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Invalidity of Tokyo guidelines in acute biliary pancreatitis: A multicenter cohort analysis of 944 pancreatitis cases

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Abstract

Background: There is a noteworthy overlap between the clinical picture of biliary acute pancreatitis (AP) and the 2018 Tokyo guidelines currently used for the diagnosis of cholangitis (AC) and cholecystitis (CC). This can lead to significant antibiotic and endoscopic retrograde cholangiopancreatography (ERCP) overuse.

Objectives: We aimed to assess the on-admission prevalence of AC/CC according to the 2018 Tokyo guidelines (TG18) in a cohort of biliary AP patients, and its association with antibiotic use, ERCP and clinically relevant endpoints.

Methods: We conducted a secondary analysis of the Hungarian Pancreatic Study Group's prospective multicenter registry of 2195 AP cases. We grouped and compared biliary cases (n = 944) based on the on-admission fulfillment of definite AC/CC according to TG18. Aside from antibiotic use, we evaluated mortality, AC/CC/AP severity, ERCP performance and length of hospitalization. We also conducted a literature review discussing each criteria of the TG18 in the context of AP.

Results: 27.8% of biliary AP cases fulfilled TG18 for both AC and CC, 22.5% for CC only and 20.8% for AC only. Antibiotic use was high (77.4%). About 2/3 of the AC/CC cases were mild, around 10% severe. Mortality was below 1% in mild and moderate AC/CC patients, but considerably higher in severe cases (12.8% and

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21.2% in AC and CC). ERCP was performed in 89.3% of AC cases, common bile duct stones were found in 41.1%.

Conclusion: Around 70% of biliary AP patients fulfilled the TG18 for AC/CC, associated with a high rate of antibiotic use. Mortality in presumed mild or moderate AC/CC is low. Each of the laboratory and clinical criteria are commonly fulfilled in biliary AP, single imaging findings are also unspecific—AP specific diagnostic criteria are needed, as the prevalence of AC/CC are likely greatly overestimated. Randomized trials testing antibiotic use are also warranted.

KEYWORDS
2018 Tokyo guidelines, antibiotic use, biliary acute pancreatitis, cholangitis, cholecystitis, endoscopic retrograde cholangiopancreatography, ERCP, mortality, stones

INTRODUCTION

Acute pancreatitis (AP) is a common and potentially dangerous cause of abdominal pain in the adult emergency department. Its incidence varies between 4.6 and 100/100,000/year in the general population, with a documented continuous increase across the globe.[1,2] Despite the increasing incidence, its mortality is decreasing—most papers attribute this to advances in diagnostic methods and the improving care over the last decades.[2]

Several factors can induce AP, one of the most common being biliary obstruction, which accounts for around 40% of all cases.[3] In such instances, the obstruction will increase the pressure in the pancreatic ducts and promote the passage of bile acids into the pancreatic duct, which will, in turn, lead to increased Ca^{2+} entry into the acinar cells, initiating premature enzyme activation and autophagy.[4,5] In addition to inducing AP, obstructions in the biliary tree can also lead to increased pressure, distention, ischemia, and bacterial invasion in the biliary tree, provoking acute cholangitis (AC) and acute cholecystitis (CC).[6] AP is a sterile inflammatory process and does not require empiric antibiotic therapy; however, antibiotics are necessary if AC or CC is present.[7]

There is a significant overlap between the clinical picture of biliary AP and the diagnostic criteria of AC and CC. According to the 2018 Tokyo guidelines, the diagnosis of AC is based on systemic inflammation, cholestasis, and imaging alterations, while for the diagnosis of CC, abdominal pain, systemic inflammation, and imaging signs (including bile stone in the gallbladder) are necessary—many of which can be present in biliary AP.[8,9] Accurate distinction of these pathologies is crucial not only to prevent antibiotic overuse but also because endoscopic retrograde cholangiopancreatography (ERCP) is recommended in all patients with features of AC.[10]

Our aim was, to examine in a cohort of biliary AP patients, the on admission prevalence of AC and CC according to the 2018 Tokyo guidelines, the ensuing antibiotic use and ERCP performance, what this means in terms of the prognosis of the AP episode and after careful evaluation, to put all this into a clinical context.

Key summary

The established knowledge on this subject

- Biliary pancreatitis is mostly (around 80% of cases) caused by spontaneously passing stones.
- Less frequently, biliary obstruction can also lead to acute cholangitis or cholecystitis.
- There seems to be a significant overlap between the 2018 Tokyo guidelines for cholangitis and cholecystitis and the clinical, laboratory and imaging alterations in biliary pancreatitis.

