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https://doi.org/10.31925/farmacia.2026.3.12 **ORIGINAL ARTICLE**

ANTIBIOTIC THERAPY STRATEGIES IN ACUTE BILIARY PANCREATITIS: A RETROSPECTIVE COHORT STUDY

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Abstract

Antibiotic therapy in acute biliary pancreatitis remains debated, as early pancreatic inflammation is frequently sterile and current guidance supports antimicrobials only for confirmed or strongly suspected infection. We performed a retrospective observational analysis of 139 patients with acute pancreatic pathology of biliary aetiology to describe real-world antibiotic strategies and their association with markers of severity. Antibiotics were administered in 83.5% of cases. Antibiotic exposure was associated with higher admission leukocyte count (p = 0.002), amylase (p = 0.014), lipase (p = 0.03), total bilirubin (p = 0.008), direct bilirubin (p = 0.022), and longer length of stay (median 12 *versus* 9 days; p = 0.018). Among treated patients, carbapenem-based regimens (n = 32) were associated with ICU admission more frequently than non-carbapenem regimens (34.4% *versus* 14.3%; p = 0.02) and with lower total bilirubin (p = 0.024), while length of stay did not differ significantly (p = 0.26). Overall, antibiotic escalation appears to reflect perceived clinical severity, highlighting the importance of targeted antibiotic prescribing and stewardship.

Rezumat

Antibioterapia în pancreatita acută biliară rămâne un subiect controversat, întrucât inflamația pancreatică precoce este frecvent sterilă, însă în practica clinică reală, antimicrobienele sunt utilizate frecvent empiric. Scopul studiului a fost evaluarea strategiilor de antibioterapie și a asocierii acestora cu markerii de severitate clinică și biologică într-un lot de pacienți dintr-o cohortă retrospectivă de 139 de pacienți internați cu pancreatită acută biliară. Tratamentul antibiotic a fost administrat la 83,5% dintre pacienți. Utilizarea acestora s-a asociat semnificativ cu leucocitoză (p = 0,002), valori crescute ale amilazei (p = 0,014), ale lipazei (p = 0,03), ale bilirubinei totale (p = 0,008) și ale bilirubinei directe (p = 0,022), precum și cu o durată mai lungă a spitalizării (p = 0,018). Terapia pe bază de carbapeneme s-a asociat semnificativ cu internarea în terapie intensivă (p = 0,02), fără diferențe semnificative în durata spitalizării comparativ cu regimurile antibiotice non-carbapenem (p = 0,26). Rezultatele sugerează că escaladarea antibioterapiei reflectă severitatea percepută clinic, subliniind necesitatea implementării principiilor de stewardship antibiotic.

Keywords: acute biliary pancreatitis, antibiotics, carbapenems, intensive care, therapeutic management

Introduction

Biliary aetiology is one of the most common causes of acute pancreatitis worldwide and accounts for a substantial proportion of emergency hospital admissions related to gastrointestinal pathology. Over the past decade, the global incidence of acute pancreatitis has continued to rise, with biliary aetiology remaining the most frequent in many regions. Although the majority of cases follow a mild and self-limiting course, approximately 15 - 20% of patients develop moderately severe or severe disease, characterised by persistent organ failure, local complications such as pancreatic necrosis, which brings with it increased risk of infectious events. This subgroup contributes disproportionately to morbidity, mortality, prolonged hospitalisation, and healthcare costs (1-6). The pathophysiology of acute biliary pancreatitis is a complex process that involves early activation of pancreatic enzymes, acinar cell injury, microcirculatory impairment, and systemic inflammatory response. Importantly, pancreatic necrosis that develops during the early phase of the disease is initially sterile. Bacterial infection of necrotic tissue often occurs later in the disease course and derives from bacterial translocation from the gut lumen, facilitated by intestinal barrier dysfunction and altered microbiota. The distinction between sterile inflammation and infected necrosis is critical in guiding therapeutic

decisions, particularly regarding antibiotic administration (7-12).

Despite the well-established fact that early pancreatic inflammation is not infected, distinguishing systemic inflammatory response syndrome (SIRS) from true infection remains clinically challenging. Elevated inflammatory markers, such as leukocyte count and C-reactive protein, could reflect sterile inflammation rather than bacterial infection. Even procalcitonin, though more specific, cannot always reliably distinguish infected necrosis in the early phase. Imaging techniques such as contrast-enhanced computed tomography play an important role in identifying necrosis and guiding intervention, yet radiologic signs of infection may appear only several days after onset. Consequently, clinicians are frequently confronted with diagnostic uncertainty during the early course of the disease (13-15).

For decades, antibiotic therapy in acute pancreatitis has been a subject of intense debate. Earlier clinical practice favoured routine prophylactic antibiotic administration in patients with predicted severe disease, based on the hypothesis that preventing infection of necrotic tissue would improve outcomes. However, subsequent randomised controlled trials and meta-analyses failed to demonstrate consistent benefits in terms of mortality reduction or prevention of infected necrosis. These findings led to a paradigm shift toward a more restrictive approach (16-18).

International guidelines now recommend against routine prophylactic antibiotics in acute pancreatitis. Antibiotic therapy is indicated only in cases of confirmed or strongly suspected infection, including infected pancreatic necrosis, acute cholangitis, bacteraemia, or other extra-pancreatic infectious complications. In acute biliary pancreatitis specifically, antibiotic use may be justified in the presence of concomitant cholangitis or persistent biliary obstruction, as well as coexistent acute cholecystitis, which is common, especially when associated with systemic signs of infection (19-23, 24, 25).

Nevertheless, real-world clinical practice often diverges from guideline recommendations. Empirical antibiotic therapy is frequently initiated in patients with severe clinical presentation, persistent organ dysfunction, elevated inflammatory markers, or prolonged hospitalisation, even in the absence of microbiological confirmation. This discrepancy reflects the difficulty of distinguishing sterile inflammation from early infection, as well as the perceived need to act pre-emptively in critically ill patients (13, 18, 26, 27, 28).

From a pharmacotherapeutic standpoint, the selection of antibiotic regimens also varies considerably. Broad-spectrum agents, including carbapenems, are often preferred for patients with severe disease or suspected infected necrosis due to their excellent pancreatic tissue penetration and broad antimicrobial coverage. However, escalating to broad-spectrum therapy may contribute to antimicrobial resistance, fungal superinfection, and increased healthcare costs, raising concerns regarding antibiotic stewardship in this population (7, 10, 18, 28, 29).

Given these considerations, evaluating actual prescribing patterns and their association with objective markers of severity is essential. Understanding whether antibiotic therapy reflects confirmed infection or merely perceived clinical severity may help refine therapeutic strategies and support more rational antimicrobial use. Therefore, the present study aimed to analyse antibiotic utilisation in a retrospective cohort of patients with acute pancreatic pathology of biliary origin and to explore the relationship between antibiotic strategies and clinical and biochemical markers of severity (13, 26, 27, 30).

Materials and Methods

Study design and setting

A retrospective, observational, single-centre study was conducted using a clinical database, including 139 patients admitted with acute pancreatitis of biliary origin at a single university hospital in Romania (the University Emergency Hospital Bucharest) over 9 years, from January 2017 to September 2025. Institutional electronic medical records, patient physical charts, and the surgical registry were used to retrieve data. Cases were selected using ICD-10 codes (K85 for acute pancreatitis and K80.xx for cholelithiasis). Informed consent for the use of data for study purposes and treatment was obtained from all patients included in the study, in accordance with the current country legislation and hospital policy. The data collected were anonymised before analysis. Hospital Ethics Committee approved the study - Approval no 6917/14.12.2022 and extension 30.09.2025, and it was conducted in accordance with the Declaration of Helsinki, revised in 2024. STROBE guideline was used for data reporting.

