UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
„CAROL DAVILA“ DIN BUCUREȘTI

Str. Dionisie Lupu 37, sector 2, București, 020021, România, www.umfcd.ro, email: rectorat@umfcd.ro

2025

UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
SCHOOL OF MEDICINE

Etiological, evolutionary and therapeutic characteristics in acute cholangitis

SUMMARY OF THE DOCTORAL THESIS

Doctoral supervisor:
PROF. UNIV. DR. HABIL. DIACONU CAMELIA CRISTINA

Doctoral student:
COZMA MATEI-ALEXANDRU

2025

Content

1. Introduction 2

2. Working hypothesis and general objectives 2

3. General research methodology 4

3.1. Materials and methods 4

3.1.1. Establishment of study groups 4

3.1.2. Obtaining and processing data and bile samples 5

3.1.3. Ethical considerations 5

3.1.4. Statistical analysis of the obtained data 6

3.2. Results 6

3.2.1. General characteristics of patients included in the study 6

3.2.2. General characteristics of acute cholangitis episodes 7

3.2.3. Etiologies of acute cholangitis 8

3.2.4. Microbiological agents involved in the etiopathogenesis of acute cholangitis 9

3.2.5. Antibiotic resistance rates 10

3.2.6. Involvement of multidrug-resistant microorganisms 13

3.2.7. Antibiotic treatment used 14

3.2.8. Microbiological evolution in recurrent episodes of acute cholangitis 15

3.2.9. Risk factors associated with infection with a multidrug-resistant microorganism 15

4. **Discussions** 15

5. Original elements and future prospects 21

6. Conclusions 23

7. Selective bibliography 25

List of published scientific papers 27

1. INTRODUCTION

Acute cholangitis (AC) is an infectious disease of the intra- and extrahepatic biliary tract (BT), frequently associated with a high rate of morbidity, organ dysfunction, and death. The prevalence has increased globally to 8–12 cases/100,000 people, mainly due to the increasing incidence of gallstone disease and malignant common bile duct (CBD) strictures. Systemic infection occurs in up to 20% of cases, and the mortality rate has remained around 10%, despite a significant decline in recent years with the widespread implementation of endoscopic interventions. Because of the severe potential, treatment should be initiated as soon as possible, and it consists of prompt fluid and electrolyte rebalancing, broad-spectrum antibiotic therapy, and early restoration of bile flow.

Antimicrobial resistance (AR) is a significant cause of morbidity, mortality and additional unnecessary medical costs globally, responsible for over 5 million deaths annually. AC makes no exception, with the increasing prevalence of multidrug-resistant (MDR) microorganisms in recent years leading to an increase in the number of complications and mortality rates.

Although this is a major problem globally, there are significant variations at national or even regional level, with high consumption of broad-spectrum antibiotics and a series of socio-economic aspects (ineffective infection control, population density and national tourism profile) being the most relevant proven risk factors (RFs).

Unfortunately, even if there are currently multiple studies in the international literature that have investigated the local microbiological particularities of patients with AC, most of them are retrospective or unicentric, and data on geographical differences in AR rates, it's evolution according to the endoscopic history of patients, and the involvement of MDR microorganisms on the prognosis of these patients are rare.

2. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

The present study aims to analyse the microbiological profile of patients with AC from two referal university centres – Colentina Clinical Hospital (CCH) in Bucharest, Romania and Haut-Lévêque Hospital (HLH) in Bordeaux, France – by comparing the resistance rates to commonly used antibiotics, based on the etiological agents isolated from bile cultures collected during endoscopic retrograde cholangiopancreatography (ERCP). Given that the data in the literature are

often partial or outdated, this study aims to provide a detailed, comparative and updated picture of the bacterial profile involved in AC in two regions with distinct epidemiological and cultural particularities.

In Romania, even if there are few retrospective studies on this topic, the present research represents the first prospective initiative that directly compares the microbiological profile and antibiotic resistance between a Romanian and a French university centre. The study was designed based on two main hypotheses.

The first hypothesis assumed that AR rates would be higher in the Romanian group, due to increased antibiotic consumption and insufficient implementation of infection control and antibiotic use policies.

The second hypothesis assumed that AR rates among patients with a history of endoscopic procedures or biliary stent placement, would be higher, due to anatomical and local microbiome changes favouring colonization with opportunistic and MDR germs. Thus, the study tracks the differences between the two centres in terms of pathogens, susceptibility profile and the impact of clinical or procedural risk factors, providing a relevant picture of the current epidemiological context specific to each region.

The major objective of the present study is to compare the antibiotic resistance patterns of the main etiological agents identified in bile cultures performed in two referral university centres in Romania and France, and, last but not least, to present these data in a comparative manner with the latest available epidemiological reports.

The specific objectives of the study are:

- Identification, based on bacterial cultures obtained from bile samples, of the main etiological agents involved in the etiopathogenesis of AC and their correlation with different RFs of the included patients.
- Determining resistance patterns to antibiotics frequently used in everyday medical practice and comparing data from the two medical centres.
- To identify the MDR bacteria involved and to establish possible correlations between their presence and various clinico-biological parameters, such as the severity of the disease, serum C-reactive protein (CRP) or white blood cells (WBC) levels, peri- and post-procedural complication rates, length of hospitalization or reintervention rate within the same hospitalization.

- Establishing possible correlations between the history of endoscopic instrumentation and various clinico-biological parameters, such as the degree of severity, the rate of peri- and post-procedural complications or the duration of hospitalization, or microbiological parameters, such as the presence of MDRs.
- Collection of microbiological data during several successive episodes of AC and comparative evaluation of AR rates within infections with the same etiological agent.
- Correlating data obtained from current practice (real-world data) with those reported in international recommendations or by governmental organizations monitoring the AR phenomenon in order to establish the level of concordance between clinical reality and epidemiological trends described at the population level.

3. GENERAL RESEARCH METHODOLOGY

3.1. Materials and methods

3.1.1. Establishment of study groups

The present study included 143 patients in the CCH study group and 62 patients in the HLH group. All included patients had a positive culture from bile samples taken during minimally invasive BT decompression procedures. In total, they experienced 256 episodes of AC during the study period (189 in CCH and 67 in HLH). Since some patients had multiple episodes of AC requiring endoscopic BT decompression, we opted to consider all positive bile cultures processed during the study period. 257 positive bile cultures and associated antibiograms were processed (190 in CCH and 67 in HLH), which led to the identification and analysis of 436 etiological agents (241 in CCH and 194 in HLH).

The included patients simultaneously met the following inclusion and exclusion criteria:

A. Inclusion criteria

- patients diagnosed with AC according to Tokyo 2018 Guidelines criteria and who presented a positive bile culture during hospitalization;
- patients who signed informed consent;
- patients over 18 years of age ;

- patients with complete medical history, socio-demographic, clinical, biological, imaging data existing in the IT system of the institutions involved;

B. Exclusion criteria

- patients who did NOT sign the informed consent or did NOT agree to participate in the study;
- patients who could NOT sign the informed consent or could NOT agree to participate in the study due to associated pathologies (e.g. critically ill patients, patients with psychiatric illnesses, patients with major neuro-cognitive disorders/dementia/mental retardation);
- patients under 18 years of age;
- patients with incomplete medical history, socio-demographic, clinical, biological, imaging data unidentified in the IT system of the institutions involved;

3.1.2. Obtaining and processing data and bile samples

The information included in the database was collected from the electronic archive of the two centres (Hipocrate System – CCH, respectively DxCare – HLH), from the observation records, discharge notes, imaging and laboratory archives, through a standardized data collection form. For patients who underwent ERCP, Olympus TJF-Q190V or TJF-Q185V therapeutic duodenoscopes were used, and CBP cannulation was performed with TRUEtome™ sphincterotomy (4.4F) and 0.035 inch Dreamwire™ guidewire (Boston Scientific). 5–10 ml of bile were aspirated before contrast medium injection, and the samples were collected in sterile urine culture tubes and quickly transported to the bacteriology laboratory of each centre. The sample collection and processing scheme is presented in **Figure 3.1.**

3.1.3. Ethical considerations

This study was conducted in compliance with the rules of research ethics and medical deontology, with the approval of the Ethics Committee of the CCH (approval no. 10/12.09.2022) and with the approval of the Ethics and Medical Research Committee of the Bordeaux University Hospital Center (Research Ethics Committee of the Bordeaux Centre for Ethics and Health Research - reference number: CER-BDX 2023-171).

3.1.4. Statistical analysis of the obtained data

Statistical analysis was performed with Microsoft Excel, GraphPad Prism 10 and SPSS 29.0. Data distribution was assessed using normality tests (D'Agostino & Pearson, Anderson-Darling, Shapiro-Wilk, Kolmogorov-Smirnov). Data with normal distribution were analyzed using Welch's T test, and those with non-normal distribution using Mann-Whitney test. The significance threshold was $p<0.05$.

