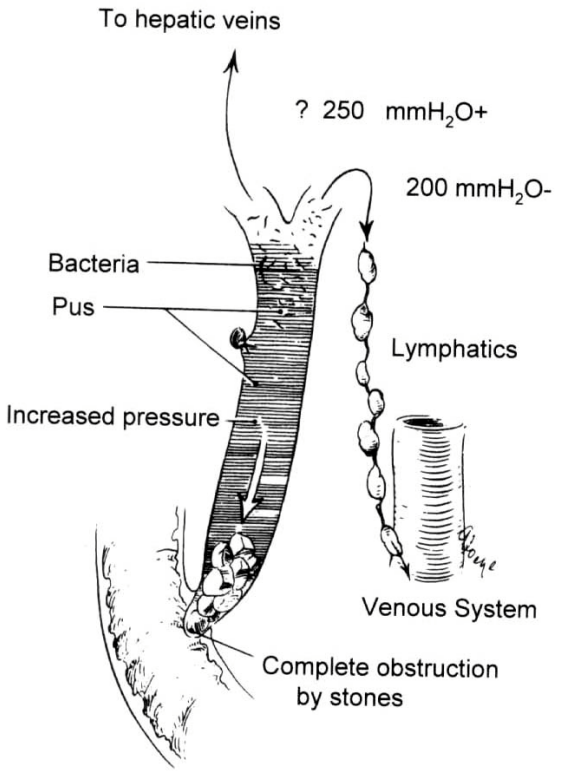

Figure 1. Diagram of the pathophysiology of cholangitis. With permission of Pitt and Longmire (12).

options will be presented along with outcome data in patients with and without the "toxic" form of cholangitis.

3. PATHOPHYSIOLOGY

Normally, the biliary tree is sterile. Acute cholangitis results from the combination of biliary tract obstruction and infection. With normal biliary flow, the presence of bactibilia is usually of little significance because concentrations of bacteria do not increase, and intraductal pressure is not elevated. However, when biliary obstruction is present, an increase in intraductal pressure ensues with continuing bile secretion. Eventually, in the presence of biliary obstruction, biliary pressures approach the secretory pressure of bile, 25-30 centimeter (cm) of water H_2O) (3). Given diminished bile flow, any bacteria that are present will have time to proliferate. Although the exact mechanism of bacteremia is unknown, systemic bacteremia can result from increased intrabiliary pressure when biliary bacteria reflux into hepatic veins and perihepatic lymphatics (Figure 1) (3). In addition, the systemic release of inflammatory mediators such as tumor necrosis factor (TNF), soluble TNF receptors, p55, p75, interleukin-1 (IL-1), 6 (IL-6) and 10 (IL-10) can produce profound hemodynamic effects in the "toxic" form of cholangitis which can take a week to return to normal levels (4).

3.1. Obstruction

Normally, biliary ductal pressures range from 7 to 14 cm. H_2O (5). However, intraductal pressure can rapidly rise to 20 to 30 cm H_2O with either partial or complete obstruction (5). Systemic reflux of radiolabeled biliary bacteria can occur at biliary pressures greater than 15 cm of H_2O (3). The reticuloendothelial system within the normal liver kills the vast majority of bacteria that enter the liver, with an estimated 10% entering the systemic circulation. With a diseased liver, however, a greater proportion of bacteria may reflux causing a systemic bacteremia.

Experimental and clinical models strongly suggest that clinical cholangitis is not produced by infected bile without obstruction, or by obstruction without infected bile. In a canine model, Huang *et al* demonstrated that blood cultures were sterile when the biliary pressure was less than 20 cm of H_2O but became positive when intraductal pressure exceeded 25 cm H_2O (6). Bile infected with 10^5 organisms did not produce bacteremia and illness unless biliary obstruction was present (7). Csendes *et al* documented that patients with "toxic" acute cholangitis had intrabiliary ductal pressures that were significantly higher than either patients with gallstones but without common ducts stones, or patients with common duct stones but without cholangitis (8).

3.2. Bacteria

In normal patients, the gallbladder and biliary tree are sterile (9). However, in the presence of gallstones within either the gallbladder or biliary tree, positive cultures are seen in 15-50% and 70-90%, respectively (10, 11, 12). Moreover, in patients with complete ductal obstruction secondary to malignancy only 25-40% of patients have positive cultures. In a recent study of patients with proximal cholangiocarcinoma, intraoperative bile cultures in patients who did not undergo preoperative endoscopic retrograde cholangiopancreatograpgy (ERCP) were positive in 7 (37%) of 19 patients compared to 23 (55%) of 42 patients who did undergo preoperative ERCP. If a preoperative bile stent had not been placed, 14% of bile cultures were positive, while 69% of bile cultures were positive when a preoperative stent had been placed (13). Interestingly, the method of biliary decompression, percutaneous (65% positive) versus endoscopic (100% positive), also made a difference in the presence of bactbilia. Nomura *et al* demonstrated that patients with biliary malignancy who were treated with percutaneous transhepatic biliary drainage (PTBD) developed both increasing bactbilia (77%) and cholangitis (22%) over time. In 78% of patients, intestinal flora was detected in bile. Catheter malfunction or the presence of undrained bile ducts induced cholangitis (14). Advancing age also increases the likelihood of a positive bile culture, and the elderly frequently present with the more toxic form of cholangitis (15).