Study population

The inclusion criteria were the diagnosis of acute biliary pancreatitis defined by at least two of the following: upper abdominal pain, serum lipase more than 3x normal value (normal lipase value 12-53 U/l) and imagistic pancreatic inflammation (mainly obtained by ultrasound and/or CT in selected cases), corroborated with cholelithiasis. All patients were adults aged 18 or older, both male and female.

On the other hand, the exclusion criteria used were as follows: cases that had incomplete data (a minimum of blood tests that included leukocyte, platelet and haemoglobin count, pancreatic enzymes, hepatic enzymes, total and direct bilirubin levels, fibrinogen as well as imagistic studies that corroborated the biliary origin of acute pancreatitis to meet the diagnosis criteria); acute pancreatitis of other aetiologies, such

as ethanolic, hypertriglyceridaemic or post-ERCP; other pancreatic pathologies (chronic pancreatitis, pancreatic malignancies); patients that refused treatment or requested premature discharge.

Data collection and variables

Age, sex, and admission diagnosis were collected; the latter was based on limited clinical and paraclinical data available at the Emergency Department, as all patients presented with acute abdominal pathology and the diagnoses were heterogeneous. Still, the common element was acute pancreatitis of biliary origin. Data also collected included hospitalisation duration, intensive care unit (ICU) admission, mortality, ERCP (endoscopic retrograde cholangiopancreatography), surgical procedures and their timing, discharge diagnosis, and comorbidities.

Regarding the laboratory parameters, leukocyte count (3600 - 10200/μL normal range), serum amylase (30 - 118 U/L normal range), serum lipase (12 - 53 U/L normal range), total bilirubin (0.3 - 1.2 mg/dL normal range), direct bilirubin (0 - 0.3 mg/dL normal range), fibrinogen (238 - 498 mg/dL normal range), AST (0 - 50 U/L normal range), ALT (0 - 50 U/L normal range), urea (17 - 43 mg/dL normal range), creatinine (0.67 - 1.17 mg/dL normal range) and glycemia (74 - 106 mg/dL normal range) were collected. CRP or procalcitonin levels were not consistently measured in most cases included in the retrospective study, and, as a consequence, they were not included in the analysis.

The imaging data collected include ultrasound, contrast-enhanced CT, and MRI when available, including data on CBP diameter and potential lithiasis, and pancreatic and peripancreatic collections when present; all patients had at least an ultrasound upon admission. The Balthazar score was sometimes recorded during CT interpretation, but it was not consistently applied across the cohort.

Microbiological data, such as drainage cultures, bile cultures, or blood cultures, were inconsistently obtained throughout the cohort; as a result, microbiological confirmation of infection could not be consistently assessed.

Severity classification

Severity scoring systems, such as Revised Atlanta Classification (RAC), BISAP or APACHE II could not be used to stratify the cohort as they were not systematically available in this retrospective study from lack of complete data (for example inconsistent reporting of organ failure) and as such severity was assessed indirectly using surrogate markers that included leukocyte count, bilirubin levels, ICU admission and length of hospital stay rather than by composite scoring systems;

We used an estimated RAC for stratifying the cohort, using available data: severe in case of death and/or recorded multiple organ failure and/or ICU stay longer than 48 hours; moderate for short ICU stay, in cases of recorded complications of the disease, for surgical reinterventions and in the absence of severe criteria as stated above; the rest of the cases included in the analysis were considered mild as they lacked the severity criteria.

Antibiotic therapy

Antibiotic therapy was recorded for each patient, including monotherapy and combination regimens, by using electronic hospital records and patients' physical charts.

Data were available only for in-hospital antibiotic use, and only those used for the specific admission diagnosis were considered meaningful for this study.

Antibiotic therapy was considered only if the duration of administration exceeded 24 hours; a single dose or a duration of therapy of less than 24 hours falls under the term antibioprophylaxis, as stated in the hospital regulations.

Antibiotic regimens were classified as carbapenem-based or non-carbapenem-based, as these were the most commonly used ones. Carbapenem-based regimens included meropenem or imipenem-cilastatin, mostly as monotherapy and occasionally associated with metronidazole or vancomycin; non-carbapenem regimens included beta-lactam/beta-lactamase inhibitor combinations: ampicillin-sulbactam alone or in association with metronidazole, piperacillin-tazobactam in single therapy; cephalosporins: cefuroxime or ceftriaxone alone or in combination with metronidazole; occasionally, fluoroquinolones (ciprofloxacin) were used in single therapy.

All patients who received carbapenem-based regimens were included in the carbapenem group, as a few had prior antibiotherapy with other regimens that were escalated.

Outcome measures

The primary outcome used was the association between clinical, imagistic and laboratory parameters and antibiotic use. Secondary outcomes included the association between antibiotic use and ICU admission (ICU criteria: severe organ(s) and/or system(s) failure), length of hospital stay (admission-to-discharge in days), in-hospital mortality, and ERCP performance.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 and Microsoft Excel 2021. Continuous variables were expressed as medians and interquartile ranges or means ± standard deviation, depending on distribution, while categorical variables were expressed as absolute numbers and percentages. Comparisons between categorical variables (such as antibiotic administration, ICU admission, ERCP performance, or mortality) were performed using the Chi-square test. When the expected frequency in contingency tables was lower than 5 in more than 20% of cells, Fisher's exact test was applied as a more appropriate method for small sample sizes. The Mann-

Whitney U test was used to compare continuous variables between two independent groups (*e.g.*, leukocyte count, pancreatic enzyme levels, bilirubin levels, or length of hospital stay).

Results and Discussion

Of the 265 cases of acute biliary pancreatitis screened during the 9 years of the study, many lacked the minimum criteria for inclusion (126 cases that either did not have confirmation of biliary aetiology or lacked complete biochemical data). The study finally enrolled 139 subjects, of whom 90 were females (64.7%), and 49 were males (35.3%). The mean age of patients was 59.6 ± 19.5 years, with a median age of 62 (IQR 31).

Pancreatitis form was mostly mild or moderate (128 cases), 11 cases had severe forms from the onset, as categorised by the patients' charts; when we applied the estimated RAC 109 (78.42%), cases were mild, 15 were moderate (10.79%), and 15 were severe (10.79%) (Figure 1). Moreover, 93 cases had an admission diagnosis of acute cholecystitis with pancreatitis, and none had a diagnosis of cholangitis associated with the main one at admission or discharge. However, based on indirect clinical data (ERCP within 24 - 48 hours), cholangitis was suspected in 8 cases. This heterogeneity reflects real-world clinical practice, where acute biliary pancreatitis frequently coexists with other biliary pathologies. Given that these conditions have different indications for antibiotic therapy, their inclusion in a single cohort must be considered when interpreting antibiotic prescribing patterns.

