Biliary Tract Infection or Colonization with *Elizabethkingia meningoseptica* after Endoscopic Procedures Involving the Biliary Tract

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Abstract

Objective This study was performed to investigate the clinical significance of detecting *Elizabethkingia meningoseptica* in the bile.

Methods We herein report a case series of biliary colonization or infection with *E. meningoseptica*. Twenty patients with *E. meningoseptica* recovered from the bile were treated at a 4,300-bed teaching hospital in China between January 2009 and December 2012. The clinical information for the cases of *E. meningoseptica* recovered from the bile and the microbiological data of the *E. meningoseptica* isolates were examined.

Results Most of the 20 patients were not immunocompromised, although they had cholelithiasis and had recently received antimicrobial agents. All cases were treated with indwelling nasobiliary tubes and endoscopic retrograde cholangiopancreatography and/or endoscopic sphincterotomy prior to the detection of *E. meningoseptica* in the bile. The average time between the placement of the nasobiliary tube and the detection of *E. meningoseptica* in the bile was 6.6 days. *E. meningoseptica* caused cholangitis in five cases, one of which also involved secondary septicemia, and colonized the nasobiliary tubes or biliary tract in the remaining 15 cases. All but two patients recovered and were discharged. Two patients died of septicemia; *E. meningoseptica* and *Escherichia coli* were the causative pathogens in one case and other organisms were the causative pathogens in the other.

Conclusion *E. meningoseptica* is an unusual causative pathogen of healthcare-associated cholangitis. Cholangitis resulting from this bacterium is generally associated with good outcomes, although secondary septicemia can be life-threatening.

Key words: *Elizabethkingia meningoseptica*, *Chryseobacterium meningosepticum*, cholangitis, biliary tract infection, colonization

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Introduction

Elizabethkingia meningoseptica, named *Chryseobacterium meningosepticum* prior to 2005 (1) and *Flavobacterium meningosepticum* prior to 1994 (2), is a saprophytic Gram-negative bacterium that was widely distributed in the environment. As an opportunistic pathogen, *E. meningoseptica* has been reported to cause a variety of infections, including abdominal infections, endocarditis, eye infections, meningitis, pneumonia, osteomyelitis, septic arthritis, septicemia and

skin and soft tissue infections (3-6). Infections caused by *E. meningoseptica* are primarily healthcare associated and occur in newborns and immunocompromised adults (3). A few outbreaks due to this opportunistic pathogen have also been reported (7-10). Furthermore, recovery of *E. meningoseptica* from bile samples has been documented (3, 11), although it remains rare. Furthermore, the clinical significance of identifying *E. meningoseptica* in the bile is unclear. A total of 20 patients with *E. meningoseptica* recovered from bile samples were identified at West China Hospital. We herein report the characteristics of these patients.

Materials and Methods

Patients and setting

West China Hospital of Sichuan University is a 4,300-bed referral teaching hospital in Chengdu, Sichuan province, western China. Between January 2009 and December 2012, there was a total of 20 patients in whom *E. meningoseptica* was recovered from bile samples. A case investigation form was used to collect the demographic data, medical history, underlying diseases, clinical manifestations, laboratory results, treatments and outcomes of the cases.

Bacterial isolates and antimicrobial susceptibility testing

The bile samples were generally collected by puncturing nasobiliary tubes using needles and syringes and processed using standard laboratory protocols. Species identification and *in vitro* susceptibility testing of *E. meningoseptica* isolates were performed using the Vitek II (bioMérieux, Durham, USA) automated system. The interpretation of the minimum inhibitory concentrations was made based on standards for non-*Enterobacteriaceae* set by the Clinical and Laboratory Standards Institute (12).

