

CHALLENGES IN THE TREATMENT AND FOLLOW UP OF ACUTE PANCREATITIS

Ph.D. Thesis

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I. Preface and general introduction

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract requiring acute hospitalization; it is associated with significant morbidity and mortality worldwide, with an increasing incidence of 5–100/100,000 cases per year. Gallstones are the leading cause of acute pancreatitis in developed countries and account for a range between 16 and 70% of all cases. Also, there is evidence that up to 20% of idiopathic AP cases are caused by microlithiasis. It is generally accepted that endoscopic retrograde cholangiopancreatography (ERCP) combined with endoscopic sphincterotomy (EST) is the effective treatment method in acute biliary pancreatitis (ABP) complicated with cholangitis. Additionally, same-admission cholecystectomy reduces the risk of recurrent gallstone-related complications in mild ABP with a very low risk of cholecystectomy-related complications. With adequate treatment of the stone disease, recurrent pancreatic attacks are rarely associated with biliary aetiology. However, in some instances, ABP can recur for various reasons. This can be due to a common bile duct (CBD) stone not detected at the first episode, stones migrating from the gallbladder into the CBD, or stones developing in the bile duct after cholecystectomy.

Moreover, some patients are not fit for endoscopic or surgical therapy because of old age or comorbidities. This repetitive inflammation of the pancreas can lead to irreversible damage of pancreatic parenchyma, namely chronic pancreatitis (CP). CP is an end-stage disease with no specific curative therapy; therefore, an early diagnosis is crucial.

I aimed to determine the role of ERCP and EST and stone clearance in ABP and provide an overview of the general use of ERCP in Hungary. Furthermore, we analyzed the rate of recurrent acute pancreatitis events and the changing biomarkers to diagnose early chronic pancreatitis (ECP) in an extensive international cohort analysis.

As we examined these two suggested clinical problems in separate projects, two different chapters are discussed below.

II. Chapter I. - Acute biliary pancreatitis (ABP)

II.1 Introduction

One of the main etiological factors in the pathogenesis of AP is the obstruction of the ampulla of Vater by gallstones or sludge or by hypertrophy of papilla and bile reflux into the pancreatic duct, contributing to 35–60% of all AP cases. This subtype of AP is termed acute biliary or gallstone pancreatitis (ABP). Bile refluxing into the pancreatic ductal system induces toxic calcium signals, mitochondrial injury, and adenosine triphosphate (ATP) depletion in acinar and ductal cells. These mechanisms decrease the intraluminal pH and enhance trypsinogen activation leading to severe inflammation of the pancreas. The accurate diagnosis of the cause of AP is essential because it affects the therapeutic strategy. In ABP, approximately 80% of patients have a mild attack, but in 15–20%, AP is complicated by substantial morbidity and mortality. In patients with a severe AP, 5-10% mortality via local or systemic complications can rise to 15-20%. Without definitive treatment of the biliary stone disease, the risk of a recurrent attack is about 30-50% within the next several months.

The diagnosis of AP is based on the recommendation by the IAP (International Association of Pancreatology) /APA (American Pancreatic Association) guidelines. It requires at least 2 of 3 criteria: (1) abdominal pain; (2) serum amylase and/or lipase increased three times greater than the upper limit of normal; and/or (3) radiographic evidence of pancreatitis.

ABP is usually more common in women. An increase in serum liver enzyme concentrations might help in the prediction of gallstones. An elevated alanine aminotransferase (ALAT) level is the best laboratory indicator of biliary pancreatitis; a level of more than three times the upper limit of normal has a positive predictive value of 95% for biliary pancreatitis. However, a normal ALAT does not exclude gallstones as a cause. The dilation of the CBD greater than 8 mm in a patient with an intact gallbladder aged ≤ 75 years and >10 mm in patients aged >75 years indicates biliary obstruction. The finding of cholecystolithiasis or biliary sludge lends further support to the diagnosis of ABP. Although transabdominal ultrasound scan (USS) is the best tool to detect gallbladder stones, with an overall accuracy of over 95%, it is much less accurate in an emergency setting, detecting stones in only 70–80% of cases. Therefore, patients with a negative abdominal USS for biliary stones but with clinical signs and biochemical parameters suggestive of a biliary cause should have a differential diagnosis of ABP and

undergo repeated imaging to reveal potential gallstones. Endoscopic ultrasound (EUS) is a critical modality for detecting gallstones, and it can prevent an unnecessary ERCP and its complications in patients with suspected CBD stones.

