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Study protocol of the FRENCH24-ANIS study: postoperative anti-infective strategy following pancreaticoduodenectomy in patients with preoperative biliary stents—an intergroup FRENCH-ACHBT-SFAR prospective randomized controlled trial

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Abstract

Background Despite advances in surgical techniques and care, pancreatoduodenectomy (PD) continues to have high morbidity and mortality rates. Complications such as sepsis, hemorrhage, pulmonary issues, shock, and pancreatic fistula are common postoperative challenges. A key concern in PD outcomes is the high incidence of infectious complications, especially surgical site infections (SSI) and postoperative pancreatic fistula (POPF). Bacteriobilia, or bile contamination with microorganisms, significantly contributes to these infections, increasing the risk of early postoperative complications. The occurrence of SSI in patients who undergo hepatobiliary and pancreatic (HPB) surgeries such as PD is notably higher than that in patients who undergo other surgeries, with rates ranging from 20 to 55%. Recent research by D'Angelica et al. revealed that, compared to cefoxitin, piperacillin/tazobactam considerably lowers the rate of postoperative SSI. However, these findings do not indicate whether extending the duration of antibiotic treatment is beneficial for patients at high risk of bacterial biliary contamination. In scenarios with a high risk of SSI, the specific agents, doses and length of antibiotic therapy remain unexplored. The advantage of prolonged antibiotic prophylaxis following PD has not been established through prospective studies in PD patients following biliary drainage.

Methods This is an intergroup FRENCH-ACHBT-SFAR multicenter, open-labelled randomized, controlled, superiority trial comparing 2 broad-spectrum antibiotic (piperacillin/tazobactam) treatment modalities to demonstrate the superiority of 5-day postoperative antibiotic therapy to antibiotic prophylaxis against the occurrence of surgical site infections (SSI) following pancreaticoduodenectomy in patients with preoperative biliary stents. The primary endpoint of this study is the overall SSI rate, defined according to the ACS NSQIP, as a composite of superficial SSI, deep incisional SSI, and organ/space SSI.

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In addition, we will analyze overall morbidity, antibiotic resistance profiles, the pathogenicity of bacteriological and fungal cocontamination, the impact of complications after bile drainage and neoadjuvant treatment on the bacteriological and fungal profile of biliculture and cost-effectiveness.

Conclusion This FRENCH24-ANIS study aims to evaluate 5-day post-operative antibiotic therapy combined with antibiotic prophylaxis on the occurrence of surgical site infections (SSI) following pancreaticoduodenectomy in patients with preoperative biliary stents.

Trial registration ClinicaTrials.gov number, NCT06123169 (Registration Date 08–11–2023); EudraCT number 2021–006991-18; EUCT Number: 2024–515181-14–00.

Keywords Pancreaticoduodenectomy, Surgical site infection, Biliary drainage, Antibiotic therapy, FRENCH24-ANIS, FRENCH group, ANIS trial

Background

In hepatobiliary pancreatic surgery for periampullary tumors, pancreatoduodenectomy (PD) is a prevalent operation. Despite advancements, the morbi-mortality rates of PD remain high, with a French study reporting 73% of cases globally and 41% of cases having major complications, including sepsis, hemorrhagic, pulmonary complications, shock, and pancreatic fistula [1].

A significant risk factor for infectious complications, particularly surgical site infections (SSI) and postoperative pancreatic fistula (POPF), is bacteriobilia – bile contamination by microorganisms [2, 3]. The presence of bacteria in bile during surgery is linked to early postoperative infectious complications. Large surveys [4, 5] highlight the problem of SSI in general surgery but lack specific data on pancreatic and liver resections. The incidence of SSI in patients who underwent hepatobiliary and pancreatic (HPB) surgery was greater than that in patients who underwent other surgeries, with rates between 20 and 55% [6–8].

Until recently, the French Society for Anesthesia and Intensive Care (SFAR) of the Infectious Diseases Society of America recommended a first- or second-generation cephalosporin uniformly as an antimicrobial prophylaxis for any PD [9, 10]. Single-institution studies suggest improvements in SSI with routine broad-spectrum antibiotics for PD [7, 11], and this practice has now been validated by the American randomized trial reported by D'Angelica et al. [12], which showed that the postoperative SSI rate was significantly lower among patients receiving piperacillin/tazobactam as antimicrobial prophylaxis (19.8%) than among those receiving cefoxitin (32.8%).

PD for patients who have previously undergone preoperative biliary drainage (PBD) is becoming more common and is routinely performed endoscopically. None of the abovementioned societies specify the management of PBD according to their guidelines, but PBD is a key risk factor for bacteriobilia, where the incidence of SSI following PD exceeds 50% [8, 13].

In high-risk situations for SSI, the management and prophylaxis of infection after PD are of interest, and Macedo et al. reported that most surgeons administer perioperative antibiotics beyond 24 h after surgery (52%) [14]. The additional benefit of prolonged antibiotic prophylaxis following PD is questionable.

