CHALLENGES IN ACUTE PANCREATITIS: DIAGNOSIS, ETIOLOGY AND TREATMENT

Ph.D. Thesis

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I. Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, et al. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020;20(4):608-616. IF: 3.629

II. Mosztbacher D, Farkas N, Solymár M, Pár G, Bajor J, Szűcs Á, et al. Restoration of energy level in the early phase of acute pediatric pancreatitis. World Journal of Gastroenterology. 2017;23(6):957. IF: 3.3

III. Zsoldos F, Párniczky A, Mosztbacher D, Tóth A, Lásztity N, Hegyi P. Pain in the early phase of pediatric pancreatitis (PINEAPPLE Trial): pre-study protocol of a multinational prospective clinical trial. Digestion. 2016;93(2):121-6. IF: 2.088

SCIENTIFIC METRICS

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TABLE OF CONTENTS

I. INTRODUCTION

Acute pancreatitis (AP) is one of the most common reasons for gastrointestinal hospitalizations in adults. AP has an annual incidence of 13-45 per 100,000 persons and is increasing worldwide as a result of better awareness of the disease and obesity-related gallstone formation and hypertriglyceridemia (HTG). AP represents a remarkable disease burden for healthcare systems and patients' quality of life. This burden is further increased by the development of a severe disease course which is accompanied by increased length of hospitalization (LOH), elevated rate of complications, intensive care unit (ICU) stay, the need for invasive interventions, and mortality.

According to the revised Atlanta classification, the severity of AP is categorized as mild, moderately severe, and severe. Severe acute pancreatitis (SAP) develops in 15-20% of AP cases; however, better understanding of the underlying mechanism may provide possibilities for decreasing severity. Although the pathomechanism of AP is still unclear, the most common etiological factors such as bile acids, fatty acids generated from triglyceride (TG), and non-oxidative ethanol metabolites (fatty acid ethyl esters, FAEEs) were shown to elevate the intracellular Ca^{2+} concentration, causing mitochondrial damage and a resultant adenosine triphosphate (ATP) and energy depletion in the exocrine pancreas. In addition, hypercatabolism secondary to pancreatic and extrapancreatic inflammation further aggravates the energy deficit. This leads to inhibited fluid and bicarbonate secretion with resultant secretory block and intrapancreatic trypsinogen activation.

Furthermore, HTG contributes to systemic pro-inflammation and local hypoxia-induced acidosis caused by hyperviscosity. HTG is the third most common cause of AP, and is responsible for up to 15% of AP cases. AP related to TG above 5.6 mmol/l should be considered as suspected hypertriglyceridemia-induced acute pancreatitis (HTG-AP), and AP associated with TG over 11.3 mmol/l is confirmed as HTG-AP. Importantly, the occurrence of AP increases with the increase in TG level. There is a 5% possibility of developing AP if TG exceeds 11.3 mmol/l, and this rises to 10–20% if TG elevates to over 22.6 mmol/l. In addition, HTG was shown to increase the risk of the development of SAP and aggravate the severity of AP compared to alcoholic and biliary etiologies. Accordingly, initial and appropriate lipid-lowering therapy may be beneficial in the case of HTG-AP; however, detailed analysis and evidence-based therapy for HTG-AP is missing.

In contrast, early enteral nutrition (EEN) as early ATP restoration has been shown to be beneficial in AP compared with nil per os (NPO) therapy. Moreover, energy supply given by enteral nutrition in AP patients was shown to be beneficial as a first-line treatment compared to total parenteral nutrition (TPN) for several reasons: (i) EEN significantly decreases pathogenic bacteria in the stool and alteration of intestinal flora; (ii) gut plays an important role as a barrier in the immune system and EEN is able to optimize intestinal permeability; (iii) this mucosal barrier integrity decreases the bacterial translocation from the gut, therefore resultant bacteremia and levels of serum endotoxins are reduced; (iv) EEN has a favorable effect on immune dysregulation caused by SAP which can reduce the rate of pancreatic infection, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome as well as duration of ICU stay. Overall, enteral nutrition either via oral, nasogastric- or nasojejunal tube feeding has been shown to be beneficial regarding visual analogue pain score, LOH, systemic infection, multi organ failure (MOF), need for surgical interventions, and mortality. Additionally, enteral nutrition further improves the outcome of AP if it is started within 48-72 hours. The type of enteral nutrition is administered based on disease severity. Three of the recent and most up-to-date guidelines for AP in adults have shown the positive effect of early nasogastric and nasojejunal tube feeding in moderately severe and SAP. Moreover, nasogastric tube feeding was shown to be as safe and as effective as nasojejunal tube feeding in SAP. In the case of patients with predicted mild AP, oral feeding is preferred as soon as possible. Despite the fact that the clinical characteristics of AP differ by age, nutritional guidelines for childhood-onset AP are limited and adopted from the adult protocols and no systematic review is available concerning the role of EEN in children.