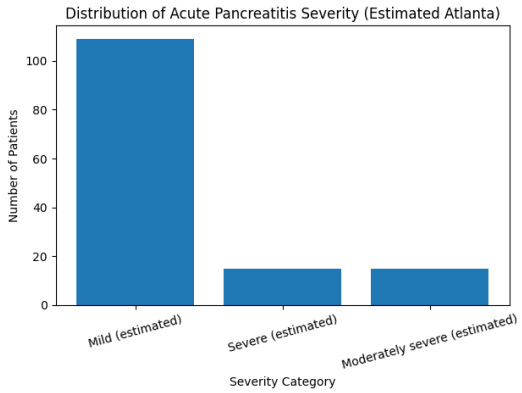

Figure 1.
Estimate RAC of the cohort

In the entire cohort, the median laboratory values were as follows, and are shown in comparison to the estimated severity in Figure 2: leukocytes: 11.3 (IQR: 8.7 - 16.4) × 10^3/μL; amylase: 1039.0 (IQR: 407.5 - 2114.0) U/L; aipase: 2774.0 (IQR: 1237.0 - 5649.5) U/L; total bilirubin (BT): 1.95 (IQR: 1.17 - 4.07) mg/dL; direct bilirubin (BD): 1.00 (IQR: 0.31 - 2.47) mg/dL; fibrinogen: 400.0 (IQR: 351.5 - 455.5) mg/dL; AST: 219.0 (IQR: 95.5 - 360.0) U/L; ALT: 262.0 (IQR: 116.0 - 403.0) U/L; urea: 33.0 (IQR: 24.0 - 45.0) mg/dL; creatinine: 0.90 (IQR: 0.76 - 1.10) mg/dL; glucose: 115.0 (IQR: 96.0 - 148.0) mg/dL.

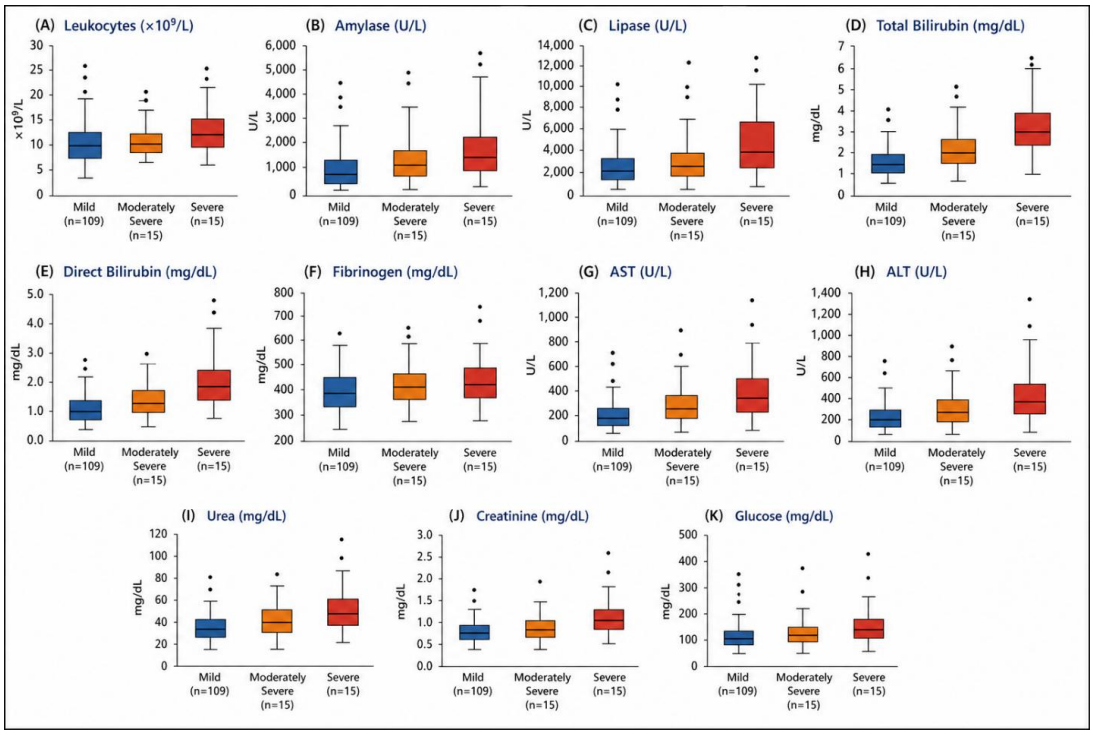

Figure 2.
Estimated severity *versus* median laboratory findings

As for management, 35 cases (25.18%) required ERCP performed between 0 and 13 days after onset; 107 (76.98%) benefited from cholecystectomy during hospitalisation between days 2 and 20 after hospitalisation, after normalisation of pancreatic blood enzymes.

ICU admission was necessary for 25 patients, representing 18% of all cases. The outcome was favourable (patients were discharged in good condition) in all 124 cases of mild and moderate pancreatitis, of which 24 patients had a hospital stay of 7 days or less, 100 patients had a hospital stay of more than 7 days, and 4 patients had an estimated RAC severe disease. The outcome was poor in the 11 cases of severe pancreatitis from the onset, resulting in the patients' demise (overall in-hospital mortality of 7.9%). Median hospital stay was 11 days, with an IQR of 8 - 15 days.

Antibiotic therapy was administered in 116 of the 139 patients (83.5%), reflecting the high prevalence of empirical antibiotic use in acute pancreatic and biliary pathology. The duration of antibiotic therapy was 4.5 days (IQR 3 - 7). In the antibiotic-positive group, a wide range of antibiotic regimens was observed, with beta-lactam/beta-lactamase inhibitor combinations and carbapenems being the most frequently used classes.

Antibiotic regimens for analysis were categorized as carbapenem-based (meropenem or imipenem, alone or in combination), totalising 32 patients, or non-carbapenem-based therapies, including beta-lactam/beta-lactamase inhibitor combinations (51 patients), cephalosporins (23 patients), and other antibiotics commonly used in biliary infections (such as metronidazole or fluoroquinolones, usually as associated antibiotics for the former groups) for a total of 84 patients. Regarding the length of antibiotic therapy, the median was 7 days (IQR 5 - 10) in the carbapenem group, and 4 days (IQR 3 - 6) in the non-carbapenem group. It was observed throughout the cohort that cases escalated to broader-spectrum antibiotics were continued on that regimen until termination of antibiotherapy. The distinction between these groups was based on broad-spectrum versus non-broad-spectrum antibiotics (Figure 3).

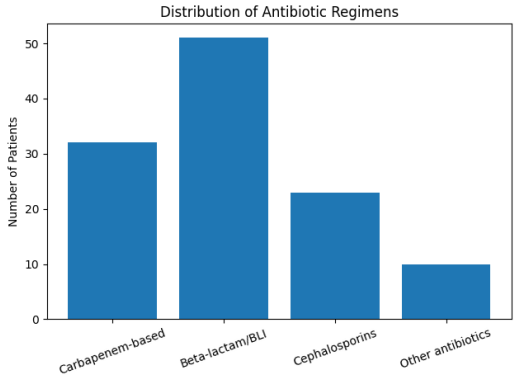

Figure 3.
Frequency of antibiotic regimens in the cohort

No statistically significant association was observed between the admission diagnosis (acute pancreatitis, mild, moderate or severe, associated with acute cholecystitis in 93 cases) and the administration of antibiotic therapy (p-value 0.268), suggesting that the initial diagnosis did not primarily drive antibiotic use but rather by clinical evolution and perceived severity (Table I and Figure 4).