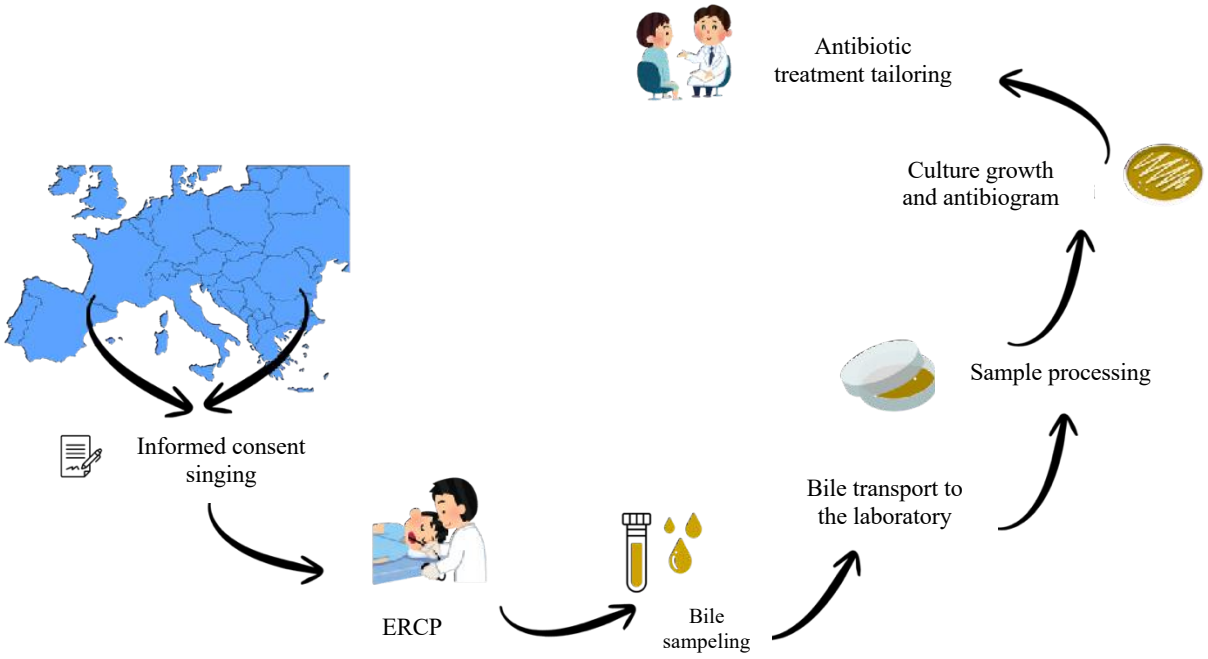


Figure 3.1. Ilustration of bile sample collection and processing.

3.2. Results

3.2.1. General characteristics of patients included in the study

The Colentina study group consisted of 83 (58.04%) male patients and 60 (41.95%) female patients. The age of the patients included in the study was within the range [41.89] years, and the mean age was 68.49 ± 10.40 years. Of the total number of patients, 77 (53.84%) had a history of sphincterotomy and had a biliary stent already installed at the time of admission.

The Haut-Lévêque study group consisted of 40 (64.51%) male patients and 22 (35.48%) female patients. The age of the patients included in the study ranged from [46.88] years, with a mean age of 70.34 ± 9.02 years. Of the total number of patients in this study group, 21 (33.87%) had a history of sphincterotomy and had a biliary prosthesis already installed at the time of admission. The distributions by sex and age of the study groups are illustrated in **Figures 3.2 and 3.3.**

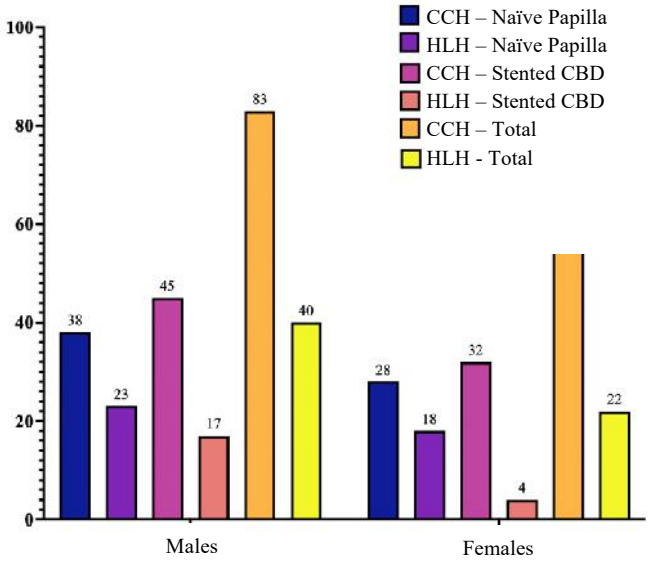


Figure 3.2. Gender distribution in both hospitals

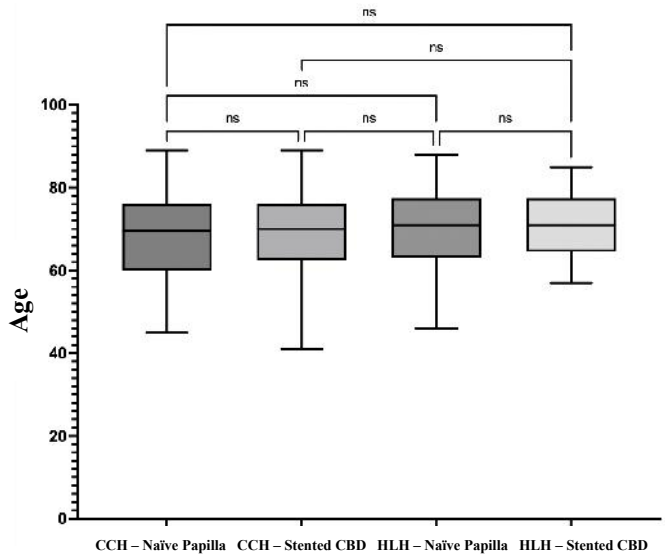


Figure 3.3. Age distribution in both hospitals

3.2.2. General characteristics of CA episodes

The vast majority of patients (n=110) in the CCH group had a single episode of AC during the study period, and in the HLH group, only 5 patients had two recorded episodes of AC. The majority of documented AC episodes were recorded among patients with biliary stents (103 cases, 54.5% - CCH and 42, 62.68% - HLH), (**p=0.0225**) **.**

The length of hospital stay was significantly longer in the CCH group, with a mean of 5.64 days compared to 3.35 days in the HLH group (**p<0.0001**). 64 (44.75%) of those admitted to the CCH and 17 (27.41%) to the HLH group were diagnosed with type 2 diabetes mellitus (T2DM), 91 (63.63%), 22 (35.48%) with hypertension, and 39 (27.28%) and 12 (19.35%) with heart failure, respectively. Of the mentioned comorbidities, only T2DM was associated with a longer duration of hospitalization in the CCH group (6.8 days vs. 5.1 days, **p=0.041**) and with a higher incidence of post-ERCP acute pancreatitis (PEP) (odds ratio/OR=1.508, 1.069–2.128, **p=0.019**).

Complications occurred in 57 (30.15%) of the CCH group and 13 (19.40%) of the HLH group (p=0.1107). These were PEP, post-endoscopic sphincterotomy bleeding, post-sphincterotomy perforation, and post-ERCP acute cholecystitis.

The most common post-procedural complication was represented by PEP which, within the CCH group, had an incidence of 20.63% (complicating 39 episodes of AC). RFs associated with the occurrence of PEP were: T2DM (OR=1.508, 1.069–2.128, p=0.019), benign and malignant ampullary carcinoma (OR=5.487, 1.94–15.516), p<0.001 and distal cholangiocarcinoma (OR of 3.255, 1.178–8.992, p<0.001), serum BT levels, OR=1.049, 1.023–1.075, p<0.001, and difficult cannulation of the CBD (OR=3.734, p<0.001) or Wirsung duct (OR=1.454, p=0.022) during ERCP. On the other hand, the only procedural variable analysed that showed a significant negative association was Wirsung duct stenting, OR=0.485, **p=0.016** .

Transfer to the intensive care unit was required in 26 episodes (13.75%) in the CCH group and in 4 episodes (5.97%) in the HLH group, with the difference being not significant (p=0.1206). In contrast, endoscopic reintervention performed during the same hospitalization was significantly more frequent in patients in the CCH study group, being required in 22 cases (11.64%), compared to only 2 (2.98%) in the HLH group (**p=0.0483**). According to the Tokyo score of severity proposed by the Tokyo Consensus in 2018, the vast majority of cases were represented by mild forms (corresponding to the Tokyo I score), representing 140 episodes (74.04%) of CA within CCH and, respectively, 45 episodes (67.16%) within HLH.

3.2.3. Etiologies of acute cholangitis

Malignant stenosis of the CBD was the most common cause of AC in both study groups, being identified in 83 (56.64%) of the patients in the CCH group and in 47 (75.80%) of the patients in the HLH group. This trend was maintained within the patient subgroups, being also more frequent in the patients with biliary stent in both medical units, reaching 77.92% in the CCH subgroup and 76.19% in the HLH, but also in the subgroup of patients with naive papilla within the HLH (75.60%).

Within the CCH group, the most common etiologies of AC were represented by choledocholithiasis, with a prevalence of 32.17%, peri-hilar cholangiocarcinoma (24.48%), and cephalo-pancreatic neoplasm (17.48%), and among HLH patients, the predominant etiologies were represented by pancreatic head neoplasm, responsible for 37.06% of cases, and by distal (14.52%) and peri-hilar (11.29%) cholangiocarcinoma (**Figure 3.4**).