Not only therapeutic, but also diagnostic pediatric guidelines for AP are adopted from adult protocols. It is not surprising that the overall incidence of acute pediatric pancreatitis (APP) is lower compared to the adult population (1 per 100,000 persons or even less versus 13-45 per 100,000); however, two major studies have proven that the real incidence of APP (3.6–13.2 per 100,000) is much higher than we previously thought. The reason is probably multifactorial, but it has been published by Morinville et al., that diagnostic workup influences the incidence of the disease. Their data showed that increased pancreatic enzyme testing could account for 94% of the change in all AP admissions in childhood, suggesting that APP is an underdiagnosed disease. However, there are factors which make the diagnosis of APP challenging: (i) abdominal pain is a common complaint in kids; 50% of the cases are in the category of pain-predominant functional gastrointestinal disorder with no significant

morbidity; (ii) hospitals cannot afford to measure serum amylase/lipase in every child experiencing abdominal pain; (iii) the clinical course of AP, pancreatic exocrine function, and radiological preferences differ by age; (iv) pediatric trials are lacking, so diagnostic criteria for APP are based on the consensus of expert pediatric pancreatologists, but not on evidence-based pediatric data and the recently published APP guideline has low evidence as well. Evidence-based medicine (EBM) guidelines are not available to provide proper instruction concerning the necessity of diagnostic tests for AP during abdominal pain in children. Therefore, most of the ordered pancreatic enzyme tests and abdominal ultrasonography (US) are based on individual pediatrician experience, and APP may be delayed or underdiagnosed as a result of the decreased awareness of diagnostic workup.

In contrast with the current diagnostic practice, there is significant importance in recognizing and diagnosing AP in childhood. Acute recurrent pancreatitis (ARP) develops in 10-35% of children following an initial AP, and idiopathic ARP is likely to be a transition phase between AP and chronic pancreatitis (CP) with 1-3.79 years of median time. However, based on a multicenter study, 16% of the pediatric CP patients had no documented prior episode of ARP. ARP and CP are of great importance because both are associated with a notable disease burden by pain, exocrine and endocrine dysfunction, frequent ER visits, hospitalizations, and school absenteeism. The most common risk factors of CP are alcohol and smoking in adults; however, these are uncommon in children. Pediatric ARP and CP are frequently associated with pancreatobiliary obstructions in ~30% and genetic abnormalities in up to 73%. Genetic involvement was shown to carry the fastest rate of progression from AP to CP. These data highlight the necessity of an appropriate and evidence-based diagnostic guideline for childhood-onset AP.

II. AIMS

As a pediatric resident I recognized the importance of evidence-based clinical practice compared to decisions based on the experiences of individual physicians. First, we aimed to perform a review of our current clinical practice, estimate the real incidence of APP and provide a fast, simple, and authentic scoring system that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme tests and abdominal US when a child has abdominal pain. Therefore, we established an international, multicenter observational clinical trial called PINEAPPLE (Pain IN the EArly phase of Pediatric Pancreatitis).

We aimed to review the literature to analyze the effect of EEN versus NPO therapy on the outcome of APP, and to aggregate the information in childhood onset AP, leading to a higher statistical power and more robust point estimate than is possible from the individual studies.

Finally, we aimed to perform a cohort analysis for investigating the dose-dependent effect of HTG on AP and providing data for further prospective randomized clinical trials.

III. DOSE-DEPENDENT EFFECT OF HYPERTRIGLYCERIDEMIA ON ACUTE PANCREATITIS

III.1. Methods

AP patients (n=1435) over 18 years old were enrolled in the prospectively collected international, multicenter AP registry operated by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2017. Post-hoc cohort analysis was performed on 716 AP cases who underwent TG measurement within 72 hours of admission. AP was diagnosed based on International Association of Pancreatology/American Pancreatic Association (IAP/APA) and HPSG evidence-based guidelines.

The threshold of the normal TG value was determined at 1.7 mmol/l. Six groups were established based on the Endocrine Society Clinical Practice Guideline and previously published clinical data related to HTG-AP : Group 1: <1.7 mmol/l; Group 2: 1.7–2.19 mmol/l; Group 3: 2.2–5.59 mmol/l; Group 4: 5.6–11.29 mmol/l; Group 5: 11.3–22.59 mmol/l; and Group 6: ≥22.6 mmol/l. In the case of each variable, elevated TG groups (Groups 2-6) were compared with the normal TG group (Group 1).

Seventy-three variables were collected from each AP case. Local complications, organ failure, and severity were defined based on the revised Atlanta classification. The 716 cases investigated showed the same epidemiological and major outcome distribution as the total cohort (1435 cases), demonstrating that our patient population represents a normal AP cohort.

The registry received ethical permission from the Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU) in 2012, and all the patients provided written informed consent to participate.

Prior to analysis of the dataset, descriptive statistical tools were used to describe the basic characteristics. Mean and standard error of the mean were calculated for continuous variables, whereas the incidence in each group was determined for categorical variables.

