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Title: Pneumococcal Biliary Tract Infections - How Rare Are They?

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Corresponding Author: Dr. Tetsuya Yagi,

Corresponding Author's Institution: Nagoya University Graduate School of Medicine

First Author: Hiroshi Morioka, M.D.

Order of Authors: Hiroshi Morioka, M.D.; Mitsutaka Iguchi, M.D.; Mitsuru Odate, M.D.; Masaki Yoneda, M.D.; Futoshi Ushijima, M.D.; Aki Hirabayashi, M.D.; Nobuyuki Tetsuka, M.D.; Yuka Tomita, M.D., Ph.D. ; Daizo Kato, M.D.; Tetsuya Yagi, M.D., Ph.D.

Abstract: Purpose:
Pneumococcal biliary tract infections (PBTIs) were reported as rare due to the bacterium's bile solubility. The purpose of this study was to determine the occurrence and clinical characteristics of PBTIs.

Methods:
A retrospective cohort study was conducted from January 2006 to August 2014 at a tertiary referral university hospital in Japan. Patients with a blood or bile culture positive for Streptococcus pneumoniae diagnosed with definite cholangitis or cholecystitis according to Tokyo Guideline 2013 were enrolled in this study. Data on demographics, underlying diseases, biliary devices in use, penicillin susceptibility, disease severity, treatments, and outcomes were collected.

Results:
During 104 months, 48 cases of positive blood cultures and 13 cases of positive bile cultures were recorded, and after excluding 43 and 5 of these, respectively, a total of 10 patients were diagnosed with PBTI (3 patients had both bile- and blood-culture positivity). Most patients (9/10) had biliary tract problems and biliary devices in place. Notably, among 37 adult pneumococcal bacteremia patients, bacteremic PBTIs occurred in 13.5%. All patients recovered from the PBTIs.

Conclusions:
PBTIs were not rare; conversely, they were a relatively common cause of pneumococcal bacteremia in this center treating a high volume of biliary tract illnesses.

Suggested Reviewers: Hiroshige Mikamo M.D., Ph.D.

mikamo@aichi-med-u.ac.jp
He conducted pneumococcal research in Japan, and top ID doctors in Japan. He certainly knew the the importance of this paper.

Hanako Kurai M.D.
hanamushi@nifty.com
She is one of the famous, efficient ID clinician in Japan. She is specialist of oncologic ID, thus she understand importance of our paper.

Noritaka Sekiya M.D.
n-sekiya@cick.jp
He is also the famous young specialist in oncologic ID. He understand the importance of our paper.

Opposed Reviewers: WK Luk WK
She was the author of previous pneumococcal biliary tract infections.

Pneumococcal Biliary Tract Infections – How Rare Are They?

Hiroshi MORIOKA[1) 2)], Mitsutaka IGUCHI[1)], Mitsuru ODATE[3) 4)], Masaki YONEDA[5)], Futoshi USHIJIMA[6)], Aki HIRABAYASHI[1) 2)], Nobuyuki TETSUKA[1) 2)], Yuka TOMITA[1)], Daizo KATO[1)], Tetsuya YAGI[1) 2)]

1) Department of Infectious Diseases, Nagoya University Hospital
2) Department of Infectious Diseases, Nagoya University Graduate School of Medicine
3) Department of Respiratory Medicine, Nagoya University Graduate School of Medicine
4) Department of Bacteriology, Nagoya University Graduate School of Medicine
5) Department of Psychiatry, Nagoya University Hospital
6) Department of Respiratory Medicine and Clinical Immunology, Toyota Kosei Hospital

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Corresponding author: Tetsuya YAGI, M.D., Ph.D.
Department of Infectious Diseases, Nagoya University Hospital
Address: 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, 466-8550, Japan
Tel:+81-52-744-2955
tyagi@med.nagoya-u.ac.jp

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Introduction

Streptococcus pneumoniae typically causes pneumonia, otitis media, sinusitis, and meningitis. However, unusual pneumococcal infections are also reported (1). Pneumococcal biliary tract infections (PBTIs: cholangitis, cholecystitis) were recognized as rare pneumococcal infections because of the bile solubility of the bacteria (2). We conducted this study to determine the epidemiology and characteristics of PBTIs.