In a recent systematic review and meta-analysis that evaluated SSIs in patients who underwent perioperative (within 24 h) versus prolonged antibiotic (over 24 h) prophylaxis after PD, the authors reported that among patients with PBD (5 studies reporting on 577 patients), organ/space infection rates were lower with prolonged antibiotic treatment compared with perioperative antibiotic treatment (OR 2.09, 1.43 to 3.07) [15].

With respect to the duration of postoperative antibiotic treatment, no clear consensus exists among 3, 5 or 7 days.

Prolonged antimicrobial prophylaxis, though offering extended infection protection, carries significant risks. The rising incidence of antimicrobial resistance (AMR) poses a global healthcare crisis, rendering long-standing antimicrobial agents less effective. In surgery, antibiotic prophylaxis is standard to prevent surgical site infections (SSI), one of the most common hospital-acquired infections. The growing AMR incidence complicates SSIs with resistant bacteria, leading to worse surgical outcomes, longer hospital stays, extended antibiotic therapy, higher revision surgery rates, and increased mortality. In Europe, around 33,000 deaths annually are due to drug-resistant infections, with more than half being healthcare-acquired [16]. Prolonged antibiotic use also causes adverse side effects: gastrointestinal disturbances, renal toxicity, hepatotoxicity, allergic reactions, fungal infections, and hematological effects.

Despite the lack of clear data and guidelines, no prospective study has compared antibiotic prophylaxis with pre- and postoperative antibiotic therapy in PD patients post-PBD.

We focused on high-risk bile contamination cases, aiming to compare two broad-spectrum antibiotics (piperacillin/tazobactam) to determine the superiority of 5-day

postoperative therapy over prophylaxis for SSI in patients with PBD. The FRENCH24 ANIS study, supported by FRENCH, ACHBT, and SFAR, aims to harmonize practices and address the lack of guidelines. Additionally, we seek to assess the incidence of biliary fungal contamination and conduct a medicoeconomic study on the impact of global and surgical site infections on healthcare costs. Findings will, finnaly, guide better patient outcomes and promote responsible antimicrobial stewardship in surgery [17].

Methods/design

Study organization and coordination

The FRENCH24-ANIS trial is designed and coordinated by L.S. (M.D., Ph.D.).

The FRENCH24-ANIS trial is conducted as a randomized, prospective multicenter study involving the participation of the Fédération de Recherche en Chirurgie (FRENCH) network. The coordinating center is represented by Rouen University Hospital—Normandy University (France). The investigators intend to include 27 participating centers. This research was financially supported by a Clinical Research Hospital Program grant (PHRC N 2020 n°20–0494) from the French Ministry of Health.

Study objectives

The main objective of this study is to compare 2 broad-spectrum antibiotic (piperacillin/tazobactam) treatment modalities to demonstrate the superiority of 5-day postoperative antibiotic therapy over antibiotic prophylaxis against the occurrence of surgical site infections (SSIs).

The primary endpoint of this study is the overall SSI rate, defined according to the ACS NSQIP as a composite of superficial SSI, deep incisional SSI, and organ/space SSI. The SSI definition used was deliberately the same as that used in the study by D'Angelica [12, 18], in order to compare the results of the two trials (Table 1).

The secondary objectives, with complications/morbidity assessed at 90 days, are as follows:

- Evaluation of the overall morbidity associated with the different treatment modes by recording surgical complications
- Evaluation of antibiotic resistance profiles and their impact on postoperative complications
- Assessment of the pathogenicity of bacteriological and fungal cocontamination
- Evaluation of the impact of complications after bile drainage and neoadjuvant treatment on the bacteriological and fungal profile of biliculture
- Cost effectiveness analysis

Patients and inclusion and exclusion criteria

All adult patients (age ≥ 18 years) who are candidates for PD performed for periampullary neoplasms following endoscopic or radiological preoperative biliary drainage.

The exclusion criteria were as follows:

Table 1 SSI definition according to Mangram et al. [18]

Superficial SSI is an infection that involves only skin or subcutaneous tissue of the surgical incision. An infection occurs within 30 days after the index operation and the infection involves only skin or subcutaneous tissue of the incision and at least one of the following:
a. Purulent drainage, with or without laboratory confirmation, from the superficial incision
b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision that is deliberately opened by the surgeon, unless incision is culture negative
d. Diagnosis of superficial incisional SSI by the surgeon or attending physician

Deep incisional SSI is an infection which involves deep soft tissues. Deep soft tissues are typically any tissue beneath skin and immediate subcutaneous fat, for example, fascial and muscle layers. It is an infection that occurs at the surgical site within 30 days after the principal operative procedure and involves deep soft tissues and at least one of the following:
a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (> 38.0° C, localized pain, or tenderness, unless the site is culture-negative
c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
d. Diagnosis of a deep incision SSI by a surgeon or attending physician

Organ/space SSI is an infection that involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation. It is an infection that occurs within 30 days after the principal operative procedure and involves any of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during the operation and at least one of the following:
a. Purulent drainage from a drain that is placed through a stab wound into the organ/space. This does not apply to drains placed during the principal operative procedure, which are continually in place, with continual evidence of drainage/infection since the time of the principal operative procedure
b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
d. Diagnosis of an organ/space SSI by a surgeon or attending physician