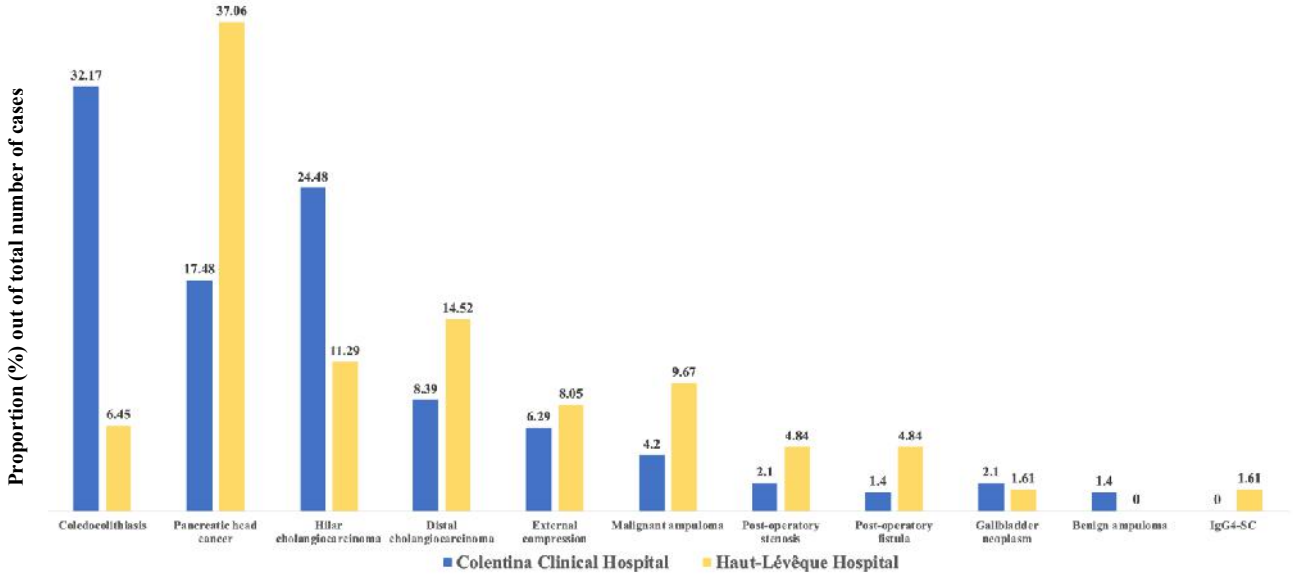


Figure 3.4. Distribution by etiology.

After performing the comparative analysis using the Fisher test, we observed significant differences only between the two main study groups in the case of choledocholithiasis (**p<0.0001**), extrinsic compression of the CBD (**p=0.0168**), pancreatic-head neoplasm (**p=0.0038**) and peri-hilar cholangiocarcinoma (**p=0.0379**). We also obtained a significant difference after comparing the subgroups of patients with naive papilla from both medical units who had pancreatic-head neoplasm as the etiology of AC (**p=0.0008**).

3.2.4. Microbiological agents involved in the etiopathogenesis of acute cholangitis

Of the 190 positive bile cultures obtained in the Colentina group, 78 (41.05%) were recorded in the subgroup of patients with naive papilla, and 112 (58.95%) were collected in the group with a biliary stent present. Regarding the HLH study group, of the 67 positive cultures, 42 (62.69%) belonged to the subgroup with naive papilla, and only 25 (37.31%) were collected from patients with an already present biliary stent, with a significant difference being observed between the two study groups (**p=0.0027**).

In the Colentina study group, the most frequently identified microorganisms were those of the genera *Escherichia* (74, 30.70%), *Pseudomonas* (68, 28.21%), *Klebsiella* (40, 16.59%), *Enterococcus* (37, 15.35%) and *Enterobacter* (7, 2.90%). In the Haut-Lévêque study group, the most frequently identified etiological factors were represented by microorganisms of the genera *Enterococcus* (58, 29.81%), *Escherichia* (22, 11.34%), *Streptococcus* (21, 10.82%), *Enterobacter* (20, 10.30%), *Candida* (16, 8.24) and *Klebsiella* (14, 7.21%) (**Figure 3.5**).

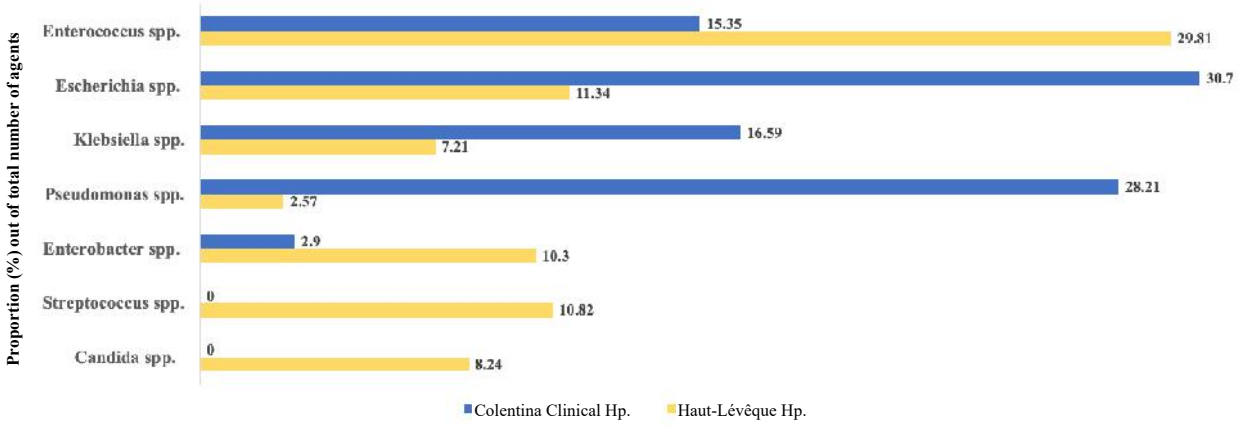


Figure 3.5. The most important etiological agents of CA in the two study groups (%).

3.2.5. Antibiotic resistance rates

In most cases, with a few exceptions, such as metronidazole, piperacillin/tazobactam, amoxicillin/clavulanic acid and colistin, the resistance rates to the antibiotics of interest were higher in the CCH group. Furthermore, after comparative analysis using Fisher's exact test, many of these differences were also statistically significant, such as in the case of resistance to ceftriaxone (**p=0.03**), ciprofloxacin (**p<0.0001**), levofloxacin (**p<0.0001**), meropenem (**p=0.0003**), cefazolin (**p<0.0001**), cefepime (**p<0.0001**) and cefotaxime (**p<0.0001**), to which a significant percentage of the microorganisms identified in the CCH study group are resistant. At the same time, we detected significant differences between the two main study groups also in terms of resistance rates to piperacillin/tazobactam (**p<0.0001**) or amoxicillin/clavulanic acid (**p<0.0001**), these being higher among the HLH group.

Subsequently, we calculated the resistance rates to the same antibiotics but within the subgroups of both study groups (Naive Papilla vs. Stent Placement). We thus observed in the CCH group, higher resistance rates in patients with an already installed biliary stent (except for

cefazolin, colistin, linezolid and cefotaxime), while in the Haut-Lévêque group, the distribution is more balanced, with higher resistance rates being found in patients without endoscopic history. We detected significant differences between the two CCH subgroups for ciprofloxacin (**p=0.045**), levofloxacin (**p=0.012**), cefazolin (**p=0.042**) and linezolid (**p=0.034**). However, for the HLH subgroups, the differences observed were not significant. The differences between the AR rates of the two groups and subgroups of interest in both medical units are illustrated in **Figure 3.6** and in the Heatmap diagram below (**Figure 3.7**).