Not only is the presence or absence of bacteria in the biliary tree important, but also the absolute concentration of organisms in the biliary tree is greater in patients with acute cholangitis when compared with patients with common duct stones or patients with gallstones (16). Csendes *et al* showed that $>10^5$ organisms was seen in 0% of normal patients, 3% of patients with

symptomatic gallstones, 36% of patients with common duct stones but without cholangitis, and 85% of patients with acute cholangitis (16).

The origin of biliary bacteria is not precisely known. Possible explanations include ascending infection from the duodenum, lymphatic spread, vascular spread from portal venous or hepatic arterial flow, or seeding from a chronically infected gallbladder (17). Because the bacteriology of the duodenum and infected bile are similar, the ascending infection theory is most plausible. Normally, the sphincter of Oddi prevents bacterial reflux into bile. Lymphatic flow is caudad from the liver to the duodenum; thus, this mechanism of infection is somewhat unlikely (18). Hepatic arterial infection and resulting hepatic abscesses do occur but in only a small percentage of patients with cholangitis. The degree of biliary tract obstruction and severity of disease is related to the proportion of patients with positive microorganisms located in the hepatic parenchyma (19).

In 1964, Dineen demonstrated that portal venous bacteremia resulted in bacterial infection and that the concentration of bacteria was related to the degree of biliary obstruction (18). Portal venous bacteremia has been demonstrated in patients with cholangiohepatitis. However, not all patients with portal venous bacteremia were ill. One possible explanation for this observation is that the bacteria, and/or its by-products and inflammatory mediators are destroyed in the liver by an efficient hepatic reticuloendothelial system that eliminates bacteria by excretion into the biliary tree and subsequent elimination in stool. Several studies (4, 20, 21, 22) have demonstrated the role of the circulating cytokines in the bile and serum in acute cholangitis.

Serum endotoxin levels are elevated in patients with cholangitis and decrease after endoscopic drainage (22). Interleukin-6 levels were examined by Akiyama and colleagues in both serum and bile in patients with acute cholangitis (20). The rate of decrease of bilirubin following percutaneous drainage correlated directly with IL-6 levels in bile, suggesting that this potent inflammatory mediator may have a role in maintaining illness following drainage (21). In a more recent study, Kanazawa *et al* demonstrated that bile endotoxin levels decreased more slowly after PTBD in patients with acute cholangitis when compared with those with a remote history of cholangitis. In addition, these authors demonstrated that both bile and serum levels of IL-1 receptor antagonist (IL-1ra), IL-6 and IL-8 were higher in patients with acute cholangitis, and even higher in patients with severe disease. Five hours after PTBD, serum IL-6 and biliary endotoxin levels were directly correlated, suggesting a direct role of biliary decompression in diminishing both intraductal biliary pressure and systemic cytokine levels (21).

In the rat model used by Rapier *et al*, constant infusion of bacteria retrograde into the biliary tree resulted in an increase in intraductal pressure and a proportional increase in bacteremia. In this model, bacterial reflux into the blood stream occurred via intracellular pathways, and preexisting biliary obstruction was not a major determinant of bacteremia. Though this model provides important information about obstruction and bacteremia, the rat does not have a gallbladder and, thus, is not equivalent to the human situation. The gallbladder is enormously efficient at absorption of water and may function to relieve some biliary pressure when a distal ductal obstruction is present. Obviously, an infected gallbladder itself can serve as a source of biliary infection (23).

4. ETIOLOGY OF OBSTRUCTION

Biliary obstruction is most commonly caused by choledocholithiasis, benign strictures, postoperative anastomotic strictures and malignant processes. In the past, up to 80% of all cases of biliary obstruction and cholangitis were caused by choledocholithiasis (11). Depending on hospital location and referral patterns today, malignancy and congenital problems account for the majority of patients at a tertiary referral centers (24). In addition, the use of biliary stents, both endoscopic and percutaneous, has increased the incidence of bacterial infection.

At many institutions over the last four decades, there has been a change in the microbiology and etiology of many surgical infectious diseases. In part, this change can be explained by tertiary referral and differing treatment options, such as biliary stents and aggressive chemoradiotherapy for biliary and pancreatic malignancies. At the Johns Hopkins Hospital from 1952-1978, choledocholithiasis was by far the most common etiology of cholangitis. However, in the last two decades, malignant obstruction and sclerosing cholangitis have been seen with increasing frequency (9, 10).