Definitions

The clinical significance, i.e., infection or colonization, of *E. meningoseptica* isolates was determined based on the presence of a biliary tract infection according to clinical manifestations, laboratory data and ultrasound, computerized tomography or magnetic resonance imaging findings obtained within two days of the collection of the specimens from which *E. meningoseptica* was isolated. Cholangitis and cholecystitis were diagnosed using the criteria of the Tokyo guidelines (13, 14). Healthcare-associated infection or colonization was defined as the acquisition of *E. meningoseptica* after 48 hours of admission to our hospital. Antimicrobial therapy for *E. meningoseptica* was considered to be appropriate if the isolates were susceptible to the agents administered. Death due to *E. meningoseptica* infection was defined as death within two weeks of infection in the absence of other known causes (15).

Results

The 20 patients included 12 men and eight women, 22 to 89 years of age, with a median age of 52 years (Table 1). Only four patients were older than 65 years. Fifteen of the 20 patients were not in an obvious immunocompromised condition, while the remaining five patients had diabetes (n=2) or carcinoma (n=2) or had undergone liver transplantation (n=1). Most (17/20) of the patients had biliary tract illnesses, while half had pancreatitis. Among the biliary tract illnesses, cholelithiasis was the most common condition, observed in 13 cases, followed by carcinoma, anomalous pan-

creaticobiliary ductal union and common bile duct stricture, present in one or two cases each. One patient had biliary tract obstruction; however, the exact cause remained unclear. Fourteen of the 20 patients received antimicrobial agents, mostly cephalosporins (nine cases) or carbapenems (four cases), within one month before collection of the specimen that grew *E. meningoseptica*. All of the patients were treated with indwelling endoscopic nasobiliary drainage (ENBD) tubes and endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic sphincterotomy (EST) or both prior to the detection of *E. meningoseptica* in the bile. Some patients also underwent other operations involving the biliary tract, such as choledochotomy, choledochoscopy and cholecystectomy (Table 1). The time between the placement of the nasobiliary tube and the detection of *E. meningoseptica* in the bile ranged from 0 (the same day) to 24 days, at 6.6 days on average.

In all but two cases, *E. meningoseptica* was the sole microorganism recovered from a single bile specimen; the remaining two patients had either *Acinetobacter baumannii* or *Stenotrophomonas maltophilia* isolated together with *E. meningoseptica* from the same bile specimen. Three patients had *E. meningoseptica* recovered from two bile specimens collected at different time points, and *E. meningoseptica* was isolated from blood in one (case no. 13) of these three cases. Four patients had other bacteria, including *A. baumannii* in all four cases, *Enterococcus faecium* in three cases and *Klebsiella pneumoniae* in two cases, recovered from bile specimens collected at different time points. Two of these four patients also had blood cultures that grew other bacteria, either *Escherichia coli* or *E. faecium*. All *E. meningoseptica* isolates were considered to be healthcare associated.

E. meningoseptica was considered to be causative pathogen of cholangitis in five cases and as a microorganism colonized in the nasobiliary tube or biliary tract in the remaining 15 cases. All five patients with cholangitis due to *E. meningoseptica* met the criteria of the Tokyo guidelines for a definitive diagnosis of cholangitis, including systemic inflammation, cholestasis and imaging of biliary dilatation, stones or stricture (13). Among the five cases of cholangitis, *E. meningoseptica* was either the only microorganism identified or the first bacterium recovered and was isolated from specimens collected within two days of the onset of cholangitis. One patient (case no. 13) developed septicemia caused by *E. meningoseptica* secondary to cholangitis. In 12 of the 20 cases, *E. meningoseptica* was considered to have colonized the nasobiliary tube or biliary tract, rather than caused an infection, due to the absence of biliary tract infection. Two patients were admitted to our hospital due to cholangitis, and their manifestations of the disease were gradually resolving at the time at which the specimens that grew *E. meningoseptica* were collected. Therefore, *E. meningoseptica* was regarded to have colonized the patients in both cases. One patient (case no. 15) developed cholangitis beyond 48 hours after admission and was therefore considered to have a

Table 1. Characteristics of the Patients with *E. Meningoseptica* (*Em*) Recovered from the Bile

