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Original article

Infectious complications of non-surgical biliary tract manipulation in paediatric patients. Role of antibiotic prophylaxis

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ABSTRACT

Background: Infections related to non-surgical manipulation of the biliary tract (NSMBT) are common events despite periprocedural antibiotic prophylaxis (PAP). Since June 2017, our local protocol has indicated a 24-h regimen of intravenous piperacillin–tazobactam for this purpose.
Objective: We aimed to describe the incidence and characteristics of NSMBT-related paediatric infections, define risk factors for their development, and analyse adherence to our PAP protocol.
Materials and methods: Epidemiological, clinical, and microbiological data were collected in consecutive NSMBT procedures performed in paediatric patients (<18 years) in our centre (2010–2019).
Results: 113 procedures in 37 patients, median age 4 years (IQR 1–8), were included. Main underlying diseases were biliary atresia (32%) and cancer (14%). Sixty-eight percent had undergone liver transplant and 70% hepaticojejunostomy. In 44 procedures (39%), the intervention was performed during the course of infection and previously prescribed antibiotic treatment was maintained. In the other 69, PAP was specifically indicated for NSMBT; antibiotic adequacy increased from 35% to 100% after June 2017. In total, 32 NSMBT-related infections (28%) occurred, mainly in the first 24 h post-procedure (72%); no deaths happened. Causative pathogens were Gram-negative rods (64%), Gram-positive cocci (28%), and *Candida* spp. (8%). Main related risk factors were hepaticojejunostomy, biliary obstruction, and liver transplant.
Conclusions: NSMBT in children entails a significant infection risk, even under antibiotic prophylaxis, being hepaticojejunostomy the main risk factor. Infectious complications mainly occurred immediately after the procedure. After establishing a PAP protocol, 100% of interventions received appropriate prophylaxis, decreasing antibiotic exposure time and potentially, the length of hospital stay.

Complicaciones infecciosas de la manipulación no quirúrgica de las vías biliares en pacientes pediátricos. Función de la profilaxis antibiótica

Palabras clave:
Vías biliares
Trasplante de hígado
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RESUMEN

Antecedentes: Las infecciones relacionadas con la manipulación no quirúrgica de las vías biliares (MNQVB) son acontecimientos frecuentes, a pesar de la profilaxis antibiótica periprocedimiento (PAP). Desde junio de 2017, nuestro protocolo local indica una pauta de 24 h de piperacilina/tazobactam por vía intravenosa para este fin.

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Objetivo: El objetivo era describir la incidencia y las características de las infecciones pediátricas relacionadas con la MNQVB, definir los factores de riesgo para su desarrollo y analizar el cumplimiento de nuestro protocolo de PAP.
Materiales y métodos: Se recogieron datos epidemiológicos, clínicos y microbiológicos en procedimientos consecutivos de MNQVB realizados en pacientes pediátricos (< 18 años) en nuestro centro (2010-2019).
Resultados: Se incluyeron 113 procedimientos en 37 pacientes, con una mediana de edad de 4 años (RIC 1-8). Las principales enfermedades subyacentes fueron atresia biliar (32%) y cáncer (14%). El 68% se había sometido a un trasplante de hígado y el 70% a una hepaticoyeyunostomía. En 44 procedimientos (39%), la intervención se realizó durante el transcurso de la infección y se mantuvo el tratamiento antibiótico recetado previamente. En los otros 69, la PAP estaba indicada específicamente para la MNQVB; la eficacia de los antibióticos aumentó del 35 al 100% después de junio de 2017. En total, se produjeron 32 infecciones relacionadas con la MNQVB (28%), principalmente en las primeras 24 h posteriores al procedimiento (72%); no se produjo ninguna muerte. Los patógenos causantes fueron bacilos gramnegativos (64%), cocos grampositivos (28%) y *Candida* spp. (8%). Los principales factores de riesgo relacionados fueron la hepaticoyeyunostomía, la obstrucción biliar y el trasplante de hígado.
Conclusiones: La MNQVB en niños conlleva un importante riesgo de infección, incluso con profilaxis antibiótica, y la hepaticoyeyunostomía es el principal factor de riesgo. Las complicaciones infecciosas se produjeron sobre todo inmediatamente después del procedimiento. Después de establecer un protocolo de PAP, el 100% de las intervenciones recibieron la profilaxis adecuada, disminuyendo el tiempo de exposición a los antibióticos y, potencialmente, la duración de la estancia hospitalaria.