Patients and Methods

This research was performed at Nagoya University Hospital (NUH, 1035 beds) in Aichi prefecture, Japan. NUH is a tertiary care, university-affiliated hospital and cancer center. From January 2006 to August 2014, microbiological data and patient records of NUH were retrospectively reviewed.

PBTIs were defined by (a) isolation of *S. pneumoniae* from blood or bile and (b) definite cholangitis or cholecystitis according to Tokyo Guideline 2013 (TG2013) (3, 4). Exclusion criteria for the purposes of this study were as follows: 1) age <18 years; 2) other concurrent pneumococcal infections; 3) previous pneumococcal bacteremia within 30 days; 4) discordance between isolated pathogens from blood and bile; 5) polymicrobial bile culture and negative or no blood culture: other pathogens were dominantly observed on gram staining; 6) previous PBTIs within 30 days.

At NUH, *S. pneumoniae* had been confirmed by colony morphology and the optochin test; however, the bile solubility test had not been routinely performed. Antimicrobial susceptibility tests were performed by the broth microdilution method with MicroScan WalkAway (BECKMAN COULTER, Brea, CA, USA), according

to the manufacturer's manual. Strains of *S. pneumoniae* isolated from blood cultures were preserved during this study period. Thus, they were re-identified by the bile solubility test (5) and *lytA* alleles analysis (6).

The data extracted from patients' records were as follows: age, sex, type of occurrence (hospital-acquired: PBTIs appeared 48 hours or more after admission; community-acquired: PBTIs appeared on admission or within 48 hours after admission), results of blood and bile cultures, underlying illness, presence of acid suppression, biliary devices in use, splenectomy, pneumococcal vaccination history, penicillin susceptibility, severity grading score according to TG2013 (3, 4), treatment, and 30-day mortality.

The study protocol was approved by the institutional review board of Nagoya University Graduate School of Medicine (No. 7084).

Results

From January 2006 to August 2014, a total of 55,318 sets of blood cultures were obtained at NUH; 6,293 of these were positive, and *S. pneumoniae* was isolated from 73 sets obtained from 48 patients. Of these, 43 patients were excluded, as follows: <18 years old, 11; diagnosed with specific other pneumococcal infections, 32 (16 pneumonia, 3 bone, skin and soft tissue infection, 2 meningitis, 2 others, and 9 unknown origin). Thus, 5 patients were included by blood culture results. Of note is that bacteremic PBTIs occurred in 13.5% (5/37) of adult pneumococcal bacteremia patients.

Bile culture results during the study period were as follows: 5,815 bile cultures were positive among a total of 9,198. A total of 20 *S. pneumoniae* cultures (0.34% of the total positive bile cultures) were positive in 13

patients, and among these, 5 were excluded, as follows: asymptomatic carrier in bile, 2; previous PBTIs within 30 days, 1; <18 years old, 1; and discordant culture results, 1. Thus, 8 patients were diagnosed with PBTIs by positive bile cultures.

A total of 3 patients had positive cultures for both bile and blood, and therefore 10 patients were enrolled in this study.

Additional tests were performed for 5 strains isolated from blood cultures. All strains were comfirmed to be bile soluble and had the typical *lytA* gene. In conclusion, all 5 strains were reconfirmed as *S. pneumoniae*.

Table 1 shows the demographic and clinical characteristics of the 10 PBTI cases. The median age of the patients was 68 years and 9 were male. In all, 7 PBTIs were hospital-acquired infections. A total of 9 cases had biliary tract problems: 4 cholangiocalcinoma, 2 gallbladder carcinoma, 2 pancreatic head carcinoma, and 1 post-choledochojejunostomy. All of them had biliary devices, as follows: 4 endoscopic naso-biliary drainage, 4 endoscopic biliary stents, 2 percutaneous transhepatic-cholangio drainage, and 1 retrograde transhepatic biliary drainage devices. Only 1 case with cholecystitis had neither an apparent bile duct problem nor a biliary device. Acid-reducing agents were administered to 4 cases prior to PBTI episodes. Neither splenectomy nor pneumococcal vaccination history was found. As for severity grading: of 8 cholangitis cases, 4 were grade 1 and the other 4 cases were grade 2. All cases of cholecystitis (3 cases) were grade 1 severity. Beta-lactam monotherapy were administered to all cases as definitive therapy. All strains of *S. pneumoniae* were penicillin susceptible, and all patients recovered from the PBTIs.