According to the revised Atlanta classification, the severity of AP is classified into three categories based on clinical course and morphologic findings: 1. Mild – No organ failure and no local or systemic complications; 2. Moderate – Transient organ failure resolving within 48 hours and/or presence of local complications; 3. Severe – Persistent organ failure longer than 48 hours. Organ failure is defined as a score of 2 in 1 or more of the three organ systems described in the modified Marshall score.

Management of ABP requires two treatment strategies: conservative medical treatment and ERCP, which is the gold standard interventional strategy in ABP to achieve biliary decompression. Although most cases of ABP are self-limiting and there is no need for invasive treatment because most gallstones spontaneously pass to the duodenum. The American Society for Gastrointestinal Endoscopy (ASGE) practice guideline suggested a stratified approach to investigate suspected choledocholithiasis. If suspicion of gallstone is intermediate, sequential EUS and ERCP have to be the preferred approach. In cases of concomitant acute cholangitis, the need for urgent ERCP within 24 hours is recommended. In predicted severe ABP without cholangitis, early ERCP did not reduce the major complications or mortality based on the results of the APEC trial. Most international guidelines recommend that ERCP be performed within 72 hours in patients with bile duct obstruction without cholangitis. However, there is still no definite consensus about the optimal timing for endoscopy. On the other hand, without apparent signs of cholangitis or obstruction, the indication of ERCP in the setting of ABP is still debated because of the lack of available evidence. Despite the studies noted above, optimal comprehensive endoscopic management of ABP still lacks clear evidence.

National and international guidelines support cholecystectomy in mild ABP during the index hospital admission to prevent recurrent biliary events.

II.2 Materials and methods

Altogether, 691 patients in 14 centers were enrolled, and their data were prospectively collected in the AP registry between January 2013 and August 2015. The AP diagnosis was made following the IAP/APA guidelines. We selected ABP patients who fit the criteria previously laid down by the Dutch Pancreatic Study Group. Other causes of AP were excluded. Detailed

data on the outcomes for ERCP were collected on patients with ABP. Descriptive statistical tools were used to characterize our cohort. To determine differences between continuous parameters, depending on the data distribution, we used the independent Student's t-test or the Mann–Whitney U test for two groups and one-way ANOVA with the Bonferroni post-hoc test or Kruskal–Wallis test in comparing more than two groups. We used the Chi-square test or Fisher's exact test to analyze the relations between the factors under examination. All analyses were performed with SPSS 24 statistical software (IBM Corporation).

II.3 Results

Biliary etiology was found in 356 (51.5%) patients, while 335 (48.5%) patients had other etiological factors. Among the subjects with ABP, there were more women, and they were older than patients with a different etiology [204/356 (57.3%) vs 106/335 (31.6%) ($P < 0.001$)] and mean age [61.5 ± 17.32 vs 51.47 ± 15.73 years ($P < 0.001$)]. The course of pancreatitis with biliary etiology was milder in contrast to non-ABP disease [mild ABP: 248/356 (69.7%) vs non-ABP: 183/335 (54.6%); moderately severe ABP: 86/356 (24.2%) vs non-ABP: 121/335 (36.1%); severe ABP: 22/356 (6.2%) vs non-ABP: 31/335 (9.2%) ($P < 0.001$)]. There was no difference in mortality between the two groups [ABP: 8/336 (2.4%) vs non-ABP: 13/322 (4.0%) ($P = 0.242$)] [73]. ABP occurs more commonly in women [204/356 (57.3%) female vs 152/356 (42.7%) male]. In almost 10% of the cases, ABP developed after a cholecystectomy [35/356 (9.4%)] and more frequently in women [28/204 (13.9%) vs 7/152 (4.6%) ($P = 0.004$)]. According to the revised Atlanta classification, the majority of the cases (69.6%) were mild, 24.2% were moderate, and 6.2% were severe. Mortality was 2.4% in total and the median length of hospital stay was 9 days. Both mortality and length of hospital stay showed significant differences between the mild, moderate, and severe groups. Necrosis developed in 11.8% of cases, mostly in severe AP.