Bilio-pancreatic ascariasis as a cause of acute cholangitis has been reported with increasing frequency in tropical and subtropical countries, with over 1 billion people worldwide infected with this parasite. The *Ascaris lumbricoides*, a roundworm, causes infection by ingestion of eggs, which hatch in the duodenum, releasing the larvae stage of this parasite. The larvae penetrate the small bowel mucosa and enter the venous circulation. On reaching the lungs, the larvae break into the alveoli, and ascend into the bronchial tree. In the oropharynx they are swallowed and then mature adult worms cause a wide variety of symptoms including acute cholangitis, gallstone formation, cholecystitis, liver abscess, pancreatitis and small bowel obstruction. In most cases of acute cholangitis secondary to ascarias (Figure 2), the roundworms are located in the common bile duct (95%), with evidence of a damaged ampulla and worms seen on endoscopy (86%) (25).

5. CLINICAL PRESENTATION

The clinical presentation of patients with acute cholangitis can be extremely varied. About 5% of patients present with “toxic” cholangitis, that is they are severely ill in septic shock as previously noted. Much as the etiology of cholangitis has changed over the last 40 years, so too has the clinical presentation. In the state of California, the spectrum of gallstone disease included biliary colic in 56%, acute cholecystitis in 36%, acute pancreatitis in 4%, choledocholithiasis in 3%, gallbladder cancer in 0.3%, and

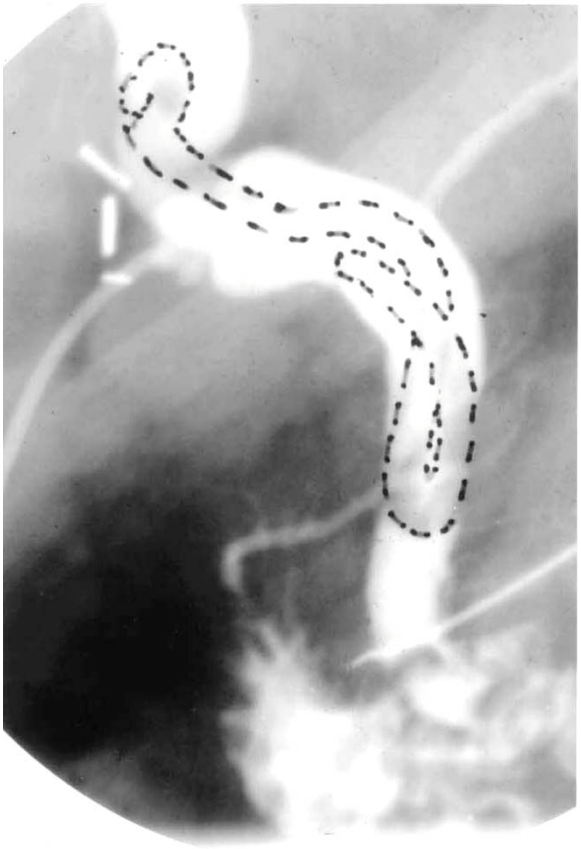

Figure 2. Cholangiogram demonstrating an Ascaris causing obstruction and cholangitis.

cholangitis in only 0.2%. (26). However, these data may be skewed by the need for a cholecystectomy as part of the presentation definition.

Most patients with acute cholangitis present in their fifth or sixth decade of life (24). The classic triad of Charcot of fever, jaundice, and abdominal pain is seen in less than one-third of patients today. Most patients have two of the three components, but fever, which is non-specific, is usually one of the components. The fact that only two-thirds of patients are jaundiced at presentation, compared with the almost uniform presence of jaundice in the past, is certainly a distinct change due to the increased use of biliary stents (9, 24). Abdominal pain, even when present, is usually mild. In spite of the varied clinical symptoms of presentation of cholangitis today, the incidence of the severe form of "toxic" cholangitis has remained constant at approximately 5% of all cases of cholangitis.

The physical examination of a patient, much like the clinical presentation, is somewhat variable. The combination of jaundice and mild right upper quadrant tenderness may be seen in as many as two-thirds of patients. The presence of severe tenderness on physical examination should prompt consideration of an alternative diagnosis such as acute cholecystitis.

6. DIAGNOSIS

The diagnosis of cholangitis should be considered in any patient who presents with fever, jaundice, or right upper quadrant pain. The differential diagnosis of patients with these symptoms and a history of gallstones, previous biliary reconstruction, or indwelling biliary catheters, certainly should include acute cholangitis. Virtually all patients with cholangitis will have some abnormality in laboratory information. The vast majority of patients will have an elevated white blood cell count greater than 10,000/millimeter^3 (mm), often between 14-20,000/mm^3 (24, 27, 28, 29). As in any life threatening infection, in a small minority of patients with overwhelming gram-negative sepsis or in patients with the Acquired Immunodeficiency Syndrome (AIDS), leukopenia may be seen.