Discussion

PBTIs have been anecdotally reported previously (2, 7, 8); however, the epidemiology and clinical characteristics of PBTIs remain uncertain. Canet et al. reported 1 PBTI among 39 hospital-acquired pneumococcal bacteremia cases (9), and Taylor also reported 3 PBTIs among 2,064 unusual pneumococcal infections (1). We evaluated both blood and bile cultures, and found 10 cases of PBTIs in a 104-month period at a single center. To the best of our knowledge, this article reports the analysis of the largest number of PBTIs to date.

In this study, 9 of 10 cases had underlying biliary tract problems and biliary devices. These patients have been reported to be at high risk for general biliary tract infections (10), and PBTIs as well (2, 7, 8). The ascending route was suspected as the main cause of PBTIs. Luk et al. reported that the concentration of bile salts in biliary tract infections was so low that the bile solubility test using the patient's bile was negative (7). In our study, the patients' bile concentrations may have been too low to prevent biliary tract infections by bile-soluble pathogens. Only 1 case had no underlying bile tract illness or biliary device. Megas et al. also reported the case of a healthy woman with severe pneumococcal cholecystitis; the occurrence of PBTIs without biliary illness was thought to be quite rare (11). In this case, a proton pump inhibitor might have inhibited the sterilization of *S. pneumoniae* in the gastrointestinal tract and helped with the invasion into the bile duct.

Most PBTIs were found to be hospital-acquired; thus, clinicians could consider early administration of antibiotics and additional biliary drainage. All cases of *S. pneumoniae* were penicillin-susceptible, and

β-lactams were effective in all cases. All these factors led to the favorable outcomes.

NUH is one of the highest volume centers for treatment of cholangiocarcinoma in the world (12). As a result, many patients with biliary tract malignancy tend to present to NUH from all over the country. This specific patient population might lead to the distinctive blood culture results of the current study. PBTIs may not be rare, but a relatively common cause of pneumococcal bacteremia at least in high-volume centers for treatment of biliary tract illness.

PBTIs occurrence might have been underestimated because *S. pneumoniae* is fastidious, even when using standard identification techniques, and may be more affected by bile. Microbiological technicians may not perform identification tests for *S. pneumoniae* because they may think *S. pneumoniae* cannot grow in bile. Knowledge of the actual occurrence of PBTIs should be spread in order to detect more PBTIs.

This study has several limitations. First, this study was conducted in one specific hospital. Second, *S. pneumoniae* isolates from bile were not preserved; thus, the tests to reconfirm bacterial identification that were performed for blood isolates could not be performed for those from bile. The possibility of biliary tract infections caused by optochin-susceptible α-streptococci could not be excluded. Finally, we could not perform capsular serotyping and determine the vaccination history, so the effectiveness of vaccination for PBTIs could not be determined. Further multicenter studies are warranted to reveal the precise epidemiology and clinical characteristics of PBTIs in the current pneumococcal vaccination era.

Conflicts of interest:

All authors declare that they have no conflicts of interest.