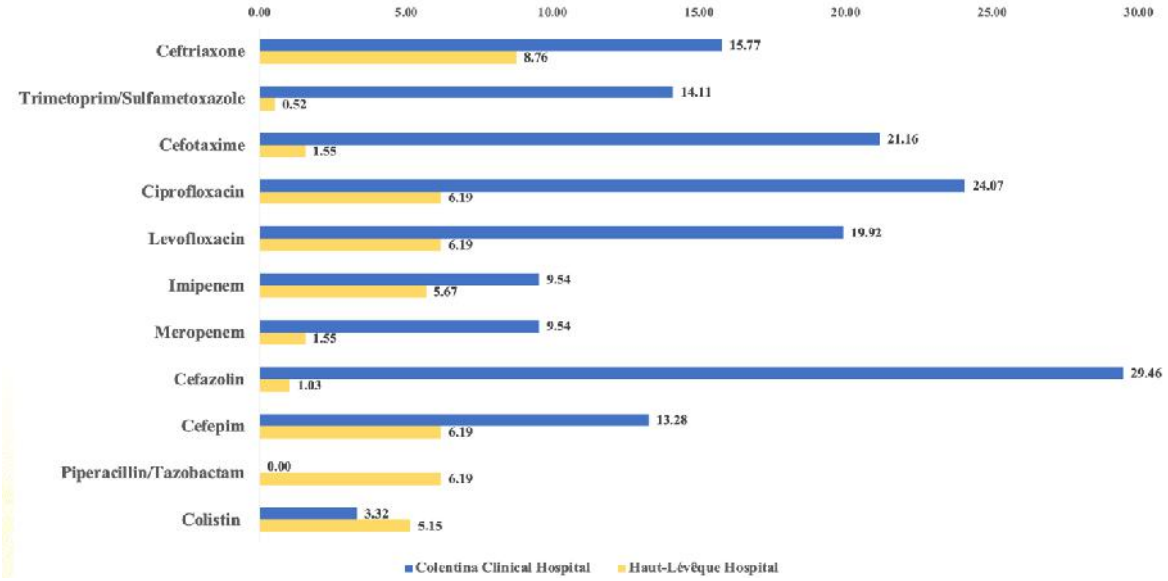
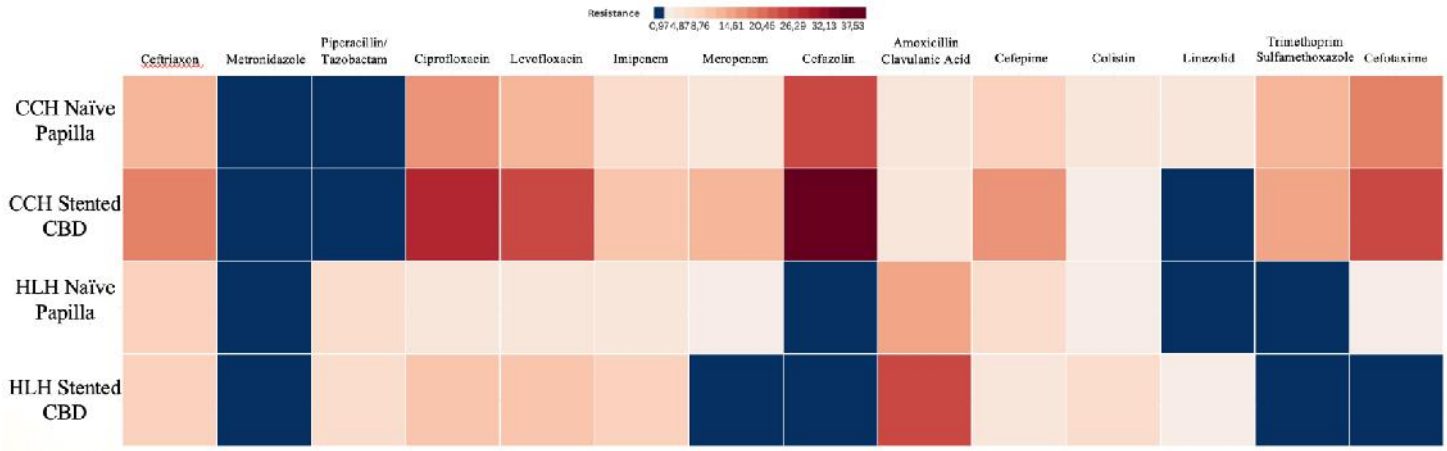
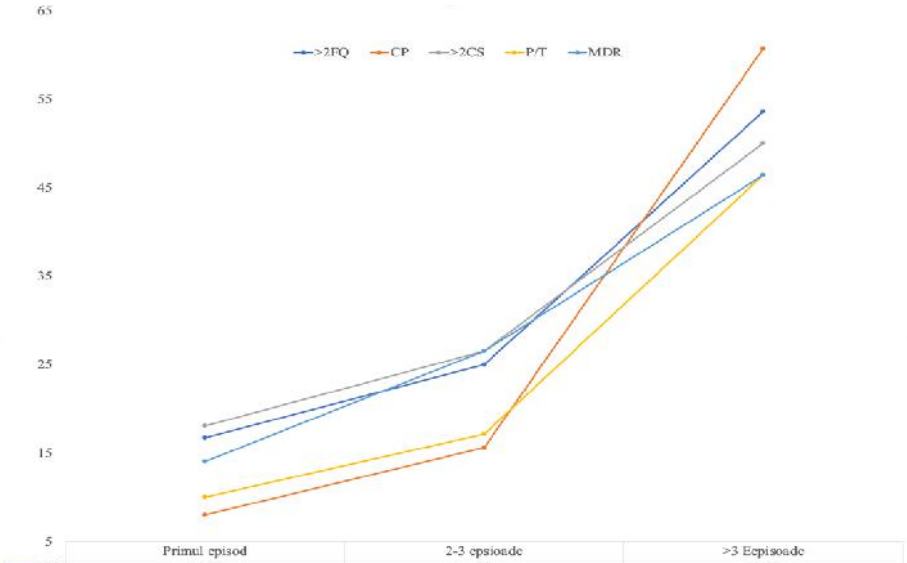


Figure 3.6. AR rates of etiological agents identified in both medical units.

Figure 3.7. Heatmap diagram highlighting differences between subgroups of patients within the same medical units.





	Primul episod	2-3 episoade	>3 Episoade
>2FQ	16.77	25	53.57
CP	8.05	15.62	60.71
>2CS	18.12	26.56	50
P/T	10.06	17.18	46.42
MDR	14.09	26.56	46.42

Figure 3.8. Evolution of complex resistance with the increase in the number of CA episodes (% of resistant microorganisms). * >2FQ - at least two antibiotics from the fluoroquinolone class; >2CS - at least two antibiotics from the 3rd/4th generation cephalosporin class; CP - antibiotics from the carbapenem class; P/T - piperacillin/tazobactam, MDR - multidrug-resistant bacteria

As can be seen in **Figure 3.8** , the evolution of complex resistance (to at least two fluoroquinolone antibiotics, to at least two 3rd/4th generation cephalosporin antibiotics, to carbapenem antibiotics or to piperacillin/tazobactam) progressed with the increase in the number of previous episodes of AC (a single episode vs. 2-3 previous episodes vs. more than 3 episodes), the difference between the 3 categories being significant (**p<0.001**) for all 4 types of complex resistance. At the same time, the share of identified MDR microorganisms was significantly higher with the increase in the number of episodes of AC in the patients' history (**p<0.001**).

3.2.6. The involvement of multidrug-resistant microorganisms

Of the total 241 microorganisms isolated in the CCH study group, 51 (21.16%) were identified as multiresistant, while in the HLH study group, only 15 (7.73%) of the 194 microorganisms were classified in this category, the difference between the two groups being statistically significant (**p<0.0001**). Their exact type and number is detailed in **Table 3.1** . We thus observed that in the HLH group there were only three types of such microorganisms, the majority

of them (14, 93.33%) being represented by extended-spectrum β-lactamases (ESBL) producing bacteria or by microorganisms resistant to macrolides, lincosamides and streptogramins (MLS). In contrast, within the CCH study group, the resistance spectrum is significantly more diverse, with microorganisms belonging to almost all major antimicrobial resistance categories being identified, including ESBLs, carbapenemase-producing enterobacteria (CPE), vancomycin-resistant enterococci (VRE), and high level aminoglycoside-resistant enterococci (HLAR).

Table 3.1. Multidrug-resistant microorganisms identified in both medical units.

Multidrug-resistant microorganisms	Colentina Clinical Hospital			Haut-Lévêque Hospital		
	Total (n=51)	Naive Papilla (n=11)	Biliary Stent (n=40)	Total (n=15)	Naive Papilla (n=7)	Biliary Stent (n=8)
Extended-spectrum β-lactamase (ESBL)-producing microorganisms	28	4	24	6	4	2
Carbapenemase-producing Enterobacteriaceae (CPE)	7	1	6	0	0	0
Carbapenemase-producing Enterobacteriaceae - metallo-β-lactamase New Delhi (CPE-NDM)	2	0	2	0	0	0
Vancomycin-resistant enterococci (VRE)	5	3	2	0	0	0
Macrolide, lincosamide and streptogramin resistant microorganisms (MLS)	0	0	0	8	2	6
Highly aminoglycoside-resistant enterococci (HLAR)	7	2	5	0	0	0
Other*	2	1	1	1	1	0

*Others - Citrobacter freundii MDR, Acinetobacter baumannii XDR

3.2.7. Antibiotic treatment used

Within the CCH study group, the most frequently used empirical antibiotics were the ceftriaxone - metronidazole combination, administered in 121 episodes of AC, representing 64.02% of the total, and as for the HLH group, the piperacillin / tazobactam combination was the most frequently used empirical antibiotic, being administered in 30 episodes of AC (44.77%), followed by the amoxicillin / clavulanic acid combination in 9 cases (13.43%) and, subsequently, a series of antibiotic combinations used in 3 episodes (4.47%) of AC each: ceftriaxone - amoxicillin / clavulanic acid, trimethoprim / sulfamethoxazole, respectively piperacillin / tazobactam - amikacin.