Abnormalities of liver function tests are common in patients with cholangitis. The pattern and degree of liver function abnormalities has been correlated to the etiology of the biliary obstruction (24). In patients with a malignant obstruction, a higher elevation of alkaline phosphatase was observed (531 vs. 278 international units (IU), $p< 0.05$) when compared with patients who had a benign biliary obstruction. Patients with benign disease more often have elevations of transaminase values, likely secondary to an acute common duct obstruction.

Hyperbilirubinemia (>2.2 milligram/deciliter (mg/dl)) has been correlated with clinical treatment failure in patients with acute cholangitis (30). Although liver function abnormalities are usually seen in patients with acute cholangitis, many other disease processes can have these non-specific elevations in liver function values. Specifically, sepsis of any origin and hepatitis must be considered. The presence of entirely normal liver function tests is unusual in patients with cholangitis.

Serum amylase may also be elevated in some patients with acute cholangitis (10). These patients usually have choledocholithiasis as the etiology of their cholangitis. In patients with “toxic” cholangitis, additional systemic signs of sepsis such as thrombocytopenia, prolongation of prothrombin time and disseminated intravascular coagulation may occur (31). The serum tumor marker CA19-9 has been evaluated in patients with cholangitis, even in benign disease (32). With therapy, the elevated CA19-9 returns to normal.

The diagnosis of acute cholangitis is not a radiographic diagnosis, though often multiple studies are employed and are necessary to help determine the etiology and treatment plan. Radiographs of the abdomen are rarely helpful in establishing this diagnosis. Occasionally, radiopaque gallstones may be seen or, even more rarely, pneumobilia may be detected (27). Nucleotide scans are helpful in establishing the diagnosis of acute cholecystitis but not cholangitis. Ultrasonography and computerized tomograhic (CT) scans can visualize dilated biliary ducts or may find a potential etiology for cholangitis, such as common duct stones or a pancreatic mass, but these studies

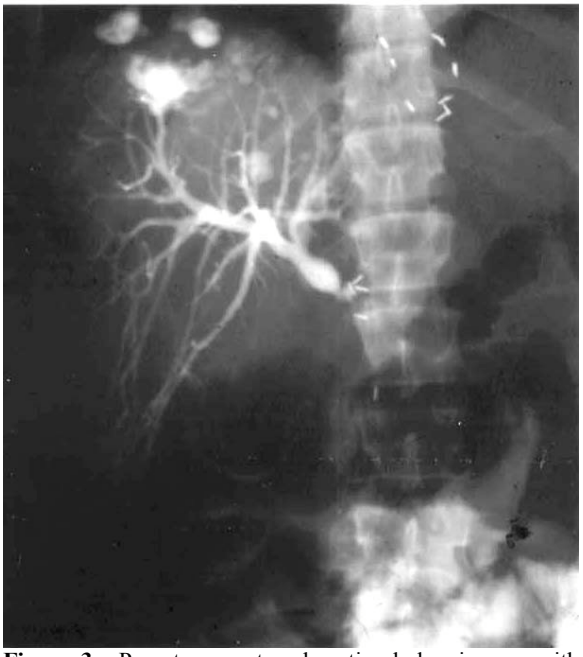

Figure 3. Percutaneous transhepatic cholangiogram with biliary obstruction and microabscesses.

do not establish a diagnosis of acute cholangitis. Ultrasonography can be useful in detecting parasites.

At some time point in the patient's clinical course, either in acute treatment or in defining ultimate management, cholangiography will be required. Direct cholangiography via the endoscopic (ERC) or percutaneous (PTC) route is equally informative (Figure 3). If common duct stones or a periampullary tumor is suspected, in general, the endoscopic route is preferred. On the other hand, if a perihilar tumor is expected, the percutaneous route has some advantages. Cholangitis can be a complication of either procedure, but with appropriate attention to biliary pressures, a generally low incidence of 3-7% can be expected (33, 34, 35).

Today, magnetic resonance cholangiopancreatography (MRCP) is a valuable tool in the identification of biliary tract pathology. MRCP, in a noninvasive fashion with a resolution comparable to invasive cholangiography, can demonstrate the presence of ductal pathology including calculi and strictures. However, MRCP is a diagnostic modality, and usual therapy is also required when acute cholangitis is present.