- Patients with known and documented allergies to any of the penicillins, cephalosporins, or β-lactamase inhibitors. Appropriate assessment and allergy testing are needed to confirm reported penicillin allergies prior to exclusion.
- Patients who are otherwise ineligible to receive the antibiotics in this study
- Patients with a known bacterial infection present at the time of surgery or who received antimicrobial therapy within 7 days prior to surgery
- Other pancreatic resections (distal pancreatectomy, total pancreatectomy, enucleation, ampullectomy)
- Absence of preoperative biliary drainage
- Surgical or anesthesiological contraindications

    - Noncontrolled congestive heart failure – non-treated angina – recent myocardial infarction (in the previous year) – noncontrolled AHT (SBP > 160 mm or DBP > 100 mm, despite optimal drug treatment), long QT
    - Major noncontrolled infection
    - Severe liver failure
    - Creatinine clearance (CrCl) ≤ 40 mL/min

- Medical, psychological or legal conditions that would not permit the patient to complete the study or sign informed consent
- Any significant disease, which, in the investigator's opinion, would exclude the patient from the study
- Pregnant or parturient or breastfeeding woman or absence of contraception
- Person deprived of liberty by an administrative or judicial decision or person placed under judicial protection, under guardianship or supervision
- Simultaneous participation in another interventional study with the same primary end point

Study design and setting

The FRENCH24-ANIS trial is an intergroup FRENCH-ACHBT-SFAR multicenter, open-label randomized, controlled, superiority trial comparing 2 broad-spectrum antibiotic (piperacillin/tazobactam) treatment modalities to demonstrate the superiority of 5-day postoperative antibiotic therapy to antibiotic prophylaxis for the occurrence of surgical site infections (SSI) following pancreaticoduodenectomy in patients with preoperative biliary stents. (Version No 2 of 03/25/2024 of the study protocol).

Overall, 27 French high- or intermediate-volume pancreatic surgery centers (hospitals) will participate in the present study. At least one of the surgeons or anesthesiologists at each center will be involved in the 3 groups that sponsor the research: the French Federation of Research in Digestive Surgery (FRENCH) program, the French Association of HPB Surgery and Transplantation (ACHBT) group and the French Society of Anesthesiology and Intensive Care (SFAR) group. On average, they each perform between 0.5 and 4 PDs a week, and we expect that approximately half of them will be included in the present study. A total of 326 patients are planned to be recruited over 24 months at 27 centers, i.e., 0.5 patients per month per center.

The inclusion visit will be scheduled for patients in the month before surgery in the Department of Surgery. The investigator will check for inclusion and noninclusion criteria. The surgeon will inform the patient about this study and answer questions. The patient will then be given a period of reflection in order to make a decision. If the patient agrees to participate in this study, then the patient and the surgeon will sign the consent form. The surgeon will proceed with randomization before the surgical procedure.

After completion of all the screening evaluations (with all the inclusion criteria satisfied and none of the exclusion criteria met) and signing of the informed consent forms, all eligible patients will be randomly assigned to one of the treatment arms. The randomization can be performed by the surgeon between the day prior to the surgery and the first incision of the surgery (D-1 to D0).

Randomization will be performed using the Interactive Web Responses System based in the research informatics server at Rouen University Hospital.

Figure 1 shows the study design.

A 90 days follow-up will be performed with the help of electronic health records (HER) for readmissions in the same center and a physical visit. If the patient does not come to the planned visit, a phone call to the patient and general practitioners will be performed to collect information about readmissions and complications that have not been identified in the EHR.

Experimental plan

In the "experimental" arm, 5 days of antibiotic therapy (ABT)* will be administered intravenously. The ABT will consist of 4 g/500 mg piperacillin/tazobactam, diluted in 50 ml of 0.9% NaCl, given intravenously at the beginning of surgery and continued at 12 g/1500 mg daily (4 g/500 mg every 8 h) after surgery until bile culture results are obtained:

- If bile cultures are negative, ABT will be stopped.
- If bile cultures are positive and sensitive to piperacillin/tazobactam, the same treatment will be continued until postoperative day 5.

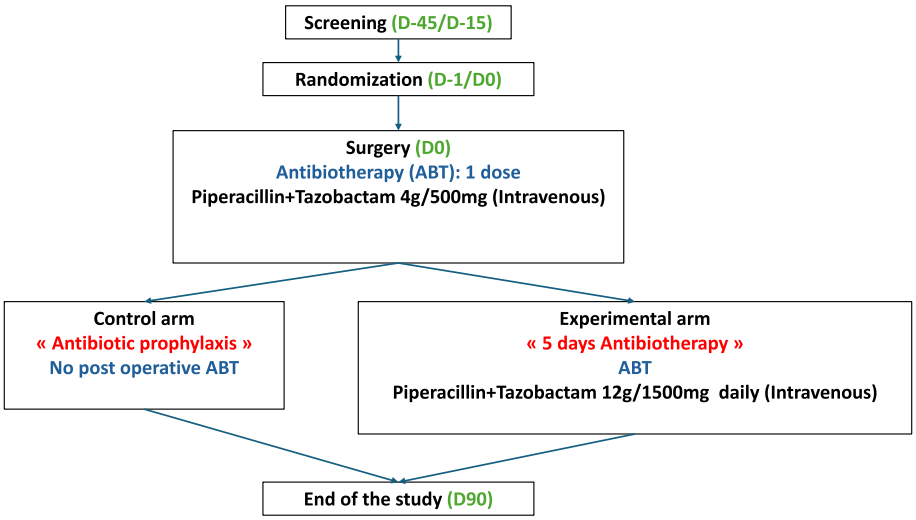

Fig. 1 FRENCH24-ANIS study design

- If bile cultures are positive and resistant, the treatment will be adapted to the cultures for an effective duration of 5 days.

