Microbiological study and antimicrobial susceptibility of bile in biliary therapeutic endoscopy

Analyse bactériologique de la bile en endoscopie interventionnelle biliaire

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RÉSUMÉ

Prérequis: L'endoscopie interventionnelle bilio-pancréatique est invasive, comportant un risque non négligeable de complications infectieuses.

But : Déterminer les germes les plus fréquemment isolés lors de l'endoscopie bilio-pancréatique et étudier leur sensibilité aux antibiotiques, afin d'adapter l'antibiothérapie en cas de sepsis, voire de justifier une antibioprophylaxie.

Méthodes: Une analyse microbiologique des prélèvements de bile effectués lors de la cholangiopancréatographie rétrograde endoscopique a été réalisée. L'indication de l'examen endoscopique était une lithiase de la voie biliaire principale dans 48% des cas et une sténose biliaire maligne ou bénigne dans respectivement 18% et 32% des cas. En cas d'isolement de germes, un antibiogramme était réalisé.

Résultats : Quarante quatre prélèvements de bile ont été analysés. La culture de bile était positive dans 93% des cas. Les germes les plus fréquemment isolés étaient l'Escherichia coli (26,8%), l'Entérocoque (17%), le Klebsiella (14,6%), l'Entérobacter (14,6%) et le Pseudomonas (9,7%). La culture des prothèses biliaires était positive dans 91% des cas. Les germes les plus fréquemment retrouvés étaient l'Entérocoque (27%), le Pseudomonas et le Klebsiella qui étaient notés dans respectivement 18% des cas. L'Escherichia coli et l'Entérobacter n'étaient mis en évidence que dans 9% des cas. Plusieurs antibiotiques ont été testés sur les germes isolés. L'imipenème avait la meilleure activité antimicrobienne (sensibilité de 100%) suivi de la colistine (94%), la tobramycine (93%), l'amikacine (89,6%) la gentamycine (85,2%) et la ceftazidine (812). Par contre, l'association amoxicilline-acide clavulanique et l'ofloxacine n'étaient sensibles que dans respectivement 66% et 60% des cas. Par ailleurs, l'antibiogramme montrait que la ceftazidine était l'antibiotique le plus efficace sur l'Escherichia Coli (sensibilité de 83%). Des germes multi-résistants étaient notés dans 22% des cas.

Conclusion: Cette étude montre que le système biliaire est un milieu à haut risque septique, particulièrement en cas de changement de prothèse biliaire, où les germes sont fréquemment multi-résistants. Ainsi, les indications de l'antibioprophylaxie devraient être rediscutées et la culture de bile devrait être systématique permettant d'optimiser le traitement antibiotique.

Mots-clés

Culture de bile, antibiogramme, cholangiopancréatographie rétrograde endoscopique, lithiase de la voie biliaire principale, prothèse biliaire.

SUMMARY

Background: Biliary obstruction together with bacterial colonization of the bile duct may lead to development of acute cholangitis. The reported incidence of infectious complications may reach up to 10%. Nevertheless, no antibiotic prophylaxis is administered routinely, prior to endoscopic therapeutic procedures.

Aim: To investigate the presence and degree of biliary bacterial colonization during endoscopic retrograde cholangiopancreatography (ERCP) in patients with biliary obstruction. Furthermore, we evaluated antibiotic therapy regimens, which would cover the bacterial species obtained by ERCP and subsequent culture in each patient.

Methods: Forty-four patients with biliary obstruction who underwent an ERCP with biliary drainage were prospectively included.
The primary indication of ERCP was choledocholithiasis (48%), followed by benign biliary strictures (32%) and malignant bile duct obstruction (18%). Bile cultures were obtained by means of bile aspiration via the cannulation catheter. Aerobic and anaerobic cultures were prepared from all obtained specimens and the isolated organisms were identified. In the case of positive cultures, an in-vitro resistance test for different antibiotics was performed.

Results: The overall positive rate of bile culture was 93%. The organisms cultured were Escherichia coli (26.8%), Enterococcus (17%), Klebsiella (14.6%), Enterobacter (14.6%) and Pseudomonas (9.7%) in decreasing order. In-vitro testing of different antibiotics was carried out in these 41 isolates. Imipenem showed the best antimicrobial activity (sensitivity, 100%), followed by colistin (94%), tobramycin (93%), amikacin (89.6%), gentamycin (85.2%) and ceftazidin (82%). Amoxicillin/clavulanic acid and ofloxacin were less sensitive (66% and 60% respectively). Ceftazidin was the most effective antibiotic on Escherichia coli (sensitivity 83%). Multi-resistant organisms were noted in 22% of the cases.

Conclusions: Escherichia coli was found to be the pathogen most frequently detected in bile following endoscopic interventions in the biliary tract. Enterococci and Klebsiella were found in bile cultures with an incidence exceeding 10%. In view of the in-vitro test results, amoxicillin/clavulanic acid or quinolons are not suitable antibiotics for the prophylaxis of biliary infections. Moreover, Gram-positive bacteria such as Enterococcus are emerging as causative microorganisms. If these organisms are isolated, antimicrobial drugs should be replaced by narrower-spectrum antimicrobials.

