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**Antibiotic prophylaxis and infection treatment in cephalic duodenopancreatectomy:
case series from a tertiary hospital in Portugal (2017-2020) and protocol proposal**

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RESUMO

Apesar dos avanços na técnica cirúrgica da duodenopancreatectomia cefálica, as complicações peri-operatórias continuam a ser uma causa major de morbimortalidade nestes doentes. As infeções são como as mais comuns e requerem, muitas vezes, longos cursos de antibioterapia, prolongando os internamentos e custos inerentes. Este trabalho visa analisar a casuística do Hospital de Santa Maria entre 2017 e 2020, por forma a traçar o perfil microbiológico e o padrão de resistência das bacteriobílias e das infeções e os fatores preditores de infeção nestes doentes, nomeadamente no que concerne a meios complementares de diagnóstico invasivos. Interpretando os dados, pretendemos definir novas estratégias para adequar a profilaxia cirúrgica e o tratamento empírico das complicações infecciosas, ajustando-os à epidemiologia local, conforme já sugerido em estudos anteriores. De acordo com o nosso estudo, a Colangiopancreatografia Retrógrada Endoscópica aumenta a taxa de bacteriobília. A profilaxia cirúrgica preconizada nas *guidelines* internacionais tem uma taxa de eficácia de 5.9%. Propomos a colheita de amostras de bÍlis pós-manipulação em CPRE e estudo de colonização retal de Enterobacterales produtoras de carbapenemases e/ou *Enterococci* resistentes à vancomicina, para ajuste da profilaxia cirúrgica no âmbito de uma consulta pré-operatória de Infecciologia (integrada no Programa de Prevenção e Controlo de Infeções e Resistência aos Antimicrobianos nacional). Se estes dados não estiverem disponíveis, sugerimos profilaxia cirúrgica com piperacilina/tazobactam (e tigeciclina se fatores de risco associados). Sugerimos ainda a colheita de amostras de bÍlis durante a cirurgia e tratamento da bacteriobília. As infeções deverão ser tratadas de acordo com os agentes isolados na bacteriobília ou, se indisponível, com meropenem, amicacina e vancomicina, até estarem disponíveis os resultados culturais.

Palavras-chave: duodenopancreatectomia, profilaxia, antibióticos, infeção, bacteriobília

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ABSTRACT

Despite the advances in the surgical technique of cephalic duodenopancreatectomy, perioperative complications remain a major cause of morbimortality in these patients. The most common complications are infectious and usually require long courses of antibiotics as well as long hospital stays, which have huge costs. This work aims to analyze the cases of Hospital de Santa Maria between 2017 and 2020 to outline the microbiological profile and resistance patterns of both the bacteriobias and the infections in these patients. We also analyzed predictive factors of infection, namely invasive procedures. After analyzing the data, we plan to define new strategies to tailor antibiotic prophylaxis and empirical treatment of infectious complications, according to local epidemiological data, which had been suggested in previous studies already. According to our data, it seems Endoscopic Retrograde Cholangiopancreatography increases the rate of bacteriobias. Surgical prophylaxis advocated in international guidelines has an efficacy rate of 5.9%. We suggest routine collection of bile samples after ERCP procedures and, combined with rectal colonization of the patients (for carbapenemase-producing Enterobacterales and/or Vancomycin-resistant *Enterococci*), later adjustment of surgical prophylaxis in a pre-operative Infectious Disease Consultation integrated in the National Program for Infection Control and Prevention of Antimicrobial Resistance. If these data are unavailable, then patients should receive prophylaxis with piperacillin/tazobactam (plus tigecycline depending on the risk factors). Additionally, we suggest routinely collection of bile samples intra-operatively and later treatment of bacteriobias. Infectious complications should be treated according to bacteriobias isolates or, if unavailable, with meropenem plus amikacin and vancomycin, until culture results are available.

Keywords: duodenopancreatectomy, prophylaxis, antibiotics, infection, bacteriobias

This work was approved by the Ethics Committee on February 19th, 2021.

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LIST OF ACRONYMS

2GCS – second-generation cephalosporin

2/3GCS-S – susceptible to second and third generation cephalosporins

3GCS – third-generation cephalosporin

AB – antibiotic

AMC-R – acquired resistance to amoxicillin/clavulanate

AMK-R – acquired resistance to amikacin

AP – aspiration pneumonia

ASA – American Society of Anaesthesiologists

BA - bacteriemia

BB - bacteriobilia

BMI – body mass index

Clinda-R – acquired resistance to clindamycin

CPE – carbapenemase-producing Enterobacterales

CPKP – carbapenemase-producing *Klebsiella pneumoniae*

CST-R – acquired resistance to colistin

DGE – delayed gastric emptying

ERCP – endoscopic retrograde cholangiopancreatography

ES – endoscopic sphincterotomy

ESBL – extended-spectrum beta-lactamases

ESGE – European Society of Gastrointestinal Endoscopy

FOS-R – acquired resistance to Fosfomycin

HA – hospital admission

HPB – hepato-pancreato-biliary

IAA – intra-abdominal abscess

IAI – intra-abdominal infection

IC – infectious complication

IO – infections of other systems

IOBC – intra-operative bile culture

LZD-R - acquired resistance to linezolid

MDR – multidrug resistant

Metro-R – acquired resistance to metronidazole

MRCP – magnetic resonance cholangiopancreatography

MRSA – methicillin-resistant *Staphylococcus aureus*

MS – multi-susceptible

NPWT – negative pressure wound treatment

NSBL – narrow spectrum beta lactamase

OI – other infections

OPD – open duodenopancreatectomy

PBD – preoperative biliary drainage

Pen-R – acquired resistance to penicillin

POPF – postoperative pancreatic fistula

PPCIRA – Plano de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos

PPH – postpancreatectomy haemorrhage

PPCDP – pylorus-preserving cephalic duodenopancreatectomy

PPX – prophylaxis

PTBD – percutaneous transhepatic biliary drainage

PTC – percutaneous transhepatic cholangiography

QN-R – acquired resistance to fluoroquinolones

RS – rectal swab

SCIP – surgical care improvement project

SD – standard deviation

SOIC – site of infection cultures

SRP – sensitivity and resistance pattern

SSI – surgical site infection

TET-R - acquired resistance to tetracycline

TGC-R – acquired resistance to tigecycline

TLPD – total laparoscopic duodenopancreatectomy

TMP/SMX – trimetropim-sulfametoxazol

TZP-R - acquired resistance to piperacillin/tazobactam

UTI – urinary tract infection

VAN-R - acquired resistance to vancomycin

VRE – vancomycin-resistant *Enterococcus spp.*

VSE – vancomycin-susceptible *Enterococcus spp.*

XDR – extensively-drug resistant

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1. INTRODUCTION:

Bile is usually a sterile liquid due to several physiological mechanisms, such as the competence of the sphincter of Oddi (preventing the reflux of intestinal content) as well as the composition of bile itself, which has bile salts (with bacteriostatic properties) and immunoglobulin A (Armiñanzas & Herrera, 2016).

The gut microbiota also offers protection against pathogenic microorganisms because it has immunomodulatory properties and can also regulate metabolic processes; microorganisms can change their metabolism drastically as a way to respond to certain environmental factors (Wang et al., 2015).

The isolation of microorganisms in the biliary tree is called bacteriobilia and is related with several risk factors that have been studied in the past, for example: increased age, biliary lithiasis, personal history of neoplasm or coronary disease, masculine gender, high ASA index, previous manipulations of the biliary tree, among others. What has not yet been well understood and still is the topic of much controversial debating is whether this bacteriobilia can play a role as far as the patients' outcomes are concerned, namely after pancreatic surgery. Many studies about this have been performed in the past but the results are not consistent (Armiñanzas & Herrera, 2016). The first study suggesting that bacteriobilia may have a role in post-surgical infectious complications was published by Wells in 1989 (G. R. Wells et al., 1989) and many others have since then further researched this topic.

There is evidence that subjects who have multidrug resistant bacteria in their bile have an increased risk of developing post-operative infectious complications (Sudo et al., 2007)(Carlo et al., 2018). On the other hand, it has also been shown that postoperative complications also have an influence on the microbiota of the biliary tree (F Scheufele et al., 2017).

It should be noted that multidrug-resistant (MDR) bacteria have become a major challenge globally, brutally increasing mortality and treatment costs worldwide, and have disseminated across the globe, becoming an epidemic problem; thus the importance of tackling this problem (Grundmann et al., 2017; Tzouveleakis et al., 2012).

Initially it was thought that pancreatic juices and bile created an environment far too hostile for the survival of microorganisms but it was later proven that some can survive, such as *Enterococcus spp.* and *Enterobacter spp* (Maekawa et al., 2018).

1.1. CANCER

Pancreatic and hepatobiliary tumours are associated with poor prognosis due to being highly invasive and highly resistant to chemotherapy (Kleeff et al., 2016).

Ampullary and periampullary tumours (tumours of the head or neck of the pancreas, distal tumours of the bile duct, tumours of the ampulla of Vater, tumours of the second part of the duodenum) represent 5% of all gastrointestinal tumours and are most common in the 7th decade of life. The most frequent signs/symptoms are jaundice, weight loss, pruritus, and abdominal pain. Other less frequent manifestations include anorexia, generalized weakness, depression, iron deficiency anemia, nausea, pancreatitis, dyspepsia or elevation of hepatic enzymes (Lucena & Barros, 2018). In patients who have this kind of neoplasms, surgery remains the only possible cure. Still, only about 20% of the patients have resectable tumours. Pancreatic cancer for instance remains the 4th or 5th cause of cancer-related death in the most developed countries, considering it is highly resistant to the available therapies (Raimondi et al., 2009). Duodenopancreatectomy is a very complex and invasive procedure, and it should be noted that the factor that influences prognosis the most is the pathological diagnosis. For instance, patients with resected head of pancreas ductal carcinoma have a 5-year survival of about 20-25% (Vincent et al., 2011), whereas patients who have node-positive disease have a survival rate of about half of that (Allen et al., 2017). Other types of tumours, such as neuroendocrine tumours, have better prognosis with a survival rate of about 60% at 5 years if the disease is localized (Halfdanarson et al., 2008).

1.2. PREOPERATIVE BILIARY DRAINAGE

PBD was initially introduced in clinical practice about 50 years ago in order to improve post-operative outcomes, as it is known that performing surgery in jaundiced patients increases the risk of post-operative complications (Van Der Gaag et al., 2010). Furthermore, it is known that biliary obstruction increases the risk of bacteriobilia because it increases the risk of bacterial translocation and it was thought PBD could

solve this problem (Kuzu et al., 1999). The beneficial effects of PBD were mostly found in smaller studies, which weren't randomized and were poorly designed (Van Der Gaag et al., 2010). Kloek *et al.* stated that the putative beneficial effects of PBD (such as the correction of impaired haemostasis) had not been demonstrated, and thus remain theoretical (Kloek et al., 2010).

It remains unclear whether these patients should proceed immediately to surgery or have a PBD (Dimitriou et al., 2019; Fang et al., 2013). Even though surgery is the only curative option, there is clear evidence that patients benefit from a multidisciplinary approach (Pomakova & Segal, 2014).

Some authors indicate that PBD should be performed in cases of cholangitis or whenever surgery cannot be performed briefly. Furthermore, bilirubin levels of 5g/dL and above are also indication for PBD, as this is the cut-off associated with decreased liver function (Krüger et al., 2019). It is important to note that some older studies could not find an association between serum levels of bilirubin and rate of complication or length of hospital stay (Ngu et al., 2013).