Introduction

Non-surgical manipulation of the biliary tract (NSMBT) includes endoscopic transpapillary procedures and percutaneous transhepatic procedures. The indications for these two techniques are well-defined in children and oriented towards the diagnosis and treatment of pancreatic or biliary diseases, such as obstructive cholestasis, congenital or acquired biliary tract stenosis, and chronic pancreatitis.[1–4]

Under normal conditions, the biliary tract is sterile,[5,6] but manipulation of the biliary structures can lead to local (mainly cholangitis) and systemic infectious complications due to the close communication between the biliary tract and duodenum.[7] The main pathogens implicated in these infections are gram-negative rods (in particular, *Enterobacterales* and *Pseudomonas* spp.), and Gram-positive cocci (e.g., *Enterococcus* spp. and *Staphylococcus aureus*). *Candida* species are less commonly involved.[8–9]

In controlled conditions, non-surgical manipulation of a naive biliary tract is considered a clean-contaminated procedure, with a reported infection rate of 1–15%.[10–11] Risk factors for procedure-related infectious complications have been well described in adults, with the most important being biliary obstruction, which increases the incidence of bacteraemia to 18%.[6,11–16] Other risk factors are liver transplantation, endoscopic access, and immunosuppression (severe neutropenia, haematological malignancies, and stem cell transplantation).[11,14,17]

Little is known about NSMBT-related infectious complications in children. The few available published series exclude liver transplant patients, and information about risk factors is not provided.[3,4,10]

The need for periprocedural antibiotic prophylaxis for NSMBT is controversial.[17–31] Some studies have shown that antibiotic prophylaxis seems useful to prevent bacteraemia, but not local infectious complications such as cholangitis.[11,13,18,20] According to the recent guidelines of the British Society of Gastroenterology,[14] the American Society of Gastrointestinal Endoscopy,[11] the European Society of Gastrointestinal Endoscopy, and the United European Gastroenterology,[20] antibiotic prophylaxis is indicated in liver transplant recipients and patients with pancreatic pseudocyst, severe neutropenia, advanced haematological malignancy, and biliary disorders with prevision of incomplete biliary drainage. As related data in children are scarce, prophylactic recommendations in children have been extrapolated from studies in adults.

The scheme of periprocedural antibiotic prophylaxis (PAP) should be adapted to the local antimicrobial resistance patterns in each centre and to the characteristics of the patients treated. A wide variety of antibiotics have been used throughout the years, but there is no consensus regarding the prophylactic regimen for the paediatric population.

The aim of this study was to describe the epidemiology of infectious complications after NSMBT in a single paediatric reference hospital, define potential risk factors for these infections in children, and analyse adherence to our current antibiotic prophylaxis protocol.

Patients and methods

Study design

Our hospital is a tertiary care centre with a nationwide referral unit for Paediatric Hepatology and Liver Transplantation in Spain. Since June 2017, protocols for antibiotic prophylaxis and treatment of infection have been designed jointly with the Paediatric Infectious Diseases Unit within the framework of our local Paediatric Antibiotic Stewardship Program. A retrospective study was conducted including all consecutive NSMBT procedures in paediatric patients (<18 years of age) from August 2010 to December 2019.

