Kritična razmišljanja

Critical considerations

Bile and bacteria

Žolč in bakterije

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Bile and bacteria in health

With very few exceptions, humans without hepatobiliary disease have sterile bile in the bile ducts and the gallbladder. In contrast, the portal venous blood carries not only endotoxins, absorbed by the intestinal mucosa, to the liver, but also bacteria that have passed, actively or passively, through the intestinal mucosal lining into the intra- and submucosal capillaries. It is assumed that, under normal conditions, the reticuloendothelial system of the liver (the Kupffer cells) destroys such microorganisms by phagocytosis.

The pattern of biliary infection

The clinical spectrum of biliary infections is very broad – from a bacteriological report of positive bile culture in an asymptomatic patient or a rather trivial infection confined to the wound to very severe conditions, such as symptomatic biliary infections combined with septicaemia. The latter may be fatal due to, for example, formation of a liver abscess, endotoxinaemia, intravascular coagulation, renal failure or a combination of two or more of these.

The incidence of biliary infection and the clinical picture

Only 10-20 % of the patients with gallstone disease, without clinical signs of acute cholecystitis or any other biliary infection, show positive cultures of their gallbladder bile. Although the reported results and opinions differ, there seems to be general agreement that acute cholecystitis is caused primarily by chemical factors, for example reflux of pancreatic juice into the bile ducts, or disturbances in the arterial blood supply or a combination of both. Infection of the gallbladder wall and content seems to be a later secondary problem giving rise to positive cultures in only one third of the cases and severe septic complications in even fewer. There is a higher incidence of positive cultures in elderly patients, however. Clinical biliary infection is also generally more common, more severe and more dangerous in elderly patients.

The incidence of bacteria in the bile in patients with stones in the bile ducts varies between 50% and 75%, virtually regardless of whether the patients show clinical signs of a biliary infection or not. Neither the presence of jaundice nor the behaviour of the ductal stones seem to influence the demonstrable incidence of bacteria in the bile.

The bile duct bile from an "untouched" patient shows positive cultures in 0-30% of the cases with malignant biliary obstruction and in 50-75% of those with benign bile duct stenosis. There is one exception: primary sclerosing cholangitis (PSC). Cultivation of the bile from a patient with PSC, achieved under sterile conditions, for example, by means of percutaneous transhepatic bile duct puncture, usually shows no bacterial growth in contrast with the conditions after endoscopic retrograde bile duct cannulation.

Some patients, not yet having been seen by any physician, suffer from septicaemia as a presenting feature. Charcot's triad in septic cholangitis – intermittent fever, possibly with chills or shivering, jaundice and upper, mostly right-sided, subcostal abdominal pain - is well known. Pain and fever are seen regularly along with intrahepatic abscess formation of biliary origin, sometimes accompanied by rigors. Occasional patients may present with circulatory collapse followed by oliguria and renal failure owing to infection with endotoxaemia. Unattended, this may finally become irreversible and thus fatal.

Biliary obstruction increases the bile duct pressure and compromises the bile flow, which results in bile duct dilation and interruption of the enterohepatic circulation, respectively. An increased pressure within the obstructed dilated ducts may destroy the delicate fragile structures of the space of Disse and allow infected bile to enter directly into the bloodstream, thus risking clinical septicaemia. The intraductal pressure may also be critically increased by inadvertent overloading of the bile ducts at direct cholangiography. This can be avoided by evacuating an amount of bile that at least corresponds to the amount of contrast dye that will be infused. Increased formation and resorbtion of endotoxins occur in biliary obstruction. These are brought to the liver by the portal venous blood and affect the hepatocytes and the Kupffer cells with many consequences such as: decreased synthesis of albumin, haem, enzymes and lipoproteins; decreased phagocytosis, s-zinc, endotoxin elimination, bile transport, drug metabolism and drug clearance; and a release of O2-radicals and cytokines, such as acute phase proteins, interleukin and leukotrienes.

Morphology in biliary infection

Infection of the bile within obstructed bile ducts, regardless of the nature of the obstruction, may lead to suppurative cholecystitis or suppurative cholangitis and septicaemia. This may contribute to, or be fully responsible for, the development of renal failure. The responsible agent in "untouched" bile ducts is, in the vast majority of cases, Escherichia coli or coliform bacteria. After surgery and interventional procedures, especially when leaving T-tubes or percutaneous or transpapillary indwelling catheters in place for some days, bile culture may demonstrate a wide spectrum of different species. A single species can be isolated in about 40% of positive bile cultures, two species in nearly one third, and three or four in the major portion of the remaining cases.