The significant and/or new findings of this study?

- 70% of 944 biliary pancreatitis patients fulfilled the diagnostic criteria for cholangitis and/or cholecystitis on admission—in contrast with the described 80% spontaneous stone passage.
- At the same time, endoscopic intervention revealed common bile duct stones in only 41% of proposed cholangitis patients.
- These results suggest that the use of the 2018 Tokyo diagnostic criteria is questionable in the context of pancreatitis, as it grossly overestimates the prevalence of cholangitis and cholecystitis.
- The considerable number of false positives leads to the overuse of endoscopic interventions and antibiotics—77% of patients received antibiotics in our cohort.

MATERIALS AND METHODS

This paper presents a secondary analysis of a prospective, international cohort of AP patients. Between 2012 and 2019, 2195 adult AP cases were collected. 944 biliary AP cases were grouped according to the on-admission fulfillment of the Tokyo Guideline 2018 criteria for

definite AC[8] or CC,[9] as outlined in Table 1. Imaging alterations were accepted within the first 72 h (since on-admission abdominal imaging was not a requirement for inclusion in the AP registry), while laboratory values were accepted only on admission. Similarly, only on-admission values of these parameters were taken into account for determining AC and CC severity.

For this analysis, we used prospectively collected data from the AP registry, including epidemiological data, symptoms, laboratory parameters, organ failure (according to the modified Marshall scoring system), complications, AP severity (as recommended by the revised Atlanta classification), and mortality.[11] We also retrospectively evaluated imaging results for biliary alterations to determine the fulfillment of the 2018 Tokyo criteria for AC and/or CC. To compare groups, we used chi-squared and Fisher exact tests in case of dichotomous variables, and Student's *t*-test and single-factor ANOVA for continuous variables. The prospective observational study received its ethical approval in 2012 (22254–1/2012/EKU), the institution's human research committee approved the study, all participants provided written informed consent. The study conforms to the ethical guidelines of the Declaration of Helsinki.

A detailed version of this "Methods" section is available in our Supplementary Material S1.

RESULTS

Table 2 shows the baseline characteristics of included participants, divided based on the on-admission definite fulfillment of the Tokyo criteria for both AC and CC, only for CC, only for AC, and for neither condition.

22.5% of 944 biliary AP patients fulfilled the diagnostic criteria only for CC, 20.8% only for AC, 27.8% for both conditions. Interestingly, no significant differences were observed regarding AP severity; however, there was a tendency of lower mortality when neither AC nor CC were present on admission (0.7% as opposed to 1.5%–3.8%; $p = 0.106$). Antibiotic use was highest when both AC and CC were present (90.5%), around 80% with either one present, and still 61.3%, when neither was found. From this 61.3% (168 cases), information on why antibiotics were initiated was ascertainable for 101 cases. In 70 cases, it was for later developed/suspected AC or

TABLE 1 Tokyo guidelines for acute cholangitis and cholecystitis.

Tokyo criteria for acute cholangitis **Suspected: At least 1 from domain A and 1 from B/C** **Definite: At least 1 from each domain**		**Tokyo criteria for acute cholecystitis** **Suspected: At least 1 from domain A and 1 from B** **Definite: At least 1 from each domain**	
A	Fever	A	Murphy's sign
	WBC count < 4 or > 10 G/L or CRP ≥1 mg/dL		RUQ mass/tenderness/pain
B	Jaundice (total bilirubin ≥2 mg/dL)	B	Fever
	ALP/GGT/AST/ALT > 1.5x upper limit		WBC count < 4 or > 10 G/L or CRP ≥3 mg/dL
C	Biliary dilatation or evidence of etiology (stricture, stone, stent, etc.) on imaging	C	Characteristic imaging findings (pericholecystic fluid, gallstone/debris, wall ≥ 4 mm, enlargement)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; RUQ, right upper abdominal quadrant; WBC, white blood cell.

TABLE 2 Baseline characteristics.