Antibiotic management

Up to June 2017, antibiotic prophylaxis was designed by the treating physician, considering the most frequent pathogens in our setting and previous colonisation. The current local prophylactic protocol, established in June 2017, recommends administration of intravenous piperacillin–tazobactam for 24 h (first dose at anaesthesia induction) for all paediatric patients undergoing NSMBT. As there is a lack of general consensus in the paediatric literature about the most appropriate antibiotic in this setting, piperacillin–tazobactam was chosen according to the microbiology of our centre and its favourable safety profile. In the case of known local colonisation or infection by a resistant microorganism in the previous 6 months, prophylaxis is adjusted to the antimicrobial resistance pattern. When the patient is receiving antibiotic treat-

ment for an active infection at the time of NSMBT, the antibiotic scheme is maintained if it is microbiologically appropriate.

Study definitions

NSMBT-related infectious complications were defined as follows: fever with no known source (temperature ≥38 °C with no other abnormality); procedural site infection[32] (PSI, an infection that occurs after a procedure in the part of the body where it took place), divided into incisional PSI (skin, subcutaneous tissue or deep soft tissue infection) or organ/space PSI (cholangitis[33]: systemic inflammation (fever/chills or abnormal laboratory data [C reactive protein, white blood cells]), cholestasis (jaundice or abnormal liver function tests) and imaging abnormalities (biliary dilatation or evidence of its cause [stricture, stone, stent, etc.]); and bacteraemia (fever with a positive blood culture for a compatible microorganism not considered a contaminant microorganism). Depending on the time of presentation, complications were classified as early (onset during the first 24 h) or late (onset between 24 h and 7 days after the procedure). In the active infection group, as the NSMBT was performed after a minimum of 48 h of antibiotic treatment, we considered a NSMBT-related infectious complication the reappearance of fever, exacerbation of other symptoms and/or deterioration of laboratory tests after the procedure.

Antibiotic prophylaxis was defined as the antibiotics used to reduce the risk of infection derived from a procedure. Antibiotic treatment was considered as the antibiotics aimed to cure an ongoing active infection at the time of the procedure.

Appropriate prophylaxis was defined as a regimen adhering to the protocol. Inappropriate prophylaxis was defined as deviations from the established scheme with regard to drug selection, duration, or both.

To evaluate the impact of our current prophylaxis protocol, we excluded interventions in which patients were receiving antibiotic treatment for an ongoing infection (the active infection group), thus including only the interventions in which patients had no infection at the time of the procedure and received antibiotic with a prophylactic purpose. The prophylaxis group was divided into two categories: before June 2017 and starting in June 2017, to analyse adherence to the protocol and compare the incidence of complications between these groups. Although there was no protocol before June 2017, the current recommendations were considered the optimal scheme for evaluating prophylactic practice over the entire study period.

Multidrug-resistant strains were defined as those resistant to 3 or more antibiotic families, including extended-spectrum beta-lactamase (ESBL) and intrinsic *Stenotrophomonas maltophilia* resistance.[34]

Data collection

NSMBT procedures were identified from the Paediatric Hepatology and Liver Transplant database. The following data on the study patients were collected from the electronic medical records: demographics (sex and age); underlying disease (biliary atresia, hepatic malignant tumours, others); potential risk factors for infectious complications (liver transplant recipient, hepaticojejunostomy, endoscopic access, biliary obstruction, severe neutropenia and other immunocompromised states, current infection, sex); perioperative antibiotic prophylaxis (route of administration, drug, duration); infectious complication (day, type, outcome); microbiological data (culture results, time from the procedure to sample collection); and outcome.