One of the most frequent indications for PBD is obstructive jaundice, which can lead to kidney and heart failure, hepatic lesion, impaired haemostasis, and immune disorders. The bile flow can be restored before surgery and can be performed using different techniques: PTBD, using radiological guidance (MRCP) or ES followed by stent placement using ERCP techniques (Fang et al., 2013). Alternatives to ERCP are needed in approximately 5% of the patients, who have distorted biliary tree anatomy. It should also be noted that the placement of a stent is associated with an extra risk of haemorrhage, perforation, cholangitis and pancreatitis (Freeman, 2003).

The pre-operative manipulation of the biliary tree is the risk factor for bacteriobilia that has been studied the most thoroughly this far and yet not every essay has reached the same conclusions, and thus it is still debated today. The most unanimous conclusion has been that each centre for hepato-pancreato-biliary surgery should perform their own research to determine the microbiologic profile of infections in its patients and after that adjust the antibiotic prophylaxis to make it more tailored and suitable. Some studies show no differences whereas some meta-analyses have pointed out a higher incidence

of complications, such as surgical site infection. It should be mentioned that surgical site infections represent 20% of healthcare-associated infections and double both the costs of treatment and length of stay in these patients (Shepard et al., 2013; Zimlichman et al., 2013).

Over 50% of patients have had a PBD when they first have a consultation with a hepatobiliary surgeon. A lot of physicians decide to do PBD on their patients (even if there is no formal indication for it) to achieve some symptomatic relief and reverse the pathological effects of jaundice (Jenkins et al., 2013)(Fang et al., 2013). Another factor that could lead to performing PBD is time, since it is legitimate to perform a PBD on a patient who has no formal indication for it if the waitlist for surgery is too long, because most hospitals are unable to respond to the demand and wouldn't operate all patients promptly (De Pastena et al., 2018) (Ngu et al., 2013). In 2017, a study published by Roberts et al. showed that avoiding PBD and operating patients earlier using the fast track pancreatic surgery strategy can reduce the infectious complications after surgery (Hu et al., 2019; Roberts et al., 2017).

Garcea *et al.* only identified an increased risk of surgical site infection and could find a positive link between positive bile cultures and both mortality and morbidity (Garcea et al., 2010). Jagannath *et al.* reached the same conclusion but also stated that the positivity of intra-operative bile cultures had a negative influence on post-operative outcomes (Jagannath et al., 2005).

The meta-analyses by Fang *et al.* and Scheufele *et al.* showed an increased overall post-operative complication rate (Fang et al., 2013)(Scheufele et al., 2017). Ngu *et al.* specify that PBD only seems to increase the rate of Clavien Grade I (wound-related infections mostly) complications, stating that the rate of more serious complications remains the same as the one observed in patients who haven't undergone PBD. Furthermore, patients who require repeated PBDs have an even higher risk of infectious complications (Ngu et al., 2013). The length of stay doesn't seem to be increased by PBD (Fang et al., 2013; Florian Scheufele et al., 2017). In 2009, a study by Herzog et al showed that patients undergoing PBD by means of ERCP have a higher risk of developing cholangitis, especially if a stent had been placed. 12% of patients developed cholangitis if a stent

had been placed whereas only 8% developed cholangitis if no stent had been placed. In the group of patients who hadn't been submitted to ERCP, only 3% developed cholangitis (Herzog et al., 2009). Further studies should analyse whether infection by resistant bacteria has a direct negative impact on the outcomes of surgery (Herzog et al., 2009).

Herzog stated that only 15% of patients who do not undergo ERCP prior to surgery have bacteriobilia, whereas patients undergoing PBD have a 98% chance of having a positive intra-operative blood culture. This latter group of patients also have a significantly higher risk of having a polymicrobial bile duct culture (51% vs 13%). The rate of complications in this study; however, was equal among patients (Herzog et al., 2009).

An adequate and tailored antibiotic prophylaxis (adjusted to each hospital's profile of microorganisms and their resistances) could have a positive influence on the rate of peri-operative complications (Dimitriou et al., 2019).

The vast majority of PBD are performed via ERCP, which protocol involves the administration of prophylactic antibiotics. According to Krüger *et al*, this prophylaxis doesn't alter in a consistent fashion the later development of bacteriobilia or even cholangitis. The direct biliary instillation of ciprofloxacin has been tested but didn't show positive results (Krüger et al., 2019). The last Cochrane meta-analysis about antibiotic prophylaxis when performing ERCP found that, while reducing bacteraemia and seeming to prevent septicaemia in patients undergoing elective ERCP, the effect was not as evident in another subgroup who had uncomplicated procedures. The authors however state further research into the topic is necessary to evaluate whether prophylaxis at the time of ERCP could reduce the rate of infections after surgery following PBD (Brand et al., 2010).

While PBD clearly helps reduce bilirubin levels (patients undergoing PBD present lower levels of bilirubin both pre- and post-operatively), it is also associated with an increase in pro-inflammatory serological markers post-operatively, namely white cell count, neutrophil count and C-reactive protein (Ngu et al., 2013).

The Cochrane review on this topic written in 2012 concludes that there are no sufficient data to either support or refute PBD on patients with obstructive jaundice. PBD could be associated with severe adverse effects and therefore, the safety of this procedure is not yet well established. According to that review, PBD shouldn't be used out of randomized clinical trials. However, most studies used in this revision are old and could contain data which are no longer relevant in current surgical practice (Fang et al., 2012).

A more recent study of De Pastena *et al.* in which 1500 cases were analysed aimed to understand the impact of PBD on post-operative outcomes as well as determine a cut-off serum level of bilirubin that would highlight which patients could benefit from a PBD. As far as the outcomes are concerned, the results were similar to previous studies and the authors concluded that patients who had been submitted to PBD (and stent placement) have a higher chance of suffering infectious complications (mainly wound infections but also abdominal collections and even sepsis) (De Pastena et al., 2018).

What De Pastena *et al.* could also demonstrate was that post-operative complications were more common in patients whose serum bilirubin was higher than 7,5mg/dL (namely global morbidity, acute kidney failure, needing a second surgical intervention and longer hospital stays). The rate of second surgeries is mostly because these patients suffer post-pancreatectomy haemorrhage twice as often as the patients with lower levels of bilirubin. This happens due to liver impairment that causes a haemorrhagic diathesis that ultimately leads to PPH. In this study, 80% of the complications that required a second surgical intervention were of haemorrhagic nature. Therefore, the authors propose that patients with bilirubin levels above 7,5mg/dL should be submitted to PBD because the higher rate of infectious complications (related to PBD) still is beneficial for patients, as it lowers the chances of haemorrhagic complications and therefore the chances of needing a second surgery. All in all, the authors state that PBD is associated to less post-operative complications than bilirubin levels above 7,5mg/dL. Thus, there seems to be a clear subgroup of patients that benefit from the restoral of enterohepatic circulation prior to surgery (De Pastena et al., 2018).

The way in which PBD can influence the mortality is not yet well established. Fang *et al.* figured there is no difference in mortality between patients performing PBD and those

who do not. However, there are not enough studies comparing these groups of patients in the long term, and therefore such conclusions can only refer to short term outcomes. Yet, significantly higher morbidity has been found in patients performing PBD, as well as slightly superior length of hospital stay. One of the complications of this procedure that can lead to a second hospitalization is the development of cholangitis (which incidence has been estimated at 26%)(Van Der Gaag et al., 2010).

Some of the limitations of these studies about the influence of PBD on mortality and morbidity are, for example, whether this technique is performed correctly. It is known that a very short drainage time could not be sufficient to achieve the desirable effects, whereas a prolonged drainage time could result in an increased rate of complications related to the procedure as well as in a progression of the tumour (Fang et al., 2013). However, the time elapsing between performing PBD and undergoing surgery doesn't influence the rate of infectious complications or the rate of bile culture positivity (Ngu et al., 2013). Earlier studies came to different results, reporting that drainage for less than 6 weeks was associated with higher rates of positive blood cultures (Jagannath et al., 2005).

1.3. SURGICAL TREATMENT

There are several different surgical techniques to manage these tumours but the main one is the Whipple procedure. Thirty years ago, a very high mortality was associated with duodenopancreatectomy, which has been brought down to under 5% in specialised centres due to considerable improvements in the surgical technique and in the field of intensive care medicine, which has also ameliorated long-term survival (Kaufman & Coleman, 1993; Neoptolemos et al., 1997). Besides that, regionalization to high-volume centres and better management of common complications have also led to a decline in mortality (Narayanan et al., 2018).

The last Cochrane review published in 2016 tried to compare pylorus-preserving duodenopancreatectomy and the duodenopancreatectomy (classic Whipple – in which part of the pancreas, the gallbladder, the duodenum, the pylorus, and the distal part of the stomach are removed) for treatment of peri-ampullary and pancreatic carcinoma. The authors concluded that the evidence available showed no difference between the

procedures, as far as mortality, morbidity and survival are concerned but highlighted the need for further future better designed studies, given the methodological heterogeneity they could find. However, perioperative outcomes seem to slightly favour PPCPD (Hüttner et al., 2016).

Open duodenopancreatectomy (OPD) is the standard surgical approach to resect ampullary neoplasms, although in recent years the number of patients submitted to laparoscopic duodenopancreatectomy (TLPD) has increased largely (Chapman et al., 2017).

1.4. POSTOPERATIVE COMPLICATIONS

Despite the evolution in recent years, post-operative complications remain a big problem, affecting 30% to 50% of all patients even in specialised centres (Maxwell et al., 2020). Most common complications are: pancreatic fistulas, delayed gastric emptying, wound infections and intra-abdominal abscesses. Infectious complications are the primary cause of post-operative morbidity and happen in about 33% of pancreaticoduodenectomies and in one quarter of distal pancreatectomies (De Pastena et al., 2017; Kelly et al., 2011; Vollmer et al., 2012).

The interesting thing about post-operative pancreatic fistula is that in certain patients it can be avoided using a post-operative drainage system, which in turn increases the risk of infectious complications. Thus, it is difficult to find the balance, but other studies reveal the early drain removal in low-risk patients diminishes morbidity rates as well as duration of hospital stay (Kagedan et al., 2015; Kawai et al., 2006).

A study by Narayanan *et al.* explored the differences between early post-operative mortality causes (within 30-90 days) and late post-operative mortality causes (until 1 year after surgery). The authors not only found that they differ significantly but also that the latter have been poorly studied and defined until now. The most common causes for early post-operative death were multisystemic organ failure (mostly due to sepsis, aspiration or haemorrhage), whereas the most common causes resulting in death between 91 and 365 days after surgery were cancer recurrence as well as debility/frailty. It should also be noted that, even though 30-day post-operative mortality rate is around 1,1%, it raises to a value of 16.5% throughout the first year after surgery. The authors

further suggest that, even though further studies are required, better patient selection (involving a more thorough staging process) and timely management of debility and malnutrition (including preoperative rehabilitations programmes) could help reduce this late post-operative mortality rate (Narayanan et al., 2018).

1.4.1. INFECTIOUS COMPLICATIONS AND ANTIBIOTIC PROPHYLAXIS REGIMENS

One of the most frequent complications after pancreatic surgery is the surgical site infection (SSI), which occurs in about 10% of the patients. It is defined as an infection, happening within 30 days after surgery, involving the skin or subcutaneous tissue (superficial incisional SSI), fascia and muscle layers (deep incisional SSI) or organ spaces manipulated during surgery (organ/space SSI) (Report, 2019). In this context, in 2006 the Surgical Care Improvement Project (SCIP) implemented measures to reduce the incidence of SSIs by recommending administration of antibiotics prior to incision (Berenguer et al., 2010). However, the rate of SSIs, especially in surgical procedures involving the pancreas and the biliary tree remains high (Saeed et al., 2015). The American Society of Health System Pharmacists' guidelines recommend cefazolin (a first-generation cephalosporin), cefoxitin or cefotetan (2GCS), ceftriaxone (3GS) or ampicillin-sulbactam for procedures involving the biliary tract (Bratzler et al., 2013). Other authors state that this coverage is not enough for these procedures and broader-spectrum antibiotics, such as piperacillin/tazobactam should be considered (Donald et al., 2013). It is also known that SSIs decrease overall survival as an independent prognostic factor, but also because they delay adjuvant chemotherapy (Chikhladze et al., 2019).