The reports on the bacteriological isolates in patients with infected bile are usually in agreement. Aerobes dominate in the Western countries with Gram-negative species varying between 50% and 90% (E. coli dominating) and Klebsiella aerogenes

as the second most common. Gram-positive species range between 10% and 30% and are dominated by Streptococcus faecalis, followed by beta-haemolytic streptococci, staphylococci aureus and coagulase-negative staphylococci. Anaerobes e.g. Bacteroides fragilis and Clostridium perfringens may be found in up to 15%. The prevalence and incidence rates of anaerobes are much higher in Eastern countries e.g. in hepatic abscesses of biliary origin or in Asiatic cholangiohepatitis.

In our material, bile samples drawn simultaneously from a PT catheter located in a peripheral portion of a segmental bile duct and from a T-tube in the common bile duct in the same patient have shown identical species of bacteria, only with occasional exceptions.

The colony count of bacteria ranges between 10^2 and 10^9 per ml in bile duct bile obtained from bile samples drawn by PT puncture of the bile ducts or via the spontaneous bile flow from an indwelling T-tube. Slightly wider variation is seen in bile samples drawn from the gallbladder by puncture at surgery or percutaneously.

Iatrogenic inducement of biliary infection

Biliary infection can be one of the most severe complications of invasive procedures and of surgery on the biliary tract. Such infections cannot always be avoided, but it is necessary to take every possible precaution to minimise the risks.

Some radiological procedures, such as T-tube cholangiography, ERC and PTC, carry a certain, but low, risk of biliary infection somewhat higher at ERC than at PTC. A relatively higher risk of infection is connected not only with surgical entero-biliary anastomoses but also with interventional therapeutic biliary procedures e.g. endoscopy of the bile ducts and the pancreatic duct as well as placement of an endoprosthesis through the region of sphincter of Oddi at ERC or PTC when required.

Almost without exception, the bile will become infected when a direct connection between the bile ducts and the gut excludes the protective function of the sphincters at the choledochoduodenal junction. Bile culture will show growth of one or more species regardless of the technique used for the barrier-free connection. There is a risk that an ascending cholangitis will ensue, sometimes with severe clinical symptoms, but surprisingly often without.

With the passage of time, the biliary infection will fairly often become symptomatic and progress to septicaemia, even with a fatal outcome. Symptomatic biliary infection seems to occur more often after ERC than after PTC, which may be due to the fundamental difference, ERC being a contaminated procedure, whereas PTC is performed under sterile conditions. We are, however, of the opinion that such complications occur more often when the procedure in question has been employed without sufficient care, not "lege artis". A new hand's suboptimal technique can always be improved by training. Clear medical malpractice seems to be rare.

Provided that the width of the anastomosis is adequate, a surgical entero-biliary anastomosis has a low rate of serious clinical cholangitis necessitating treatment.

Positive bile culture is common but clinical cholangitis is rather uncommon after placing a PT endoprosthesis and, if present, it is usually not serious. It can be managed by careful rinsing or flushing of the prosthesis with saline solution, or by replacement and, if this is not effective, by antibiotics. A relatively higher incidence of septic cholangitis seems to burden endoprostheses inserted at duodenoscopy. This infection is best handled by replacement of the endoprosthesis combined with antibiotics, but the high incidence of septic cholangitis in malignant obstruction of the upper and middle third of the common duct has consequently changed the previously positive attitude to the use of endoscopic endoprostheses into a more sceptical one at some endoscopy centres.

Specific conditions are present in patients suffering from a Klatskin tumour. The tumour may isolate one or more hepatic segments by obstructing their draining bile ducts. The effect of an otherwise well-placed endoprosthesis may be ruined by septic cholangitis comprising one (or more) of the segmental ducts. Claude Ligouri reported the results from endoprostheses placed at ERC in Klatskin tumours as “devastating”.

In principle, it is therefore necessary to ensure adequate bile drainage from all segments of the liver to avoid this dreaded complication. In practice, this sometimes means that multiple prostheses have to be placed. This is more difficult at duodenoscopy than with the PT approach.