The timing of cholangiography can be important. With the exception of patients who have "toxic" cholangitis, cholangiography should be delayed until fever has resolved (36). Lai and colleagues have suggested that ERCP should be delayed for 72 hours after the patient has defervesced when performed for diagnostic reasons alone. In patients who have a malignant obstruction or recent cholangitis, the incidence of ERCP-associated cholangitis is higher; and thus, these patients warrant early elective biliary decompression (37). Alternatively, MRCP may have a role in some patients in the future when the reason for the cholangiography is diagnosis and planning, rather than therapy.

7. MICROBIOLOGY

Today, organisms most often isolated are the gram-negative aerobes, *Escherichia coli* and *Klebsiella pneumonia*, the gram-positive enterococci and the gram-negative anaerobe, *Bacteroides fragilis* (38, 39, 40, 41). However, the bacteriology of the biliary tree has changed over the last forty years (Table 1). The more resistant gram-negative organisms *Pseudomonas* and *Enterobacter* are being seen with increasing frequency (24, 42). Anaerobes, such as the *Bacteroides* species, continue to play a small, but significant, role in biliary infection (39, 43). *Candida* species are increasingly isolated from both bile and blood cultures. In analyzing failures of therapy, Thompson *et al* found that isolation of Candida, pan-resistant bacteria, and more than two bacteria are associated with clinical treatment failures (30).

Systemic signs such as high fever, rigors, and particularly hypotension signify that gram-negative bacteremia is likely in patients with acute cholangitis. In the Saharia series, 50 of 78 patients with acute cholangitis had blood cultures drawn shortly after admission, and 20 patients (26%) had bacteremia (27). *E coli* and *Klebsiella* species accounted for 17 of these 20 cases. In the series from 1990, 21% of patients with cholangitis had bacteremia, but *E coli* and *Klebsiella* species represented a much smaller proportion of the total number of isolated organisms (24). In the study by Sugiyama and Alomi, positive blood cultures were seen in 63 of 134 patients (47%) (15). Though positive blood cultures were slightly more common in elderly patients (56% vs. 44%) this difference did not achieve statistical significance and suggests that the underlying obstruction and infection have a high tendency for bacteremia, irrespective of underlying medical and physical condition.

8. TREATMENT

Patients with acute cholangitis represent a wide spectrum of illness. A small number of patients with mild forms of acute cholangitis may be treated with oral antibiotics as an outpatient. An equally small minority of patients with the "toxic" form of cholangitis may require intensive care admission, invasive monitoring, and the use of vasoactive agents to support blood pressure. Maintenance of euvolemia is important to preserve organ function, and hydration is usually required. Occasionally, in spite of adequate volume replacement blood pressure support with a vasoactive agent is required. The selection of vasoactive agents is dependent on the individual hemodynamics of each patient. The routine use of renal dose dopamine remains unproven and is no longer recommended (44, 45).

8.1. Antibiotic Therapy

Antibiotics remain the cornerstone of therapy for all patients with acute cholangitis. However, the specific agent selected for use should be based on an institutional

Table 1. Biliary Bacteriology at The Johns Hopkins Hospital

	1976-1978	1983-1985	1986-1989
Bile Culture	(N=40)	(N=48)	(N=96)
	% of Patients		
Escherichia coli	55	55	39
Klebsiella species	41	32	54
Enterococcus	41	55	34
Bacteroides species	28	9	15
Enterobacter species	0	33	34
Pseudomonas species	0	23	24

experience with cholangitis. If the microbiology is unknown at a particular institution, empiric antibiotic selection must include the gram-negative aerobes and, possibly, enterococci.

Gram-negative aerobes are well covered by the ureidopenicillins, carbapenems, fluoroquinolones, and the third generation cephalosporins. Ureidopenicillins, such as piperacillin, offer the advantage of gram-positive coverage, including the enterococci and of anaerobic coverage (24). When combined with a beta-lactamase inhibitor such as tazobactam, piperacillin offers extended and improved coverage against organisms today that have acquired resistance. In *Klebsiella* species, these Extended Spectrum Beta-Lactamases (ESBLs) are present in as many as 25% of all organisms and cause resistance to usual agents, especially the penicillin derivatives. The carbapenems, imipenem and meropenem, also cover the gram-negatives, the gram-positives, and the anaerobes. These two agents have been successfully utilized as monotherapy for abdominal or unknown sepsis even in critically ill patients (46).

Most fluoroquinolones today do not cover the anaerobes, but have improved gram-positive coverage when compared with first generation fluroquinolones. Since the withdrawal of trovafloxacin, the approved existing quinolones should not be used without additional anaerobic coverage. Because of the increased isolation of *Pseudomonas* from biliary sepsis, in ill patients one should consider an empiric treatment regimen that covers *Pseudomonas*. This strategy would include agents such as piperacillin, cefipime, a fourth generation cephalosporin, and the carbapenems, to name a few. Though most experts would agree that *Pseudomona*s should be treated with two drugs, this recommendation has actually never undergone rigorous study. The data supporting this practice comes from randomized controlled trials with monotherapy. Patients with *Pseudomonas* isolated are frequently and statistically more likely to fail with monotherapy.