Frenette *et al.* studied the infections associated to each surgical procedure, thereby adapting the prophylaxis regimens using antibiotic stewardship techniques and then analyzed the impact of these interventions on the rate of postoperative SSIs and came to a significant reduction of more than 50% in the rate of SSIs (Frenette et al., 2016).

Most abdominal surgeries have well defined SSI rates and factors influencing their occurrence. As this did not happen for hepato-pancreato-biliary surgery, in 2020 Mentor *et al.* did a meta-analysis on the topic to find that the risk factors for an SSI after pancreatic resection are: pancreaticoduodenectomy (compared to distal

pancreatectomy), open surgery (vs. laparoscopic), POPF, PBD, radiotherapy, chemotherapy, high pre-operative bilirubin levels, male gender, high BMI and high ASA index. Furthermore, they could state that no preventive measures had this far shown any improvements, with the only promising preventive intervention being the use of NPWT (negative pressure wound treatment), which still needs further studying (C. I. Wells et al., 2019) (Mentor et al., 2020).

In 2018, Stack *et al.* tried to look for associations between patient factors, the type of procedure and factors related to the antibiotic prophylaxis and looked for an association with the development of SSI. They conducted a retrospective study comprised by 300 patients submitted to HPB procedures other than transplants (all of which had been given prophylactic antibiotics) and found that 65% of patients who developed SSI had been given drugs to which the bacteria were resistant to. The most frequently isolated organisms were *Enterococcus spp.*, *E. coli* and *Enterobacter spp.* but after statistical analysis the authors concluded that adding drugs with anti-enterococcal and/or anti-pseudomonal activity showed no reduction on the risk of developing SSI. The authors found that patient and procedure factors were the only factors predicting SSI, contrary to the spectrum of activity of the antibiotics given. Male gender, prior ERCP with stent, smoking and beta-lactam allergy were significantly linked to developing SSI; as were open procedures and procedures lasting longer than 4 hours (Stack et al., 2018). The association between the increased risk of developing a SSI and beta-lactam allergy had been reported in other studies as well, such as that of *Blumenthal et al.* (Blumenthal et al., 2018). Other studies have also demonstrated that the organism isolated in post-operative SSI after HPB procedures is resistant to the antibiotics used as prophylaxis in over 50% of the cases (Fong et al., 2016; Gavazzi et al., 2016).

In 2018, De Pastena *et al.* tried using a rectal swab (detecting enteric colonization of MDR bacteria) to find concordance between the microorganisms in the preoperative RS and in the intraoperative bile cultures, and to assess whether the colonization had influence on the postoperative outcomes. They found that patients who had a positive rectal swab had a higher mortality and morbidity rate due to a higher number of infectious complications (namely SSI, abdominal collections, etc.), although there was no difference in the rates of POPF, DGE or PPH. In fact, multivariate statistical analysis

proved that infectious complications and mortality were the only independent factors that could be linked to a positive RS. Besides, they also detected a good correlation among the RS culture, the intraoperative bile cultures as well as the organisms later isolated in patients with infectious complications. This study therefore proves that RS could become part of antibiotic stewardships programmes to readily detect colonized patients and therefore implement strategies to diminish nosocomial diffusion as well as transmission to relatives or caregivers upon discharge of such bacteria. This strategy could also help profiling MDR bacteria trends within each centre, therefore contributing to better surveillance and infection control programmes. Ultimately, it could also be used to tailor more aggressive prophylaxis schemes for higher-risk patients (such as the ones previously submitted to PBD) (Pastena et al., 2018).

In 2019, Dimitriou *et al.* tried to understand if prophylactic antibiotics given in the context of pancreatic resections were adequate and analysed the influence of PBD on post-operative septic complications. The authors tried to always isolate a microorganism in bile cultures and understand whether the antibiotics given were effective against that microorganism. They also reckoned that PBD significantly increased bacteriobilia but doesn't increase overall mortality, which the authors relate to it not increasing the rate of serious complications (like PPH or fistulas). Still, PBD significantly increased the rate of surgical site infections in their study (Dimitriou et al., 2019). The authors isolated the microorganism in every infectious situation and also figured that it is not possible to establish a link between a certain microorganism and a certain infectious complication (Dimitriou et al., 2019). Lee *et al.* however found a link between the isolation of ESBL enterobacteria and the risk of developing organ failure (Lee et al., 2015).

PBD has been shown to not only increase the incidence of bacteriobilia but also alter the microbiological profile of such bacteriobilia, by rising the frequency of enterobacteria. In about 48% of the patients included in the study, there was at least one microorganism resistant to standard antibiotic prophylaxis (amipicilin + sulbactam (2g+1g)). However, after performing antibiotic sensitivity testing, the authors realised that the most effective drug for prophylaxis would be imipenem, which given the very broad spectrum should not be used as prophylaxis. Therefore, this study did not succeed in identifying

alternative and more effective antibiotics to be used as prophylaxis and so it is stated that each centre should perform their own studies (Dimitriou et al., 2019; Krüger et al., 2019). Krüger *et al.* also suggest that ampicillin + sulbactam is adequate and sufficient in patients who have not had previous PBD. However, bile cultures should still be performed routinely, should antibiotic therapy need adjustments.

Other studies came to similar conclusions as far as ideal prophylaxis is concerned. Sudo *et al.* suggested that the most suitable choice would be a fourth-generation cephalosporin (for example ceftazidime) or the association of imipenem-cilastatin, which present a rate of resistance (even for patients who have undergone PBD) of 9% and 5%, respectively. The authors further state that, for patients who haven't been submitted to PBD, a first-generation cephalosporin would be appropriate for more than 90% of the cases in Japan where the study was carried out. The authors therefore defend that antibiotic prophylaxis should be different according to the patient's PBD status (Sudo et al., 2014). In 2020, Stecca *et al.* also advocated for a broad-spectrum prophylaxis in all patients (proposing the same regimens as Sudo et al. had), stating that bile cultures should be performed routinely to then adequate antibiotic therapy based on antibiograms. These authors added to all immunocompromised patients should additionally receive antifungal prophylaxis (Stecca et al., 2020).

Donald et al. studied the sensitivity rate of the prophylactic regimens recommended by the Surgical Care Improvement Project, which are for abdominal surgery: cefotetan, cefoxitin, cefazolin with metronidazole or ampicillin with sulbactam (Rosenberger et al., 2011). The authors found that the most commonly isolated microorganisms were *Enterococcus spp.* (which are intrinsically resistant to cephalosporins) and *Enterobacter spp.* which are also frequently resistant to the regimens recommended by SCIP. The authors therefore decided to use alternative prophylactic regimens, such as piperacillin-tazobactam or tigecycline and experience a decrease in the rate of SSIs of about 80% (Donald et al., 2013). The problem of using piperacillin-tazobactam as prophylaxis is that it is a broad-spectrum antibiotics and may actually be one of the reasons why enterococci have emerged as a problem in the last few years (Prieto et al., 2016). Krüger *et al.* suggest that the use of piperacillin + tazobactam as prophylaxis can be considered in situations of high clinical risk (Krüger et al., 2019).

Other authors state that half of the isolations cannot be seen as pathogenic (Park et al., 2014). This allied to the fact that bacteriobilia doesn't lead to increased mortality has led to several debates about whether bile cultures should be performed in a systematic fashion in all patients. It is however unanimous that it is valuable and helpful in situations of active infection in order to adjust antibiotic therapy. Yet, the authors admit further studies are necessary (Armiñanzas et al., 2016).

Mohamed et al. showed that targeted antibiotic therapy given for 10 days post-surgery reduced SSIs from 12% in the control group to 3% and recommends treating bacteriobilia. As other authors, they did not find a significant difference in the incidence of other complications (Mohammed et al., 2014).

Another problem identified by Maxwell *et. al* is the frequent discordance between the microorganisms isolated in bile cultures performed intra-operatively and the ones isolated afterwards in site of infection cultures (SOIC). This study showed a match of only 31,3% and the match between sensitivity and resistance patterns (SRPs) was even weaker. Other studies however have found values between 22% and 100% (Maxwell et al., 2020). These findings suggest that doctors should take other factors into account (besides the bile culture results) when prescribing therapy for these patients.

Thus, the efficacy of prophylactic antibiotics in these patients is still discussed, not only due to the high rate of infections that still occur today (despite administration of antibiotics) but also due to the increase in ESBL Enterobacteriaceae and carbapenemase-producing Enterobacteriaceae infections. The role of bile cultures is still vital for antibiotic stewardship purposes but its value as far as prognosis is concerned is far more controversial. Still, an unanimous conclusion is that every hospital/centre for HPB surgery should conduct their own studies and interpret their findings, in order to develop a more tailored approach to this problem (Maxwell et al., 2020).

2. METHODS

2.1 Settings

This is a retrospective study conducted at Hospital de Santa Maria, a tertiary hospital in Lisbon, Portugal, approved by the local Ethics Committee on February 19, 2021.

Our aim was to assess the infectious complications after oncological cephalic duodenopancreatectomy in patients 18 and older.

Basic demographic data was analyzed, as well as the patients' relevant history, such as prior surgical interventions, prior antibiotic administrations, hospital length of stay and infection history, as well as survival times and post-operative complications. Concerning the infectious complications, microbiological data as well as resistance patterns were also collected.

All perioperative and microbiological data were gathered in a local scientific database.

2.2. Case ascertainment

Non-pregnant patients with pancreatic neoplasms requiring surgical treatment from January 1, 2017 to December 31, 2020 were identified through the database of the Surgery Department of this hospital (n = 76). 20 patients were excluded due to the irresectability of their tumors, whereas 20 patients were excluded due to the anatomical location of their tumors, which made the most suitable surgical approach one other than the cephalic duodenopancreatectomy. 2 patients were excluded because the final diagnosis was not a tumor. An additional patient was excluded as he was infected at the time of surgery. Overall, 33 hospitalized subjects were enrolled in this study.

2.3. Definitions

Antibiotic prophylaxis for surgery was only considered in cases where the complete regimen lasted shorter than 48 hours and was begun before the surgical procedure. In our hospital, prophylaxis is administered to all patients and usually consists of cefazoline or ceftriaxone + metronidazole, if the patient has history of previous invasive procedures.

Bacteriobilia can be defined as the bacterial colonization of the biliary tree. Although bile is usually sterile, bacteriobilia isn't an infection, as it isn't usually followed by clinical or laboratorial findings suggestive of infection. Therefore, it doesn't count as an infectious complication in our study, although patients still received targeted antibiotic treatment directed at these microorganisms.

Conversely, **infectious complications** were considered when there were clinical or laboratorial findings suggestive of infection. They were subdivided into surgical site infections, intra-abdominal infections (which consisted of more serious, deeper infections, such as intra-abdominal abscesses and cholangitis), bacteremia (when microorganisms were isolated from blood cultures) and infections of other systems (in our study, we found only aspiration pneumonias and urinary tract infections).

When both intra-operative bile cultures and site of infection cultures were available, the isolated microorganisms were compared and concordance between samples assessed. We categorized **concordance** into three levels: discordant, partially concordant, and totally concordant. Discordance was defined as the occurrence of two or more different specimens between samples. Partial concordance happened when there was only one different specimen after comparing the two samples. Total concordance was present when all specimens isolated were the same in both cultures.

The microbiological specimens were examined according to standard microbiological procedures of our microbiology laboratory. Susceptibility for the tested antibiotics were analyzed in this study. The number of detected sensitivities and resistances was related to the number of bacteria in each group, even though not all antibiotics were tested for all genera. This procedure allowed comparability between groups.