Microbiology procedures

Blood and bile fluid samples were collected. Blood was obtained by peripheral venous puncture or through a central venous catheter and bile from a biliary external or internal-external drain, if present. Blood cultures were performed in BacT/ALERT bottles (bio-Mérieux Inc., Marcy-l'Etoile, France) and bile samples were cultured in solid and conventional liquid media for aerobic and anaerobic bacterial growth. Both types of samples were incubated for 6–7 days. Isolated microorganisms were identified by biochemical and metabolic tests or mass spectrometry (Vitek 2 ID Cards and Vitek MS MALDI-TOF, respectively, both from bio-Mérieux Inc., Marcy-l'Etoile, France). Antimicrobial susceptibility was assessed by microdilution testing (Vitek 2 AST Cards, bio-Mérieux Inc. France) or diffusion in agar (by discs, Rosco Neo-Sensitabs Taastrup, Denmark; and E-test strips, bio-Mérieux Inc., Marcy-l'Etoile, France) according to the CLSI (Clinical and Laboratory Standards Institute) recommendations from 2009 to 2013 and to the EUCAST (European Committee for Antimicrobial Susceptibility Testing) recommendations from 2014 to 2017.

Ethical aspects

The local Ethics Committee for Clinical Investigation approved the study in December 2018 (PR(AMI)526/2018).

Statistical analysis

Each NSMBT procedure was considered separately in the statistical analysis. In the risk factors analysis, procedures were stratified according to liver transplant status, presence of a hepaticojejunostomy, biliary obstruction, current infection, and route of access.

Categorical variables are expressed as the number and percentage. Quantitative variables are expressed as the median and interquartile range. The odds ratio and 95% confidence interval (95%CI) were calculated in the risk factors analysis. Univariate analysis was performed for the risk factors. Statistical analyses were performed with the "R" statistics program (R version 3.5.2 (2018-12-20), Copyright 2015, The R Foundation for Statistical Computing).

Results

Patients and procedures

Thirty-seven patients were included, of them 26 patients had undergone liver transplantation; among the transplant recipients, the most frequent underlying diseases were biliary atresia (11 patients), malignant liver tumours (5), metabolic disease (4), and others (6); all had a Roux-en-Y hepaticojejunostomy except for 2 patients with Wilson's disease, in whom the choledochal duct was maintained. The aetiologies other than transplantation (11/37) included bile duct lithiasis/biliary sludge (6 patients), cholestasis of unknown origin (2), and others (3 patients, including 1 patient with biliary atresia and a Kasai portoenterostomy).

During the study period, 113 NSMBT procedures were performed in the 37 patients (median 2 procedures/patient): 10 underwent 1 procedure, 10 had 2, and 17 had 3 or more. Median age at the time of the procedure was 4 years (IQR 1–8 years). Thirty-eight percent of the procedures were performed in males. Seventy-eight procedures took place before June 2017 and 35 after this date.

As to the distribution of previously described risk factors, 77 (68%) procedures were performed in liver transplant recipients (median time from the transplant to the procedure, 8 months

Table 1
Risk factors, prophylaxis characteristics and infectious complications, by previous infection status and existence of a local prophylaxis protocol (implemented in June 2017).

	Prophylaxis group total $n = 69$			Active infection group $n = 44$ (%)	Total $n = 113$ (%)
	Before June 2017 $n = 48$ (%)	From June 2017 $n = 21$ (%)	p value		
Sex					
Male	21 (44)	7 (33)	0.41	15 (34)	43 (38)
Age (at the procedure)	4	7		4	4
Median, IQR (years)	1–8	2–16		1–7	1–8
Risk factors					
Liver transplant	28 (58)	16 (76)	0.16	33 (75)	77 (68)
Hepaticojejunostomy	25(52)	15 (71)	0.18	39 (89)	79 (70)
Biliary obstruction	26 (54)	12 (57)	0.81	16 (36)	54 (48)
Endoscopic access	9 (19)	3 (15)	0.65	2(5)	14 (12)
Other immunocompromised	0	0	0.68	0	0
Drug used					
piperacillin–tazobactam	36 (75)	17 (81)	0.47	16 (36)	69 (61)
Meropenem	5 (10)	4 (19)	0.48	13 (30)	22 (19)
Cefoxitin	2 (4)	0	0.59	0	2(2)
Ciprofloxacin	1 (2)	0	0.85	0	1 (1)
Ceftazidime	0	0	0.68	2 (5)	2 (2)
Amoxicillin-clavulanate	0	0	0.68	1 (2)	1 (1)
Combined therapy	0	0	0.68	12 (27)	12 (11)
None	4 (8)	0	0.33	0	4 (4)
Prophylaxis duration					
24 h	17 (35)	21 (100)	**<0.01**		
Longer than 24 h	27 (56)[a]	0	**<0.01**		
Appropriate prophylaxis	17 (35)[a]	21 (100)	**<0.01**		
Inappropriate prophylaxis					
Drug used	1 (2)	0	0.85		
Duration> 24 h	25 (52)	0	**<0.01**		
Both drug and duration	1 (2)	0	0.85		
No prophylaxis	4 (8)	0	0.33		
Infectious complications, time					
Early	9 (19)	7 (33)	0.31	7 (16)	23 (20)
Late	5 (10)	1 (5)	0.48	3 (7)	9 (8)
Infectious complications, type					
Fever with no source	4 (8)	1 (5)	0.62	0	5 (4)
Cholangitis with no bacteraemia	6 (13)	5 (24)	0.24	7 (16)	18 (16)
Cholangitis with bacteraemia	4 (8)	2 (10)	0.87	3 (7)	9 (8)