	CC + AC	CC	AC	Neither	*p*
n (% of total)	262 (27.8)	212 (22.5)	196 (20.8)	274 (29.0)	
Age (years); mean ± SD	62.4 ± 16.4	63.3 ± 15.9	64.0 ± 16.3	59.5 ± 17.7	**0.014**
Female sex; *n* (%)	155 (59.1)	108 (50.9)	119 (60.7)	161 (58.8)	0.169
AP severity; *n* (%)					
Mild	210 (80.2)	152 (71.7)	165 (84.2)	223 (81.4)	0.065
Moderate	44 (16.8)	48 (22.6)	24 (12.2)	41 (15.0)	
Severe	8 (3.1)	12 (5.7)	7 (3.6)	10 (3.6)	
Mortality; *n* (%)	5 (1.9)	8 (3.8)	3 (1.5)	2 (0.7)	0.106
Receiving antibiotics; *n* (%)	237 (90.5)	167 (78.8)	159 (81.1)	168 (61.3)	**<0.001**

Note: Participants are divided into four groups based on the presence of acute cholecystitis or cholangitis according to the Tokyo guidelines. *p*-values < 0.050 appear in bold.

Abbreviations: %, percentage; AC, cholangitis; AP, acute pancreatitis; CC, cholecystitis; *n*, number; *p*, P-value; SD, standard deviation.

CC, in 14 cases "empirically" or for "elevating inflammatory parameters", and for the rest, for other reasons (urinary tract infection, pneumonia, pancreatic superinfection, etc.). A within-group comparison according to antibiotic administration can be found in our supplementary material (Supplementary Table S4).

AC and CC severity's influence on AP outcomes

Figure 1 displays how different severities of AC and CC (according to the Tokyo guidelines) were distributed and how they influenced antibiotic use, length of hospitalization (LOH), AP severity, and mortality in our cohort. With both AC and CC, about 55%–60% of the cases were mild and around 10% severe. Mortality was below 1% in mild and moderate AC and CC patients, but considerably higher in severe cases (12.8% and 21.2% in AC and CC respectively). A more apparent trend of increasing AP severity, LOH and antibiotic use was visible in CC, whereas in AC mild and moderate cases were not that clearly separated regarding AP severity and LOH. At the same time, antibiotic use in AC was the highest in the moderate and not the severe group (92.4% and 91.3%, respectively).

Common bile duct stones in AP cases with AC

In the 458 cases of biliary AP where definite AC was established according to the 2018 Tokyo guidelines, 409 (89.3%) underwent ERCP with successful canulation (Figure 2). In 12 cases, canulation was unsuccessful, and in 37 cases, ERCP was not performed, the reason for this was stated to be improving clinical and laboratory status in 18 patients; in the remainder, lack of consent, critical condition, and unstated reasons precluded the ERCP. 74% of ERCPs were performed within 24 h of hospital admission. No common bile duct (CBD) stones were identified in 58.9% of these procedures, and neither stones nor sludge was found in 46.2%.

DISCUSSION

In our prospectively collected and well-characterized cohort of AP patients, we retrospectively evaluated the presence of AC and CC according to the Tokyo Guideline 2018 among cases with biliary etiology. We also assessed the ensuing antibiotic use and how these conditions affected the clinical course of AP.

We found that according to the diagnostic criteria, either AC or CC was present in 71.0% of all biliary AP cases on admission, and as suspected, this led to a high rate of antibiotic use, around 85%, when one or both conditions were present. The question arises: are these criteria applicable in AP?

CRP elevation will be present in almost all AP episodes, regardless of biliary pathology. WBC elevation is also common, with cohort analyses of AP patients observing the mean WBC concentration to be above 10 G/L.[12] The pain in AP is characteristically an upper abdominal pain, often described as "belt-like", radiating to the back.[13] Thus the right upper abdominal quadrant (RUQ) will often be affected—in a cohort analysis of more than 1400 AP patients, 54.0% of all cases and 57.3% of biliary cases had RUQ pain or tenderness.[14] In a meta-analysis of three studies, Murphy's sign had a specificity of 87% and a subpar sensitivity of 65% for CC, and since it likely stems from the same pathophysiological process as RUQ pain—local inflammation and peritoneal irritation—it might be even less reliable in biliary AP.[15] A 3-fold elevation of AST or ALT is a good indicator of biliary etiology in AP, while ALP and bilirubin are seemingly less useful in the etiological workup.[16] Nevertheless, in our cohort, 38.2% of biliary AP patients presented with jaundice on admission, indicating that it is also a common finding. Among symptoms and laboratory components of the diagnostic criteria for AC and CC, there are ones that are less likely to be fulfilled in biliary AP uncomplicated by AC or CC and hence could be considered more specific diagnostic indicators in this context. RUQ mass is usually not found in AP, not even in the case of local complications: circumscribed fluid or necrotic masses usually take 4 or more weeks to develop, are only occasionally palpable and are adjacent to the pancreas.[11] Fever isn't necessarily a sign of infectious sequelae in AP, as it can occur in more serious systemic inflammation, predicting a severe AP course, but it is less common in non-severe cases[17]—at the same time, mild AC cases are described to exhibit only mild temperature increases.[8]