Case	Sex, Age	Year	Underlying diseases or diseases present on admission	Operations, days before the detection of <i>Em</i>	Antibiotics before, days ¹	Other bacteria Species ² , sample (date) ³	Antimicrobial treatment ⁴	Significance of <i>Em</i>	Outcome	
1	M,	60	2009	papillary cancer of duodenum	EST+ENBD, 11d; pancreaticoduodenectomy+ cholecystectomy, 0d.	+, 8d	-	CPIZ 7d, CFP-SUL 7d.	Cholangitis	Survived
2	M,	56	2009	cholelithiasis, cholecystitis, pancreatitis	ERCP+EST+ENBD, 1d	-	-	CFP-SUL 9d, CFMX 2d, AMC 4d.	Colonization	Survived
3	M,	46	2009	cholelithiasis, pancreatitis	ERCP+EST+ENBD, 0d	+, 3d	-	CFP-SUL 6d.	Colonization	Survived
4	M,	45	2009	cholelithiasis, diabetes, pancreatitis	ERCP+EST+ENBD, 6d	+, 6d	-	IMP 5d.	Colonization	Survived
5	F,	40	2009	pancreatitis, venous thrombus (left limb)	ERCP +ENBD, 2d	-	-	CFP-SUL 5d, AZT 5d.	Colonization	Survived
6	M,	39	2009	cholelithiasis, pancreatitis	choledochoscope+cholecyst estomy, 7d; ERCP+ENBD, 1d	+, 1d	-	CFP-SUL 7d	Colonization	Survived
7	M,	57	2009	pancreatitis	EST+ENBD, 1d	+, 2d	<i>Ab+Ef</i> , bile (+2d).	MER 10d, PIP-TAZ 5d.	Cholangitis	Survived
8	M,	57	2009	cholelithiasis, common bile duct stricture, pancreatitis	EST+ENBD, 4d	+, 1d	<i>Sm</i> , bile (0d)	AZT 10d.	Colonization	Survived
9	F,	63	2009	liver transplantation stoma stenosis, liver cirrhosis	ERCP+EST+ENBD, 1d	-	-	AZT 7d, PIP-TAZ 5d.	Cholangitis	Survived
10	F,	56	2010	cholelithiasis, pancreatitis	ERCP+ENBD, 10d	+, 6d	-	CTM 7d.	Colonization	Survived
11	M,	46	2010	cholelithiasis, cholecystitis, duodenal ulcer, pancreatitis	ERCP+EST+ENBD, 9d	+, 12d	<i>Kp</i> , bile (+2, +23d); <i>Ef</i> , bile (+23d).	IMP 13d, CTM 8d, IMP 4d, PIP-TAZ 9d, MFX 8d.	Cholangitis	Survived
12	M,	52	2010	cholelithiasis, diabetes, pancreatitis	EST+ENBD, 1d	-	-	CEP-SUL 11d, FOX 4d.	Colonization	Survived
13	M,	72	2010	biliary tract obstruction of unknown cause	ERCP+EST+ ENBD, 18d	+, 16d	<i>Ec</i> , blood (+1d); <i>Ab</i> , bile (+4d).	CFP-SUL 2d, IMP 2d, IMP+VAN 3d	Cholangitis, septicemia	Died
14	F,	73	2010	cholelithiasis, cholangitis, vater's diverticulum	ERCP+ENBD, 4d	+, 6d	<i>Ab</i> , bile (-4d).	CTIZ 8d.	Colonization	Survived
15	F,	52	2010	anomalous pancreaticobiliary ductal union	ERCP+ ENBD, 1d	+, NA	-	CTIZ 7d.	Colonization	Survived
16	M,	41	2010	cholelithiasis	EST+ENBD, 23d; choledochoscopy, 0d	+, 20d	-	LMOX 7d.	Colonization	Survived
17	F,	22	2011	cholelithiasis, cholecystitis, hemolytic anemia	laparoscopic splenectomy +cholecystectomy, 7d; ERCP+EST+ENBD, 6d	+, 18d	-	LMOX 3d.	Colonization	Survived
18	F,	89	2011	cholelithiasis, cholecystitis, cholangitis	ERCP+EST+ENBD, 7d; choledochotomy+ cholecystectomy, 5d	-	-	CFP-SUL9d, MER 21d.	Colonization	Survived
19	F,	31	2011	cholelithiasis	ERCP+ENBD, 2d	-	-	AZT 4d.	Colonization	Survived
20	M,	74	2011	cholangiocarcinoma	ERCP+ENBD+stent in common bile duct, 24d	+, 23d	<i>Kp</i> , bile (-12d); <i>Ab</i> , bile(-9, 0, +8, +19, +32d), blood (+34d); <i>Ef</i> , bile (+8, +35, +42d), blood (+32, +34d).	CFP-SUL 3d, CAZ 30d, CFP-SUL 12d.	Colonization	Died