[a] One case received 7 days of piperacillin–tazobactam adjusted to the protocol of acute hepatic failure. Bold values mean statistical significance.

[IQR 2 months – 2 years]), 79 (70%) in patients with a hepaticojejunostomy, and 54 (48%) in patients with an obstructed biliary tract. Aside from the transplanted group, there were no other immunocompromised patients. No patient was under post-transplant antibiotic prophylaxis at the time of the procedure. The access route was mainly transhepatic (99 procedures, 88%); endoscopic access was used in only 14 procedures (12%).

Ten procedures had no potential associated risk factors, 14 had 1, and 89 had 2 or more potential risk factors for NSMBT-related infections. A summary of the risk factors, prophylaxis characteristics, and infectious complications by group and time period are shown in Table 1.

Periprocedural antibiotic prophylaxis

Overall, PAP was indicated in patients with no active infection (69/113 procedures, 48 before June 2017 and 21 after this date) and was administered in 65 procedures (4 did not receive prophylaxis). The antibiotic most often used was piperacillin–tazobactam (53/69, 77%), followed by meropenem (9/69, 13%), cefoxitin (2/69, 3%), and ciprofloxacin (1/69, 1%). In 5/9 procedures in which meropenem was used, the drug was administered because of recent colonisation by a multidrug-resistant pathogen. Antibiotic duration was 24 h in 38/69 interventions (55%) and between 2 and 8 days in 27/69 interventions (39%).

On analysis of adherence to our local prophylaxis protocol starting in June 2017, we found that antibiotic prophylaxis was appropriate (by both drug selection and duration) in all procedures (100%), whereas in the previous period only 17/48 (35%) received an "appropriate" regimen ($p < 0.01$).

The remaining patients (44/113 procedures (39%), 30 before June 2017 and 14 after this date) had an active infection at the time of the intervention, and biliary obstruction was the main reason for therapeutic bile duct manipulation. Antibiotic treatment was piperacillin–tazobactam in 16/44 (36%), meropenem in 13/44 (30%), and combined therapy in 12/44 (27%).

Infectious complications

Overall, there were 32/113 cases of NSMBT-related infection (28% of procedures), which mainly occurred in the first 24 h after the intervention (23/32 cases, 72%). Twenty-six infectious complications occurred in transplant recipients (median time from the transplant, 6 months (IQR 2 months – 6 years). Regarding late infectious complications, 6/9 cases occurred in procedures with prolonged antibiotic use (3 cases had inappropriate prolonged prophylaxis and 3 cases were from the active infection group, including

Table 2
Microbiological data.