Table I
Antibiotherapy *versus* main laboratory findings

Variable	Median (IQR)		p-value
	Antibiotics	No antibiotics	
Leukocytes (x10^3/µL)	12.3 (9.2 - 17.12)	9.9 (7.3 - 11.66)	0.002
Amylase (U/L)	1193.0 (519.5 - 2260.0)	612.0 (201.5 - 1412.0)	0.014
Lipase (U/L)	2961.0 (1350.75 - 6080.0)	1596.0 (899.0 - 3125.0)	0.03
Total bilirubin (mg/dL)	2.04 (1.31 - 4.15)	1.11 (0.64 - 2.84)	0.008
Direct bilirubin (mg/dL)	1.11 (0.44 - 2.56)	0.3 (0.18 - 1.8)	0.022
Fibrinogen (mg/dL)	407.0 (357.5 - 454.75)	381.0 (331.5 - 455.0)	0.35
Urea (mg/dL)	39 (28 - 51)	28 (22 - 35)	0.021
Creatinine (mg/dL)	0.96 (0.79 - 1.18)	0.81 (0.71 - 0.96)	0.047
Glycemia (mg/dL)	121 (98 - 151)	101 (86 - 124)	0.009

Patients who received antibiotic therapy had significantly higher leukocyte counts at admission than those who did not (median 12.3 *versus* 9.9 × 10^3/µL, p = 0.002), suggesting that antibiotic initiation was associated with a more pronounced inflammatory response.

The antibiotic therapy group had significantly higher serum amylase levels at admission than those who did not receive antibiotics (median 1193.0 *versus* 612.0 U/L, p = 0.014). Similarly, admission lipase levels were significantly higher in the antibiotic-treated group (median 2961.0 *versus* 1596.0 U/L, p = 0.03), suggesting that antibiotic initiation was associated with a more severe biochemical presentation rather than the admission diagnosis itself.

Patients receiving antibiotic therapy showed significantly higher admission urea, creatinine, and glycemia values than those not receiving antibiotics (p-values of 0.021, 0.047, and 0.009, respectively),

supporting an association between antibiotic initiation and markers of systemic severity.

Patients who received antibiotic therapy had significantly higher total bilirubin levels at admission than those who did not (median 2.04 *versus* 1.11 mg/dL, p = 0.008). Similarly, direct bilirubin levels were significantly higher in the antibiotic-treated group (median 1.11 *versus* 0.3 mg/dL, p = 0.022), suggesting that antibiotic initiation was associated with more pronounced biliary involvement, possibly including biliary duct obstruction and/or cholangitis. Due to the limited number of available measurements, no valid statistical comparison could be performed for the common bile duct diameter.

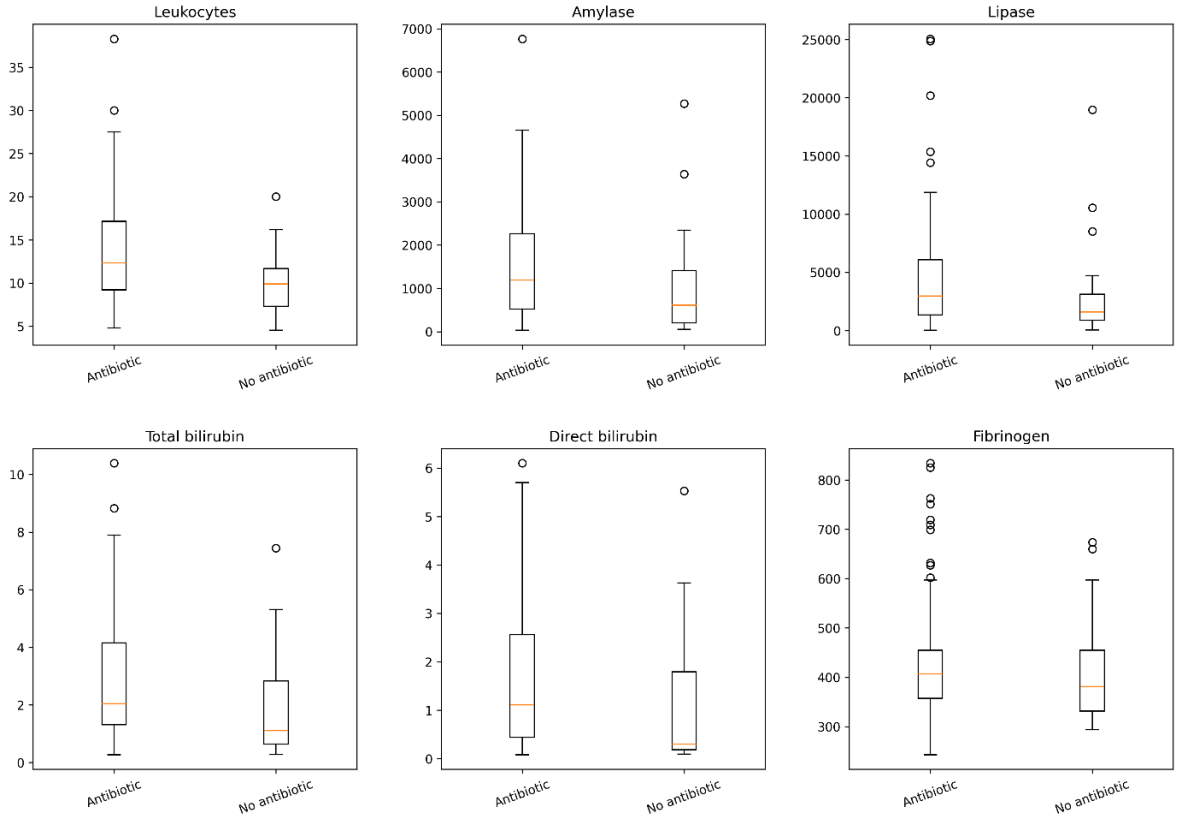

Figure 4.
Laboratory values at admission according to antibiotic therapy

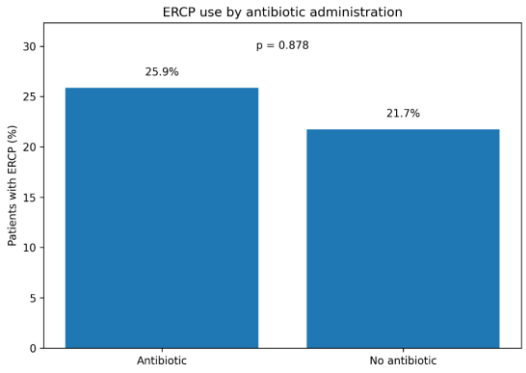

Figure 5.
ERCP stratified by antibiotic use

In contrast, admission fibrinogen levels did not differ significantly between groups (median 407.0 *versus* 381.0 mg/dL, p = 0.35), as fibrinogen levels tend to rise more slowly and reach higher peaks later in the disease progression than leukocyte count.

ERCP was performed in approximately one quarter of patients (35 cases), with a similar distribution across antibiotic strategies (Figure 5). It was observed that 30/116 (25.9%) patients receiving antibiotics underwent ERCP, while 5/23 (21.7%) patients in the no antibiotics group underwent ERCP (p value 0.878). This observation supports the concept that antibiotic therapy was often integrated into a broader therapeutic approach, including endoscopic management when biliary obstruction or cholangitis was suspected (19-21, 23, 25).