During hospitalization, the initial antibiotic regimen was modified in 38 cases of AC in the CCH group (representing 20.10% of the total episodes in this group) and in 7 cases (10.44%) in the HLH group, this difference not being statistically significant (p=0.0925). In the Colentina group, the most frequently used antibiotics in the adjusted regimen were: meropenem (n=12), imipenem/cilastatin (n=10), the combination of meropenem – metronidazole (n=3) and ciprofloxacin (n=3), and in the Haut-Lévêque group, these were piperacillin/tazobactam (n=2), the combination of piperacillin/tazobactam – meropenem (n=1), and piperacillin/tazobactam – linezolid (n=1). At the same time, in the CCH group, 26 of the 38 cases (68.42%) in which the initial treatment regimen was modified were recorded in patients with an already installed biliary prosthesis, and in the HLH group, 3 of the 7 cases (42.85%) were in the same situation.

3.2.8. Microbiological evolution in recurrent episodes of acute cholangitis

During the study period, of the 32 patients who experienced at least two episodes of AC in the CCH group, the same microorganism was isolated in 22 of them: 9 were represented by *Escherichia coli* , of which 8 developed resistance to at least one class of antibiotics, and 10 bacteria of the genus *Pseudomonas* (of which 4 developed resistance to at least one class of antibiotics of interest). At the same time, the same microorganism was isolated in only one of the patients, this one being represented by *Enterococcus faecium*, which developed resistance to imipenem.

3.2.9. Risk factors associated with infection with a multidrug-resistant microorganism

Within the CCH study group, the RFs that were associated with infection with an MMR were, in order of importance of the association: resistance to at least two antibiotics from the fluoroquinolone class, associated with an OR of 6.25 (95% confidence interval: 2.817 – 13.869), **p<0.001** , resistance to at least two antibiotics from the 3rd/4th generation cephalosporin class, OR = 6.009 (3.084 – 11.708), **p<0.001** , resistance to antibiotics carbapenems, OR of 4.45 (1.803 – 10.982), **p=0.001** , the presence of a biliary stent, having an OR of 2.847 (1.377 – 5.888), **p=0.005** and the presence of a positive blood cultures, OR = 1.646 (0.2.12 – 1.967), **p=0.042.**

In the HLH study group, the only RFs associated with the presence of an MDR bacteria were resistance to at least two fluoroquinolones, OR=19.444 (4.752 - 79.566), **p<0.001** , resistance to piperacillin/tazobactam, OR=3.508 (1.136 - 10.831), **p=0.022**, resistance to amoxicillin/clavulanic

acid, OR= 3.508 (1.136 - 10.831), **p=0.029,** and resistance to at least two antibiotics from the 3rd/4th generation cephalosporin class, OR=3.107 (0.013 – 9.533), **p=0.047** .

4. DISCUSSIONS

4.1. Analysis of general data of included patients and recorded AC episodes

The demographic and epidemiological aspects of patients with AC identified in the present study are consistent with those presented in the literature. Similar results regarding the gender of patients were also reported by Chandra et al., Sung et al. and Masadeh et al. in their prospective studies, in which they also found a male preponderance of 56%, 64.7% and 58%, respectively [2–4].

However, within the CCH group, age over 75 years was associated with a longer hospital stay (6.14 vs. 4.96 days, **p<0.0001**), with 51 (26.98%) of the 189 recorded episodes involving patients over 75 years of age. At the same time, it was also associated, only in the CCH study group, with a higher rate of admission in the ICU (12 episodes - 6.34%) (**p<0.019**). These results are consistent with both numerous prospective studies and the latest edition of the TG18 guidelines, which demonstrated a transfer rate to the ICU of 39% in patients over 80 years of age, significantly higher (p<0.001) than in those aged 65–79 years (23.2%), thus underlining the significance of age in the prognosis of patients with AC [5–7].

The mean length of hospital stay was significantly longer in the CCH group, with a duration of 5.64 days compared to 3.35 days in the HLH group (**p<0.0001**). Other authors have identified a variable mean length of hospital stay in other prospective investigations, such as the investigation by Raghhupatruni et al. which identified a mean length of hospital stay between 5 and 7.5 days depending on the severity of the AC, or the study by Patel and colleagues who observed a length of hospital stay between 4 and 11 days depending on the time elapsed until ERCP [8,9].

T2DM was associated with a longer length of hospital stay in the Colentina group (6.8 days vs. 5.1 days, **p=0.041**) and a higher incidence of PEP (OR=1.508, 1.069–2.128, **p=0.019**). Similarly, Khoury et al. identified T2DM as an independent RF for developing AC among patients with choledocholithiasis (OR 1.93, 1.26–2.96, p=0.002), and in their investigation, T2DM was associated with a longer length of hospital stay (p=0.01) and higher mortality in the first 30 days (OR=2.285, 1.161–4.497, p=0.017) [10–12].

4.2. Etiology of acute cholangitis

The results of the present study are similar to those identified in the literature. Regarding the nature of CBD obstruction, most prospective studies in the literature have identified benign obstruction (including choledocholithiasis in this category) as the most common etiology of AC. These include the studies conducted by: Kaya et al. (which included 91 patients, of whom over 87% had a benign etiology), Negm et al. (46%), Lee et al (over 70% of cases), Chandra et al. (68%), Goo et al. (58%), Gromski et al. (68%) and Patel et al. (85%) [2,9,13–17]. Studies that observed a predominance of malignant etiology include those conducted by Schneider et al. (52%), Sung et al. (70.3%), Masadeh et al. (60%), Miuțescu et al. (50.4%) and Rerknimitr et al. (70%) [3,4,18–20].

In terms of causal pathology, choledocholithiasis represented the most frequent etiology, as in the CCH group, in most international studies, such as those conducted by Patel et al. (63%), Lee et al. (22.8%), Kaya et al. (83%) or Miuțescu et al. (48.5%) [9,13,17,21]. Pancreatic-head cancer represented among the most important causes of AC, as in the HLH group, in international investigations such as those conducted by Reiter et al. (second most frequent cause, 14.7%), Kaya et al. (second most frequent cause, 7%), Miutescu et al. (second most frequent cause, 24.8%), Masadeh et al. (most frequent cause, 32%) or Melzer et al. (second most frequent cause, 18%) [4,13,18,22]. The possible difference between the two medical units can be attributed to the protocols within HLH that require bile sampling for cultures mainly in patients with oncological pathology, given their risk of recurrence and BT colonization with MDR microorganisms.

4.3. Microbiological profile of bicultures

Most studies similar to the present one have identified a similar distribution, with the already mentioned Gram-negative microorganisms being predominant in investigations such as those carried out by Kaya et al., in which over 80% of the identified microorganisms were represented by Gram-negative bacteria, Miuțescu et al. (>70%), Goo et al. (60%), Li et al (68%), or Reuken et al. (78%) were polymicrobial, demonstrating that *Enterobacteriaceae* can be found in approximately 41% of cases, *Enterococcaceae* in approximately 25%, and fungi in approximately 8%, the microbial agents with the highest prevalence being those of the *Escherichia coli* (16%) and *Enterococcus faecalis* (13%)) [13,14,21,23–25].

There are also a number of recent retrospective studies conducted by a team from Timisoara, Romania, that have studied aspects similar to our investigation, ultimately showing both similar and distinct results. Thus, in an investigation that included 488 cases of AC, the microbial agents with the highest prevalence were similar to those found in our centre, namely *Escherichia coli* (30.7%) (especially in patients with naive papilla - 36.8%, and patients who underwent sphincterotomy only (30.3%), *Klebsiella spp* . (18.4%, especially in patients with biliary stents (37.2%)), and *Enterococcus spp.* (23.6%) (predominantly in subjects who underwent both sphincterotomy and biliary stent placement (43.6%)) [18]. In another similar investigation, *Escherichia coli* and *Klebsiella spp* . were represented in similar percentages to those in CCH, but in our case, we detected a higher incidence of *Pseudomonas spp.* (28% vs. <7%) and a lower incidence of *Enterococcus spp.* (15% vs. 23.6%) [26]. In a study that included 262 patients with AC, Gram-negative bacteria were also predominant, with the authors reporting the presence of *Escherichia coli* predominated in patients with benign CBD obstruction (56.1% vs. 37.6%). *Klebsiella spp.* , *Pseudomonas spp.* and *Citrobacter spp.* were identified in 24-29%, 10-14% and 4.7-7% of cases, while *Enterococcus spp.* was identified in 18.7-24.7% of subjects with biliary obstruction. Almost 70% of blood cultures were sterile, and most of the positive cases revealed the presence of *Escherichia coli* , *Klebsiella spp.* and *Pseudomonas spp.* [27].

In contrast, we detected a distinct distribution within the HLH study group, where Gram-positive microorganisms, such as those from the genera *Enterococcus* or *Streptococcus* , predominated, totalling approximately 40% of the identified microorganisms, while Gram-negative microorganisms from the family *Enterobacteriaceae*, such as those from the genera *Escherichia, Enterobacter* and *Klebsiella*, represented only 28% of the total etiological agents isolated. Other studies that demonstrated a similar distribution are, for example, those carried out by Rupp el al. (Gram-positive microorganisms representing 57% of the total isolated ones), Negm et al. (in which, even though there was an approximately equal number of Gram-positive and Gram-negative bacteria isolated, those from the genus *Enterococcus* were by far the most frequent, 30% of the total), Kruis et al. (in which *Enteroccus* was the most frequently isolated bacterium – 31%) or Krupik et al. (in which bacteria of the genus *Enterococcus* were most frequently identified, 57%) [16,25,28,29].