II.3.1 Indications, quality indicators, and findings of endoscopic retrograde cholangiopancreatography (ERCP)

Out of the 356 ABP patients, 267 (75.0%) underwent ERCP for suspected cholangitis or cholestasis based on raised inflammatory markers with dilated biliary ducts and increased liver function tests. ERCP was not performed in 89 patients (25%), although it would have been indicated in 50 cases due to suspected cholangitis (56.2%). ERCP was omitted in these cases for various reasons, including an improving clinical picture, lack of consent from the patient,

or rapid deterioration from multi-organ failure. EUS was performed in only five patients based on the available data, with bile duct stones being identified in two cases. Magnetic resonance cholangiopancreatography (MRCP) was carried out in one patient, which reported clear bile ducts.

The key performance indicators for ERCP met the criteria set out in the ASGE guidelines. Successful biliary cannulation was achieved in 233 subjects with naïve papilla (90.7%), but the successful cannulation rate was 84.0% (216 procedures) at the first attempt. In 80 subjects, extractions of stones smaller than 1 cm were successful in 93.7% of the cases. Plastic stent placement below the bifurcation was successful in all cases after deep biliary cannulation (33/33). Perforation occurred in 1/267 (0.4%) of the cases. Clinically significant bleeding requiring blood transfusion occurred in 3/267 (1.2%) of the patients. CBD stones, sludge, and/or dilation of the bile ducts were reported in 97 (36.3%), 91 (34.1%), and 124 (46.4%) cases, respectively. Spontaneous passage of a bile duct stone was suspected in 19.5% (52/267) of the patients during ERCP. In 30 cases (11.2%), biliary pathology was not found by ERCP. Endoscopic ultrasound was carried out only in 5 cases because of limited access during the study. There were no statistically significant differences in ABP outcomes between the patients treated with or without ERCP.

II.3.2 Outcomes for ABP in relation to success rates and timing of ERCP

The success rate for bile duct cannulation in all patients was 83.5% (223/267) during the first ERCP, and any further endoscopic attempts resulted in a higher rate of success [90.6% (242/267)]. Successful cannulation was achieved in 84.0% (216/257) of patients with naïve papilla, and clearance of the bile duct was successful in 71.5% (191/267) at the first ERCP attempt. Endoscopic biliary sphincterotomy was done in 86.5% (231/267) of the ERCPs, whereas pancreatic sphincterotomy was only performed in 1.12% (3/267) of the cases. Biliary stents were placed in 12.4% (33/267) and pancreatic stents in 16.8% (45/267) of the cases. Successful cannulation was associated with significantly lower rates of local (22.9% vs. 40.9%) and systemic (4.9% vs. 13.6%) complications. Successful clearance was linked to lower rates of local complications (22.5% vs. 40.8%). Successful cannulation and clearance correlated with a less severe course of ABP and shorter hospitalization (3.6% vs. 15.9% and 4.1% vs. 12.2%, respectively). Complete failure of clearance and decompression of the bile ducts were related to a higher frequency of local complications (22.5% vs. 50%) and a more severe course of ABP (4.1% vs. 18.7%) and longer hospital stay (median 9 vs. 16 days). The majority of ERCP