In the "control" arm, only the dose of antibiotic administered at the beginning of surgery, namely piperacillin/tazobactam 4 g/500 mg of powder for injection*, diluted in 50 ml of 0.9% NaCl, will be given intravenously. An additional dose of piperacillin/tazobactam PANPHARMA 4 g/500 mg powder for injection will be administered 8 h after the first injection in the case of an extended operation time.

After surgery, the bile culture results will be obtained according to the protocol:

- If bile cultures are positive without infection symptoms, no antibiotherapy will be provided.
- If bile cultures are positive and infection symptoms occur, antibiotherapy adapted for culture will be provided. The duration of treatment will be chosen according to the clinical situation.

At the beginning of the surgery, the patient will receive a dose of broad-spectrum prophylactic antibiotics (piperacillin + tazobactam 4 g/500 mg given intravenously) 30 min before the skin incision. For each patient, four intraoperative biliary samples will be taken from two different sites: the gallbladder and the bile duct. Thus, for each patient, an antifungiogram and an antibiogram will be performed for each sampling site. The surgical procedure will be performed according to the surgeon's preferences. During this period of hospitalization, adverse events (AEs) and serious adverse events (SAEs) will be recorded.

Ninety days (± 15 days) after surgery, an end-of-the-study visit will be conducted. During this visit, the surgeon will record infectious complications, including SSIs and overall postsurgical morbidities, graded according to the Clavien–Dindo classification system and CCI score; specific morbidities due to pancreatic fistula, graded according to the International Study Group of Pancreatic Fistula (ISGPF) criteria; readmission rates; duration of hospitalization; incidence of fungal contamination; correlation between bacteriological and fungal contaminations; and bacteriological resistance profiles.

Table 1 shows the chronology of the research according to SPIRIT guidelines.

Randomization

The population in each group will be balanced at a ratio of 1:1. Simple randomization will be performed because the design is open-label. Indeed, stratified randomization, especially center stratification, will make it possible to consciously or unconsciously predict the sequence of allocations since several allocations in one group are probably followed by allocations in the other group, leading to a selection bias [19, 20]. These problems can be reduced, to an extent, by using large randomization blocks and random-sized randomization blocks, but simple randomization is the only method that guarantees independence between allocations. Kenneth et al. recommends simple randomization in non double blind controlled trials [20] since Lachin found a negligible power loss for $n \geq 200$ patients [21].

A document specifying the randomization procedure will be kept confidentially in the Biostatistics Unit (Table 2).

Table 2 Study participants' visits

	Screening	Randomization	Surgery	Post-operative hospitalization					End of the study
Study day	D_{-45}/D_{-15}	D_{-1}/D_0	D_0	D_1	D_2	D_3	D_4	D_5	D_{90}
Review inclusion / exclusion criteria	✓								
Collection of consent	✓								
WHO performance status	✓								
Demographic data	✓								
Concomitant treatment	✓								
Medical history	✓								
Blood pregnancy test	✓								
Clinical examination/ vital signs	✓		✓						✓
Laboratory testing	✓		✓						✓
Randomization		✓[a]							
Intraoperative biliary sampling (antibiogram/antifungus)			✓						
Administration of Pipe/Tazo 4 g / 500 mg (IV)			✓[b]						
Administration of Pipe/Tazo 12 g / 1500 mg (3 times 4 g / 500 mg a day every 8 h) (IV)				✓[c]	✓[d]	✓[d]	✓[d]	✓[d]	
Adapted treatment of antibiotics					✓[e]	✓[e]	✓[e]	✓[e]	
AE and SAE reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] Before the first prescription of post-operative treatment

[b] At the beginning of the surgery and 8 h after the first injection in "control" arm if the surgery lasts more than 8 h

[c] Only « experimental» arm: until bile cultures results

[d] Only « experimental» arm: if bile cultures is positive and sensitive to Pipe/Tazo

[e] Only « experimental» arm: if bile cultures is positive and resistant

The randomization list will be established in the Biostatistics Unit of the Rouen University Hospital by SAS or R software before the start of the trial and will then be saved centrally and readable by Cleanweb software (Telemedecines Technologies). Upon request via the system, the investigator will obtain the randomization number and the group to which it will be assigned. This information will be sent by the system via e-mail to the center investigator, the pharmacy and the sponsor.