The classification of microorganisms as multidrug resistant followed the definitions established by Magiorakos *et al.* **Multidrug resistance** was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, **Extensively drug resistant** was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).

2.4. Statistical analysis

All calculations were done using the statistical analysis software SPSS® (version 28.0). Differences between two subgroups were calculated using the t-test and calculations were done bilaterally (two-tailed test). Significance level was defined as a p-value lower than 0,05.

2.5. Role of the funding source

The study had no source of funding. The corresponding author had full access to all the data in the study.

3. RESULTS

Our study included 33 patients with oncological diagnoses who were submitted to cephalic duodenopancreatectomy in Hospital de Santa Maria, Lisbon, Portugal between 2017 and 2020. The mean age was 67.2 years at the time of surgery.

Table 1. Demographics and medical history of the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017, to December 31, 2020 in the Surgery Department of Hospital de Santa Maria.

Patient variables	n = 33
Age (mean \pm SD)	67.2 yrs \pm 9.3 yrs
Female / Male	20 / 13
Malignancy	33
Adenocarcinoma	29
Serous cystadenoma	1
Tubulovillous adenoma	1
Pseudopapillary	1
Neuroendocrine	1
History of hospital stays in the previous 6 months	23
History of ERCP in the previous year	20
History of antibiotic treatment in the previous 3 months	18
History of previous abdominal surgical intervention	12
History of hospital admission more than 7 days before surgery	6
History of MDR microorganism infection in the previous year	4
Beta-lactam allergy	0
Length of hospital stay in days (mean, min-max)	25.9 (7-98)

We assessed patients' history for several risk factors that had been described in previous studies, such as previous hospital stays in the 6 months before surgery (69.7%), history of ERCP in the previous year (60.6%), antibiotic use in the previous 3 months (54.5%) and history of MDR microorganism infection in the previous year (12.1%). Most of our patients had at least one of these, considering they all had oncological diagnoses that require very frequent medical attention.

Other information and relevant medical history is summarized in Table 1.

3.1. Postoperative complications

Infectious complications were the most common complications observed in our study (76.5%) and had a great range, varying from superficial surgical site infections to sepsis causing death. Out of all patients (n=33), 20 developed at least one infectious complication (60.6%). We found a total of 17 patients with bacteriobilia, eight of them later developed an abdominal infectious complication and one who later had an aspiration pneumonia. Eight patients only had bacteriobilia without infectious complications and a total of five patients had neither bacteriobilia nor infection.

Table 2. Complications following surgical treatment of the patients with pancreatic neoplasms submitted to cephalic duodenopancreatectomy from January 1, 2017, to December 31, 2020 in the Surgery Department of Hospital de Santa Maria.

Infectious complications - abdominal infections	n
Intra-abdominal abcess	11
Superficial surgical site infection	10
Bacteriemia (abdominal)	9
Sub-total	30
Infectious complications - other	n
UTI	6
Aspiration pneumonia	3
Sub-total	9
Non-infectious complications	n
Post-operative pancreatic fistula (POPF)	9
Mesenteric ischemia and reintervention	1
Post-pancreatectomy hemorrhage (PPH)	1
Pseudoaneurysm	1
Sub-total	12
Total	51

We reported 30 abdominal infectious complications in our study, which represent 76.9% of all infectious complications (n=39). Ten (33.3%) of which were superficial surgical site infections, whereas 11 (36.7%) were more serious intra-abdominal infections, such as abscesses. Bacteriemia was found post-operatively in nine cases.

The reported infectious complications from other organ systems were six urinary tract infections and three aspiration pneumonias.

Out of all 33 patients, only 11 (33.3%) developed non-infectious complications, although most were potentially life-threatening conditions. We found nine cases of POPF, although only one of these didn't have at least one infectious complication simultaneously and six of them had intra-abdominal infections. We found a case of a pseudoaneurysm, a case of mesenteric ischemia and a case of post-pancreatectomy hemorrhage.

A detailed description and list of the surgical complications reported in our study can be found in table 2.

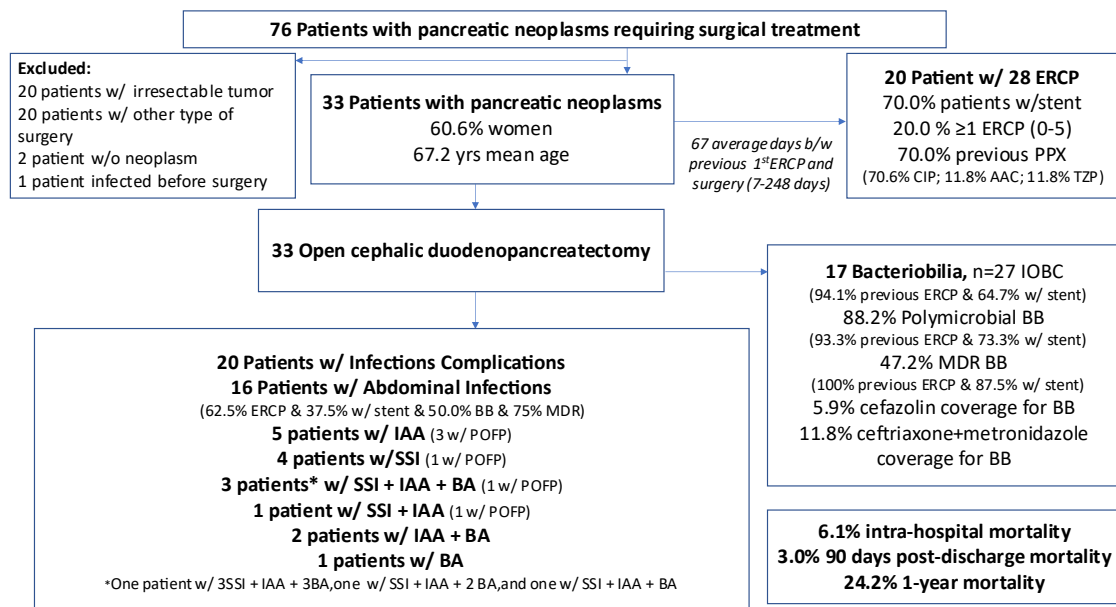


Figure 1. Detailed description of our population, exclusion criteria, number of ERCP procedures, rate of intra-operative bile cultures, infectious complications and mortality in patients with neoplasms submitted to cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 in the Surgery Department of Hospital de Santa Maria, Lisbon.

3.2. ERCP, antibiotic prophylaxis and bacteriobilia

Out of all 33 patients, 20 had performed an ERCP prior to surgery. 14 patients received antibiotic prophylaxis at this time. In our study, the most commonly used antibiotics were ciprofloxacin (70.6%) and amoxicillin/clavulanate (11.8%).

We divided these patients into two further subgroups: in the first, patients had done the last ERCP (or only one ERCP) less than one month before surgery whereas in the second this procedure had taken place somewhere between 1 and 6 months before surgery. This subdivision was aimed at figuring out whether the bacteriobilia induced by ERCP was permanent or transitory.

Regarding the rate of positive intra-operative bile cultures, it was 63.6% and 100.0% in patients who had been submitted to their last ERCP up to 1 month before surgery and between 1 and 6 months before surgery, respectively. These data are summarized in Table 3.

Table 3. Link between history of ERCP and positive intra-operative bile culture in patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 in the Surgery Department of Hospital de Santa Maria.

Last ERCP up to 1 month prior to surgery	11 (9)	Only 1 ERCP	6 (5)	Positive/ Negative IOBC*	3 (3) / 2 (1)
		Multiple ERCP	5 (4)	Positive/ Negative IOBC	4 (4) / 1 (0)
Last ERCP 1 to 6 months before surgery	9 (5)	Only 1 ERCP	7 (4)	Positive IOBC	7 (4)
		Multiple ERCP	2 (1)	Positive IOBC	2 (1)

The numbers in bold represent the number of patients submitted to stent placement during ERCP

* In one of the patients in whom a stent had been placed during a ERCP, no bile samples were collected intra-operatively

In the subgroup of patients in whom the last ERCP had been performed less than one month before surgery, bacteriobilia was present at a rate of 50.0% in patients who only had one ERCP and 80.0% in cases of multiple previous ERCP procedures.

A total of seven patients had history of multiple ERCP procedures and in these patients, the rate of positive IOBC was 85.7%. In our study, 14 patients had a stent (re)placed before surgery and, in this group, 12 patients (85.7%) had positive intra-operative bile cultures.

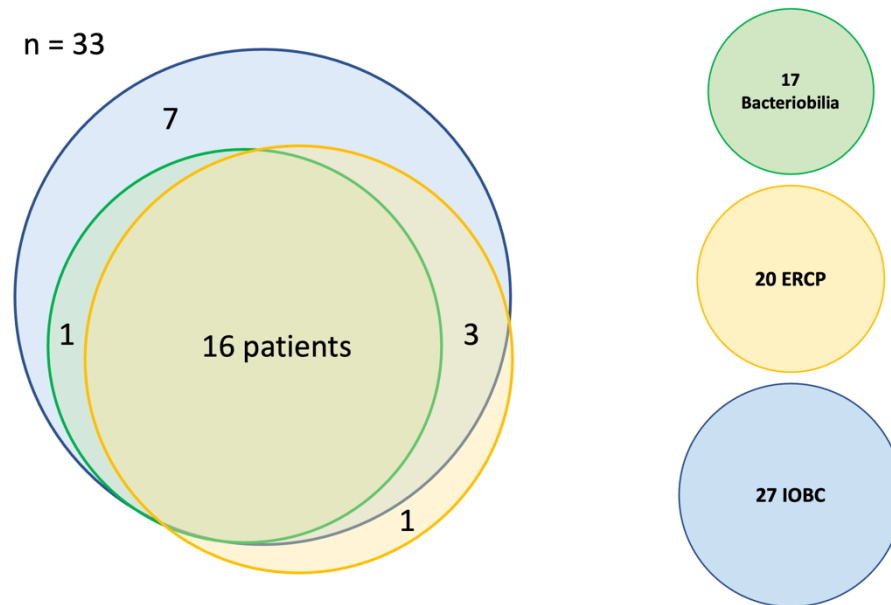


Figure 2. Distribution of patients with neoplasms submitted to cephalic duodenopancreatectomy between January 1, 2017 and December 31, 2020 in the Department of Surgery of Hospital de Santa Maria and their status regarding the intra-operative bile culture and history of ERCP.

Out of the 19 patients who were submitted to ERCP and collected IOBC before, only four (21.1%) had negative intra-operative bile cultures.

In 17 patients, positive bile cultures were collected intra-operatively, corresponding to cases of bacteriobilia and in 16 (94.1%) of these patients an ERCP had been previously performed. Only one patient (5.9%) out of the 17 with positive intra-operative bile cultures had no history of ERCP in the previous year.

Table 4. Link between history of ERCP, administration of antibiotic prophylaxis for ERCP and bacteriobilia and/or intra-abdominal infection rates in patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria

ERCP	20	14 w/ ERCP AB PPX	Bacteriobilia	5
			IAI	1
		6 w/o ERCP AB PPX	Bacteriobilia + IAI	8
			Bacteriobilia	3
No ERCP	13	IAI	IAI	6
			Bacteriobilia	1

Out of all patients undergoing ERCP, intra-abdominal infectious complications arose in 50.0%; whereas in the 13 patients that hadn't been submitted to ERCP prior to surgery, 46.2% had intra-abdominal post-operative infectious complications.

Regarding the role of antibiotic prophylaxis in ERCP, out of the 14 patients who received antibiotics before the ERCP, 9 (64.3%) developed post-operative infectious complications whereas only 1 out of the 6 (16.7%) who received no prophylaxis had at least one intra-abdominal infectious complication after the surgery, although the rate of bacteriobilia is similar between the two groups.