ICU admission was recorded in 25 patients (18.0%). From these, 23 belonged to the antibiotherapy-positive group (19.8% of the group), and from the no-antibiotic group, 2/23 cases needed ICU admission (8.7%) – presented in Figure 6. Although the proportion of patients with ICU admission was higher in the antibiotic group (19.8% *versus* 8.7%), the difference did not reach statistical significance (p = 0.250).

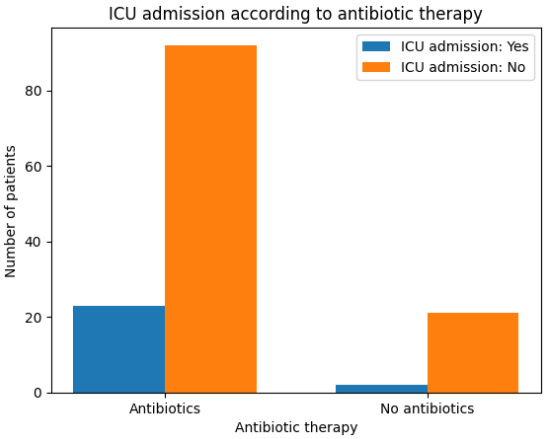

Figure 6.
ICU admission according to antibiotic therapy

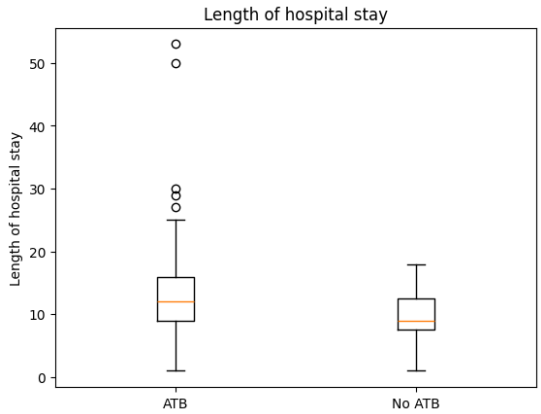

Figure 7.
Length of hospital stay according to antibiotic therapy

Patients who received antibiotic therapy had a significantly longer hospital stay than those who did not (median 12 *versus* 9 days, p = 0.018), suggesting that antibiotic use was associated with a more severe clinical course (Figure 7).

Overall, in-hospital mortality was 7.9% (11 cases out of 139 included in the cohort; Figure 8). 9 cases (7.8%) were in the antibiotic group, and 2 cases (8.7%) did not receive antibiotic therapy, with a p-value of 1. This further emphasises the hypothesis that antibiotic administration rather reflects disease severity than influences clinical outcomes.

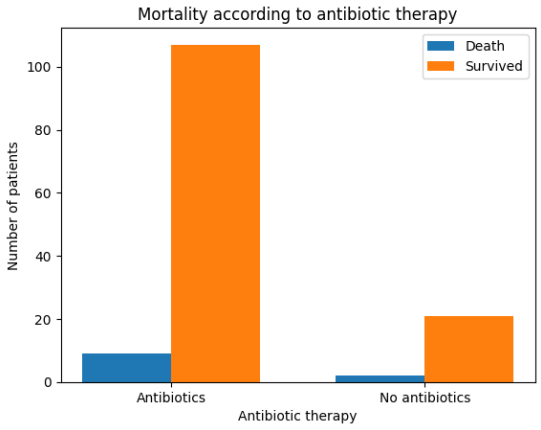

Figure 8.
Mortality according to antibiotic therapy

The analysis showed that the initiation of antibiotherapy did not correlate with ICU admission, mortality, or the decision to undergo ERCP (p = 0.25, 0.87, and 1, respectively); antibiotic use was mostly associated with markers of greater biochemical severity and longer hospitalisation, as shown in Table II.

Table II

Descriptive and analytical statistics of antibiotherapy *versus* evolution and management

Variable		**Antibiotherapy**		**P value**
		Yes	**No**	**Fisher's exact test/Chi-square**
ICU	Yes	23	2	0.25
	No	93	21	
ERCP	Yes	30	5	0.87
	No	86	18	
Evolution	Death	9	2	1
	Favourable	107	21	
Hospital stay, days (median)		12	9	**0.018**

Of the entire cohort of 139 patients, 116 received antibiotherapy; among them, we identified two main groups, based on broad-spectrum *versus* non-broad-spectrum antibiotherapy: 32 carbapenem-based (imipenem, meropenem) and 84 non-carbapenem-based (beta-lactam/inhibitor, cephalosporines, others).

The admission diagnosis as recorded in the patients 'charts did not differ significantly between carbapenem and non-carbapenem groups (p = 1.00). In contrast, when the estimated RAC was used to stratify the cohort, a statistically significant association was found between estimated Atlanta severity and antibiotic class (carbapenem *versus* non-carbapenem) (p = 0.012). The proportion of patients receiving carbapenem therapy increased with disease severity, from 22.5% in mild cases to 61.5% in severe cases (as estimated by indirect parameters), as shown in Table III and Figure 9.

Table III

Association between estimated Atlanta severity and antibiotic class (carbapenem *versus* non-carbapenem)

Estimated Atlanta severity	Carbapenem n (%)	Non-carbapenem n (%)
Mild	20 (22.5%)	69 (77.5%)
Moderately severe	4 (28.6%)	10 (71.4%)
Severe	8 (61.5%)	5 (38.5%)
Total	32	84

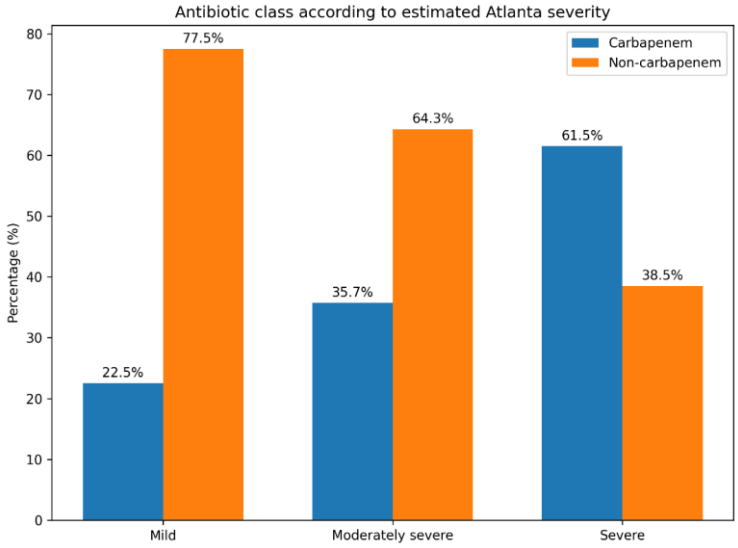

Figure 9.

Distribution of antibiotic classes according to estimated Atlanta severity

The observed association between disease severity and carbapenem use suggests that clinicians are more likely to escalate to broad-spectrum antibiotic therapy in patients with more severe presentations. This finding aligns with clinical practice patterns, although it may also reflect variability in adherence to guideline-based antibiotic stewardship, particularly in the absence of confirmed infection.

A comparison of admission laboratory parameters between carbapenem and non-carbapenem groups is shown in Table IV and Figure 10.