Assessment of efficacy

The primary endpoint of this study will be the presence of an organ/space SSI determined according to the Centers for Disease Control and Prevention's national nosocomial infection surveillance system. Organ/space SSIs include postoperative pancreatic fistula (POPF) and bile leakage, with positive culture results. Clinical examination will be performed every day to collect manifestations related to SSI and its complications. Clinical examination will include temperature, signs of sepsis or infection, and drainage output. A biological evaluation will be performed once every two days. Imaging requested according to the clinical manifestations will be recorded. The need for reoperation, radiological or endoscopic drainage, and readmission will be recorded. Assessments for pancreatic and nonpancreatic complications will be performed at the time of discharge and during follow-up by the attending surgeon.

The anonymized data of perioperative biological, clinical and radiological data (but neither prescriptions nor antibiotic blood dosages) of the electronic health record will be uploaded on a secure Web platform and reviewed by blind assessment committees composed of an infectiologist and a surgeon. They will assess the primary outcome, blind of the randomization group. To avoid the risk of unblinding by case recognition, the infectiologist and surgeon will not review patients of their center; a different committee will review their cases.

Sample size considerations

Assuming a frequency of SSI equal to 33.9% in the 5-day ATB group vs. 51.6% in the standard group (same difference as the one found by Okamura, PMID: 28,371,248) [12], 90% power and a 5% two-sided type I error rate for a chi-square test, the sample size will be 163 patients per group (326 total). Protocol deviations and losses to follow-up may reduce the statistical power, but they are expected to be rare.

In daily surgical practice, pancreaticoduodenectomy represents approximately 80% of pancreatic resections. For the last French clinical trial (PREFIPS, NCT03000946), 654 patients with PD were included during 24 months in 16 French referral centers for pancreatic surgery, ensuring the feasibility of the study in terms of recruitment.

Statistical analysis

Primary analysis and sensitivity analysis

The primary intention-to-treat (ITT) analysis will be performed. All the randomized patients will be included in the primary analysis.

If a patient dies after randomization, before surgery (even before any antibiotic treatment) or up to 90 days after surgery (or initially planned surgery if the surgery is canceled), he or she will be considered to have an SSI. If the surgery is canceled, it will be assumed that no SSI can occur. If the surgery is delayed, the patient will be kept in his randomization arm and receive the planned treatment later. The follow-up data will be reported but will not change the primary outcome analysis.

Major protocol deviations to the antiobiotherapic treatment, including prescription of the wrong antibiotherapy or no antibiotherapy at all, will be ignored. Patients will be analyzed as if they had received the intervention planned by their randomization groups. Patients who have met the exclusion criteria (inclusion error) will be included in the ITT analysis if they have been randomized. As described before, if patients receive no surgical interventions, they will not meet the primary outcome unless they die within 90 days following the surgery day initially planned.

Data on the primary outcome may be missing if patients withdraw their consent for data collection or if they are lost to follow-up.

No in-hospital loss to follow-up is expected, and loss to follow-up at 90 days is improbable even after hospital discharge.

If there is no missing data on the primary outcome, a chi-square test without continuity correction will be performed as the primary analysis, with a two-sided type I error rate set at 5%. If there is at least one missing primary outcome, the 90-day rate of SSI in each group will be estimated by the Kaplan–Meier method, with censorship at the last follow-up visit, and compared by normal approximation Wald's test with Greenwood's formula for variance on a linear scale (i.e., without log, arcsine or cloglog transformation).

A sensitivity analysis will be performed with the maximal bias hypothesis, assuming that all patients lost to follow-up in the experimental group have had an SSI and that none lost to follow-up in the control group have had any SSI after their last visit. This will be performed by a chi-square test.

A second sensitivity per protocol analysis is planned. Patients with major protocol deviations, such as patients who do not fulfill the inclusion criteria and patients who do not receive the planned antibiotic treatment, will be excluded from this analysis. Patients who would not have undergone surgery will be excluded from this analysis. The Kaplan–Meier/Greenwood method will be used to compare the two groups unless there are no patients lost to follow-up; in such cases, the chi-square test will be used.

There will be no multiple testing corrections for sensitivity analyses since they cannot substitute for the primary analysis but can only break the primary analysis when they provide inconsistent results (strong change in point estimate or confidence interval width).

The three subsequent secondary analyses (90-day Clavien–Dindo complication rate, 90-day readmission rate and duration of hospitalization) will be performed if the primary analysis is successful ($P < 0.05$), with an overall two-sided type I error rate set at 5%, owing to hierarchical testing (gatekeeping by the primary analysis) and a Benjamini–Hochberg multiple testing procedure for the three secondary analyses.

Secondary analysis: comparison of surgical complications between randomization groups

The hierarchical testing + Benjamini–Hochberg procedure applies to the secondary analysis.

Patients with several Clavien–Dindo complications will be described by the complication having the highest grade.

The proportions of patients with at least one Clavien–Dindo complication ≥ 2 will be compared between the ITT groups via the same method used for the primary analysis: the chi-square test with the maximal bias hypothesis will be used if there are 0 to 3 patients lost to follow-up, and Kaplan–Meier/Greenwood estimation will be used to determine the difference in proportions. No sensitivity analysis is planned for that outcome.