Table 5. Link between intra-operative bile cultures, their treatment and later development of intra-abdominal infections (and concordance between these infections and the microorganisms previously isolated in bacteriobilia) in patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

IOBC	Total	Tx for BB	Patients w/ IAC	MO concordance b/w BB and SOIC
Positive	17*	9 w/ coverage	1 SSI	1 Discordant
			2 IAA	2 Partial
			1 (IAA + BA)	1 Total
		7 lacking coverage	1 SSI	1 Parcial
			1 IAA**	N.A.
			1 (SSI + IAA + BA)	1 Discordant
			1 (3 SSI + IAA + 3 BA)	1 Discordant
Negative	10	N.A.	1 SSI	N.A.
			2 IAA	
			1 (IAA + BA)	
Not collected	6	N.A.	1 SSI	N.A.
			1 (SSI + IAA)	
			1 (SSI + IAA + 2 BA)	
			1 BA	

* In one patient, the antibiotics used were not tested for the microorganisms isolated.

** In one patient, it was not possible to determine the causative agent for the infectious complications

Out of 17 patients with positive IOBC (bacteriobilia), eight (47.1%) later developed abdominal infectious complications despite receiving antibiotic treatment for bacteriobilia, once data was available; the rate of abdominal infectious complications in patients with negative IOBC was 40.0%.

When bacteriobilia was confirmed, patients were given antibiotics active against the isolated agents; nine of them received drugs that were active against the microorganisms found in their bile, while seven others received ineffective antibiotic

therapies and in one patient the antibiotics used were not tested for the microorganisms isolated.

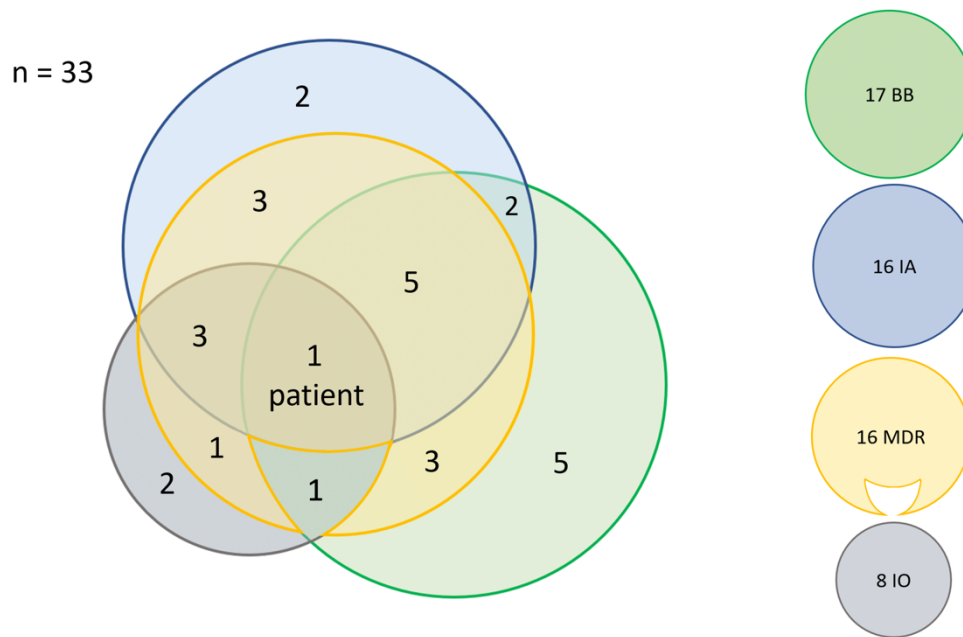


Figure 3. Distribution of patients with neoplasms submitted to cephalic duodenopancreatectomy between January 1, 2017, and December 31, 2020 in the Department of Surgery of Hospital de Santa Maria and their status regarding the intra-operative bile culture, abdominal infections, other infections or infections by multidrug-resistant microorganisms.

Out of all nine patients treated with tailored antibiotic treatment, four (44.4%) still developed intra-abdominal infectious complications. From these four patients, three revealed partial (n=2) or total concordance (n=1) between the microorganisms causing bacteriobilia and the ones responsible for the intra-abdominal infectious complications. Out of the seven patients who were not treated appropriately for bacteriobilia, four (57.1%) developed intra-abdominal infectious complications. From these four patients, two had discordant culture results while one revealed partial concordance between the microorganisms causing bacteriobilia and the ones responsible for the intra-abdominal infectious complications. There was one case in which it was not possible to determine the causative agent for the infectious complications, which was an intra-abdominal abscess and there was one other case in which the microorganisms causing the infection were discordant from those that had been previously isolated in the bacteriobilia.

The most frequently observed infectious complication was the superficial infection of the surgical site, which occurred in eight patients. Only one of these cases occurred in patients who had received appropriate antibiotic treatment for their bacteriobilia. Of the remaining seven cases, three occurred in patients who didn't receive appropriate treatment for their bacteriobilia.

3.3. Characterization of the isolated microorganisms

In this study there were a total of 52 microbiological cultures performed, 33 of which were polymicrobial whereas 19 were monomicrobial.

A total of 101 microorganisms were isolated, the 3 most frequent belonging to the following genera: *Enterococcus* (n=30), *Klebsiella* (n=20) and *Escherichia* (n = 14). A detailed description of all the isolated microorganisms may be found in Tables 6, 7, 8 and 9.

A total of 16 anaerobic microorganisms were isolated in 15 different isolates (which account for 28.9% of all isolates); they also tended to occur in concomitance with other bacterial (usually aerobic) species and were found individually in only one isolate.

In our study, 18 patients had history of recent antibiotic treatment (less than three months prior to the infection) and 16 of them had polymicrobial infections.

Additionally, in four patients, a clinical diagnosis of infection was made but no agent could be found in cultures, three of these had a diagnosis of intra-abdominal abscess and another developed an aspiration pneumonia.

We divided the isolated microorganisms into three further subgroups: the ones isolated in intra-operative bile cultures (bacteriobilia), the ones isolated from intra-abdominal infections and the ones isolated from other systemic infections (UTIs and pneumonias). A comprehensive list of the bacteria found in each subgroup is displayed in tables 6 through 9.

Table 6. Number of specimens of Gram-positive bacteria isolated in this study, the frequency of multidrug resistant strains and their distribution in different infections from the biological samples of patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Gram +		Total	BB	SSI	IAA	BA	OI	MDR
<i>Staphylococcus spp.</i>	MRSA	1				1 (1)		1
	<i>S. anginosus</i>	1	1					
<i>Streptococcus spp.</i>	Group B	1			1			
	<i>E. faecalis</i>	17	9	3	3	2	2	1
<i>Enterococcus spp.</i>	<i>E. faecium</i>	VSE	5	2 (1)	1 (1)	2 (2)		4
		VRE	2	1 (1)	1 (1)			2
	VanC Enterococci*	3	3					
	Other Enterococci**	3	2		1			

The numbers in bold represent the amount of multidrug resistant bacteria found in our study.

* VanC Enterococci comprise microorganisms bearing the VanC gene which grants resistance to both vancomycin and teicoplanin. In our study, these bacteria belong to the *Enterococcus gallinarum* and *Enterococcus casseliflavus* species.

** Other Enterococci found in our study were *E. durans* and *E. raffinosus*.

Table 7. Number of specimens of Gram-negative bacteria isolated in this study, the frequency of multidrug resistant strains and their distribution in different infections from the biological samples of patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Gram -			Total	BB	SSI	IAA	BA	OI	MDR	
Enterobacterales	<i>Klebsiella spp.</i>	<i>K. pneumoniae</i>	CPKP	8	2 (2)	2 (2)	3 (3)	1 (1)	2 (2)	8
			ESBL	5	2 (2)	2 (2)	1 (1)		1 (1)	5
			NSBL	3			1		2	
			MS	2	1	1				
	<i>K. oxytoca</i> *	p-ampC	1	1						
		MS	1	1						
	<i>E. coli</i>	NSBL	7	2 (1)	1 (1)	1 (1)	2 (2)	1	5	
		MS	7	6		1				
	SPMCE**	ampC	7	3 (1)	1	2	1		1	
	<i>Citrobacter sp.</i> ***	NSBL	2	1	1					
<i>Proteus vulgaris</i>	NSBL	1	1 (1)					1		
<i>Pseudomonas aeruginosa</i>			2	1			1 (1)		1	

The numbers in bold represent the amount of multidrug resistant bacteria found in our study.

* Out of the 2 isolated specimens of *Klebsiella oxytoca*, one exhibited plasmid-mediated AmpC beta-lactamases.

** In the SPMCE group, we included all bacteria expressing a chromosomal ampC gene, which in our study were *Morganella morganii*, *Citrobacter sp.*, *Citrobacter freundii*, *Citrobacter braakii*, *Enterobacter sp.* and *Enterobacter cloacae*.

*** Other species of *Citrobacter sp.* such as *Citrobacter koseri* didn't exhibit the same resistance gene and were therefore included in a separate group which we named *Citrobacter sp.*

Table 8. Number of specimens of anaerobic bacteria isolated in this study, the frequency of multidrug resistant strains and their distribution in different infections from the biological samples of patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Anaerobes	Total	BB	SSI	IAA	BA	OI	MDR
<i>Clostridium perfringens</i>	4	3	1				
<i>Bacteroides sp.</i>	7	3	2 (1)	2			1
<i>Prevotella sp.</i>	2	2		1			
<i>Fusobacterium sp.</i>	1	1					
<i>Parvimonas micra</i>	1		1				
<i>Veilonella parvula</i>	1	1					

The numbers in bold represent the amount of multidrug resistant bacteria found in our study.

Table 9. Number of specimens of fungi isolated in this study, the frequency of multidrug resistant strains and their distribution in different infections from the biological samples of patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Fungi	Total	BB	SSI	IAA	BA	OI	MDR
<i>Candida albicans</i>	3	2	1				
Non-albicans Candida	3		2		1		

A total of 30 MDR microorganisms were found, the most frequent being MDR *Klebsiella pneumoniae* (n=13) and *Enterococcus spp.* (n=7).

16 patients were colonized or developed at least one infectious complication which was originated by at least one multidrug resistant microorganism. The link between risk factors and multidrug resistant infection can be found in table 10.

Table 10. Link between infection by multidrug resistant bacteria and association with possible risk factors in the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

	MDR*	MDR IC	Non-MDR IC	MS IC	No IC	No IC nor BB
Total	16	13	7	0	13	5
ERCP	11	8	3	0	9	2
AB history	11	8	3	0	6	1
Previous infection	5	2	1	0	3	0
HA > 7d before Cx	4	4	1	0	0	1
BB	9	6	3	0	8	N.A.**

* Both colonization or infection by multidrug resistant bacteria were taken into account.

** In one patient, no bile samples were collected intra-operatively.

Out of the 13 patients who developed an infectious complication caused by a multidrug resistant, eight had history of recent ERCP and eight had been given antimicrobial drugs in the previous 3 months.

Among the patients who developed infectious complications caused by MDR bacteria, 30.8% had been hospitalized for longer than a week before surgery took place; conversely, among the patients who suffered no infectious complication, none of them had been hospitalized for longer than seven days before surgery. This difference is statistically significant (p-value: 0.031341)

Interestingly, the patients who had neither an infectious complication nor positive bile cultures had the lowest rate of recent antibiotic use (20.0%).

Table 11. Resistance patterns of Enterococci in the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 in the Surgery Department of Hospital de Santa Maria.

Enterococci	Total	QN-R	VAN-R	LZD-R	TET-R
Ampicillin-susceptible*	21	3/19	3/21	0/12	12/19
Ampicillin-resistant	7	4/5	0/7	0/7	6/7
Ampicillin and vancomycin-resistant	2	2/2	2/2	0/2	1/2

* Regardless of whether or not they were susceptible to vancomycin (as occurs intrinsically for bacteria bearing the VanC gene)

Table 12. Resistance of Enterobacterales in the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 in the Surgery Department of Hospital de Santa Maria.