Among patients receiving antibiotic therapy, carbapenem-based regimens were associated with significantly lower total bilirubin levels at admission compared to non-carbapenem regimens ($p = 0.024$) and carbapenem therapy was also associated with higher urea values and non-significant trends toward higher creatinine and glycemia, supporting the interpretation that escalation may have reflected systemic severity and organ dysfunction rather than biliary biochemical abnormalities alone. No significant differences were observed between groups regarding amylase, lipase, leukocyte count, or fibrinogen levels ($p > 0.05$ for all). Direct bilirubin showed a non-significant trend toward higher values in the non-carbapenem group ($p = 0.053$). The observed difference in bilirubin levels suggests that antibiotic escalation to carbapenems may not be solely driven by the degree of biliary obstruction. The lack of significant differences in inflammatory markers indicates that additional clinical factors likely influenced treatment decisions. These findings highlight variability in prescribing patterns and support the need for improved antibiotic stewardship.

Table IV

Antibiotherapy groups *versus* main laboratory findings

Variable	Median (IQR) Carbapenem	Median (IQR) Non-carbapenem	p-value
Leukocyte count (x10^3/µL)	14.5 (10.1 - 19.3)	12.02 (8.8 - 16.35)	*0.109*
Amylase (U/L)	1494 (451 - 2332)	1187 (530 - 2155)	*0.835*
Lipase (U/L)	2650 (1123 - 4780)	2965 (1424.5 - 6305)	*0.497*
Total bilirubin (mg/dL)	1.61 (1.06 - 2.6)	2.42 (1.4 - 4.24)	***0.024***
Direct bilirubin (mg/dL)	0.68 (0.35 - 1.38)	1.25 (0.55 - 2.76)	*0.053*
Fibrinogen (mg/dL)	398 (373 - 465)	408 (352.5 - 451.5)	*0.612*
Urea (mg/dL)	46 (33 - 61)	35 (26 - 46)	***0.028***
Creatinine (mg/dL)	1.06 (0.88 - 1.39)	0.90 (0.77 - 1.09)	*0.061*
Glycemia (mg/dL)	128 (108 - 167)	114 (95 - 141)	*0.074*

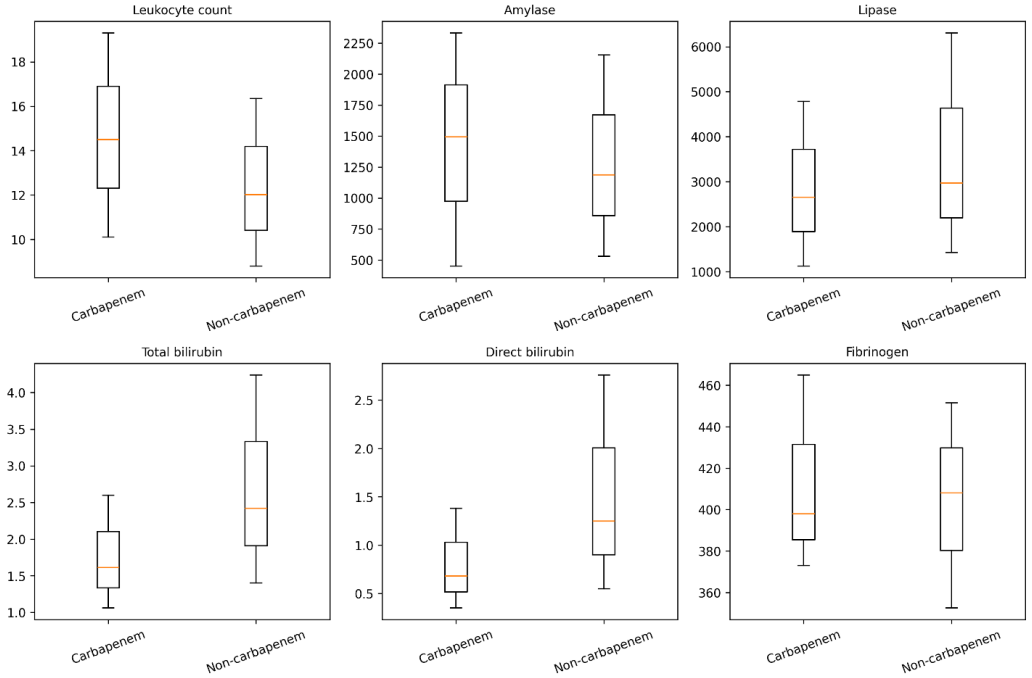

Figure 10.
Laboratory values at admission according to the antibiotic therapy group

As for ERCP performance, among the carbapenem group, 11/32 cases (34.4%) required ERCP, and 21 did not (65.6%); in the non-carbapenem group, 19/84 cases (22.6%) required ERCP, and 65 did not (77.4%), as shown in Figure 11. The distribution of ERCP procedures did not differ significantly between the two groups (p = 0.25). This finding suggests that the ERCP decision was independent of antibiotic escalation and was likely driven by obstruction of the main bile duct or suspected or confirmed cholangitis. This further supports the hypothesis of escalation to carbapenems based on overall clinical severity.

When stratified by antibiotic strategy, ICU admission was significantly more frequent among patients treated with carbapenems compared to those receiving non-carbapenem regimens (11 cases *versus* 12 cases, 34.4% *versus* 14.3%, p = 0.02) (Figure 12).

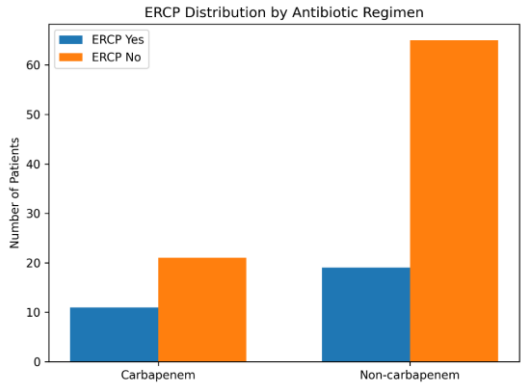

Figure 11.
ERCP distribution by antibiotic group

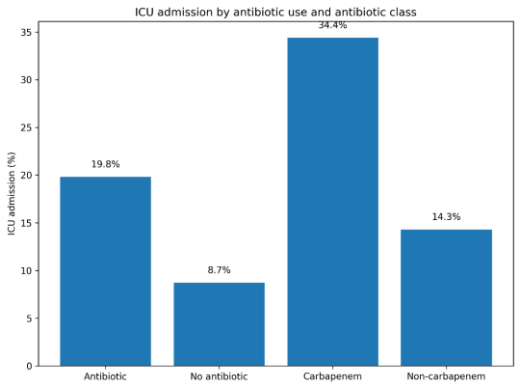

Figure 12.
ICU admission according to antibiotic use and regimen (carbapenem *versus* non-carbapenem)

These findings suggest that escalation to carbapenem therapy is associated with more severe clinical presentation, as reflected by higher ICU admission rates. This supports the hypothesis that antibiotic choice is driven by disease severity rather than representing an independent determinant of outcomes.

In the antibiotic group, hospital stay was longer in those treated with carbapenems compared to non-carbapenem regimens (median 13.5 *versus* 11 days), but this difference did not reach statistical significance (p = 0.26). This data highlights the use of antibiotics based on perceived clinical severity, with broader-spectrum antibiotics used for greater severity, which, in itself, is a determinant of length of hospital stay. The use of carbapenems in such cases does not appear to be associated with better prognosis or

shorter disease progression, but rather with perceived severity.

Overall mortality was 7.9%, with a higher proportion of deaths observed in the carbapenem group - 5/32 (15.6%) deaths as opposed to 4/84 (4.8%) in the non-carbapenem group. However, this difference did not reach statistical significance ($p = 0.11$), likely reflecting the limited sample size and the confounding effect of baseline severity.