References

1. Taylor SN, Sanders CV. Unusual manifestations of invasive pneumococcal infection. The Am J Med, **1999**;107:12S-27S.
2. Blenkharn JI, Blumgart LH. The isolation of Streptococcus pneumoniae from bile. The J Infect, **1986**;12:175-8.
3. Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). J Hepatobiliary Sci, **2013**;20:24-34.
4. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Sci, **2013**;20:35-46.
5. CDC, WHO. Laboratory Methods for the diagnosis of Meningitis caused by *Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae*. WHO MANUAL, Second edition. Available at: http:// http://www.cdc.gov/meningitis/lab-manual/full-manual.pdf
6. Llull D, Lopez R, Garcia E. Characteristic signatures of the lytA gene provide a basis for rapid and reliable diagnosis of Streptococcus pneumoniae infections. J Clin Microbiol, **2006**;44:1250-6.
7. Luk WK, Liu CL, Yuen KY, Wong SS, Woo PC, Fan ST. Biliary tract infection due to bile-soluble bacteria: an intriguing paradox. Clin Infect Dis, **1998**;26:1010-2.
8. Schirger A, Martin WJ, Morlock CG, Baggenstoss AH. Bacteremia due to Diplococcus pneumoniae associated with disease of the biliary tract. AMA arch Intern Med, **1957**;99:622-7.
9. Canet JJ, Juan N, Xercavins M, Freixas N, Garau J. Hospital-acquired pneumococcal bacteremia. Clin Infect Dis, **2002**;35:697-702.
10. Higuchi R, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, et al. TG13 miscellaneous etiology of cholangitis and cholecystitis. J Hepatobiliary Sci, **2013**;20:97-105.
11. Megas T, Mega A, Vernikos P, Pavleas I, Georgiou S, Rigas K, et al. Acute cholecystitis associated pneumococcal bacteremia and purpura fulminans. Ann Gastroenterol, **2005**;18:349-52.
12. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg, **2013**;258:129-40.

Table

Table 1. Clinical Characterictics of Patients with Pneumococcal Biliary Tract Infections

Patients	Diagnosis	Sex	Age	Onset	Blood culture	Bile culture	Other pathogen in bile	Underlying illness	Splenectomy	PPI / H2RA	Biliary devices in place	Vaccination history	Penicillin MIC	Severity	Antibiotics	30-days mortality
1	Cholangitis	M	63	HA	+	+	-	HC	-	-	EBS	ND	≦2	2	CPZ/SBT→ ABPC/SBT	Survived
2	Cholangitis	M	39	HA	+	+	+	HC	-	+	EBS, PTCD	ND	≦2	1	MEPM → MEPM	Survived
3	Cholangitis	M	74	HA	+	+	-	GC	-	+	ENBD	ND	≦2	1	CPZ/SBT→ CTRX	Survived
4	Cholangitis	M	75	HA	+	ND	ND	PHC	-	-	EBS	ND	≦2	1	CPZ/SBT→ CPZ/SBT	Survived
5	Cholecystitis	M	73	CA	+	ND	ND	Esophageal carcinoma	-	+	-	ND	≦2	1	CPZ/SBT→ ABPC/SBT	Survived
6	Cholangitis	M	38	HA	-	+	+	PHC	-	-	RTBD	ND	≦2	2	CFPM + VCM→ CTRX	Survived
7	Cholecystitis	M	71	CA	-	+	-	HC	-	-	ENBD	ND	≦2	1	FMOX→ ABPC/SBT	Survived
8	Cholangitis	M	65	HA	ND	+	-	Choledochojejunostomy	-	-	PTCD	ND	≦2	2	CPZ/SBT→ CPZ/SBT	Survived
9	Cholangitis & Cholecystisis	M	59	CA	ND	+	+	HC	-	-	ENBD	ND	≦2	1/1	FMOX→CTRX	Survived
10	Cholangitis	F	74	HA	-	+	+	GC	-	+	ENBD, PTCD	ND	≦2	2	CPZ/SBT→ CTRX	Survived

Abbreviations: PPI: proton pomp inhibitor, H2RA: H2 receptor antagonist, MIC: minimal inhibitory concentration, M: male, F: female, HA: hospital acquired, CA: community acquired, ND: no date, HC: hilar cholangiocarcinoma, GC: gallbradder carcinoma, PHC: pancreatic head carcinoma, EBS: endoscopic biliary stent, PTCD: percutaneous transhepatic cholangio drainage, ENBD: endoscopic nasobirialy drainage, RTBD: retrograde transhepatic biliary drainage, CPZ/SBT: cefoperazone/sulbactam, ABPC/SBT: ampicillin sulbactam, MEPM: meropenem, CFPM: cefepime, VCM: vancomycin, CTRX: ceftriaxone, FMOX: flomoxef