4.4. Antibiotic resistance profile of identified etiological agents

The data identified in the literature are variable. A German investigation already mentioned by Reiter et al. identified a susceptibility of Gram-positive and Gram-negative pathogens to ampicillin/amoxicillin of 68% and 3.4%, to amoxicillin/clavulanic acid of 70.4% and 20.9%, to piperacillin/tazobactam of 71.1% and 72.9%, to cefuroxime of 12.3% and 45.8%, to ceftriaxone of 12.8% and 71.7%, to cefepime of 11.9% and 80.4%, to ciprofloxacin of 2.6% and 79.6%, to meropenem of 15% and 94.8%, to gentamicin of 3.2% and 93.2%, and to tigecycline of 97.3% and 82.2%. Gram-positive bacteria were susceptible to linezolid in 97% of cases and to vancomycin in 89.1% of cases. Fungal strains were susceptible to fluconazole in approximately 76% of cases and to voriconazole, echinocandin, or amphotericin B in over 90% of cases [22].

Gromski et al. identified in the aforementioned study a susceptibility for *Escherichia coli* of 65% to ciprofloxacin, 89% to ceftriaxone and 79% to trimethoprim/sulfamethoxazole, for *Klebsiella pneumoniae* of 88% to ciprofloxacin, 96% to ceftriaxone and 91% to trimethoprim/sulfamethoxazole, and for *Pseudomonas aeruginosa* of 46% to ciprofloxacin and 70% to both ampicillin and trimethoprim/sulfamethoxazole [15].

The aforementioned Romanian studies have shown variable results. In the study that included patients with a history of cholecystectomy, AR rates showed a similar pattern, with 20–30% of cases resistant to ampicillin/sulbactam, piperacillin/tazobactam, third- and fourth-generation cephalosporins, and 15–20% resistant to fluoroquinolones and carbapenems [26]. Another investigation conducted on a group of 488 patients and which took into account the endoscopic history of the patients showed similar results to those detected in the CCH group, with resistance to ampicillin/sulbactam observed in 33.3% (especially in patients with biliary stents), to piperacillin/tazobactam in 20%, to fluoroquinolones in 15.8% (especially in patients with biliary stents, 19%), to carbapenems in 17.7%, to 3rd generation cephalosporins in 25.9% and 4th generation cephalosporins in 22.8% [18] . [27] .

An increase in resistance rates between 2003 and 2017 was also observed by Suh et al in patients with CA for ciprofloxacin, from 10% in the period 2003-2007, to 35% in the period 2013-2017, p=0.031 , and for ceftriaxone, from 12% in the period 2003-2007 to 20% in the period 2013-2017 (statistically insignificant difference) [30] As was also demonstrated in our study, AR rates are higher in patients with a history of sphincterotomy and biliary stent placement and, at the same time, increase with the number of recurrent episodes and, implicitly, with the number of

endoscopic interventions performed. Similarly, a German study by Schneider et al. showed a significant decrease in the susceptibility of identified microorganisms to ceftriaxone (p=0.035), fluoroquinolones (p<0.001), and trimethoprim/sulfamethoxazole (p=0.003). At the same time, significantly lower susceptibility was found in patients with biliary stents to ceftriaxone (p=0.014) and ciprofloxacin (p<0.001) [20].

4.5. The involvement of multidrug-resistant microorganisms

A study conducted in two German medical units by Reuken et al., which analysed a total of 1764 microorganisms isolated from 531 positive biliary cultures, identified 24 MDR bacteria (1.34%): ESBL (n=13); VRE (n=7), *Pseudomonas aeruginosa* MDR (n=4). RFs associated with such an infection were male gender (p=0.043), hospital-associated forms (p=0.047), WBC count (p 0.014) or GGT (p=0.040), presence of a biliary stent (p=0.025), presence of positive blood cultures (p=0.019), and antibiotic treatment in the last 14 days (p=0.012). Similar to our study, in this case, infection with an MDR bacteria was not associated with increased mortality, hospital stay, or a severe form of AC [24].

Sung et al. found a significant increase in the prevalence of ESBL *Escherichia* and *Klebsiella* from 2.3% during 2000–2004 to 43.9% during 2005–2009 [3]. Also from a time perspective, Suh et al. observed an increase in the prevalence of vancomycin-resistant *Enterococcus faecium strains* (from <5% to almost 20%) and penicillin-resistant *Enterococcus non-faecium* strains (from <5% to almost 10%) during 2013–2017 compared to 2003–2007, although the differences observed were not statistically significant [30].

In their prospective study of 1150 positive bile cultures and 1491 isolates, Rupp et al. detected 138 MDR bacteria (9.25%): 12 VRE, 86 non-VRE *Enterococcus faecium* , 26 ESBL, and 14 other. Furthermore, MDR microorganisms were more common in patients with a history of sphincterotomy or biliary stenting, OR=3.634 (2.124–6.219), p<0.001, and their presence was associated with significantly higher mean hepatic enzymes (p<0.001) and CRP (p<0.001).

Another study by Reiter et al. identified 58 (14.9%) MDRs from the total isolates, the most common being ESBL (36), VRE (11), MLS (9) and CRE (1) [22]. The investigation carried out in the USA by Gromski and collaborators identified 155 (23.4%) MDRs from the total of 662 identified: MRSA was detected in approx. 50% of the cases, VRE in approx. 15%, ESBL in 8% and CRE in 4% of the total [15].

In a series of investigations that analysed a cohort of 488 patients from Romania with or without a history of cholecystectomy, but also with a history of sphincterotomy or biliary stent, Miuțescu and collaborators identified a proportion of 19.9% of multiresistant bacteria: 12 ESBL (12.3%), 22 CRE (4.5%), 13 VRE (2.7%) and 2 cases of MRSA (0.4%). With the exception of MRSA, MMR were more frequently isolated in the group of patients with a history of cholecystectomy, the differences being significant for all types of multiresistance. Moreover, a higher prevalence was detected in patients with an already installed biliary stent for all categories of MMR compared to patients with naive papilla: 28.7% vs. 8.9% for ESBL ($p<0.001$), 8.5% vs. 1.1% for VRE ($p<0.001$), and 11.7% vs. 2.8% for CRE ($p<0.001$). FRs associated with MDR bacteria infection were history of cholecystectomy OR=2.45 (1.56–3.84), p=0.002, total bilirubin value, OR=1.10 (1.03–1.18), p=0.007 and PCR values, OR=1.04 (1.01–1.07), p=0.015 [18,26].

4.6. Administered antibiotic treatment

The empirical antibiotic regimen was modified in 20.10% of cases in the CCH group and in 10.44% in the HLH group (p=0.0925). The adaptation of the antibiotic regimen was performed in both medical units in case of an unfavorable evolution of the patients (increase of inflammatory syndrome markers or alteration of the general condition), despite an effective biliary drainage, and not always after the antibiogram was available. Thus, considering the relatively low proportion of patients in whom an adaptation of the initial antibiotic regimen was indeed needed, the importance of effective biliary drainage in the treatment of CA is highlighted. The most frequently used antibiotics in adjusted regimens were meropenem (n=12), imipenem/cilastatin (n=10), the combination of meropenem – metronidazole (n=3) and ciprofloxacin (n=3) in the CCH group, and piperacillin/tazobactam (n=2), the combination of piperacillin/tazobactam – meropenem (n=1), piperacillin/tazobactam – linezolid (n=1), piperacillin/tazobactam – amikacin (n=1), and, respectively, the association – piperacillin/tazobactam – linezolid – amphotericin B (n=1) in the HLH group. We thus observe that, despite the fact that the adjustment of the antibiotic regimen was less frequent in the HLH group, the options chosen were more varied. Moreover, it is important to note that, in the case of the CCH group, most therapeutic adaptations (68.42%) were made among patients with a biliary stent in place, while, in the case of HLH, 3 out of the 7 cases (42.85%) fell into this category.

In a previously mentioned study published by Reuken et al., antibiotic combinations were predominant, being used in 46% of cases, and monotherapies in 36% of cases. Similar to the results in the CCH group, ceftriaxone was the most frequently used antibiotic (43%), followed by ciprofloxacin, metronidazole, and piperacillin/tazobactam. Furthermore, the identified etiological agents were fully susceptible to empirical antibiotic therapy in 24% of monotherapy cases and in 29% of antibiotic combination cases. Adaptation of the antibiotic regimen occurred in 53% of patients initially treated with ceftriaxone, 45% of those initially treated with ciprofloxacin, 10% with piperacillin/tazobactam, and 33% of those treated with vancomycin [24] .

Similar to the two groups of patients in our study, ceftriaxone monotherapy (23.1%) or piperacillin/tazobactam (20.2%) were the most frequently used empirical antibiotic treatments in an investigation by Reiter et al., followed by ciprofloxacin (6.7%) and meropenem (4.3%). In 44.1% of cases, the initial antibiotic regimen was adjusted (56% due to the result of the antibiogram and 17.6% due to the deterioration of the patient's general condition), these patients ultimately having a significantly longer hospital stay, 9 ± 0.7 days vs. 15 ± 1.4. days, $p < 0.001$ [22] .