In summary, carbapenem use was associated with lower total bilirubin, higher urea levels, and greater ICU admission frequency, but not with significantly different length of stay or mortality, suggesting that carbapenem escalation tracked clinical severity rather than independently influencing outcomes. Carbapenem therapy was preferentially used in patients with more severe clinical presentations, suggesting a causal relationship between antibiotic choice and severity, and supporting the concept that broad-spectrum antibiotics are markers of clinical severity and biliary involvement rather than determinants of outcome.

Taken together, these results illustrate current antibiotic prescribing patterns in acute biliary pancreatitis and highlight the tendency to escalate therapy to broad-spectrum agents in severe cases, as perceived from a clinical point of view. Such findings underscore the importance of careful clinical assessment, appropriate indication, and timely reassessment of antibiotic therapy to avoid unnecessary exposure to broad-spectrum agents (13, 26, 27, 30).

The present study demonstrates a high prevalence of empirical antibiotic administration in patients admitted with acute pancreatic pathology of biliary aetiology. Antibiotic therapy was significantly associated with elevated leukocyte count, increased pancreatic enzymes, higher bilirubin levels, and prolonged hospitalisation.

Leucocytosis at admission was significantly higher among patients who received antibiotics, supporting the notion that clinicians frequently interpret elevated inflammatory markers as potential indicators of infection. However, in acute pancreatitis, systemic inflammatory response syndrome (SIRS) is common even in the absence of bacterial contamination. The early inflammatory cascade involves cytokine release, endothelial activation, and immune cell recruitment, all of which may produce laboratory abnormalities that mimic infection. This diagnostic ambiguity likely contributes to early empirical antibiotic use (13, 15, 19, 27, 30).

Similarly, higher amylase and lipase levels in the antibiotic-treated group suggest that pancreatic injury, as highlighted by biochemical intensity, influenced therapeutic decisions. Although enzyme levels do not correlate perfectly with clinical severity, higher levels of pancreatic enzymes may reinforce the perception of a more aggressive disease course. In clinical practice, such biochemical findings often coexist with abdominal pain severity and imaging abnormalities, further increasing the threshold for conservative management (13, 26, 27, 30).

Elevated total and direct bilirubin levels were also significantly associated with antibiotic administration. In acute biliary pancreatitis, hyperbilirubinemia may indicate persistent biliary obstruction or cholangitis. Even in the absence of confirmed infection, the combination of cholestasis and elevated systemic inflammatory markers may prompt antibiotic initiation. This pattern reflects the complexity of differentiating sterile inflammation from early biliary infection, especially before definitive endoscopic intervention (19-21, 23, 25).

Fibrinogen levels did not differ significantly between antibiotic and non-antibiotic groups. The slower kinetics of fibrinogen elevation may explain this compared to the leukocyte count. While fibrinogen is an acute-phase reactant, its peak values may occur later in disease progression, reducing its utility as an early trigger for antibiotic therapy. This underscores the variability of inflammatory markers, such as procalcitonin, which was used only in selected cases in this study (mainly in ICU admissions), and the need for multimodal clinical assessment (13, 14, 26, 27, 30).

A key aspect that emerges from our data is the discrepancy between guideline recommendations and real-world practice. Current guidelines recommend antibiotic therapy only in the presence of confirmed or strongly suspected infection, such as cholangitis or infected necrosis (21, 23, 26). However, in our cohort, antibiotics were administered in 83.5% of patients, despite the lack of microbiological confirmation and the absence of systematic evidence of infection. The rate of antibiotic use observed in our study appears higher than that reported in several published cohorts, which ranged from approximately 40% to 70%, depending on disease severity and study design. This discrepancy may reflect differences in clinical practice patterns, local protocols, and the level of diagnostic certainty regarding infection (8, 11, 15-18, 28).

An important aspect influencing the interpretation of our findings is the heterogeneity of the study population. Although all patients met diagnostic criteria for acute biliary pancreatitis, many presented with concomitant biliary conditions such as acute cholecystitis. These associated conditions have distinct therapeutic options, as antibiotic therapy is frequently used in acute cholecystitis, whereas uncomplicated acute pancreatitis does not require routine antibiotic administration. Therefore, the high rate of antibiotic use observed in our cohort may be explained by the presence of these coexisting biliary pathologies. At the same time, the retrospective design and the lack of standardised diagnostic criteria

for infection (including microbiological confirmation and consistent imaging data) limited our ability to precisely quantify the proportion of patients who received antibiotics outside guideline-based indications. Consequently, while our findings suggest a tendency toward empirical antibiotic use, the exact degree of inappropriate prescribing cannot be definitively established. This limitation underscores the complexity of evaluating antibiotic stewardship in real-world settings and the need for more granular prospective data to accurately assess adherence to current clinical guidelines.

In conclusion, the data suggest that antibiotic initiation was primarily driven by markers of systemic inflammation and biochemical severity rather than by microbiologically confirmed infection. A substantial proportion of patients likely received antibiotics based on clinical suspicion or perceived severity rather than established indications, highlighting a potential gap in adherence to guidelines (13, 26, 27, 30). Although microbiological data and imaging confirmation of infected necrosis were not consistently available, presenting as a major limitation to the study, this limitation reflects real-world clinical practice, where antibiotic decisions are frequently made in the absence of definitive diagnostic confirmation. This further emphasises the need for improved diagnostic strategies to guide antimicrobial therapy.

A main finding of this study is the significant association between carbapenem-based therapy and intensive care unit admission. Patients treated with carbapenems were more likely to require ICU support, indicating that broad-spectrum antibiotic escalation was predominantly reserved for more severe clinical scenarios. Importantly, this association should not be interpreted as evidence of improved or worsened outcomes due to carbapenem therapy itself, as it is biased by the use of more aggressive therapy in more clinically perceived severe cases (7, 10, 18, 28, 29).

Carbapenems are frequently considered in cases of suspected infected pancreatic necrosis, sepsis of biliary origin, or clinical deterioration despite standard therapy. Their pharmacokinetic properties, including favourable pancreatic tissue penetration and broad antimicrobial coverage, make them attractive options in high-risk settings. However, the absence of significant differences in pancreatic enzyme levels and inflammatory markers between carbapenem and non-carbapenem groups and the negative association between bilirubin levels and carbapenem use suggest that escalation was not based solely on biochemical severity but possibly on overall clinical impression, hemodynamic instability, or organ dysfunction (7, 10, 18, 29, 31).

In comparison with the antibiotic *versus* non-antibiotic groups, in which the majority of biochemical markers favoured antibiotic initiation, the carbapenem *versus* non-carbapenem analysis showed far fewer significant biochemical markers. It is the case with pancreatic enzymes, whose values appear not to correlate with carbapenem use, and with bilirubin levels, which show a negative correlation with the carbapenem group. These facts suggest that in practice, either the clinical deterioration of patients, highlighted by the significant difference in urea levels (which have a prognostic value validated by prognostic scores) or lack of clinical improvement might drive the use of perceived more potent antibiotics; moreover, in mild pancreatitis treated with non-carbapenem antibiotics there might be a clinical improvement independent of antibiotic use, but correlated to the natural progress of the disease, that made escalation unnecessary (7, 12, 13, 15, 32).