	Bile culture	Blood culture
Culture results by microbial growth		
Total	18	29
Monomicrobial	7	7
Polymicrobial	9	2
Negative	2	20
Type of microorganism isolated		
Total	18	27
Gram negative bacteria	15	8
Gram positive bacteria	7	3
Fungi	3	0
Microorganisms isolated		
Enterobacter cloacae	3	1
Klebsiella spp.	5	4
Pseudomonas aeruginosa	3	1
Stenotrophomonas maltophilia	3	1
Escherichia coli	1	1
Citrobacter freundii	1	0
Enterococcus faecalis	4	1
Enterococcus faecium	4	2
Candida spp.	3	0
Susceptibility to piperacillin–tazobactam	2/15 samples tested	2/8 samples tested
Multi-resistant strains[a]	7/15 samples tested	3/8 samples tested

[a] Multi-resistant strains: resistance to 3 or more antibiotic families, including extended-spectrum beta lactamase (ESBL) or intrinsic *S. maltophilia* resistance.

1 with haemodynamic instability); 1 infection occurred in a patient who did not receive prophylaxis and only 2 occurred in patients receiving appropriate prophylaxis.

Regarding the type of infection, there were 5 cases of fever with no identifiable source, 18 organ/space PSI (cholangitis), and 9 bacteraemia. No incisional PSI occurred. Five cases presented with haemodynamic instability (2 cholangitis and 3 bacteraemia). No NSMBT-related deaths occurred.

Infectious complications occurred in 23% (10/44) of the group with an active infection, and 32% (22/69) of the uninfected group receiving PAP ($p = 0.29$). Organ/space PSI (cholangitis) was the most common type of infection in both groups. There were no significant differences regarding the incidence of infectious complications before and after June 2017—14/48 (29%) *vs* 8/21 (38%), respectively; p = 0.46—or the incidence of bacteraemia—4/48 (8%) vs 2/21 (10%), respectively; $p = 0.87$. The clinical characteristics of the two groups were similar (Table 1).

Regarding the 5 severe cases of NSMBT-related infection with haemodynamic instability, 1 patient did not receive PAP although it was indicated, 2 received appropriate piperacillin–tazobactam prophylaxis (including the single case after June 2017), and the remaining 2 were receiving antibiotic therapy for an active infection.

Among the 32 cases of NSMBT-related infection, 20 were microbiologically confirmed (positive blood and/or bile culture for a compatible microorganism) whereas the other 12 were diagnosed only by clinical and/or analytical features. Blood culture was positive in 9/29 and bile culture in 16/18 available samples, 13 of them obtained from internal–external drainage.

The main pathogens isolated in bile culture were Gram-negative rods (15/18 cases, 83%), Gram-positive cocci (7/18 cases, 39%), and *Candida* spp. (3/18 cases, 17%). Concordance between blood and bile culture was 100% (5/5) when both samples were available and positive. Susceptibility to piperacillin–tazobactam was confirmed in 2/15 bile cultures and 2/8 blood cultures tested. Multidrug-resistant strains were isolated in 7/15 bile cultures and 3/8 blood cultures (Table 2).

Risk factors

Analysis of the overall group showed that hepaticojejunostomy was a statistically significant risk factor for infection (OR 4.11, 95%CI 1.31–12.88), and biliary obstruction was marginally significant (OR 2.30, 95%CI 0.99–5.34).

In the periprocedural prophylaxis group, hepaticojejunostomy and liver transplant status were both statistically significant risk factors (OR 3.63, 95%CI 1.06–12.39; and OR 5.11, 95%CI 1.50–17.41, respectively), whereas biliary obstruction was the only significant risk factor in the active infection group (OR 13.00, 95%CI 2.28–74.09). Neither patients' sex, the access route nor an ongoing infection were associated with an increased risk of NSMBT-related infection. The distribution of risk factors according to the development of infectious complications and the previous infection status are shown in Table 3.