In some cases, it will not at all be practicable to achieve such optimal treatment. If the predecisional work-up has shown that surgery may be possible, this is the first choice although only a palliative resection would usually be possible. If surgery cannot be contemplated, two alternatives remain. One is to refrain from risking an isolated segmental septic cholangitis and dispense with placing any endoprosthesis. The other is to face the risk and combine incompletely draining endoprostheses with antibiotics. We are inclined to recommend the former alternative.

Infected bile, biliary surgery, wound infection and sepsis

It has been very well documented in several studies that the incidence of wound infection is higher in patients with infected bile. Bacteria identified in the bile at laparoscopic surgery and other invasive procedures have been shown to be closely correlated with those isolated from cultures of pus from infected incisional wounds or from blood from septic patients.

Pus from infected wounds in patients with sterile bile at surgery regularly shows staphylococci, indicating an exogenous origin. Positive blood cultures in septic patients with documented sterile bile at surgery are seen, with very few exceptions, only when a T-tube is employed and are therefore probably also of exogenous origin. The organisms found in such positive blood cultures also correlate very well with those recovered from the T-tube bile.

Biliary surgery and antibiotics

Biliary surgery should be performed in accordance with the general rules of surgery irrespective of whether this is performed at laparotomy or laparoscopy. Dissect carefully, handle all tissues and organs gently, avoid unnecessary tearing, identify all tissues before a contemplated transection, avoid unnecessary bleeding and use efficient haemostasis. Use cautery with discretion. Do not leave necrotic tissue behind and evacuate any blood or blood clots. No extrahepatic bile duct, except the cystic duct, should ever be severed. Before opening any part of the extrahepatic bile duct, take care that all instruments for immediate suction are activated and placed in position beneath the intended opening to prevent any spillage of potentially infected bile also in laparoscopic surgery, etc.

Antibiotics cannot compensate for insufficient surgical training or be expected to improve the results of inadequate surgery or eliminate surgical complications.

There are two main schools regarding the use of antibiotics in biliary surgery. In principle, one of them uses antibiotics in all kinds of biliary surgery as a prophylactic agent; the other one recommends antibiotics only for therapeutic purposes.

The use of antibiotic prophylaxis is founded on the assumption that no infection is present in any relevant tissue. The crucial period of surgery is when potential bacteria in the bile may contaminate the injured tissues of the operative field or opened blood vessels. The prophylactic antibiotic agent should therefore be used to attain serum and tissue levels sufficient to prevent colonisation of the surrounding tissues and the blood. Very high doses of **prophylactic** antibiotics can be used without risking toxic reactions as **one single dose** usually is enough to achieve the goal. Intravenous administration of the antibiotic is to be preferred to oral or intramuscular administration, as the latter two do not readily provide the necessary high serum levels at surgery. The prophylactic antibiotic should be chosen from those not too rapidly excreted by the kidney in order to maintain a high serum level during a sufficiently long period of time.

The intestinal flora will change in patients with biliary obstruction owing to the absence of bile in the gut. This change will also increase the formation and resorbtion of endotoxins, which, brought to the liver with the portal venous blood, will meet with a decreased hepatic capacity for detoxification. Administration of **therapeutic** antibiotics and other substances in order to counteract the change in the intestinal flora and thereby decrease the formation of endotoxins in the intestines could also be contemplated.

Antibiotics are indicated in symptomatic biliary infections. An adequate antibiotic with a narrow spectrum should be used if the pathogen has been identified. The antibiotic agent should be diffusible, and chosen from those that can penetrate into inflamed tissues, be non-toxic and have no side effects at all or only a few unimportant ones. Avoid agents that carry a risk of renal toxicity, as

the kidneys may already be at risk owing to the patient's biliary disease e.g. septicaemia or biliary obstruction. It is advantageous if the agent chosen is also excreted into the bile. It will take several days for the antibiotic to penetrate the infected tissues and prolonged therapy is necessary as long as the patient's general condition improves and the strategy for surgery or drainage procedures can be decided on during a predecisional work-up period.

Remember that antibiotics can neither compensate for insufficient surgical training nor be expected to improve the results of inadequate surgery or inadequate invasive procedures. Nor can antibiotics eliminate surgical or invasive complications.