The description of Clavien–Dindo complication grades 1, 2, 3A, 3B, 4, 4A, 4B and 5 will be performed for both groups by frequency and proportion without formal statistical comparison, even in case of failure of the primary analysis, to make the meta-analysis possible on these judgment criteria. In that descriptive analysis, patients lost to follow-up will all be considered to have had no complications after having been lost to follow-up.

Secondary analysis: comparison of 90-day readmission rates between randomization groups

The hierarchical testing + Benjamini–Hochberg procedure will be used for secondary analysis.

Ninety-day readmissions will be counted from the day of surgery or planned day surgery if the surgery has been canceled.

This comparison will be performed for the ITT sample. Patients lost to follow-up will be considered not to have been readmitted unless they are readmitted before being lost to follow-up. A chi-square test will be used to compare the proportions of patients readmitted between the two randomization groups, and the absolute difference in proportions will be estimated by Wald's method.

Secondary analysis: duration of hospitalization

The duration of the initial hospitalization will be compared in this analysis. Readmission will not be considered. The duration will not be capped to 90 days, but if a patient is still hospitalized when the study terminates, his or her duration of hospitalization will be imputed at the actual timepoint he or she has already reached.

The hierarchical testing + Benjamini–Hochberg procedure will be used for secondary analysis.

Patients in the ITT sample will be compared between randomization groups for the duration of their initial hospitalization by Student's t test. The total duration of hospitalization will be taken into account for patients transferred to another hospital (sums of durations in each hospital). A patient for whom the duration of hospitalization is not known after transfer will have an imputation based on the average duration of hospitalization of patients having had a duration of hospitalization greater than the initial duration of this patient (duration of stay in the center). Patients dying during the initial hospitalization will have a hospitalization duration set at the 90th percentile of hospitalization duration or to the actual hospitalization duration if the latter is longer.

Ancillary analyses

These analyses are labeled "ancillary" because they are not aimed at assessing the experimental treatment. No multiple testing procedures are planned for these ancillary analyses. All analyses will be two-sided, with a type I error rate of 5% for each analysis.

To respond to the objective "Evaluation of antibiotic resistance profiles and their impact on postoperative complications", the antibiotic resistance of all surgical site contaminations or infections will be described by the proportion of resistance to each class of antibiotic tabulated for each germ category. Some broad categories may be defined, such as extended-spectrum beta-lactamase (ESBL) Enterobacteriaceae. Comparisons of complications will not be performed between groups with fewer than 30 patients (insufficient statistical power). If possible (more than 30 patients in each group), patients with contamination/infection caused by bacteria sensitive/intermediate to the probabilistic antibiotherapy will be compared to patients with bacteria germs resistant to the probabilistic antibiotherapy, with adjustment based on the bacterial type. Comparisons will be perfomed by Student's t tests or a general linear model (when adjusting for germ type) on the Clavien–Dindo scale (from 1 to 5, with IIIB coded as 3.5 and IVB coded as 4.5). For each patient, the worst Clavien–Dindo complication will be used as a reference.

To respond to the objective "Assessment of the pathogenicity of bacteriological and fungal cocontamination", patients with fungal contamination will be compared to patients without fungal contamination on the average Clavien–Dindo scale by a general linear model adjusted for the type of bacterial pathogen (broad categories) if there are more than 30 patients in each group.

To assess the correlation between postoperative bacteriological samples and intraoperative bile samples, the proportion of patients for whom the same pathogen is found in both samples will be estimated. In the case of polymicrobial cultures, at least one microbial pathogen must be identical between the two cultures. A contingency table of the two samples will be shown, excluding rare microbes.

To assess the correlation between bacteriological and fungal contamination, the rate of fungal contamination/infection (i.e., positive fungal sample, with or without symptoms) will be compared between patients with resistant and nonresistant bacteria. The frequency of fungal contamination/infection may be compared between the main bacterial pathogens if the sample sizes are large enough.

Discussion

Among the most prevalent complications following pancreaticoduodenectomy (PD), pancreatic fistula and infectious complications account for approximately 20 to 30% and 40 to 50% of cases, respectively [1, 22]. One of the primary risk factors for infectious complications, particularly surgical site infections (SSI) [2] and postoperative pancreatic fistula (POPF) [3], is bacteriobilia, characterized by the contamination of bile with microorganisms.

Studies have reported a greater incidence of POPF in patients with bacteriobilia than in those with a negative intraoperative bile culture (38% vs. 25%, $p < 0.03$) [3]. Additionally, biliary contamination has been associated with increased rates of intra-abdominal hemorrhage (7% vs. 1%) and wound infections (28% vs. 7%; $p < 0.03$). Notably, positive drainage fluid cultures on postoperative

days 1 (15% vs. 3%) and 3 (27% vs. 7%) were significantly more common in patients with biliary contamination ($p < 0.001$). Interestingly, cultures from drainage fluid on postoperative day 3 were found to be positive in 19% of patients, with the microorganisms detected matching those isolated from bile cultures in 100% and 88% of patients, respectively, for patients with positive intraoperative bile cultures on postoperative days 1 and 3. These findings suggest that bacteria present in spilled bile during surgery are early contributors to postoperative infectious complications.