Regarding imaging findings, in case biliary obstruction was the etiological factor of AP, a finding of gallstones or debris in the gall bladder can be anticipated. This means that all three domains of the Tokyo Guideline 2018 diagnostic criteria for CC will commonly be fulfilled in biliary AP, as demonstrated in our cohort. Multiple findings suggesting CC (cholelithiasis accompanied by thickened gallbladder wall, gallbladder enlargement and/or pericholecystic fluid) can increase our confidence in the diagnosis. However, we should note that these imaging alterations can be present next to chronic liver, renal or cardiac disease[18] and in other proximal, non-gallbladder-related inflammatory processes—as some authors suggest, even in AP *per se*.[19–21]

While the development of AC secondary to CBD stones usually requires prolonged obstruction, in around 80% of biliary AP patients, the episode is caused by a transient obstruction, the stone passes spontaneously.[4,22,23] In our cohort, 90% of proposed definite AC patients had ERCP, no CBD stones were found in 58.9%, and neither stones nor sludge in 46.2%. ERCP is unnecessary, even harmful when stones are absent, due to its approximately 7% complication rate and up to 1% mortality.[24–27] The low stone retention rate is probably due to the observation that AP is elicited by smaller bile stones (median of 3 mm in the study by Tranter et al.) or sludge.[22,23,25,28] Nevertheless, even a transient obstruction can lead to mucosal edema and bile duct dilation: despite the considerably smaller stone size in spontaneous passage patient groups, biliary dilatation is often present—a mean CBD diameter of 8.5 ± 3.8 mm was found on admission in the study by Khoury et al.; 34.1% had dilatation in Pencovich et al., 40.0% had a CBD >10 mm in Ding et al.[29–31] Albeit,