The aminoglycosides have retained excellent activity against the gram-negatives (47,48). Though aminoglycosides are inexpensive and effective, there continues to be great reluctance to use them due to perceived nephrotoxicity and ototoxicity. Patients with the "toxic" form of cholangitis are critically ill, and initial selection of appropriate empiric agents has been linked with outcome (49). This issue emphasizes the need to be familiar with both the local microorganisms and resistance patterns in your hospital.

Aminoglycosides are difficult to dose properly in critically ill patients with variable, usually markedly increased, volume of distribution, and are frequently underdosed with initial low peak levels (47,48). In gram-negative sepsis, when aminoglycosides are utilized for therapy, both time until a therapeutic peak level is reached, and low initial drug trough levels are linked to mortality (48). To account for a larger volume of distribution, the initial loading dose for gentamicin and tobramycin in the critically ill patient is 4-6 milligram/kilogram (mg/kg) (50). A peak serum level can be obtained to insure initial adequate doses. If aminoglycosides are administered on a once daily dosing schedule, then a trough level is recommended at the second dose (51). Alternatively, Nichalau *et al* have suggested that a " random" level be obtained somewhere between 6 and 14 hrs after the initial 5 mg/kg dose of gentamicin or tobramycin. These authors provide a normogram for the dosing schedule with this method (52). Using these methods, aminoglycosides have continued to be safe and effective antibiotics.

Several randomized prospective trials for the antibiotic treatment of acute cholangitis have been performed (24, 39, 53). In a study done at the Mayo Clinic, mezlocillin, an ureidopenicillin, favorably compared with the combination of ampicillin/gentamicin (53). Twenty of 24 patients (83%) of patients treated with mezlocillin were cured, compared to only nine of 24 (41%) patients treated with ampicillin/gentamicin. In addition, fewer toxic effects were seen in the mezlocillin arm. However, aminoglycosides were administered in the traditional every eight-hour dosing schedule.

In a study from Johns Hopkins, University of California Los Angeles (UCLA), and the Olive View Medical Center, 90 patients were randomized to either piperacillin or ampicillin and tobramycin (24). The cure rates of both treatment groups were similar, but the outcomes were noted to be related to the etiology of the obstruction (benign versus malignant) (Figure 4). Shingawa *et al* have also confirmed the finding that patients with malignancy were less likely to respond (63%) to antibiotics than were patients with benign disease (88%) (42).

8.2. Biliary Decompression

Initial therapeutic interventions for acute cholangitis such as hydration and antibiotics are usually successful. However, up to 15% of patients with acute cholangitis will require urgent biliary decompression for the treatment of ongoing sepsis, and delay in biliary decompression in patients with severe cholangitis has been associated with increased morbidity and mortality (54).

Non-operative means for establishing biliary decompression are now available in most hospitals (55,56). For patients with acute "toxic" cholangitis secondary to choledocholithiasis, an evidence-based approach would

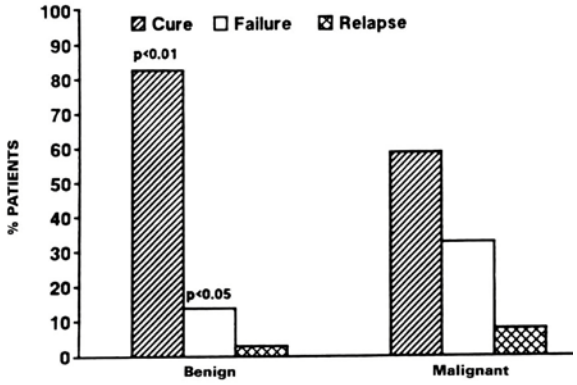

Figure 4. Outcome of cholangitis with benign and malignant obstruction. With permission of Thompson *et al* (24)

suggest that endoscopic decompression is preferred. In this seminal study, 82 patients with "toxic" cholangitis were randomized to receive either urgent endoscopic treatment or surgical decompression. Surgical decompression was associated with an increased need for ventilatory support, respiratory failure and death (32% vs. 10%) when compared to endoscopic decompression (28). Sharma *et al* reported on their experience of 89 consecutive procedures for acute cholangitis requiring biliary drainage, recommending that endoscopic sphincterotomy with stone extraction be considered only in limited cases of acute cholangitis because of increased morbidity when compared with endoscopic nasobiliary drainage (+/- sphincterotomy) (57).