¹Antibiotics used prior to the collection of the bile specimen that grew *E. meningoseptica*. +: used; -: not used. Days: duration. NA: not available.

²species: *Ab*: *A. baumannii*, *Ec*: *E. coli*, *Ef*: *E. faecium*, *Kp*: *K. pneumoniae*, *Sm*: *S. maltophilia*

³date, days before or after the collection of the bile specimen that grew *E. meningoseptica*; +, after; -, before; 0d, the same specimen.

⁴Antimicrobial agents: AMC: amoxicillin-clavulanic acid, AZT: aztreonam, FOX: cefoxitin, CAZ: ceftazidime, CFMX: cefminox, CFP-SUL: cefoperazone-sulbactam, CPIZ: cefpimizole, CTM: cefotiam, CTIZ: ceftizoxime, IMP: imipenem, LMOX: latamoxef, MER: meropenem, MFX: moxifloxacin, PIP-TAZ: piperacillin-tazobactam, VAN: vancomycin

healthcare-associated infection. This patient also had *K. pneumoniae* and *A. baumannii* isolated from bile specimens prior to the recovery of *E. meningoseptica*, and his condition had not deteriorated within two days before or after the collection of the specimen that grew *E. meningoseptica*. In addition, *A. baumannii* and *E. faecium* were repeatedly identified in multiple bile specimens collected at different time points, and the two bacteria were recovered from blood cultures. Therefore, *E. meningoseptica* was not considered to be the causative pathogen of the healthcare-associated cho-

langitis observed in case no. 15.

Although *E. meningoseptica* had simply colonized the patients in most cases, the affected patients usually had pancreatitis or cholecystitis, and all patients with *E. meningoseptica* colonization or infection were administered antimicrobial agents. However, none of the agents were appropriate with respect to the susceptibility results. Nonetheless, all but two patients recovered and were discharged. Two patients died of septicemia; *E. meningoseptica* and *Escherichia coli* were the causative pathogens in case no. 15, and *A.*

Table 2. Characteristics of the Septicemia Patients with *E. Meningoseptica* Secondary to Biliary Tract Infection

Sex	Age	Underlying diseases	Biliary tract infection	Antimicrobial	Outcome	Reference
M	56	liver transplantation	cholangitis	not available	Survived	(3)
F	66	diabetes, coronary artery disease	no information	CIP ¹	Survived	(16)
F	90	congestive heart failure	no information	CIP	Died	(16)
M	72	biliary tract obstruction	cholangitis	CFP-SUL, IMP, VAN	Died	This study

¹CIP: ciprofloxacin.

baumannii and *E. faecium* were the causative pathogens in case no. 20. Therefore, only one of the 20 patients died of infection due to *E. meningoseptica*.

All isolates in this study were resistant to aminoglycosides (amikacin, gentamicin and tobramycin), penicillins (piperacillin and ticarcillin-clavulanic), cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefepime), aztreonam, imipenem and fluoroquinolones (ciprofloxacin and levofloxacin). All but one were also resistant to piperacillin-tazobactam, with the remaining isolate being intermediate. Isolates from 11 cases were susceptible to trimethoprim-sulfamethoxazole, while the remaining isolates were resistant to these drugs.