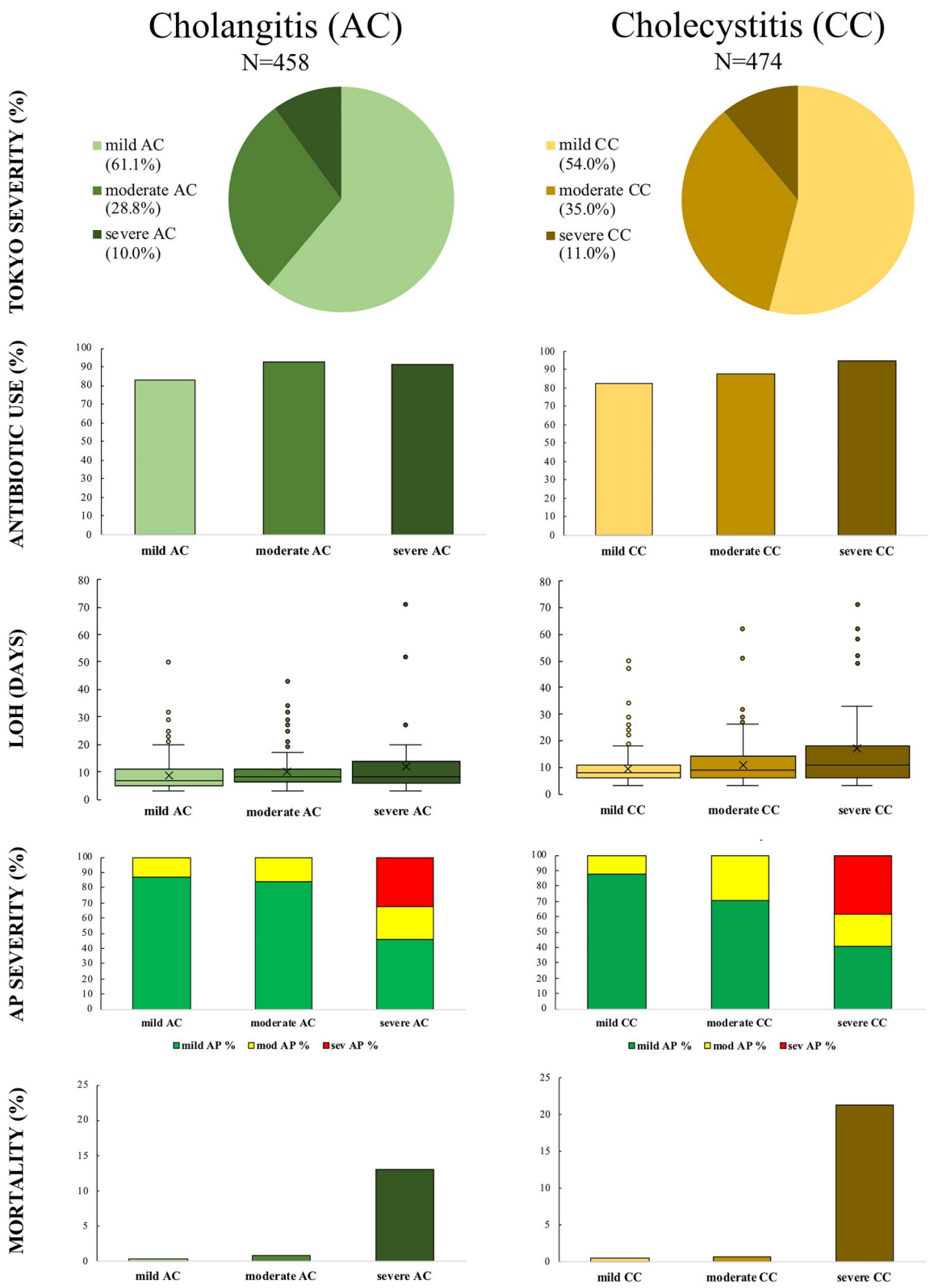

FIGURE 1 Cholangitis and cholecystitis severity's influence on acute pancreatitis. The figure displays the distribution of cholangitis and cholecystitis severity and antibiotic use, length of hospitalization, acute pancreatitis severity, and mortality in the mild, moderate and severe cholangitis and cholecystitis subgroups. %, percentage; AC, acute cholangitis; AP, acute pancreatitis; CC, acute cholecystitis; LOH, length of hospitalization.

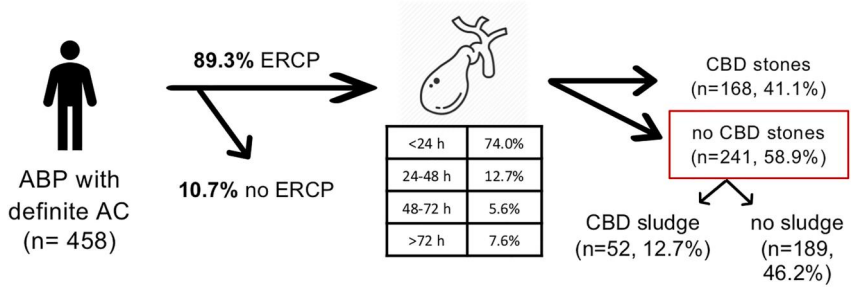

FIGURE 2 Endoscopic retrograde cholangiopancreatography in pancreatitis patients with definite acute cholangitis. ERCP was performed in 89.3% of the patients. The table within the figure demonstrates the distribution of performance according to the time from hospital admission. The ERCP identified common bile duct stones in 41.3% of the cases. %, percentage; ABP, acute biliary pancreatitis; AC, acute cholangitis; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; h, hours.

this is significantly less than what was observed in the retained stone groups in the same cohorts. This means that with detected bile duct dilatation (or even a detected smaller stone that will come to pass without intervention), the criteria for AC can also be easily fulfilled in biliary AP without the de facto presence of the diagnosed condition.

The mortality of CC varies between 0.6% and 13.5%, AC has a mortality of around 10%, up to 20%–30% in severe cases, and cohorts from the 1970s reported mortality rates exceeding 50% when patients were managed without ERCP.[32] Our cohort showed a <1% mortality in mild and moderate AC and CC cases, a 12.8% mortality in severe AC, and 21.2% in severe CC. Around 30% of severe AC and CC patients had severe AP, which can have an up to 40% mortality.[33] Next to the tendency of increasing mortality and AP severity with increasing AC and CC severity, increasing LOH was also observed. 61.3% of patients who did not fulfill the diagnostic criteria for AC nor for CC on admission received antibiotics. In our cohort, when neither AC nor CC was present on admission, in 21.5%, the rationale behind antibiotic use could not be ascertained, in 8.1%, inadequate reasons for antibiotic use were provided—showing that although diminishing, empiric antibiotic use is still a prevalent problem in AP.