Discussion

There was a substantial rate of infectious complications after NSMBT in our paediatric cohort, despite appropriate antibiotic prophylaxis. A high percentage of the patients included had biliary obstruction, a hepaticojejunostomy, or were liver-transplant recipients, and these factors were significantly associated with a risk of NSMBT-related infections. The infectious complications mainly occurred immediately after the procedure and affected the bile ducts (organ/space PSI – cholangitis–). Implementation of a prophylactic protocol enabled standardisation of the prophylaxis practice, which resulted in a decrease in the length of antibiotic prophylaxis with no increase in the infection rate.

Of particular note, the rate of infectious complications following NSMBT (28%) was higher than previously reported values (3–18%).[6,11,13,21,27] Certain features of our cohort may explain this difference. First, most of the procedures (103/113, 91%) were performed in patients with one or more potential risk factors for NSMBT-related infections, such as hepaticojejunostomy, biliary obstruction, and liver-transplantation.[10] Second, the bile duct had been manipulated previously in most of our patients, unlike the patients in other studies, in whom the bile duct was naïve.[16,18] If previous biliary tract manipulation were also considered a potential risk factor, all patients in our cohort would have at least one risk factor. Hence, this sample would represent the largest series of high-risk paediatric patients described to date.

Regarding the predisposition to infection, lack of the common bile duct (hepaticojejunostomy) was the main risk factor in both the overall cohort and in the prophylaxis group, being statistically significant in both groups. Liver transplant status followed as the second major risk factor in the prophylaxis group. Most paediatric liver recipients have a hepaticojejunostomy, because of extensive use of split livers (from cadaveric as well as live donors) and a high incidence of biliary atresia as the reason for transplant. Multivariate analysis would have been useful to assess the contribution of hepaticojejunostomy to the risk attributed to liver transplantation, but our study did not have the statistical power to perform this analysis. To our knowledge, presence of a hepaticojejunostomy has not been considered a risk factor in adults. In addition, analyzing the degree of immunosuppression of the transplant recipients would be interesting, but the design of our study did not make it possible due to the lack of standard comparators. Biliary obstruction was also a significant risk factor in the active infection group, as has been described in the literature.[11,14,20] Of note, ongoing but treated infections did not emerge as a statistically significant risk factor for further complications in our study. Moreover, in contrast to the findings in other studies, endoscopic access did not increase the infection risk, but this result could have been affected by the

Table 3
Distribution of risk factors by development of infectious complications and previous infection status.

	Infectious complication *n* (%)	No infectious complication n (%)	Odds ratio (95% confidence interval)	*p* value
TOTAL, n = 113	*n* = 32	*n* = 81		
Sex (male)	15 (47)	28 (35)	1.67 (0.72–3.83)	0.23
Liver transplant	26 (81)	51 (63)	2.54 (0.94–6.89)	0.06
Hepaticojejunostomy	28 (88)	51 (63)	4.11 (1.31–12.88)	**0.01**
Biliary obstruction	20 (63)	34 (42)	2.30 (0.99–5.34)	0.05
Endoscopic access	1 (3)	13 (16)	0.16 (0.02–1.34)	0.09
Current infection	10 (31)	34 (42)	0.62 (0.26–1.49)	0.29
PROPHYLAXIS GROUP, n = 69	(*n* = 22)	(*n* = 47)		
Sex (male)	11 (50)	17 (36)	1.76 (0.63–4.92)	0.28
Liver transplant	18 (82)	26 (55)	3.63 (1.06–12.39)	**0.03**
Hepaticojejunostomy	18 (82)	22 (47)	5.11 (1.50–17.41)	**<0.01**
Biliary obstruction	13 (59)	25 (53)	1.27 (0.45–3.54)	0.64
Endoscopic access	1 (5)	11 (23)	0.15 (0.01–1.29)	0.08
ACTIVE INFECTION GROUP, n = 44	(*n* = 10)	(*n* = 34)		
Sex (male)	4	11	1.39 (0.33–5.97)	0.65
Liver transplant	8 (80)	25 (74)	1.44 (0.25–8.09)	0.67
Hepaticojejunostomy	10 (100)	29 (85)	3.91 (0.19–77.04)	0.36
Biliary obstruction	8 (80)	8(24)	13.00 (2.28–74.09)	**<0.01**
Endoscopic access	0	2 (6)	3.91 (0.19–77.04)	0.36

Bold values mean statistical significance.

unequal distribution of access routes in our analysis (only 14/113 were endoscopic procedures).