Discussion

Recovering *E. meningoseptica* from the bile is unusual. For example, this bacterium accounted for 2.6% of microorganisms isolated from bile cultures obtained between January 2009 and December 2012 at West China Hospital, and only a few cases of *E. meningoseptica* recovered from the bile have been reported in the literature (3, 16). Nonetheless, *E. meningoseptica* can cause biliary tract infections and septicemia secondary to cholangitis, although, in most cases, this bacterium results in colonization rather than infection. It has been documented that *E. meningoseptica* is able to colonize several body sites and medical tubes, including the oropharynx (17), respiratory secretions (18), rectum (17), aerosol tubes (17) and endotracheal tubes (9, 17); however, colonization of nasobiliary tubes and/or the biliary tract has not been previously described. Three cases (3, 16) of *E. meningoseptica* septicemia secondary to biliary tract infection have been reported in the literature (Table 2). One of these patients had cholangitis, as in case no. 13 in the present study (3), whereas the type of biliary tract infection was not specified and no information regarding whether *E. meningoseptica* was isolated from the bile was provided in the other two cases (16). Two of the three patients survived after receiving antimicrobial therapy, while the remaining patient died despite receiving treatment with an agent to which the *E. meningoseptica* isolate was susceptible. The operations applied in the present study involved the biliary tract, in particular the use of an indwelling nasobiliary tube appeared to be the most important risk factor for *E. meningoseptica* colonization or infection, as all patients in this

study received an indwelling nasobiliary tube and ERCP or EST, while some patients also received choledochoscopy or cholecystectomy. Of note, unlike previous reports of *E. meningoseptica* infection or colonization at other sites, most of the present patients with biliary tract colonization or infection were not neonates, immunocompromised adults or elderly.

E. meningoseptica is intrinsically resistant to most commonly used antimicrobial agents; therefore, options for antimicrobial therapy against this opportunistic pathogen are limited. In previous reports (6, 9, 19-21), the clinical isolates of *E. meningoseptica* were always resistant to aminoglycosides and almost all β -lactams, except for piperacillin-tazobactam, and usually susceptible to trimethoprim-sulfamethoxazole and fluoroquinolones. However, unlike that found in most previous reports (6, 19), all isolates in this study were also resistant to fluoroquinolones (ciprofloxacin and levofloxacin), and none of the isolates were susceptible to piperacillin-tazobactam. In addition, almost half of the isolates were resistant to trimethoprim-sulfamethoxazole, making the selection of agents for appropriate antimicrobial treatment particularly difficult. Nonetheless, four of the five patients with *E. meningoseptica* infection survived, suggesting that host factors are critical determinants of the outcome in cases of *E. meningoseptica* infection, as previously suggested (16), and that treatments other than antimicrobial agents, such as drainage, are also critical. In addition, the susceptibility breakpoints for unusual opportunistic non-fermenting Gram-negative pathogens, such as *E. meningoseptica*, should be verified.

The present study is a retrospective analysis and therefore is associated with several limitations. For instance, the isolates were not stored for further study of their clonal relatedness, strain type and susceptibility to several antimicrobial agents that may be effective, such as vancomycin, linezolid, rifampicin and minocycline. Furthermore, no follow-up bile specimens were collected in most cases; therefore, the duration of colonization of *E. meningoseptica* could not be determined. *E. meningoseptica* can cause outbreaks as an opportunistic pathogen of healthcare-associated infections (22-24), and it is possible that the isolates reported in this series are closely related and have caused outbreaks. However, due to the absence of data for strain typing, it is impossible to confirm or exclude the presence of any outbreaks.

In summary, *E. meningoseptica* is an unusual pathogen causing colonization as well as healthcare-associated cholangitis after operations involving the biliary tract and indwelling nasobiliary tubes. Biliary colonization or infection with *E. meningoseptica* are primarily observed in patients who are neither elderly nor immunocompromised. Although the *E. meningoseptica* isolated from the bile in the present study was found to be resistant to most commonly used antimicrobial agents, *in vitro* susceptibility findings are not usually relevant to the clinical outcome, and all cases of cholangitis caused by this bacterium without secondary septicemia resolved in the present study. Although *E. meningoseptica* septicemia can develop secondary to cholangitis, it remains a very rare and life-threatening infection.

The author states that he has no Conflict of Interest (COI).

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