(64.8%) was performed during the first 24 hours after admission, in 18.4% (47/256) of them between 24 and 48 hours after admission, and in 16.8% (43/256) cases later than 48 hours after admission. A tendency of an increased rate of local complications was observed if ERCP was performed later [ERCP in 24 hours: 21.1% (35/166); between 24 and 48 hours: 23.4% (11/47); after 48 hours: 37.2% (16/43) ($P = 0.088$)]. The length of hospitalization was significantly longer in all patients if ERCP was delayed (median 8 vs. 10 vs. 13 days)

II.4 Discussion

II.4.1 Epidemiology of ABP

In this multicenter study, we analyzed prospectively collected, real-world data. The cohort gave considerable coverage of Hungarian ABP cases, and the data shown above depicted the then actual management strategies used in Hungary. Although a clear-cut diagnosis of definite cholangitis would have been desirable in our analysis, currently, there is no validated definition of cholangitis in the setting of ABP. Simple AP can result in a transient and self-resolving biliary obstruction with deranged liver function tests and dilated biliary tree, which can mimic cholangitis with the raised inflammatory markers and fever driven by pancreatitis. Thus, the definition of definite cholangitis as termed by the Tokyo criteria had to be avoided. As described in other studies, we found that patients with ABP are older, and there are more women among them than in AP of different etiologies. ABP tended to have a less severe natural course, but the mortality was the same as in other etiologies. A previously documented episode of AP occurred in more than 10% of the patients. Although data on the etiology of the previous attack was not available, we believe that the majority of the cases were likely driven by gallstone disease, similar to data reported by Bakker et al.

II.4.2 ERCP and other modalities for diagnosis and treatment of gallstone pancreatitis

ERCP was performed in 75% of the patients presenting with ABP. There are no previous cohort studies where the rate of ERCP in ABP was published and analyzed to our best knowledge. We found that our ERCP practice in ABP was in line with the current guidelines; however, we must highlight that minimal access to urgent EUS and MRCP resulted in some avoidable ERCPs. As it is well known that most ABP patients spontaneously pass stones into the duodenum, ERCP could be avoidable in more cases. The presence of cholestatic liver enzymes and dilated common bile duct are proven not to be reliable factors for detecting the presence of common bile duct stones. Hence, in patients with a clinical probability of CBD stones, ESGE

recommends performing EUS or MRCP. By performing EUS first, about two-third of ERCPs can be avoided. However, EUS has spread slowly in Hungary due to technical, personnel, and financing issues. This clinical practice is now improving.

II.4.3 Quality indicators of ERCP

The monitoring of quality indicators of ERCP is crucial in current practice as this endoscopic intervention has the highest rate of complications. Some of the key performance indicators describing the ERCP practices in our large cohort across many centers described suboptimal ERCP practices. Most importantly, a success rate of 84 % at the first attempt (216 patients) is below the quality benchmark of >90% recommended by ASGE. This may well be driven by the fact that some ERCPs were performed in low-volume centers. It also reminds us that, if indicated, high-quality ERCP with maximal pancreas protection and high competence of alternative biliary access techniques should be mandatory. One of our main findings is that failed cannulation, and bile duct clearance are associated with a higher incidence of local complications and severity of ABP. This result can be interpreted in two ways. Firstly, successful clearance and decompression of the bile ducts can result in a quicker resolution of pancreatitis and less progression leading to complications. Secondly, it may be explained by the difficult access to the bile ducts in already complicated AP, driven by difficult intubation of the duodenum, poor visualization of the papilla, limited maneuverability of the duodenoscope, and challenging cannulation of the edematous papilla. ERCPs in ABP are classified as grade 3 on the modified Schutz difficulty grade, on a scale of 1–4, where 4 represents the most difficult. High success rates can only be expected of competent, highly skilled endoscopists with substantial case numbers in ABP. Cannulation of naïve papilla was successful at first attempt in 84.1% of all ERCPs (desired: 90%), perforation occurred in 0.4% (desired: $\leq 0.2\%$), and bleeding requiring transfusion resulted in 1.2% (desired: $\leq 1\%$). We note that this analysis contained data from 267 patients, hence the two latter measures. Quality indicators of stone extraction and stenting of obstructions below the level of bifurcation met the criteria for the guidelines. The indication was suspected cholangitis in most patients, and they could have benefited from additional diagnostic imaging. A prospective national cohort from the hungarian ERCP Registry was published lately by Pécsi et al. initiated to compare patients with ABP and patients with acute cholangitis without ABP. Their data support that ERCP is more difficult in ABP than in cholangitis without ABP. It is noteworthy that they found normal descriptions of the biliary tree in 20.0% of ABP cases. This also supports our statement that acute cholangitis