A systematic review with meta-analysis by Mussle in 2016 reported a significantly increased incidence of SSI in patients with bacteriobilia (RR 2.84; CI 2.17–3.73; $p < 0.001$) [2]. SSI has been linked to prolonged hospital stays and increased healthcare costs [23, 24]. Moreover, its higher occurrence in hepatopancreaticobiliary (HPB) surgery indicates a greater economic burden in patients undergoing such procedures. HPB oncological resection complicated by SSI has been shown to reduce overall survival, both as an independent prognostic factor and by delaying or preventing adjuvant chemotherapy [25, 26].

Preoperative biliary drainage and the presence of an ampullary malignancy are strongly associated with bile contamination, with approximately 95% of these patients having positive bile cultures. Given the likely increase in the use of preoperative biliary drainage, especially in the context of neoadjuvant therapies, there is a need to optimize antibiotic prophylaxis. Therefore, extended antibiotic prophylaxis should be considered for patients at high risk of contaminating bile to reduce postoperative infectious complications.

In the absence of previous national or international guidelines, a study by D'Angelica et al. validated the use of broad-spectrum antibiotics such as the piperacillin/tazobactam combination after PD [12]. However, these studies do not provide differentiated conclusions in high-risk situations such as those involving preoperative biliary drainage. The increasing prevalence of PD in patients who have previously undergone preoperative biliary drainage, particularly in the context of neoadjuvant therapy, necessitates careful consideration of the appropriate perioperative prophylactic antibiotic and its duration, depending on the presence of PBD.

The percentage of patients with a positive bile culture (bacteriological bile contamination), whether with or without preoperative biliary drainage, is commonly less than 20% and greater than 95%, respectively [27]. PBD (in relation to bacteriological biliary contamination) and postoperative pancreatic fistula are well established as the two main factors contributing to SSI [28]. Antibiotic prophylaxis theoretically affects only contaminated bile. Therefore, stratification based on the criterion of "biliary drainage," as proposed by D'Angelica et al., is logically sound. Subgroup analysis revealed that the impact of antibiotic prophylaxis on the occurrence of SSI was not significant (OR = 0.76, 95% CI = 0.51 to 1.12). The rates of SSI in the absence of PBD were 23.1% and 28.3% in the piperacillin-tazobactam and cefoxitin groups, respectively. This difference was more pronounced and statistically significant after biliary drainage (OR = 0.38; 95% CI (0.25 to 0.58)), with SSI rates of 17.6% and 35.9%, respectively. Notably, the authors mentioned that the observed effect of piperacillin-tazobactam was nonsignificant for certain subgroups, such as participants without biliary stents, without drawing definitive conclusions [12].

Before this randomized controlled trial, several single-institution studies indicated improvements in SSI rates following the adoption of routine broad-spectrum antibiotics for PD, particularly after PBD. Indeed, Kone et al. [29] and DeGrandi et al. [30] reported a significant decrease in all-type SSI and organ-space SSI with broad-spectrum antibiotics after open PD. A subgroup analysis by Kone et al. revealed that only patients with preoperative biliary stents and/or jaundice (constituting 61% of PD patients) had a significant association between broad-spectrum antibiotics and reduced SSI.

In studies focusing on patients undergoing surgery following preoperative biliary drainage (PBD), a major risk factor for bacteriobilia, the average rate of SSI exceeded 50% [8]. For instance, Okamura's study specifically assessed the risk of SSI after hepatobiliary and pancreatic surgery with PBD and reported an overall SSI rate of 71% at 30 days [31].

To mitigate the risk of SSI associated with PBD, the adoption of a "fast track pancreatic surgery" strategy, known to reduce infectious complications after pancreatic resection, may be considered. However, the latest French recommendations suggest that PBD should be reserved for patients with jaundice associated with specific conditions, such as severe hyperbilirubinemia, angiocholitis, or renal insufficiency related to hyperbilirubinemia, or when surgery needs to be deferred for reasons such as operability assessment, renutrition, or neoadjuvant chemotherapy [32].

In the absence of guidelines or high-quality data guiding decision-making, many surgeons and institutions have developed their own antibiotic prophylaxis regimens. An international survey of hepatobiliary surgeons revealed marked heterogeneity in antibiotic choice, with 36% opting for 2nd generation cephalosporins, 19% opting for 1st generation cephalosporins, 10% opting for ampicillin with sulbactam, 9% opting for extended spectrum penicillins, and 26% selecting various other regimens [14]. Information regarding the duration and timing of prophylactic antibiotic use in pancreatic

surgery was not available, but it is estimated that approximately 70% of North American surgeons discontinue prophylactic antibiotics within 24 h of surgery. Institutional culture surveillance, institutional antibiograms, and preoperative/intraoperative bile culture data were also lacking in the dataset, highlighting the heterogeneous nature of practices in this field. Some authors have compared antibiotic prophylaxis with 1st- or 2nd-generation cephalosporins to broad-spectrum antibiotics for durations ranging from 3 to 5 days [30, 33, 34]. Additionally, several studies have compared antibiotic prophylaxis with 1st- or 2nd-generation cephalosporins to broad-spectrum antibiotics [30, 33, 35]. Droogh et al. noted the benefits of prolonged antibiotic treatment duration, with a decreased proportion of organ/space infections in patients with PBD [15].