5. ORIGINAL ELEMENTS AND FUTURE PROSPECTS

By completing this thesis, we achieved the proposed main and secondary objectives and succeeded in carrying out a comparative analysis of the microbiological profile and AR rates of microorganisms identified in bile cultures and related antibiograms in patients with AC from two reference university centres in Romania and France.

To our knowledge, although there are a number of retrospective studies conducted in our country, this is the first prospective international multicentre study comparing epidemiological data of patients with CA in Romania with a reference centre in France, a country significantly different from a socio-economic point of view, in terms of public health measures and the general population's attitude towards antibiotic consumption.

At the same time, in addition to documenting the isolated etiological agents and their rates to the most common antibiotics, we opted for an additional detailed analysis, in which we took into account the endoscopic history of the included patients, the prevalence of MDRs and their impact on the patient's prognosis, the antibiotic treatment administered both empirically and adjusted according to the antibiogram result and, last but not least, we were able to identify RFs associated in a statistically significant manner in both study groups with an MDRs infection.

Considering that both study groups come from reference university centres in each country of origin, we can state that the data obtained in this study can be extrapolated to some extent considering that a good part of the enrolled patients also come from medical units around the cities.

Moreover, one of the most important original elements of the present work is represented by its second part, namely the ability to follow a series of patients from both study groups during several episodes of recurrent CA and, in this way, being able to dynamically evaluate the evolution of the microbiological profile and antibiotic resistance rates of the identified microorganisms, our study being, to our knowledge, the first to address this aspect. Therefore, our investigation thus significantly contributes with valuable epidemiological data, in an attempt to compensate for the relatively low volume of similar information from this region (Eastern Europe).

In the future, we plan to include more patients from other similar centres in Romania in order to increase the relevance of the results obtained and to obtain a clearer picture of the local microbiological context. Furthermore, we want to create a registry to centralize the rates of AR and MDRs identified in this category of patients, with the ultimate goal of facilitating the decision of empirical treatment in medical units in Romania where taking bile samples and performing bile cultures and related antibiograms is not as accessible as in the reference university centres.

However, it is important to note that although the study is a prospective, multicentre, international one, it includes only two centres, with a relatively small number of patients compared to the incidence of AC and the number of endoscopic procedures such as ERCP performed annually in both countries.

In addition, the study was conducted over a relatively short period of time, thus limiting the follow-up of the patients' post-procedural evolution and, at the same time, there may be differences in the sample processing techniques between the two medical units, even if the declared protocols are standardized and transparent. At the same time, the lack of new generation detection methods, such as polymerase chain reaction or 16S rRNA sequencing, can be considered a limitation leading to a decrease in the overall sensitivity of the detection methods used. Last but not least, the fact that the patients in both groups came from reference university centers may lead to a selection bias, given the much more severe or complex nature of the cases resolved within them, compared to regular medical units.

6. CONCLUSIONS

1. In our study, demographic data related to age identified a mean age of 68.49 ± 10.40 years in the CCH study group and 70.34 ± 9.02 years in the HLH group, without any significant difference being observed between the two groups, the age of all patients included in the study being included in the range [41,89] years.

2. Age > 75 years was associated, only within the Colentina group, with a longer hospital stay (6.14 days vs. 4.96 days, $p<0.0001$), 51 (26.98%) of the 189 AC episodes recorded involving patients over 75 years of age, and with a higher rate of admission to the ICU ($p<0.019$).

3. The male gender predominated in both study groups, with men representing 58.04% of patients in the CCH group and 64.51% in the HLH group, the difference between the two groups not being significant in this case either ($p=0.7243$).

4. Within the CCH group, most patients (53.84%) had a history of endoscopic sphincterotomy and already had a biliary stent installed at the time of admission, while within the HLH group, most did not have an endoscopic history (33.87%), the difference being significant ($p=0.0098$).

5. A significantly higher number of patients in the CCH group experienced recurrent episodes of AC during the study (49.79% vs. 2.98%, $p<0.0001$).

6. The average length of hospital stay was significantly longer in the CCH group, 5.64 compared to 3.35 days in the HLH group ($p<0.0001$).

7. T2DM was associated with a longer duration of hospitalization in the CCH group (6.8 days vs. 5.1 days, $p=0.041$) and with a higher incidence of PEP (OR=1.508, 1.069–2.128, $p=0.019$).

8. The most common etiologies of AC were represented by choledocholithiasis, pancreatic-head neoplasm, and peri-hilar and distal cholangiocarcinoma.

9. The majority of cultures taken within the CCH group (74.73%) were monomicrobial, while the majority of cultures taken within the HLH group were polymicrobial (53.73%), with at least 3 bacteria identified.

10. Within the CCH group, the most frequently involved microorganisms were those of the *Enterobacteriaceae family* such as those of the genera *Escherichia* , *Klebsiella* or *Enterobacter* (totaling almost 40% of the total), while, in the case of the HLH group, the most frequently involved were Gram-positive bacteria such as those of the genera *Enterococcus* or *Streptococcus* , (again totalling approximately 40% of the total).

11. Within the three subgroups of interest ("Naive Papilla" CCH vs. HLH, "Biliary Stent" CCH vs. HLH and "Total" CCH vs. HLH), we observed significant differences between the two medical units for the genus *Enterococcus* , more frequent in the HLH group (p=0.0112, p=0.0205 and p=0.0003), and for the genera *Escherichia* (p=0.0143, p=0.0001 and p<0.0001) and *Pseudomonas* (p<0.0001 for all three subgroups), which were more frequent in the CCH group.

12. Within the "Biliary Stent" and "Total" subgroups, we observed significant differences for the genera *Klebsiella*, (more frequent in the CCH group; p=0.0096 and p=0.0033) and *Enterobacter*, (more frequent in the HLH group; p=0.008 and p=0.0022).

13. Resistance rates of all identified microorganisms were significantly higher in the CCH group for ceftriaxone (p=0.03), ciprofloxacin (p<0.0001), levofloxacin (p<0.0001), meropenem (p=0.0003), cefazolin (p<0.0001), cefepime (p<0.0001) and cefotaxime (p=<0.0001).

14. In the HLH group, resistance rates were significantly higher for piperacillin/tazobactam (p<0.0001) and amoxicillin/clavulanic acid (p<0.0001).

15. Within the CCH group, resistance rates were significantly higher in patients with an already placed biliary stent for ciprofloxacin (p=0.045), levofloxacin (p=0.012), cefazolin (p=0.042) and linezolid (p=0.034), while in the HLH group, resistance rates were higher in patients without a history of endoscopic surgery, but the differences were not significant.

16. Within the CCH group, the proportion of microorganisms resistant to at least two fluoroquinolones or third-generation cephalosporins, to carbapenems, to piperacillin/tazobactam, or classified as multidrug-resistant increased directly proportionally to the number of previous CA episodes (p<0.0001 for all 5 variables).

17. The MDRs rate was significantly higher in the CCH group compared to the HLH group (21.16% vs. 7.73%, p<0.0001).

18. The majority of MDRs infections in both study groups were detected in patients with an already installed biliary stent, the difference being significant only in the CCH group.

19. Involvement of an MDRs was associated only in the CCH study group with a higher risk of endoscopic reintervention during the same hospitalization (odds ratio of 4.9, p<0.001).

20. FRs associated with MDRs infection were resistance to at least two antibiotics from the fluoroquinolone class (p<0.001), respectively 3rd/4th generation cephalosporins (p<0.001), carbapenems (p=0.001), piperacillin/tazobactam (p=0.022), amoxicillin/clavulanic acid (p=0.029), the presence of a biliary stent (p=0.005) and a positive blood culture (p=0.042).

21. The preferred empirical antibiotic treatment was the ceftriaxone-metronidazole combination in the CCH group (64.02%) and piperacillin/tazobactam in the HLH group (44.77%), being changed according to the antibiogram result in 20.10% of cases in the CCH group and in 10.44% in the HLH group (non-significant difference).