is complicated to diagnose in ABP, and the lack of access to additional diagnostic tools (EUS or MRCP) resulted in many unnecessary and avoidable ERCPs. In summary, we believe that ERCP for ABP will be reduced with an accurate prediction of CBD stones as access to EUS and MRCP improves.

We did not find a significant decrease in the rate of local complications and the length of hospital stay in the cohort when ERCP was performed within two days. Evidence suggests that early ERCP in ABP with cholangitis is indicated, but our findings could not reinforce these previous data. According to APEC trial, in predicted severe ABP without cholangitis, urgent ERCP with biliary EST is proven not to be superior to early endotherapy. On the other hand, regardless of disease severity, in patients with a clear-cut diagnosis of acute cholangitis, EST should be considered as soon as possible to provide a better outcome.

III. Chapter II. - Evidence for diagnosis for early chronic pancreatitis after three episodes of acute pancreatitis

III.1 Introduction

Chronic pancreatitis (CP) is a severe condition that considerably deteriorates the quality of life and decreases life expectancy. Importantly, there is no specific curative intervention available. The diagnostic criteria for CP only allow us to detect the disease at the end-stage when 90% of pancreatic parenchyma is irreversibly damaged, resulting in endocrine and exocrine insufficiency. Cholestasis is usually temporarily caused by edema of the pancreas, obstruction or compression of the bile duct via stones, sludge, or local complications of pancreatitis. It can resolve spontaneously or via endoscopic intervention. Therefore CP with biliary etiology is not a common entity. The Japan Pancreatic Society has already defined early CP, but their definition is uncertain since it includes patient- and observer-reported components. The four leading pancreatic societies (International Association of Pancreatology, American Pancreatic Association, Japan Pancreatic Society and European Pancreatic Club) could not agree on the definition of early CP because any biomarker cannot diagnose it since all early biomarkers are nonspecific. Several pathomechanisms on progression towards CP were proposed earlier; however, extensive cohort analyses are still lacking. DeSouza et al. reported a high-quality magnetic resonance imaging (MRI) study, which was the first to demonstrate pancreas shrinkage 'after ≥ 3 attacks of AP.

III.2 Materials and methods

This study is a comparative multicentric cross-sectional study. We extracted and analyzed data from the AP and CP registries of HPSG collected between June 2012 and September 2017. Altogether, 1315 patients from the AP registry and 324 patients from the CP registry were eligible for inclusion. Diagnosis of AP was established based on the HPSG and IAP/APA guideline recommendations, while that of CP was based on the HaPanEU criteria. We formed three groups based on the morphology of the pancreas and the number of recurrent acute episodes. The first episode of AP without any chronic morphological change of the pancreas was labeled AP (983 cases). Cases with two or more episodes of AP without clinical signs and symptoms of CP or pancreatic morphological alterations were labeled recurrent acute pancreatitis (RAP) (270 cases). RAP was further divided into four subgroups based on the

number of acute episodes (RAP2: 2 episodes of AP; RAP3: 3 episodes; RAP4: 4 episodes; and RAP5 + : 5 or more episodes). RAP 5 + consisted of 30 cases). Any acute episodes based on clinical signs and symptoms and pancreatic morphological changes attributed to chronic inflammation were labeled CP (62 cases). We used descriptive statistics to characterize our cohort. To check the normality of the data, we used the Kolgomorov-Smirnov test and/or visual inspection of the Q–Q plots. We used the independent t-test, one-way ANOVA with a Tukey post hoc test to identify significant differences between groups. The association between categorical variables was examined with the Chi-square test and the Fisher's exact test, depending on the sample size. All statistical tests were performed using SPSS statistical software version 25 (IBM Corporation).