In the context of this research project, we conducted a practice study under the auspices of the FRENCH group. Our observations indicated that curative postoperative antibiotic therapy was administered in 58% of patients with PBD. This observation underscores the diversity of practices among expert centers in pancreatic surgery. In the event of introducing a probabilistic postoperative antibiotic therapy, piperacillin-tazobactam (a broad-spectrum antibiotic) was the choice for the majority of patients (58%) due to the observed resistance spectra of the primary causative microorganisms.

Surgical antibiotic prophylaxis may play a pivotal role in managing infectious complications in this patient population. The microbiological etiology of postoperative infections strongly suggests that some cases are a consequence of biliary contamination [36]. Stecca et al. reported that more than 50% of bacteriobilia cases showed resistance to the administered prophylaxis [37]. Furthermore, patients with antibiotic-resistant infections experienced significantly greater complication rates (68% vs. 39%; $p=0.04$; RR = 1.73; 95% CI = 1.012–3.214). Failure to treat bacterial infections with an appropriate antibiotic regimen nearly doubled the overall complication rate. Additionally, fungal infections, including Candida spp. and Hafnia spp., should not be underestimated, as they are present in 25% to 45% of cases. For instance, we recently reported a 25% rate of biliary fungal contamination in patients with biliary bacterial contamination [38]. Commonly implicated microorganisms include Klebsiella spp., Enterococcus spp., Escherichia spp., Enterobacter spp., Streptococcus spp., and *Pseudomonas aeruginosa* [36, 37, 39]. In most cases, cultures revealed a mixture of microbial flora rather than monomicrobial infections, with these microorganisms typically present in the gastrointestinal flora.

Given that 75% to 80% of the abovementioned pathogens following PBD exhibit resistance to classically used antibiotic prophylaxis (cefoxitin-metronidazole), broader spectrum antibiotics, such as piperacillin-tazobactam, should be considered. Despite the absence of reliable data and precise recommendations, no prospective study has been proposed to compare antibiotic prophylaxis with perioperative (antibiotic prophylaxis) or postoperative antibiotic therapy in the context of PD following PBD.

To address this gap in knowledge and provide guidance, the FRENCH24 ANIS study, supported by the FRENCH, ACHBT, and SFAR groups, is aimed to be the first prospective study focusing on this subgroup of patients who undergo surgery after biliary drainage. As a secondary objective, this study will evaluate the incidence of biliary fungal contamination, which is poorly documented in the literature. Given the significant economic impact of global and surgical site infections on healthcare costs, a health economics study is also proposed in this study.

Ethics and dissemination

Each participant will be granted a contemplation interval after the delivery of the pertinent information and prior to the endorsement of the informed consent document.

The responsibility of collecting the informed consent document prior to the participant's enrollment in the study protocol resides with the principal investigator or a delegated medical professional representing the investigator. The participant will be furnished with the informational document and a duplicate of the signed and dated informed consent form, both endorsed by the participant and by either the principal investigator or the representing physician. This exchange will occur before the participant's engagement in the research project. Furthermore, the investigator is obliged to document in the participant's medical records the methodologies employed for both securing consent and providing the necessary information aimed at obtaining said consent. The original informed consent document, bearing signatures and dates, will be retained by the investigator.

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Author's note
All communications and scientific reports pertaining to this trial will fall under the oversight and responsibility of the lead investigator. The authorship of all communications and reports will include the investigators and clinicians involved in patient management, determined by the number of patients they have included, as well as the statistician overseeing the data analysis. The FRENCH network, along with the ACHBT and SFAR groups, will be acknowledged in all publications. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. This study has been registered at ClinicalTrials.gov with the identifier NCT06123169 (Registration Date 08–11–2023).

Sponsor role
The study sponsor plays a crucial role in ensuring the successful execution and timely completion of the research project, by involving responsibilities in Oversight and Monitoring, Provision of Resources, Compliance and Reporting, Facilitation of Communication and Risk Management. A Data Monitoring Committee (DMC), appointed by the study sponsor, is tasked with the oversight of participant safety and the integrity of data during the clinical trial, ensuring that the study is conducted according to the highest ethical and scientific standards.

Authors' contributions
LS, JR, ASC, OJB: literature search and analysis. LS, ASC, OJB: study conception. AG, JR, EL: methodology. LS: drafting the article. All authors were involved in the revision of this article and in the study conception and design. Moreover, all authors have read and approved the final article and agree to be accountable for all aspects of this work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by CPP: Comité de Protection des Personnes ANSM: Agence Nationale de Sécurité du Médicament. The patients/participants provided their written informed consent to participate in this study. Any major modifications to the protocol will require a formal amendment to the protocol and must be reported to the same regulatory authorities.

Competing interests
The authors declare no competing interests.

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