More recently, Poon et al have reported their results in 184 patients with acute cholangitis secondary to gallstones in the era of laparoscopic surgery (58). These authors performed ERCP within the same day in severe cases, but usually within the second day of admission in most patients. After an initial diagnostic cholangiogram, endoscopic sphincterotomy (ES) followed by stone extraction at the same setting was performed unless the patient was hemodynamically unstable. In unstable patients, initial drainage was obtained with a polyethylene double pigtailed catheter and ES and stone extraction were performed at a later date. Interval laparoscopic cholecystectomy was performed in most patients 6 to 12 weeks later. In 175 of 184 patients, ERCP was successful, percutaneous drainage was needed in 3 and open common duct exploration in 6. Endoscopic stone clearance was successful in 132 of 175, 28 did not have a common bile duct (CBD) stone, 13 failed to clear the CBD, and 2 patients died. Recurrent biliary symptoms and cholangitis were common in patients who did not undergo interval cholecystectomy because of surgical risk (7/26) or refusal of operation (11/47). In the multivariate analysis, the gallbladder remaining in situ (Relative Risk (RR), 95% Confidence Interval (CI): 4.16, 95% CI 1.39-12.50), and a small papillotomy (RR 2.94, 95% CI 1.07-8.10) were associated with recurrent biliary symptoms (58).

Percutaneous transhepatic decompression (PTD) is a well-established technique for biliary drainage in patients with obstructive jaundice (33, 34, 35). Usually, sedation is required, and in critically ill patients, especially elderly patients or those with a depressed mental state, intubation and mechanical ventilation may be needed (15). If a patient has a proximal perihilar obstruction or a previous biliary-enteric anastomosis, percutaneous drainage may be the preferred route of biliary decompression. Though highly variable rates for morbidity and mortality have been reported, in most series urgent percutaneous decompression in patients can be done with morbidity less than 10% and a mortality rate of 5% (35, 55, 56).

In institutions where endoscopic or percutaneous biliary decompression is not available, operative drainage remains a life-saving intervention for seriously ill patients with acute cholangitis (29). Lai *et al* demonstrated that even patients with persistent shock can be successfully managed by operative decompression. He demonstrated that the outcome of 30 patients who were managed with operative decompression was not different from a similar group of patients who were successfully resuscitated prior to surgery (29). Thus, when non-operative means are not available, patients who are severely ill with cholangitis can be successful managed with timely appropriate operative intervention.

The hemodynamic status of the patient should guide the extent of the procedure in the endoscopy or interventional radiology suite and in the operating room. In an unstable patient, operative drainage alone may be life saving. Biliary drainage alone was performed in 24 of the 44 patients in the Lai series (28). Cholecystostomy is not adequate drainage and biliary decompression of some type is required. Additional, and often definitive, therapy should not be performed at the same operative procedure, when the indication for intervention has been "toxic" cholangitis and the patient remains hemodynamically unstable during surgery.

Suc *et al* recently reported the results of a multicenter randomized French trial examining the role of primary operative versus primary endoscopic treatment in symptomatic patients with suspected common bile duct stones (59). Unlike the Lai study mentioned previously, patients were not considered for entry into this study if severe acute cholangitis was present. Patients with mild cholangitis were entered into the study and comprised 43% of the patients randomized to surgery and 36% of patients randomized to the endoscopic group. The intent of the study was to examine the total number of procedures and attendant morbidity and mortality attributed to those procedures. This study concluded that surgery was beneficial as an initial therapy in this cohort because the surgical procedure was more likely to be successful, and the rate of additional procedures was lower with surgery as the initial therapy.

Mortality was not different between the groups, and major complications occurred in 4% of surgically treated patients versus 11% ($p<0.002$) in patients with endoscopic treatment (59). Length of stay in the hospital was 16 days in the surgical group compared with 12 days in

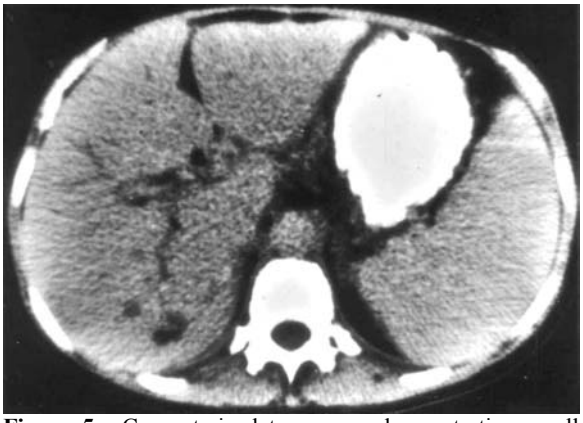

Figure 5. Computerized tomogram demonstrating small liver abscesses posteriorly on the right lobe.

the endoscopic group, but this difference did not achieve statistical significance (p=0.09). The need for cholecystectomy in patients with endoscopic initial management and the lower initial success of the procedure explained the findings in this study (59). Thus, operative therapy remains an important component of the management of patients with acute cholangitis, except in those patients with severe acute cholangitis whereby endoscopic drainage is preferred.