III.3 Results

1. One out of five patients with an acute episode suffers from RAP, as opposed to one out of twenty who has CP.

Out of the 1315 patients in the AP registry, a cohort of 983 (74.8%) patients had AP without CP, as opposed to 270 (20.5%) suffering from RAP without CP; 62 (4.7%) of the acute episodes were accompanied by already existing CP. The male/female ratio was 53.4/46.6% with AP, 64.8/35.2% with RAP, as opposed to 72.6/27.4% with CP.

2. Bidirectional changes in alcoholic and biliary etiologies in AP, RAP, and CP patients.

50.2% of AP cases had biliary origin; however, the rate of this etiological factor continuously decreased towards CP (20.7% with RAP and 11.3% with CP). The distribution of alcoholic etiology moved in the opposite direction: 19.4% with AP, 39.1% with RAP, and 51.6% in the CP group.

3. Local complications are more frequent in CP than in AP or RAP, whereas systemic complications and mortality are less so.

The demographic, epidemiological, and primary outcome parameters suggest that patients move closer to CP after each acute episode of AP.

4. Fifteen out of 102 biomarkers showed significant alterations between the AP, RAP, and CP groups.

Epidemiology-based markers [age, sex, smoking, alcohol consumption, and body mass index (BMI)], etiology-based parameters [biliary and alcoholic etiology, serum levels of bilirubin, gamma-glutamyl transferase (GGT), aspartate aminotransferase (ASAT), and alanine aminotransferase (ALAT)], laboratory value [red blood cell count (RBC)], and pancreas-dependent parameters (rate of pseudocyst formation, serum amylase, and lipase) showed significant differences between the groups. The dynamic changes of these parameters indicate that RAP represents a continuous transition from AP to CP.

5. The significant differences between the biomarkers measured during acute episodes in AP and CP disappear after 2–3 attacks.

The significant difference in eleven parameters disappears after the second episode of AP (RAP2; age, sex, etiology, alcohol consumption, bilirubin, ASAT, GGT, RBC count, pseudocysts, amylase, and lipase). The significant difference in BMI and ALAT disappears after RAP3. There is no difference in smoking after RAP4. Calculating the rate of morphological alterations after each episode revealed that 0.3% of AP, 1% of RAP2, 16% of RAP3, 33% of RAP4, and 32% of RAP5+ cases already have either computed tomography (CT)-, magnetic resonance imaging (MRI)-, transabdominal ultrasound scan (USS)- or endoscopic ultrasound (EUS) - based morphological alterations. These data indicate a stage in CP development in which biomarkers show the disease progression earlier than pancreatic morphological changes.

6. In the RAP3 group, 16% of patients already have established CP, while the figure is nearly 50% in the RAP4+ group.

These data demonstrate that three or more episodes of AP are considered a significant risk factor for the development of CP.

7. RAP patients have an average of three attacks, whereas CP patients have an average of four to five.

RAP patients had an average of 3.07 ± 1.85 AP attacks at the time of diagnosis, whereas CP patients had 3.76 ± 2.24 in the AP registry. In the CP group, the average number of attacks was 4–5 (4.07 ± 3.82).