The lack of significant difference in hospital length of stay between carbapenem and non-carbapenem groups further supports the interpretation that carbapenem use does not independently modify disease trajectory. Although median hospitalisation was longer in the carbapenem group, this difference did not reach statistical significance, suggesting that underlying severity rather than antibiotic class likely determined hospitalisation duration (7, 10, 18, 28, 29). Patients who received antibiotics had a significantly longer hospital stay compared to those who did not. This association likely reflects the selection of more severe cases for antibiotic therapy rather than a direct prolonging effect of antibiotics. Severe pancreatitis is associated with longer recovery, increased need for monitoring, and greater likelihood of complications (13, 26, 27, 30).

Prolonged hospitalisation itself may contribute to antibiotic exposure through secondary infections, invasive procedures, and extended supportive care. This creates a bidirectional relationship between severity and antibiotic use, introducing a double bias that is hard to quantify. Therefore, interpreting length of stay requires caution, as it is influenced by multiple clinical variables beyond antimicrobial therapy alone (13, 26, 27, 30).

Although mortality was numerically higher in the carbapenem group, this difference did not reach statistical significance. The relatively small sample size of severe cases may limit the ability to detect meaningful differences. Moreover, mortality in acute pancreatitis is largely driven by persistent organ failure, systemic inflammatory response, and late infectious complications rather than by the specific antibiotic regimen used. These findings reinforce the concept that antibiotic choice reflects clinical severity rather than acting as a primary determinant of outcome (7, 10, 17, 18, 28, 29).

The high rate of empirical antibiotic use observed in this cohort further emphasises the ongoing challenge of aligning clinical practice with guideline

recommendations. While caution is understandable in patients with severe presentations, the other side is the unnecessary exposure to broad-spectrum antibiotics that carries significant risks. These include the development of multidrug-resistant organisms, Clostridium difficile infection, fungal superinfection, and disruption of gut microbiota (13, 18, 26-28, 33-35).

Carbapenem overuse is of particular concern in the context of global antimicrobial resistance trends. The selective pressure exerted by broad-spectrum agents may contribute to the emergence of carbapenem-resistant Enterobacteriaceae strains and other resistant pathogens. In addition, prolonged antibiotic therapy increases healthcare costs and may complicate subsequent therapeutic options (7, 10, 18, 28, 29, 33, 36).

From a clinical perspective, our findings support several practical strategies to improve antibiotic stewardship in acute biliary pancreatitis. First, antibiotic therapy should be restricted to patients with clear clinical or radiological evidence of infection (8, 13, 15, 26). Second, early reassessment within 48 - 72 hours is essential to evaluate the ongoing need for antimicrobial therapy. Third, escalation to broad-spectrum agents such as carbapenems should be carefully justified and reserved for cases with strong suspicion of severe infection or clinical deterioration (8, 15, 26).

Implementing such measures may help reduce unnecessary antibiotic exposure and limit the emergence of antimicrobial resistance without compromising patient outcomes. However, implementing antimicrobial stewardship strategies in acute biliary pancreatitis requires clear diagnostic criteria for suspected infection, early imaging reassessment, and timely de-escalation when infection is not confirmed. Biomarkers such as procalcitonin may assist in guiding decisions, although they should not replace but be integrated by clinical judgment. Multidisciplinary collaboration between gastroenterologists, surgeons, intensivists, and infectious disease specialists may further optimize antibiotic use (13-15).

This study has several limitations inherent to its retrospective design. First, the decision to initiate antibiotic therapy was clinician-dependent and not standardized, introducing potential selection bias; also, the lack of formal scoring in most cases limited the stratification and adhesion to guidelines. Second, microbiological confirmation of infection was not available in all cases, limiting the ability to distinguish true infection from empirical treatment and whether antibiotherapy was justified by guidelines. Third, the sample size, particularly within the carbapenem subgroup, may reduce statistical power for certain comparisons. Finally, multivariate analysis was not performed, and therefore confounding factors related to baseline severity cannot be fully excluded.

Taken together, the findings of this study suggest that antibiotic therapy in acute biliary pancreatitis is closely linked to clinical perception of severity and biochemical abnormalities rather than strictly to documented infection. Broad-spectrum escalation with carbapenems appears to function as a therapeutic response to critical illness rather than as a predictor of improved outcomes.

Guideline adherence could only be explored indirectly in our study. Cholangitis was approximated based on the admission diagnosis, whereas infected necrosis could not be reliably assessed due to the absence of standardised imaging data. Nevertheless, a large proportion of patients without a diagnosis suggestive of cholangitis still received antibiotic therapy, indicating a potential deviation from recommended practice. These findings should be interpreted cautiously, as the lack of imaging data may lead to an overestimation of inappropriate antibiotic use. The observed prescribing pattern may reflect clinical uncertainty at presentation. In the early phase of acute pancreatitis, distinguishing between sterile inflammation and infection can be challenging. As a result, clinicians may initiate antibiotic therapy based on elevated inflammatory markers, biochemical abnormalities, or overall clinical severity, even in the absence of confirmed infection. While this approach may be intended to prevent complications, it may also contribute to unnecessary antibiotic exposure.

These results highlight an important gap between guideline recommendations and real-world clinical practice. Current guidelines discourage routine antibiotic use in the absence of cholangitis or infected necrosis, emphasising the importance of accurate diagnosis before initiating therapy. However, our findings suggest that this principle is not consistently applied in clinical settings. The present study adds to the existing literature by providing real-world data on antibiotic prescribing patterns and their relationship with disease severity. Unlike previous studies that focused primarily on outcomes, our analysis emphasises the discrepancy between recommended practice and actual clinical behaviour, highlighting an area for potential improvement. These results emphasise the importance of refining antibiotic decision-making processes and integrating antimicrobial stewardship principles into routine management of acute biliary pancreatitis (7, 10, 18, 28, 29).

Conclusions

In this retrospective cohort, antibiotic therapy was administered to the majority of patients with acute biliary pancreatitis, suggesting the gap between guideline recommendations and real-world clinical practice. Its association with clinical and biochemical severity markers implies that antibiotic initiation reflects perceived severity. Carbapenem-based

regimens were significantly associated with intensive care unit admission, indicating that these agents are preferentially used in patients with more severe clinical presentations. This association should be interpreted as a reflection of severity rather than a direct therapeutic effect of broad-spectrum antibiotics on outcomes. Although mortality was higher among patients treated with carbapenems, the difference did not reach statistical significance. These findings emphasise the need for careful patient stratification and judicious antibiotic selection, guided by clinical, laboratory, and imaging criteria suggestive of infection. Integrating antimicrobial stewardship principles into the therapeutic management of acute biliary pancreatitis may reduce unnecessary exposure to broad-spectrum antibiotics, limit the development of antimicrobial resistance, and support more rational, evidence-based pharmacotherapy.

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Availability of data and materials

The data generated in the present study are included in the article. Additional data may be requested from the corresponding author.

Ethics approval and consent to participate

All procedures were conducted in accordance with institutional standards, and the Hospital Ethics Committee approved the study - Approval no 6917/14.12.2022 and extension 30.09.2025. Informed consent for the use of data for study purposes and treatment was obtained from all patients included in the study, in accordance with the current country legislation and hospital policy.

AI use disclosure

During the preparation of this manuscript, the authors used artificial intelligence tools for language editing, text structuring, and manuscript organisation. The authors reviewed and revised all outputs and take full responsibility for the final content.

Conflict of interest

The authors declare no conflict of interest.

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