9. OUTCOME

In most series, the overall mortality of patients with acute cholangitis is 5%. The highest mortality occurs in the small subgroup of patients who present with "toxic" cholangitis. Several authors have suggested additional risk factors for patients who present with acute cholangitis. As might be expected, concomitant medical disease, acute renal failure, and low serum albumin are additional risk factors (29, 30, 60, 61). Patients over the age of 80 years have a poorer outcome of acute cholangitis, with a higher incidence of mental obtundation and shock (43%) when compared to younger patients (25%) (15). Not surprisingly, these elderly patients had a higher mortality (10.8%) when compared to younger patients (3.2%) (15).

In high-risk patients with "toxic" cholangitis, considerable morbidity and mortality may be expected (30, 60). These high-risk patients are at particular risk for the development of end organ dysfunction or organ failure, and careful management is necessary to prevent the development of these complications. The development of renal dysfunction and renal failure is common in this group of patients and undoubtedly is related to the combination of altered hemodynamics and low effective circulating volume from the production of inflammatory mediators released by the severe infection. Direct and indirect effects of hormonal and sympathetic control on renal blood flow can cause acute or relative renal ischemia. The maintenance of adequate intravascular volume is essential. In some cases where hepatic and renal failure is present, circulating endotoxin has been documented and has been associated with the clinical features of acute cholangitis (22). In theory, therapies directed at decreasing absorption of endotoxin through the small bowel mucosa and, thus, decreasing the amount in the portal bloodstream have been proposed. These methods include oral bile acids, lactulose, and internal bile drainage (62,63,64). These methods do not address the possibility that endotoxin could be locally produced in the liver and/or biliary tree, and their general use has not been adopted.

Gigot *et al* retrospectively demonstrated seven independent risk factors that predicted mortality following acute cholangitis (60). These factors were: 1) acute renal failure, 2) liver abscess, 3) cirrhosis, 4) high malignant strictures, 5) percutaneous transhepatic cholangiography, 6) female gender, and 7) age. In a multiple regression formula with proportional weight given to the individual factors, a score from 0-27 could be obtained. If the score was less than seven, the predicted mortality was 1.8%; while if the score was greater than seven, the predicted mortality was 49%.

A liver abscess is frequently seen in association with biliary pathology (Figure 5). The development of one or more liver abscesses considerably increases morbidity and mortality (91%) of acute cholangitis. A liver abscess should be considered in any patient with cholangitis who is either seriously ill or fails to improve after initial therapy. If multiple small abscesses are present, biliary drainage and systemic antibiotics may be all that is required. However, if a large hepatic abscess is present, usually additional drainage will be required. Most often, drainage of a liver abscess can be managed percutaneously with either aspiration or drainage, but occasional operative drainage is necessary, particularly if concurrent intraabdominal pathology is present.

In patients with acute cholangitis, the underlying cause of the biliary obstruction does have prognostic importance, as originally described by Thompson et al (24). In this study designed to evaluate antibiotic therapy, the benign or malignant nature of the biliary obstruction was an independent and important predictor of outcome (Figure 4). The initial cure rate of the patients with a benign obstruction was 83%, which compared with only 59% of patients with a malignant obstruction. In this study, there was a 5% mortality rate, but all of these patients had end-stage malignancy, and many also had liver failure and/or renal failure. This finding has been validated in another recent paper (15).

Cholangitis is a common complication in patients with biliary atresia. Risk factors and outcomes were compared for those with and without cholangitis. Irrespective of the adequacy of postoperative bile flow (good or poor), the occurrence of cholangitis was a poor prognostic sign, with 100% survival in the group that did not have cholangitis in the follow-up period. Repeated attacks of cholangitis further decreased survival (65).

Today, management decisions in patients with acute cholangitis should be based on risk factors, magnitude of illness, or etiology of obstruction. Hui and colleagues have attempted to develop a prospective scoring system that would help the clinician identify which patients

were likely to require emergency ERCP (66). In their 142 patients, 21 required emergency ERCP for failure of medical therapy. Risk factors included 1) a maximum heart rate of more than 100/min, 2) albumin of less than 30 g/L, 3) bilirubin of more than 50 mmol/L and 4) a prothrombin time of more than 14 seconds and were associated with failure of medical therapy. When none of these risk factors were present, the risk of ERCP was 1.5% versus 50.7% with one or more risk factor. This scoring system had a sensitivity of 96.8% and a specificity of 59.6% (66). Thus, identification of the highest risk patients and proposing a management strategy that incorporates aggressive supportive measures combined with early intervention may improve prognosis.

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