Enterobacterales	Total	TZP-R	FQ-R	GEN-R	AMK-R	TGC-R	FOS-R	CTX-R	CST-R
MS	10	0/10	0/10	0/10	0/10	0/8	0/9	0/10	Not tested
NSBL	13	3/13	1/13	2/13	0/13	3*/10	1/10	5/13	Not tested
ESBL	5	3/5	5/5	4/5	0/5	1/4	0/4	4/5	Not tested
ampC**	8	NA	1/8	0/8	1/8	0/7	1/7	3/7	1***/6
Carbapenemase-producing	8	NA	7/8	6/8	3/8	1/8	3/8	7/8	0/7

* One case of intrinsic resistance (*Proteus vulgaris*)

** There are seven cases of bacteria carrying a chromosomal ampC gene (all belonging to the SPMCE group described above) and one case of a plasmid-mediated ampC occurring in a specimen of *Klebsiella oxytoca*

*** One case of intrinsic resistance (*Morganella morganii*)

Table 13. Resistance of anaerobes in the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Anaerobes		Total	Pen-R	AMC-R	Clinda-R	Metro-R
Cocci		2	1	0	0	0
Bacilli	Gram +	4	0	0	0	0
	Gram -	10	5	1	2	1

We analyzed the resistance pattern of all isolates, which are as follows:

Two thirds (66.7%) of all Enterococci isolated remained susceptible to ampicillin, a narrow spectrum aminopenicillin. Tetracycline; however, was active against Enterococci in 40.0% of the cases. The rate of susceptibility to fluoroquinolones, such as ciprofloxacin, was of 70.0%. There were five cases of resistance to vancomycin but in three of those cases, ampicillin was still active against the isolated Enterococcus, meaning there were only two isolates (6.7%) in which neither ampicillin nor vancomycin would have been a valid option. In these two cases, the isolates remained susceptible to linezolid, to which there were no resistances in our study (0%).

The specimen of MRSA which was isolated had acquired resistance to ciprofloxacin and clindamycin, remaining however susceptible to all other non-beta-lactamic anti-MRSA drugs tested.

Both isolates belonging to the *Streptococcus spp.* genus remained susceptible to penicillin and all other drugs tested, namely clindamycin.

As for the Gram negative, we isolated a total of 44 Enterobacterales and 2 specimens of *Pseudomonas aeruginosa*.

In the Enterobacterales group, 20.4% are multisusceptible bacteria, 34.1% produced narrow-spectrum beta-lactamases (susceptible to second and third generation cephalosporins), 11.4% are ESBL producers, 15.9% are ampC-producers and 18.2% are carbapenemase producers.

In our study, we report a resistance rate of 47.7% to piperacillin/tazobactam in this group.

We report 13 cases of resistance to fluoroquinolones, which renders a resistance rate of 29.5% (ranging from 0% in narrow-spectrum beta-lactamase producers, 12.5% in ampC-producers, 87.5% in carbapenemase-producing bacteria and 100% in ESBL-producers).

Furthermore, we reported 4 cases of acquired resistance to amikacin which makes up for a resistance rate of 9.1%. Similar resistance rates were found for tigecycline and fosfomycin, which were 6.8% and 11.4%, respectively.

As for colistin, it is not routinely tested in our laboratory but, when few options were available, namely in cases of multidrug resistance it was tested and no cases of acquired resistance were reported in our study.

Unlike what we saw for Enterococci, none of the drugs tested for Enterobacterales was effective against all the bacteria included in the group.

Regarding the two specimens of *Pseudomonas aeruginosa* isolated, one was multidrug resistant, as it was resistant to, among others, piperacillin/tazobactam, meropenem and ciprofloxacin. The other specimen, on the contrary, had no acquired resistance to the tested antimicrobial agents.

As for the resistance in fungi, only one specimen of *C. glabrata* was resistant to fluconazole.

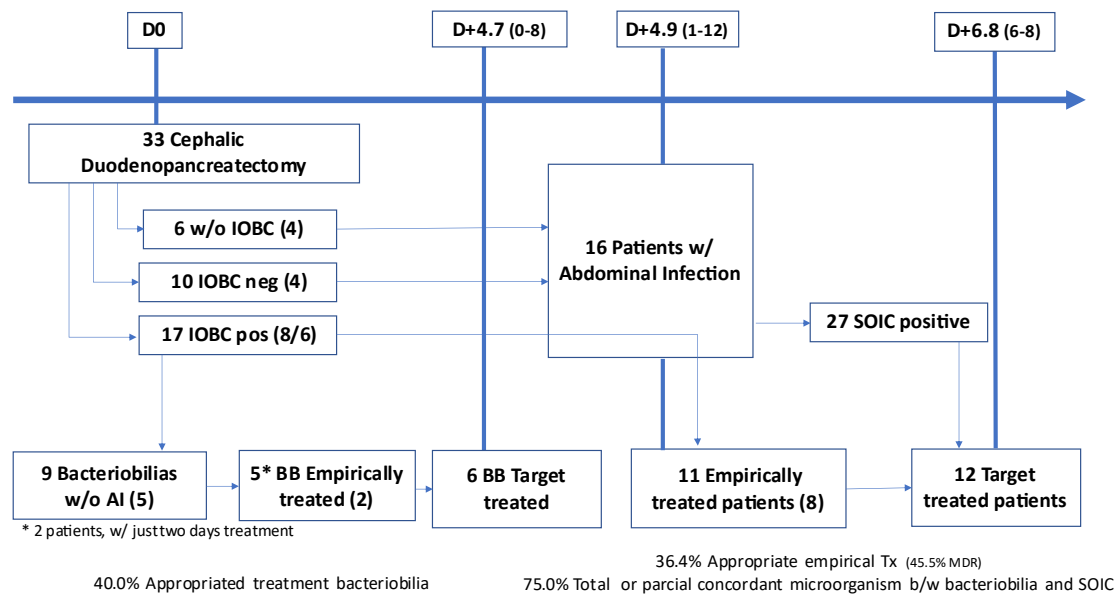
Acquired resistance in anaerobes was much more infrequent when compared to other bacteria. Anaerobic bacteria are subdivided into three subgroups, the cocci (*Veillonella parvula*), the gram-positive bacilli (*Clostridium perfringens*) and gram-negative bacilli (comprising the *Bacteroides*, the *Fusobacterium* and the *Prevotella* genera). The latter subgroup was the one where resistances were most frequently found. Resistance to penicillin was, by far, the most commonly seen. It occurred in 6 (37.5%) bacteria; we describe one case of penicillin resistance in a coccus and five others in gram-negative bacilli. Clindamycin resistance was found in two isolates of gram-negative anaerobic bacilli (12.5%). We only report one case of resistance to both metronidazole (6.3%) and one case of resistance to amoxicillin/clavulanate (6.3%), both occurring in the gram-negative cocci group. We only found one case of a multidrug resistant anaerobic

microorganism, which was a specimen of *Bacteroides fragilis* resistant to penicillin, clindamycin and metronidazole, maintaining its susceptibility to amoxicillin/clavulanate.

Resistance patterns of the microorganisms are presented in Tables 11, 12 and 13.

3.4. Antibiotic therapy

Only five patients in our study didn't use antibiotics, either before or after the surgery. The average duration of antibiotic therapy in our study was of 19.3 days and on average each patient completed 1.6 different antimicrobial regimens (empiric and targeted).



The numbers between brackets represent the number of patients who go through to the following square of the figure. For example, the numbers (8/6) after "17 IOBC pos" means that out of the 17 patients who had a positive intra-operative bile culture, eight later developed an abdominal infectious complication and six were treated empirically.

Figure 4. Detailed description of our population regarding rate of intra-operative bile cultures, abdominal infectious complications and history of antibiotic treatment in patients with neoplasms submitted to cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 in the Surgery Department of Hospital de Santa Maria, Lisbon.

Empirical treatment for bacteriobilia was considered when antibiotics were initiated immediately after surgery and was appropriate in only 40.0% of cases. When patients displayed signs of infections, empirical antibiotics were also initiated (4.9 days (on average) after surgery) and, in these cases, the chosen regimens were appropriate in 36.4% of cases.

On average, targeted treatment for bacteriobilia was initiated 4.7 days after bile samples were collected intra-operatively, whereas targeted therapy for infectious complications was only initiated 6.8 days after surgery on average.

Table 14. List of empiric antibiotic regimens used in patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Empiric therapy			Total	Appropriate
Single-drug regimen	β-lactams	Amoxicilin	1	0
		Amoxicilin/clavulanate	1	0
		Ceftriaxone	1	0
		Piperacilin/tazobactam	7	3
		Ertapenem	2	0
		Meropenem	3	1
	Non β-lactams	Fosfomicin	1	0
		Tigecyclin	1	0
Combination regimen	Ceftriaxone + Metronidazole		3	1
	Ciprofloxacin + Metronidazole		1	0
	Piperacilin/tazobactam + vancomycin		1	0
	Piperacilin/tazobactam + tigecycline		2	0
	Ertapenem + Tigecycline		1	0
	Meropenem + Vancomycin		1	0
	Meropenem + Linezolid		1	0
	Meropenem + Tigecycline + Linezolid		1	1
	Ceftazidim/avibactam + Vancomycin + Doxycycline + Anidulofungin		1	1
Total			29	7

Table 15. List of targeted antibiotic regimens used in patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

Target therapy		Total	Adequate	
Single-drug regimen	β -lactams	Ampicilin	1	1
		Amoxicilin/clavulanate	4	3
		Piperacilin/tazobactam	2	1
		Ertapenem	1	1
		Meropenem	4	3
	Non β -lactams	Fosfomicin	1	1
		Tigecyclin	1	1
Combination regimens	Amoxicilin/clavulanate + TMP/SMX		1	1
	Amoxicilin/clavulanate + Metronidazole		1	1
	Amoxicilin/clavulanate + TMP/SMX + Anidulafungin		1	1
	Amoxicilin/clavulanate + Linezolid + Fluconazole		1	1
	Cefuroxime + nitrofurantoin		1	1
	Cefotaxime + Metronidazole + Anidulafungin		1	0
	Ceftazidim/avibactam + Tigecycline		1	1
	Ceftazidim/avibactam + Tigecycline + Linezolid		1	1
	Ceftazidim/avibactam + Gentamicin + Linezolid		1	1
	Piperacilin/tazobactam + tigecycline		1	0
	Piperacilin/tazobactam + tigecycline + anidulafungin		1	1
	Ertapenem + Tigecycline		1	1
	Ertapenem + Linezolid + Fluconazol		1	1
	Meropenem + Fluconazol		1	0
	Meropenem + Vancomycin		1	0
	Meropenem + Tigecycline + Colistin		2	2
Tigecycline + Colistin		1	1	
Doxycycline + fosfomicin		1	1	
Total		33	26	

We also analyzed what therapeutics surgeons prescribed once the patients developed infectious complications, both before and after culture results. Out of all 29 antibiotic regimens prescribed empirically, only seven were appropriate, meaning that only 24.1% of these regimens were active against the microorganism causing the infection. Despite this, on many occasions, broad-spectrum antibiotics were used. In fact, the most frequently used drugs were piperacillin/tazobactam (which was used 7 times as monotherapy and 3 times in combination with other antimicrobial agents) and meropenem (used 3 times in monotherapy and 3 times in combined regimens). In total, these two drugs were used in 16 out of the 29 (55%) antimicrobial drug regimens prescribed empirically but were appropriate in only 5 cases (31.3%).

Most common reason for failure of empiric regimens were carbapenemase-producing *Klebsiella pneumoniae* which occurred in seven cases, the occurrence of specimens from

the *Enterococcus* genus, which was responsible for five cases of failure, the occurrence of fungal specimens which accounted for three cases of failure. Other reasons include the occurrence of ampC bacteria and *Pseudomonas aeruginosa*.