As to the microbiological findings, the microorganisms isolated were the same as those described in previous reports. Our analysis showed 100% concordance between blood and bile culture when both samples were available and positive. In polymicrobial bile cultures, the most virulent microorganism is the one that reaches the bloodstream, and these were mainly Gram-negative rods, in accordance with previous reports.[35,36] The bile culture material was obtained from external or internal-external drains, although in the latter case it was difficult to interpret the role of the microorganism as the source of the infectious complication (colonisation *versus* infection). As would be expected, only a minority of pathogens were susceptible to the standard prophylactic regimen (piperacillin–tazobactam): 2/15 biliary cultures and 2/8 blood cultures. Prior manipulation of the hepatobiliary tissue disrupts the anatomical and physiological mechanisms of the biliary tract and favours colonisation by pathogens, which, after frequent instrumentation and exposure to prophylactic regimens, develop resistance against commonly used antibiotics.[37,38] Multidrug-resistant strains were isolated in 7/15 bile cultures and 3/8 blood cultures. Nonetheless, in our opinion, these results should not lead to changes in the prophylactic antibiotic scheme. A significant increase in the incidence of infections (overall and severe bacteraemic complications) did not occur despite this shorter approach, and infectious complications also occurred in patients receiving prolonged, broader spectrum antibiotic regimens. Instead, we believe that careful selection of patients requiring NSMBT is mandatory.

Regarding the antibiotic regimen and the impact of our local protocol, the predominant prophylactic scheme before June 2017 consisted of a longer-than-24-h antibiotic approach. Starting in June 2017, 100% of interventions received appropriate prophylaxis according to the local Paediatric Antimicrobial Stewardship Program, permitting a decrease in the antibiotic exposure time and potentially, the length of hospital stay. Despite the shorter length of antibiotic prophylaxis after June 2017, there were no significant differences in the incidence of infectious complications between the 2 time periods ($p = 0.46$), including bacteraemia ($p = 0.87$).

Most of the complications from June 2017 onwards were organ/space PSI – cholangitis–, which theoretically, is not preventable despite periprocedural antibiotic prophylaxis, according to the recent literature.[11,13,18,20] Finally, 72% of NSMBT-related infections in our series were early complications, and late complications predominantly occurred in procedures with prolonged antibiotic use, either for prophylaxis or therapy. Hence, it is important to underscore the need to avoid lengthy antibiotic prophylaxis, as it has shown no added benefit and may increase the risk of adverse events and, potentially, generation of antimicrobial resistance.

Our study has several limitations. First, it is a retrospective analysis and subject to the inherent limitations of this type of study, including the fact that assessment of complications was based on written medical records. Second, because there are no standardised guidelines to define the microbiological interpretation (infection *versus* colonisation) when samples are obtained from an internal-external drain, the results are interpreted subjectively depending on the patient's clinical status and the expertise of the treating physician. Third, the risk of misinterpretating a NSMBT-related infectious complication in the active infection group, or the fever with no source as fever related to an infection. Fourth, the relatively small sample prevented us from performing multivariate analysis, which could have provided important information about risk factors. Finally, the lack of a control group without PAP prevented us from evaluating the true impact of antibiotic prophylaxis.

To conclude, NSMBT entails a high risk of infectious complications in children, mainly those lacking a common bile duct, even under antibiotic prophylaxis. An appropriate but shorter prophylactic regimen did not lead to an increased incidence of infectious complications. Further collaborative studies are needed to establish unified definitions and specific indications regarding the periprocedural antibiotic approach in paediatric patients undergoing NSMBT.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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