III.4 Discussion

There is much data available on AP and CP; however, much less is known about RAP and ECP. Two nationwide studies have already highlighted that repetitive inflammation of the pancreas can lead to CP according to the SAPE model. In a cross-sectional epidemiological study, Masamune et al. showed that 26.5% of ECP cases had previous acute episodes. We investigated uniformly and prospectively collected 130,744 pieces of high-quality data from 1315 patients in our international cohort. Our epidemiological analysis revealed that one out of five AP patients suffers from RAP, whereas one out of twenty suffers from CP, similarly to data reported by the Japanese cohort studies. Of note, almost all the CP cases (98%) had a previous episode of AP, which is surprisingly high compared to previous data by Olesen et al. (47%). We found 15 variables that were significantly different in the first AP and CP, and, importantly, the differences start disappearing after recurrent episodes of AP. Epidemiological data showed that the male gender, younger age, and lower BMI are associated with RAP and CP, which data are in accordance with the findings of the Cleveland cohort. Concerning ages, no further changes were observed after the third attacks of AP (45.7 ± 16.5 y), suggesting that three or more AP attacks may be a separate group of RAP. One of the key findings of this study is that the incidence of recurrent episodes increases the risk of CP development. The first two attacks have small effects (0–1%) on the odds for developing CP, whereas the third and fourth (16–50%) episodes have large ones. At least three factors could explain the striking difference between RAP2 and RAP3: (1) the biliary etiology decreased from 24.9% to 9.3%, whereas the alcoholic etiology elevated from 37.6% to 48.8%. While the biliary etiology is usually a one-time hit on the pancreas, alcohol has a continuous deteriorating effect. (2) RAP3 occurs in a more damaged pancreas, which is confirmed by our experimental settings. (3) RAP3 seems to be more severe than RAP2 (mortality: 4.7% vs 2.3%; systemic complications: 4.7% vs 2.3%). Our significant biomarkers clearly showed bidirectional changes in alcoholic and biliary etiologies in AP, RAP, and CP patients.

National and international guidelines support cholecystectomy in mild ABP within the same index hospital admission to prevent further recurrent biliary events based on, among others, the PONCHO trial. In patients who are unfit for cholecystectomy because of old age or comorbidities, an elective EST is offered to reduce recurrent biliary events after an ABP attack. Before the routine cholecystectomy era, biliary AP was even more frequent in RAP than in general AP. Using endoscopic and/or surgical therapy, the biliary etiology in CP (11.3%) is five

times less than in the first episode of AP (50.1%); furthermore, it also suggests that repetitive episodes are one of the critical determinants of CP.

We report that the on-admission elevation of serum lipase and amylase levels decrease from AP to CP via RAP. The episode-dependent decrease in the elevation of amylase activity highlights the loss of acinar cells in the pancreas and the reduction of pancreatic enzyme secretion/leakage from acinar cells. Importantly, these data also indicate that the three-fold elevation of serum pancreatic enzymes may not be suitable for setting up a diagnosis in patients suffering from RAP. Taken together, we suggest that three or more episodes of RAP can be considered as ECP.

IV. Conclusions

1. Indication and benefit of ERCP in patients with ABP but without a clear-cut diagnosis, cholangitis remains a contentious issue.
2. There is no validated definition of cholangitis in ABP, so the Tokyo guideline should not be used for interpretation.
3. ERCP and cannulation of papilla is difficult in ABP (Shutz grade 3). Failed cannulation and bile duct clearance are associated with a higher incidence of local complications and severity of ABP.
4. Suboptimal ERCP practices are likely to be associated with poorer outcomes of ABP.
5. Invasive procedures should be performed by experts in high-volume centers.
6. Quality indicators of ERCP must be closely monitored.
7. Non-invasive diagnostic approach (EUS, MRCP) should be maximized to select the most suitable subgroup of ABP patients for ERCP.
8. RAP represents a continuous transition from AP to CP.
9. There is a stage in CP development in which biomarkers show the disease progression earlier than pancreatic morphological changes.
10. Three or more episodes of AP are considered a significant risk factor for the development of CP.
11. Using endoscopic and/or surgical therapy, the biliary etiology in CP is five times less than in the first episode of AP; furthermore, it also suggests that repetitive episodes are one of the key determinants of CP.

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