The main conclusion of our study is that, according to the currently accepted diagnostic criteria (the 2018 Tokyo guidelines), AC and CC are prevalent in biliary AP, as is antibiotic use. Clinicians should be aware that most of the parameters used in the diagnostic criteria of AC and CC are naturally present in biliary AP; thus, their applicability is questionable. While alternative diagnostic criteria or a change in clinical practice cannot yet be suggested based on our results, we strongly urge the performance of interventional studies in patients where the diagnosis of AC or CC is based upon less reliable parameters or is unlikely and the risk of mortality is lower. Most authors recommend antibiotic therapy in all CC cases, but their use in non-severe cases is debated.[34,35] As highlighted above, the reliability of the diagnostic criteria for CC in biliary AP is likely low; thus, the use of antibiotics in this context is even more questionable, especially in patients with limited imaging alterations (e.g., only gallbladder stones/sludge). Grade I-III AC patients are recommended to receive antibiotics, until 4–7 days after the successful elimination of the obstruction.[34] However, as discussed above, most biliary AP episodes are caused by small, spontaneously passing stones or sludge and not a prolonged obstruction leading to AC. Thus, a randomized controlled trial of biliary AP patients initially diagnosed with AC (especially predicted mild or moderate, where mortality is low) testing the immediate cessation versus continuation of antibiotics after a negative ERCP or negative EUS is warranted. It is also likely that the use of EUS and magnetic resonance cholangiopancreatography will gain greater importance in the management of patients with AP and CBD stones—future studies should also focus on determining accurate imaging features that indicate a high chance of spontaneous stone passage. Such outlined investigations and measures could reduce excessive antibiotic use and lower the number of unnecessary ERCPs, positively impacting resistance patterns and healthcare costs.

Strengths and limitations

Our study is the first to describe the presence of AC and CC in biliary AP, which is a frequently occurring and important clinical question, greatly determining the management of patients. We observed AC and CC in the majority of patients, indicating that the applicability of their diagnostic criteria is questionable in this context. Parallelly, we found overwhelming antibiotic use. Our cohort comes from multiple centers and countries, containing more than 2000 AP patients. While some of the data used in this analysis (mainly the imaging alterations of the biliary system) was collected retrospectively, most of the data used were collected prospectively and in a uniform manner and validated in multiple tiers to ensure the quality of the data. The prospective collection of the laboratory and clinical data necessary for evaluating AC and CC was conducted with a high quality and almost all patients had pancreatic and biliary imaging on admission.

The most important limitation is that imaging reports had to be evaluated retrospectively and were not uniformly structured and phrased. However, since this is a cohort of AP patients, the description of the biliary system was routinely included. Hence, the diagnosis was ascertainable, but this did limit more specific investigations—for example, in cases where the biliary tree was without pathological alterations, parameters such as gallbladder wall

thickness were rarely described. Detailed imaging information was only available for Hungarian centres, limiting the generalizability of our results.

Implications

For practice: AC and CC are overdiagnosed in biliary AP because of the reduced applicability of the guidelines in this condition. This most likely leads to a high rate of antibiotic use. The Tokyo guidelines should not be used generally to decide on antibiotic therapy in AP.

For research: Future research should aim to identify biliary AP-specific diagnostic criteria for AC and CC and randomized controlled studies testing antibiotic use in patients that are likely misdiagnosed.

AUTHOR CONTRIBUTIONS

In determining authorship, we referred to the guidelines of the International Committee of Medical Journal Editors. Each author provided sufficient contribution to the concept of the work (Márk Félix Juhász, Nelli Farkas, Bálint Erőss, Andrea Szentesi, Péter Hegyi, Andrea Párniczky), data acquisition (Márk Félix Juhász, Rebeka Tóháti, Viktória Adrienn Jászai, Regina Molnár, László Czakó, Áron Vincze, Bálint Erőss, Andrea Szentesi, Ferenc Izbéki, Mária Papp, Péter Hegyi, Andrea Párniczky), analysis (Márk Félix Juhász, Rebeka Tóháti, Viktória Adrienn Jászai, Regina Molnár, Nelli Farkas, Péter Hegy, Andrea Párniczky), interpretation (Márk Félix Juhász, Rebeka Tóháti, Viktória Adrienn Jászai, Regina Molnár, László Czakó, Áron Vincze, Bálint Erőss, Andrea Szentesi, Ferenc Izbéki, Mária Papp, Péter Hegyi, Andrea Párniczky). All authors worked on drafting the manuscript and/or revising it critically for important intellectual content; all authors approved the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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