Key-words

Bile culture, microbiology, antimicrobial susceptibility, endoscopic retrograde cholangiopancreatography, choledocholithiasis, biliary stent

Biliary obstruction together with bacterial colonization of the bile duct may lead to development of acute cholangitis. Cholangitis or biliary sepsis is a complication of endoscopic retrograde cholangiopancreatography (ERCP). They occur mainly following therapeutic ERCP in the setting of an obstructed biliary system. The reported incidence of infectious complications may reach up to 10%. Nevertheless, no antibiotic prophylaxis is administered routinely, prior to endoscopic therapeutic procedures. Antibiotic prophylaxis and antibiotic therapy must consider the spectrum of microorganisms, which is found in these situations.

The aim of the study was to investigate the presence of biliary bacterial colonization during ERCP in patients with biliary obstruction. Furthermore, we evaluated antibiotic therapy regimens, which would cover the bacterial species obtained by ERCP and subsequent culture in each patient.

METHODS

Samples of bile from 44 patients with biliary obstruction who underwent an endoscopic retrograde cholangiopancreatography (ERCP) were prospectively included for microbiological analysis. The primary indication of ERCP was choledocholithiasis in 21 cases, followed by benign biliary strictures in 14 cases and malignant bile duct obstruction in 8 cases. One patient had a biliary complication of hydatid cyst of liver. Twelve patients from them underwent ERCP to change an obstructed plastic biliary stent. Bile cultures were obtained by means of bile aspiration from the bile duct in a sterile syringe via the cannulation catheter during ERCP. The bile was transferred into a sterile blood collection tube and transported at room temperature to the microbiology laboratory. Aerobic and anaerobic cultures were prepared from all obtained specimens and the isolated organisms were identified. In the case of positive cultures, an in-vitro resistance test for different antibiotics was performed.

RESULTS

Bacteriology of bile

The overall positive rate of bile culture was 93%. The organisms cultured in bile were Escherichia coli (26.8%), Enterococcus (17%), Klebsiella (14.6%), Enterobacter (14.6%) and Pseudomonas (9.7%) in decreasing order. The bacteriology of cultures is illustrated in table 1.

Antimicrobial susceptibilities of isolated bacteria

In-vitro testing of different antibiotics was carried out in these isolates (table 2). Multi-resistant organisms were noted in 22% of the cases. Imipenem showed the best antimicrobial activity (sensitivity, 100%), followed by colistin (94%), tobramycin (93%), amikacin (89.6%), gentamycin (85.2%) and ceftazidin (82%). Amoxicillin/clavulanic acid and ofloxacin were less sensitive (66% and 60% respectively). Ceftazidin was the most effective antibiotic on Escherichia coli (sensitivity 83%). Antibiotic sensitivities of the isolates bacteria are shown in figure 1.

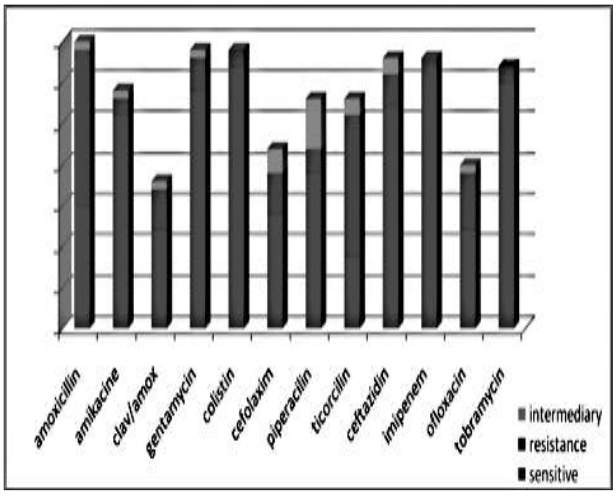
Table 1: Bacteriology of positive bile cultures

Isolated bacteria	Bile (n=44)	
	n	%
Positive cultures	41	93
Escherichia coli	11	26.8
Enterococcus	7	17
Enterobacter	6	14.6
Klebsiella	6	14.6
Pseudomonas	4	9.7
Streptococcus D	3	7.3
Staphylococcus	2	4.8
Proteus	2	4.8

Table 2: Antimicrobial sensitivities

Antibiotic	In vitro-testing n	Sensitivity n (%)	Resistance n (%)	Intermediary sensitivity n (%)
Amoxicillin	35	15 (43)	19 (54)	1
Amikacin	29	26 (89.6)	2 (7)	1
Clavulanic a.-	18	12 (66)	5 (28)	1
amoxicillin	34	29 (85.2)	4 (12)	1
Gentamycin	34	32 (94)	2 (6)	0
Colistin	22	14 (63)	5 (23)	3
Cefotaxim	28	19 (68)	3 (11)	6
Piperacillin	28	9 (32)	17 (61)	2
Ticorcillin	33	27 (82)	4 (12)	2
Ceftazidin	33	33 (100)	0 (0)	0
Imipenem	20	12 (60)	7 (35)	1
Ofloxacin	32	30 (93)	2 (7)	0
Tobramycin				