As for the targeted therapies (drugs prescribed after receiving the results of microbiological data), we identified a total of 33 drug regimens. As for these therapies, we considered 26 of them to be adequate (78.8%). There were four cases in which the drugs used still weren't active against the microorganism causing the infection. In the remaining three cases in which the antibiotics weren't adequate it was because the regimens needed de-escalation according to culture results. It is impressive that broad-spectrum antibiotics are still among the most used drugs even when therapies are guided by culture results.

3.5. Mortality and length of hospital stay

The intra-hospital mortality rate is 6.1% with only two cases reported. Both of these patients died in septic shock. We report only one case of 90-day mortality, a patient who required a re-intervention due to an anastomotic dehiscence and died in hypovolemic shock. The remaining patients were alive for longer than one year after surgery. There are five patients who are still alive but whose surgery happened less than one year ago. Therefore, the 1-year mortality rate is 24.2%.

Table 16. Link between infection by multidrug resistant bacteria and association with possible risk factors in the patients with pancreatic neoplasms requiring cephalic duodenopancreatectomy from January 1, 2017 to December 31, 2020 of the Surgery Department of Hospital de Santa Maria.

	< 15 d hospital stay	> 15 d hospital stay	p-value	< 1 year mortality	> 1 year mortality	p-value
Total	15	18		7	21	
Infectious complications	5	15	0.003179	7	13	>0,05
MDR	4	12	0.014513	4	10	>0,05
Non-infectious complication except POPF	1	1		1	1	

Mortality was not assessed in five patients because surgery occurred less than one year ago, and these patients are still alive.

In our study, infectious complications occurred more often in longer (> 15 days) (83.3%) hospital stays when compared to shorter stays (< 15 days) (33.3%) – this difference is statistically significant (p-value: 0.003179); and are associated with < 1 year mortality (100%) comparing to > 1 year mortality (61.9%).

We could find a similar association for multidrug resistant bacteria infection/colonization. In < 15 days hospital stays, infections caused by MDR bacteria occurred at a rate of 26.7%, whereas in > 15 days hospital stays, multidrug resistant bacteria occurred at a rate of 66.7% - this difference is statistically significant (p-value: 0.014513). In terms of mortality, the rate of MDR in < 1 year mortality was 57.1% and in > 1 year mortality it was 47.6%.

4. DISCUSSION

It has been known for very long that pancreatic surgery procedures come with a high rate of complications, despite improvement in the surgical technique that resulted in a great decrease in mortality. Mortality can be lower than 5% in some high-volume centers (Neoptolemos *et al.*, 1997). Morbidity remains high and the focus is now on perioperative measures that could reduce it. It is also universal that the most common cause of complications is infectious and that is what we observed in our population, too.

As previously described in the literature, SSIs are the most frequently reported infectious complication following this procedure (Saeed *et al.*, 2015). They occur in very high rates after biliopancreatic surgery, rates vary from 30% to 50% according to previous studies (Maxwell *et al.*, 2020). In our study, infectious complication rate was estimated at around 60.6%. Although SSIs were frequent in our study, they may be underestimated, since samples are not routinely collected for microbiological analysis in mild cases, and these can be managed empirically in association with non-pharmacological strategies. Besides, when more severe infectious complications occur simultaneously, the latter tend to be the main focus of treatment, and this could lead to not documenting the SSI.

In our hospital, since bile cultures are not routinely performed when patients undergo ERCP, we cannot tell whether the microorganisms infecting the patients after the surgical procedure were already colonizing the biliary tree at the time of the ERCP. We believe that collecting bile samples routinely at the end of ERCP procedures could help tailor antibiotic prophylaxis prior to surgery and could also help figure whether bacteriobilia happens during the ERCP or surgery.

There is no standard regimen defined in the ESGE guidelines, which advise against routine use of prophylactic antibiotics before ERCP and only recommend its use in specific cases, namely if incomplete biliary drainage is anticipated or if the patient is immunocompromised. These guidelines state, however; that if the physician chooses to use antibiotics prior to the intervention, then he should opt for a drug active against Gram-negative bacteria and adjusted to local epidemiology (Reco & Ions, 2020).

Our results could suggest that not using prophylaxis for ERCP may be beneficial in terms of infection rates, although there are some factors behind the rationale of choosing to use antibiotics that could explain it. Physicians tend to prescribe antibiotics more easily in patients whose condition is more concerning and who are therefore more vulnerable and thus, more prone to infection. Another factor that could explain this difference is that using antibiotics could select more aggressive pathogens that would ultimately cause infections after surgery. Besides, there is a high prevalence of quinolone-resistant bacteria in Portugal and ciprofloxacin was one of the most used drugs for prophylaxis; this could also explain why there seems to be no benefit in using antibiotics as prophylaxis for ERCP in our study. Furthermore, our sample is also small which could lead to a degree of bias.

Although the bile is usually a sterile fluid, most patients with pancreatic neoplasms undergo at a certain point invasive diagnostic and therapeutic procedures (most frequently ERCPs) that allow bacterial colonization of the biliary tree (bacteriobilia). This association has been proven in previous studies but is still widely debated (Herzog et al., 2009; Krüger et al., 2019).

The results of our study concur with those from previous studies by Herzog *et al.* and Krüger *et al.*, that showed an increase in the rates of bacteriobilia after ERCP. Unfortunately, and because collection of bile samples intra-operatively was not a standard procedure before, this was not done in six patients in our study. The use of surgical prophylaxis can also negatively affect the growth yield of bile cultures. Besides, bile is toxic for most bacteria and bile cultures don't always yield appropriate results (Strohäker et al., 2021).

In our study, the rate of bacteriobilia in patients with history of ERCP in the previous year is 80.0% whereas in patients without history of ERCP in the previous year, this rate is 7.7%. Considering the data related to ERCP procedures, the factors that seem to influence the rate of bacteriobilia may be waiting longer than 1 month for surgery after ERCP (100.0%) as well as the placement of a stent (85.7%) and/or multiple ERCP procedures (85.7%). These data make us reconsider that doing PBD (using ERCP

procedures) to achieve symptomatic relief to delay surgery might be harmful to patients, as it increases the rate of bacteriobilia.

Whereas it might not be perfectly clear that bacteriobilia should or should not be treated according to the microbiological analysis, it seems that these data could be helpful to determine what antibiotic regimen should be used once a patient starts displaying signs of infection (Maxwell et al., 2020). Although bacteriobilia seems to be a poor predictor of infectious complications, it seems it might be useful in predicting what microorganisms could potentially cause future infections and thus could allow a more rapid initiation of adequate antibiotic therapy, reducing the risk of serious infections and ultimately sepsis. In our study, we couldn't find a difference between the rate of abdominal infectious complications in the group with bacteriobilia and the group with negative IOBC (47.1% vs 40.0%). However, when bacteriobilia was appropriately treated, the rate of abdominal infectious complications was 44.4% and when it was not appropriately treated, this rate was 57.1%. Furthermore, there was a concordance rate (including partial concordance) of 75.0% between the microorganisms causing infectious complications and the ones that had been previously isolated in intra-operative bile cultures. Therefore, we believe that the appropriate treatment of bacteriobilia might have prevented the development of some infectious complications and therefore bacteriobilia be routinely treated until better literature is available.

According to previous studies, bacteriobilia doesn't seem to increase mortality, as it only increases the likelihood of developing non-severe complications, such as SSIs. This is matter is still debated and there is no definitive conclusion, as further larger studies are needed. In our study, out of all patients who developed SSIs, four (40.0%) had bacteriobilia, 30.0% had negative intra-operative bile cultures and in the additional 30.0% no bile culture had been collected. Therefore, the rate of patients with bacteriobilia who later developed SSIs in our study ranges from 40.0% to 70.0%.

The current formal guidelines suggest the use of cefazolin as antibiotic prophylaxis for this surgery. However, literature suggests adjusting this regimen according to local epidemiological data and resistance pattern of isolates could be beneficial and could

reduce infection rates (Dimitriou et al., 2019; Donald et al., 2013; Krüger et al., 2019; Stecca et al., 2020; Sudo et al., 2014).

As for our cohort, it seems that when defining a standard antibiotic prophylaxis for this surgical procedure, it would not be reasonable to use cephalosporins, given the high prevalence of enterococcal infections in this population. Enterococci are intrinsically resistant to all cephalosporins, and they represent 29,7% of all isolates, meaning that this would automatically make prophylaxis ineffective in almost one third of all isolates.

The second most frequently isolated microorganisms were those belonging to the *Klebsiella spp.* genus, against which cefazolin is active, unless acquired resistances arise, which was the case in 85.0% (n=17) of all *Klebsiella spp.* isolates in our study. Cefazolin also offers coverage against 50% (n=7) of the specimens of *E. coli* isolated in our study. Unfortunately, some other members of this order are intrinsically resistant to this drug, such as *Morganella morganii*, *Enterobacter spp.*, *Citrobacter freundii* and *Proteus vulgaris*, all of which were found in our study. Considering ceftriaxone, it would cover all the *E. coli* and *Proteus spp.* isolated (n=15), six out of the 20 *Klebsiella spp.* isolated and none of the SPMCE group; therefore, the coverage rate for Enterobacterales would be 50.0%.

Cefazolin and ceftriaxone don't offer anaerobic coverage, unlike ceftiofur, which would mean these drugs wouldn't be active against an additional 16.0% of all our isolates.

According to our data, cefazolin would have been active against 5.9% (one case) of the intra-operative bile cultures and ceftriaxone combined with metronidazole would be active against two cases of IOBC (11.8%).

Anaerobes are part of the commensal flora of the gut in general and the biliary tract and malignancies are a predisposing factor for anaerobic infections. (Finegold, 1993) This could explain the high rate of anaerobic microorganisms in our population. It seems reasonable to include drugs with anti-anaerobic activity when considering antibiotic prophylaxis for these patients. In our cohort both associations of beta-lactams/beta-lactamase inhibitors (such as amoxicillin/clavulanate or piperacillin/tazobactam) and

metronidazole seem to be a good option, with only one case of resistance reported for each of the two drugs.

Interestingly, all fungal infections but one occurred in patients with history of antibiotic use. The only case in which this did not happen occurred in a patient that had been recently submitted to another surgical intervention and in whom a ERCP had been performed without antibiotic prophylaxis. It is also noteworthy that fungal organisms were always associated with the occurrence of at least one bacterial species.

Regarding the need to add antifungal agents to prophylaxis regimen, it seems unnecessary for the general population but should be considered in specific cases, especially if there is any recent history of recent use of broad-spectrum antibiotics. In our population, fluconazole seems to be a good option, as only one case of resistance was found. Besides, literature also suggests that we should pay attention to the immune status of the patient, as several comorbidities and/or history of recent manipulation of the biliary tree may contribute to patients' immune suppression and thus facilitate fungal colonization.

After analyzing our data of intra-operative bile cultures, we found a very high prevalence multidrug resistant microorganisms, as well as microorganisms intrinsically resistant to many antibiotics (such as bacteria carrying the ampC gene). No single drug in our study would have been effective against all microorganisms isolated in intra-operative bile cultures, which is why double regimens would be more effective.

The patients in our study require frequent medical attention and most of them have history of invasive procedures or radiotherapy/chemotherapy (which contribute to a degree of immunosuppression), which is why we believe a prophylaxis regimen using broad-spectrum antibiotics is justifiable.

For a better prophylaxis regimen, we suggest a colonization study prior to surgery (for example by performing routine bile cultures during ERCP, as mentioned above) and tailoring the prophylaxis accordingly. We suggest prophylaxis with piperacillin/tazobactam and if the patient is colonized by VRE or carbapenemase-producing Enterobacterales, we suggest adding tigecycline to the regimen. Tailored

broader-spectrum regimens should be used according to previous isolations whenever necessary. For example, it doesn't seem to be necessary to target *Pseudomonas aeruginosa* unless it has been previously isolated, as it was a rare isolate in our study.