7. SELECTIVE BIBLIOGRAPHY

1. Cozma MA, Găman MA, Diaconu CC, Berger A, Zerbib F, Mateescu RB. Microbial Profile and Antibiotic Resistance Patterns in Bile Aspirates from Patients with Acute Cholangitis: A Multicenter International Study. Antibiotics. 4 July 2025;14(7):679.
2. Chandra S, Klair JS, Soota K, Livorsi DJ, Johlin FC. Endoscopic Retrograde Cholangio-Pancreatography-Obtained Bile Culture Can Guide Antibiotic Therapy in Acute Cholangitis. Dig Dis. 2019;37(2):155-60.
3. Sung YK, Lee JK, Lee KH, Lee KT, Kang CI. The Clinical Epidemiology and Outcomes of Bacteremic Biliary Tract Infections Caused by Antimicrobial-Resistant Pathogens. American Journal of Gastroenterology. 2012 Mar;107(3):473-83.
4. Masadeh M, Chandra S, Livorsi D, Johlin F, Silverman W. Evaluation of Biliary Bacterial Resistance in Patients with Frequent Biliary Instrumentation, One Size Does Not Fit All. Dig Dis Sci. December 2018;63(12):3474-9.
5. Miura F, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. J Hepato Biliary Pancreat. January 2018;25(1):31-40.
6. Inan O, Sahiner ES, Ates I. Factors associated with clinical outcome in geriatric acute cholangitis patients. Eur Rev Med Pharmacol Sci. April 2023;27(8):3313-21.
7. Christeven R, Frandy F, Andersen A. Acute Cholangitis: An Update in Management Based on Severity Assessment. InaJGHE. July 21, 2020;19(3):170-7.
8. Raghhupatruni P, Gopalakrishna R, Ankarath V, Sadasivan S. Profile and Outcome of Patients with Acute Cholangitis in a Tertiary Center in South India. Journal of Digestive Endoscopy. September 2021;12(03):127-32.
9. Gaduputi V. Acute Cholangitis: Does the Timing of ERCP Alter Outcomes? 2016;
10. Khoury T, Sbeit W. Diabetes mellitus is associated with a higher rate of acute cholangitis among patients with common bile duct stones: A retrospective study. Medicines. 2022 Jan 28;101(4):e28687.
11. Murata A, Matsuda S, Kuwabara K, Ichimiya Y, Fujino Y, Kubo T. The Influence of Diabetes Mellitus on Short-Term Outcomes of Patients with Bleeding Peptic Ulcers. Yonsei Med J. 2012;53(4):701.
12. Cozma MA, Dobrică EC, Shah P, Shellah D, Găman MA, Diaconu CC. Implications of Type 2 Diabetes Mellitus in Patients with Acute Cholangitis: A Systematic Review of Current Literature. Healthcare. November 2, 2022;10(11):2196.
13. Kaya M, Beştaş R, Bacalan F, Bacaksız F, Arslan EG, Kaplan MA. Microbial profile and antibiotic sensitivity pattern in bile cultures from endoscopic retrograde cholangiography patients. World J Gastroenterol. 2012 Jul 21;18(27):3585-9.
14. Goo JC, Seong MH, Shim YK, Lee HS, Han JH, Shin KS, et al. Extended Spectrum-β-Lactamase or Carbapenemase Producing Bacteria Isolated from Patients with Acute Cholangitis. Clin Endosc. 2012;45(2):155.

15. Gromski MA, Gutta A, Lehman GA, Tong Y, Fogel EL, Watkins JL, et al. Microbiology of bile aspirates obtained at ERCP in patients with suspected acute cholangitis. Endoscopy. Nov 2022;54(11):1045-52.
16. Negm AA, Schott A, Vonberg RP, Weismueller TJ, Schneider AS, Kubicka S, et al. Routine bile collection for microbiological analysis during cholangiography and its impact on the management of cholangitis. Gastrointestinal Endoscopy. 2010 Aug;72(2):284-91.
17. Lee CC, Chang IJ, Lai YC, Chen SY, Chen SC. Epidemiology and Prognostic Determinants of Patients with Bacteremic Cholecystitis or Cholangitis. Am J Gastroenterol. 2007 Mar;102(3):563-9.
18. Miutescu B, Vuletici D, Burciu C, Bende F, Ratiu I, Moga T, et al. Comparative Analysis of Antibiotic Resistance in Acute Cholangitis Patients with Stent Placement and Sphincterotomy Interventions. Life. 2023 Nov 13;13(11):2205.
19. Rerknimitr R, Fogel EL, Kalayci C, Esber E, Lehman GA, Sherman S. Microbiology of bile in patients with cholangitis or cholestasis with and without plastic biliary endoprosthesis. Gastrointestinal Endoscopy. 2002 Dec;56(6):885-9.
20. Schneider J, De Waha P, Hapfelmeier A, Feihl S, Rommler F, Schlag C, et al. Risk factors for increased antimicrobial resistance: a retrospective analysis of 309 acute cholangitis episodes. Journal of Antimicrobial Chemotherapy. 2014 Feb 1;69(2):519-25.
21. Miuțescu B, Vuletici D, Burciu C, Turcu-Stiolica A, Bende F, Rațiu I, et al. Identification of Microbial Species and Analysis of Antimicrobial Resistance Patterns in Acute Cholangitis Patients with Malignant and Benign Biliary Obstructions: A Comparative Study. Medicine. 2023 Apr 6;59(4):721.
22. Reiter FP, Obermeier W, Jung J, Denk G, Mahajan UM, De Toni EN, et al. Prevalence, Resistance Rates, and Risk Factors of Pathogens in Routine Bile Cultures Obtained during Endoscopic Retrograde Cholangiography. Dig Dis. 2021;39(1):42-51.
23. Li K, Jiang S, Fu H, Hao Y, Tian S, Zhou F. Risk Factors and Prognosis of Carbapenem-Resistant Organism Colonization and Infection in Acute Cholangitis. Infect Drug Resist. 2022;15:7777-87.
24. Reuken PA, Torres D, Baier M, Löffler B, Lübbert C, Lippmann N, et al. Risk Factors for Multi-Drug Resistant Pathogens and Failure of Empiric First-Line Therapy in Acute Cholangitis. Galdiero M, editor. PLoS ONE. 2017 Jan 11;12(1):e0169900.
25. Kruis T, Güse-Jaschuck S, Siegmund B, Adam T, Epple HJ. Use of microbiological and patient data for choice of empirical antibiotic therapy in acute cholangitis. BMC Gastroenterol. December 2020;20(1):65.
26. Miutescu B, Vuletici D, Burciu C, Bende F, Ratiu I, Moga T, et al. Comparative Analysis of Microbial Species and Multidrug Resistance Patterns in Acute Cholangitis Patients with Cholecystectomy: A Single-Center Study. Diseases. 2024 Jan 6;12(1):19.
27. Miuțescu B, Vuletici D, Burciu C, Turcu-Stiolica A, Bende F, Rațiu I, et al. Identification of Microbial Species and Analysis of Antimicrobial Resistance Patterns in Acute Cholangitis Patients with Malignant and Benign Biliary Obstructions: A Comparative Study. Medicine. 2023 Apr 6;59(4):721.
28. Krupik Y, Ariam E, Cohen DL, Bermont A, Vosko S, Shirin H, et al. Do the Results of Bile Cultures Affect the Outcomes of Patients with Mild-to-Moderate Ascending Cholangitis? A Single Center Prospective Study. Diagnostics. 2025 Mar 11;15(6):695.
29. Rupp C, Bode K, Weiss KH, Rudolph G, Bergemann J, Kloeters-Plachky P, et al. Microbiological Assessment of Bile and Corresponding Antibiotic Treatment: A Strobe-Compliant Observational Study of 1401 Endoscopic Retrograde Cholangiographies. Medicines. 2016 March;95(10):e2390.
30. Suh SW, Choi YS, Choi SH, Do JH, Oh HC, Kim HJ, et al. Antibiotic selection based on microbiology and resistance profiles of bile from gallbladder of patients with acute cholecystitis. Science Rep. 2021 Feb 3;11(1):2969.

List of published scientific papers

Articles published as lead author in Clarivate Analytics indexed journals (with impact factor) (first author, last author, corresponding author)

1. **Cozma, M.-A** .; Dobrica, E.-C.; Shah, P.; Shellah, D.; Gaman, M.-A.; Diaconu, CC Implications of Type 2 Diabetes Mellitus in Patients with Acute Cholangitis: A Systematic Review of Current Literature. Healthcare 2022, 10, 2196. https:// doi.org/10.3390/healthcare10112196

   Impact Factor: 2,800 (Q2) – at the date of publication

   https://www.mdpi.com/2227-9032/10/11/2196

2. **Cozma MA,** Gaman MA, Srichawla BS, Dhali A, Manan MR, Nahian A, Marsool MDM, Suteja RC, Kutikuppala LVS, Kipkorir V, Gaman AM, Diaconu CC. Acute cholangitis: a state-of-the-art review. Ann Med Surg (London). 2024 May 15;86(8):4560-4574. two: 10.1097/MS9.0000000000002169. PMID: 39118745;

   Impact Factor: 1,700 (Q2) – at the date of publication

   https://journals.lww.com/annals-of-medicine-and surgery/fulltext/2024/08000/acute_cholangitis__a_state_of_the_art_review.41.aspx

3. **Cozma MA,** Angelescu C, Haidar A, Mateescu RB, Diaconu CC. Incidence, Risk Factors, and Prevention Strategies for Post-ERCP Pancreatitis in Patients with Biliopancreatic Disorders and Acute Cholangitis: A Study from a Romanian Tertiary Hospital. Biomedicines. 2025 Mar 17;13(3):727. doi: 10.3390/biomedicines13030727. PMID: 40149703;

   Impact Factor: 3.9 (Q1) – at the date of publication

   https://pubmed.ncbi.nlm.nih.gov/40149703/

4. **Cozma, M.A.,** Găman, M.-A., Diaconu, C.C., Berger, A., Zerbib, F., Mateescu, R.B. Microbial Profile and Antibiotic Resistance Patterns in Bile Aspirates from Patients with Acute Cholangitis: A Multicenter International Study. Antibiotics, 2025 14(7), 679. https://doi.org/10.3390/antibiotics14070679 ;

   Impact Factor: 4.6 (Q1) – at the date of publication

   https://www.mdpi.com/journal/antibiotics