Figure 1: Antimicrobial sensitivities



DISCUSSION

Bacteria may enter the biliary tract by two routes: haematogenous or retrograde. The haematogenous route involves the translocation of enteric bacteria across the bowel wall to portal vein, hepatic sinusoid and via the space of Disse into bile. For the retrograde route duodenal

bacteria migrate through the ampulla and into the biliary system. In a healthy biliary tract, there are anatomical barriers to both these route (tight junctions between hepatocytes prevent bacteria entry into the bile, competence of the sphincter of Oddi bars the retrograde route, immunoglobulins excreted into the bile, bile salts). These mechanisms normally combine to keep bile sterile in 'healthy' individuals [1].

Disease of the biliary tract circumvents or negates these protective mechanisms and results in the presence of bacteria in the bile (bacterobilia). Obstruction of the biliary system from either benign or malignant causes has marked effects on the antibacterial defenses. As well as preventing flushing of bacteria, obstruction reduces biliary immunoglobulins production, increases translocation of gut flora into the portal vein, reduces Kupffer cell function and disrupts the tight junction between hepatocytes. Iatrogenic intervention such as endoscopic sphincterotomy, choledochostomy or endoprosthesis removes the normal ampullary barrier between bile duct and duodenum. Moreover, bacteria adhere to biliary stents perpetuating potential infection [1].

In this study, we noted that more than 90% of bile cultures were positive. In others series, bacterobilia was found in 50 to 98% [2-7]. Much of the variation can be explained by clinical differences (acute vs. elective procedures) and improvements in culture techniques. In our study, high prevalence of bacterobilia can be also explained by contamination of samples during the procedure. Use of bile trap could probably decrease contamination. Culture was positive in 91% of obstructed biliary stents. Dermibarg et al. reported contamination of all bile duct stents in a study of 51 cholangitis due to occluded stents [8]. More frequent isolated bacteria are Gram-negative, with Escherichia coli found in 27%, Klebsiella and Enterobacter in 15%. This is reported by majority of authors [2-7]. This bacterial flora found in bile is almost enteric origin. This implies that retrograde bacterial colonization is more important than haematogenous. In 6 cases, unusual bacteria like Pseudomonas were isolated, more frequently in obstructed plastic biliary stent (18.5% vs. 9.7%). In literature, widest variation is seen in the prevalence rate of Pseudomonas, which ranges from 0 to 25% and may reflect prior instrumentation of the biliary tract or antibiotic usage [1, 8]. Poorly sterilized endoscope or percutaneous drain may induce iatrogenic introduction of unusual bacteria such as Pseudomonas or Staphylococci [1].

The choice of an antimicrobial regimen for cholangitis should take into account the antibiotic sensitivities of bacteria colonizing biliary tree, the antibiotic excretion into bile and whether biliary obstruction or bacteriaemia is present. Traditionally, cephalosporins, aminoglycosides and quinolons have been used empirically to provide antibiotic coverage in patients with biliary sepsis, pending culture results. However, these antibiotics were chosen based on results from surgical bile specimens [6-9].

In our study, Imipenem showed the best antimicrobial activity. Amoxicillin/clavulanic acid and ofloxacin were less sensitive. However, amoxicillin/clavulanic acid and quinolons are available in orally administered forms; these are favoured as the antibiotics of choice in patients with biliary obstruction for majority of authors [1-6]. In accord with some authors, Imipenem need to be reserved for serious infections or in the case of evident resistance against standard antibiotics [10].

The use of prophylactic antibiotics before ERCP is recommended by many authors especially in the presence of an obstructed biliary system [11-22]. Nevertheless, systematic antibiotic prophylaxis may contribute to overuse of antibiotics and emergence of resistance strain. In a recent meta-analysis [13], the authors conclude that prophylactic antibiotics reduce bacteriaemia and seem to prevent cholangitis and septicaemia in patients undergoing elective ERCP. In the subgroup of patients with uncomplicated ERCP, the effect of antibiotics may be less evident. Further research is required to determine whether antibiotics can be given during or after an ERCP if it becomes apparent that biliary obstruction cannot be relieved during that procedure.

CONCLUSION

Escherichia coli was found to be the pathogen most frequently detected in bile following endoscopic interventions in the biliary tract. In view of the in-vitro test results, amoxicillin/clavulanic acid and quinolons were less sensitive. Nevertheless, use of quinolons can be recommended because they effectively penetrate in an obstructed biliary tree and can be administered orally. Other antibiotic, like Imipenem, need to be reserved for serious infections or in the case of evident resistance against standard antibiotics.

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