Recent studies suggest that healthcare-associated intra-abdominal infections carry a high risk of multi-drug resistance and thus suggest regimens providing coverage against resistant gram-negative bacilli, such as ESBL-producing Enterobacterales and *P. aeruginosa*. Furthermore, a special note is made for postoperative infections, for which an agent with anti-enterococcal activity should be added. Suggested regimens are, among others, meropenem, imipenem, doripenem, piperacillin/tazobactam or other combination regimens, such as ceftazidime or cefepime plus metronidazole. These latter regimens lack anti-enterococcal activity and therefore ampicillin or vancomycin should be added for extra coverage. The authors also suggest adjusting these regimens according to each patient's risk factors.

In our study, most patients were given broad-spectrum antibiotics empirically, once they developed infectious complications. Although this is known to increase the risk of new resistances, it is recommended in recent studies. The problem with our cohort is that, despite the frequent use of broad-spectrum antibiotics, in many occasions the chosen regimen still wasn't active against the causative microorganism, possibly because of the lack of consideration for the available epidemiological data. Empirical treatment for abdominal infections was appropriated in only 36.4% of cases.

Another reason that could justify the constant use of broad-spectrum antibiotics is the clinical status of most of our patients, all of which had not only a cancer diagnosis but had also been submitted to a major surgery, leaving them particularly fragile to serious complications.

The use of broad-spectrum antibiotics in our population was enormous and most patients underwent long periods of antimicrobial treatment (on average, the duration of antibiotic therapy was 19.3 days and each patient completed 1.6 different antimicrobial regimens), which not only increased costs and length of hospital stays but also increase the risk of emergence of new multidrug resistant strains of bacteria. We therefore reinforce the need for stewardship strategies for antibiotic use in hospitals,

especially before choosing a broad-spectrum antibiotic or when there are no culture data available, which can prevent the spread of resistant isolates. This seems to be crucial in maintaining and increasing treatment options in the future.

Despite culture results, 21.2% of all targeted antibiotic therapies were inadequate. In 4 of the cases in which therapy was inadequate, the chosen antibiotic regimen wasn't active against the isolated microorganism. In the remaining 3 cases, de-escalation was needed and was not performed, which we correlate with the difficulty in choosing the best drug for polymicrobial infections that often involve multi-drug resistant bacteria. We believe this could be solved by routinely involving an infectious diseases specialist when infections are polymicrobial or the resistance pattern is uncommon.

Given the high rate of multidrug resistant organisms, we suggest starting empirical therapy (when IOBC are negative or unavailable) once signs of intra-abdominal infection are present with meropenem plus amikacin and vancomycin, which provides double Gram-negative coverage and VSE coverage at the same time. When IOBC are positive, then we suggest tailoring antibiotic therapy accordingly. The suggested empirical regimen is based on the high frequency multi-drug resistant Gram-negative bacteria (including carbapenemase-producing) and ampicillin-resistant Enterococci. Cultures should be performed as quickly as possible, and de-escalation should follow as soon as results are out. Given the high vulnerability in most of these patients, we believe starting an aggressive combination regimen early could avoid bacteremia and thus reduce the risk of sepsis.

It has been perfectly outlined that all infectious complications are associated with a great increase in the length of hospital stays and therefore comes with much higher monetary costs. Therefore, it is in the physicians' best interest to develop strategies that help avoid such complications (De Pastena et al., 2018).

As for longer hospital stays (lasting longer than 15 days), our data suggests these are associated with a higher frequency of infectious complications (83.3%), comparing to their occurrence in stays lasting less than 15 days (33.3%). The rate of MDR didn't differ between the two groups.

The intra-hospital mortality rate in our study is 6.1% and 90-day mortality rate is of 3.0%. The 1-year mortality rate is 24.2%. Infectious complications are associated with < 1 year mortality (100%) and occur less frequently in > 1 year mortality (61.9%).

Our data therefore suggests that infectious complications are a major determinant of the length of hospital stays, as stated in previous studies and are a cause of short-term mortality (< 1 year).

Other factors that could influence mortality rates and should be included in further studies are the ASA classification and local recurrence or disease progression.

5. CONCLUSIONS/RECOMMENDATIONS

After analyzing our data and for improvement in patient care, we suggest:

That bile samples should be collected routinely at the end of ERCP procedures (after manipulation of the biliary tree). These data should be used to tailor surgical prophylaxis for these patients. Besides, given the high frequency of quinolone-resistant bacteria in Portugal, we believe prophylaxis with amoxicillin/clavulanate would be more suitable for first ERCP procedures. In cases of repeated ERCP and/or recent history of antibiotic use and/or recent hospital stay, ceftriaxone should be preferred.

Moreover, we stress that ERCP procedures should be performed as close to the date of surgery as possible, preferably less than 30 days before surgery. If the placement of a stent is necessary, then Percutaneous Transhepatic Cholangiography (PTC) should be considered, as this technique might be associated with a lower risk of infection.

Furthermore, a rectal colonization study of VRE and/or carbapenemase-producing Enterobacterales should be performed and the patients' history of infections or colonizations as well as antibiotic use should be mapped. These data should be used for risk stratification and to then tailor surgical antibiotic prophylaxis.

Hospital admissions should take place at most 48 hours before surgery, as longer stays increase the patients' risk of developing infectious complications caused by MDR bacteria.

For the general population, and when no data on the patient is available, prophylaxis with piperacillin/tazobactam is sufficient.

If the patient has risk factors for MDR infection, we suggest combining piperacillin/tazobactam with tigecycline.

Several risk factors have been associated with infection by multidrug resistant microorganisms, such as history of ERCP (especially if repeated procedures have been done or a stent has been placed), recent use of antibiotics, long hospital stays and previous infections; all of these should prompt the physician to use the more aggressive version of the prophylaxis regimen.

Then, we suggest collecting bile samples routinely again intra-operatively and treating bacteriobilia accordingly, if it is present. Should signals of infection arise, then the patients should receive tailored antibiotic treatment (adapted according to previous data available) or empirically start a regimen with meropenem plus amikacin and vancomycin until culture results are available.

Given the complexity of this matter and the growing problem of antimicrobial resistances, we suggest the implementation of a pre-operative Infectious Disease consultation performed by a physician with antimicrobial stewardship expertise and integrated in the national PPCIRA program.

Our recommendations are summarized in Figure 5.

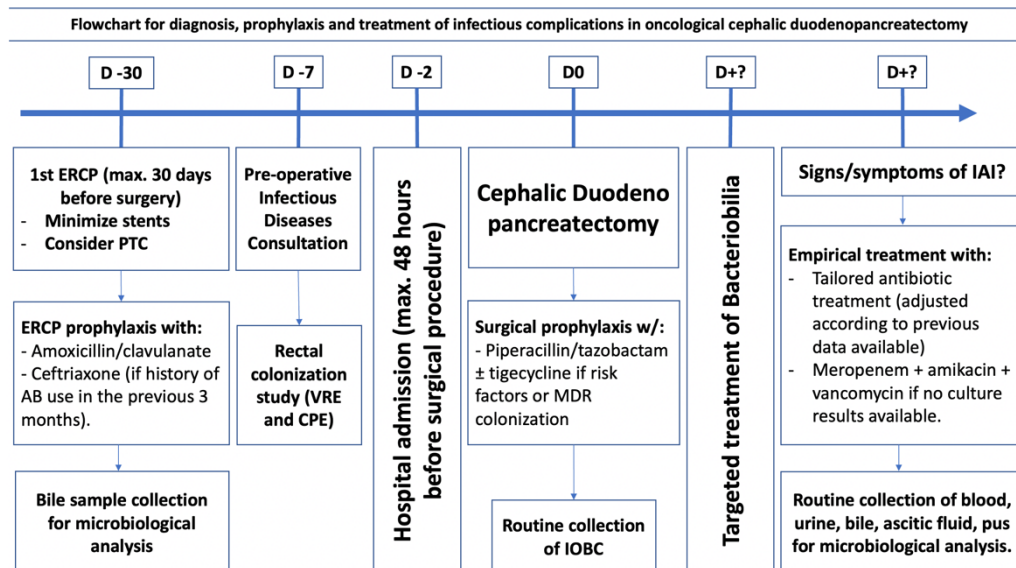


Figure 5. Flowchart for diagnosis, prophylaxis and treatment of infectious complications following cephalic duodenopancreatotomy in oncological patients.

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7. ANNEXES

7.1. ANNEX 1: Approval of the Ethics Committee



Presidente
Prof. Doutor João Forjaz Lacerda
Vice-Presidente
Prof.ª Doutora Helena Cortez-Pinto
Membros
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Prof.ª Doutora Dulce Brito
Doutora Carla Fonseca
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Exma. Senhora

Dra. Carla Mimoso Santos

Serviço de Doenças Infecciosas

Centro Hospitalar Universitário Lisboa Norte, E.P.E.

Lisboa, 22 de Março de 2021

Nossa Ref.º N.º 473/20

Assunto: Projeto "Profilaxia antibiótica em doentes submetidos a cirurgia bílio-pancreática: casuística do Centro Hospitalar Lisboa Norte (entre 2017 e 2020) e proposta de protocolo"

Relator: Prof.ª Doutora Helena Cortez-Pinto

Pela presente se informa que o projeto citado em epígrafe, obteve, na reunião ocorrida em 19 de Fevereiro de 2021, parecer favorável da Comissão de Ética, considerando-se observados os imperativos que fundeiam as Boas práticas clínicas, os preceitos internacionalmente reconhecidos de qualidade ética e científica que devem ser respeitados na conceção e na realização dos estudos clínicos que envolvam a participação de seres humanos.

No uso das competências próprias constantes do disposto no Decreto-Lei. N.º 97/95 de 10 de Maio, e no exercício das suas funções em observância ao deliberado na Lei n.º 21/2014 de 16 de Abril, que aprova a lei da investigação clínica, na sua atual redação alterada pela Lei n.º 73/2015 de 27/07/15, complementada pelo Decreto-Lei n.º 80/2018 (DR n.º 198-2018, Série I de 2018/10/15) que reforça o papel das comissões de ética no contexto da instituição em que se integram, na sua missão de contribuir para o cumprimento de princípios da ética e da bioética, na prestação de cuidados de saúde e na realização de investigação clínica, e ainda em harmonia com os regulamentos internos do CHULN, com os códigos deontológicos, as convenções, e as recomendações constantes das declarações e diretrizes internacionais designadamente as Declarações de Helsínquia a de Tóquio, da Organização Mundial de Saúde e da União Europeia, a Comissão de Ética avaliou o projeto, que considera obedecer aos requisitos éticos fundamentais que devem ser respeitados, refletindo o primado da dignidade e da integridade humanas.

Encontra-se assegurado o direito à integridade moral e física do participante, cumpre as precauções essenciais, cujo desígnio visa minimizar eventuais danos para os seus direitos de personalidade, bem como o direito à privacidade e à proteção dos dados pessoais que lhe dizem respeito, respeitando os imperativos refletidos no Regulamento Geral sobre a Proteção de Dados (RGPD) entrado em vigor em 25 de Maio de 2016 e plenamente aplicável a partir de 25 de Maio de 2018, (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27/04/16), de 27 de abril, publicado no Jornal Oficial da União Europeia, no dia 4 de Maio de 2016, e na Lei n.º 58/2019, de 8 de Agosto

Mais se informa que o referido estudo foi autorizado pelo Sr. Diretor Clínico, Dr. Luís Pinheiro

Com os melhores cumprimentos

O Presidente da Comissão de Ética do CAML


Prof. Doutor João Forjaz Lacerda

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7.2. ANNEX 2: Urkund Report



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