Depending on the distribution of the data, the independent Student's t-test or Mann–Whitney U test was used to evaluate differences between continuous parameters. The chi-square test or Fisher's exact test was conducted to analyze the relations between categorical variables. We compared the confidence intervals (CI) of the proportions to investigate differences in the incidence of moderately severe cases between groups. A p-value less than 0.05 ($p \leq 0.05$) was determined as statistically significant. All analyses were performed using IBM-SPSS Statistical Software Version 25 (IBM Corporation, Armonk, NY, USA).

III.2. Results

In our cohort, 30.6% (n=219) of the patients presented with elevated TG level (≥1.7 mmol/l). HTG was significantly and dose-dependently linked to younger age and male gender. In 7.7% of AP cases (n=55), TG level was above 11.3 mmol/l, which is considered as a causative etiological factor. In 56.4% of these cases, HTG-AP patients had no other etiology described; however, raised TG level was also accompanied by alcohol in 38.2% of these cases and by biliary etiology in 5.4%, showing that HTG-AP is associated with other etiologies in a substantial number of cases. Data from patients' medical history revealed that HTG is significantly and dose-dependently linked to obesity and diabetes mellitus (DM). The amount of previous AP in the medical history was higher in the HTG group compared to the normal TG group. HTG was significantly related to increased heart rate. Regarding the laboratory parameters on admission showing significant differences with HTG, amylase, lipase, sodium, and calcium were associated inversely; however, glucose, C-reactive protein (CRP), cholesterol, red blood cell count (RBC), hemoglobin, and hematocrit were related in parallel with TG level. On admission, laboratory parameters consistent with cholestasis suggested that HTG is less common in cases with biliary etiology. The parallel rise in gamma-glutamyltransferase (γGT) and TG levels confirms that alcohol consumption is linked to HTG. The rate of local complications, including peripancreatic fluid collection, pancreatic necrosis, and DM was significantly and dose-dependently increased with TG level. Organ failure, including heart and renal failure, and maximum CRP level were significantly and dose-dependently raised by TG level; however, respiratory failure and maximum white blood cell count (WBC) did not show any significant differences by HTG. As regards severity, TG level above 11.3 mmol/l was associated with a significantly higher rate of moderately severe AP and longer hospital stay, whereas TG level above 22.6 mmol/l was significantly related to severe AP as well. Due to the low event rate, the effect of HTG on mortality could not be determined.

Plasmapheresis was carried out in 36.4% (20/55) of the HTG-AP cases; 85% of these patients had an initial TG level higher than 22.6 mmol/l, and the average TG level was 70.1±10.0 mmol/l.

III.3. Discussion

According to the previously published literature, HTG is the third most common cause of AP (7.7%). However, it seems more than likely that the incidence of HTG-AP is higher than is usually recorded. Our analysis revealed that TG measurement is performed in just 50% (716/1435) of AP cases within the first three days of admission, and most probably this rate is even lower in centers that provide no data. Furthermore, our data also confirmed additional etiological factors (alcohol and biliary disease) besides HTG in 43.6% of HTG-AP cases, and showed a dose-dependent relation between obesity (body mass index), pre-existing DM, and HTG. Our data suggests that HTG-AP should be suspected in the case of significant alcohol consumption, poorly controlled DM, and obesity. Although our data clearly show that biliary obstruction may be associated with HTG, serum TG was measured in just 44.3% (266/601) of the biliary AP cases. Furthermore, in the case of biliary AP, there is no recommendation for TG measurement. Our data analysis confirmed that HTG is significantly linked to younger age and male gender. This is not surprising, since underlying genetic abnormalities behind HTG contribute to younger manifestation, and alcohol-related HTG affects the male gender and younger ages more. In contrast, biliary etiology is accompanied by a higher rate for the female gender and older population.

Diagnosing AP in the presence of HTG can be challenging due to in vitro interference between plasma TG levels above 5.6 mmol/l (with grossly turbid plasma) and determination of amylase and lipase activities. Our data confirmed a significant reduction of amylase and lipase levels with the elevation of TG.

HTG was shown to be a toxic agent and dose dependently initiates local and systemic pathological processes. In accordance with these data, our analysis confirmed that local complications, organ failure, severity and LOH were significantly increased by HTG. The overall mortality of AP is ~1% based on the literature and 1.5% in our cohort, but we could not perform a further subgroup analysis because of the low event number.

In our cohort, plasmapheresis was carried out in 36.4% of the HTG-AP cases. Although our data clearly suggest that the severity of AP is significantly elevated above the 11.3 mmol/l TG level, the average TG level was 70.1±10.0 mmol/l in patients with plasmapheresis, and

85% of these cases had a TG level over 22.6 mmol/l. We could not state any further conclusions regarding the therapy because of incomplete data and lack of randomization as a result of the cohort feature of the dataset.

Our study has several limitations. Although all data were collected prospectively, all questions were raised retrospectively. Cases were included in the analysis with TG measurement within the first three days of admission, but unfortunately only 50% of the entire cohort met the inclusion criteria. We attempted to minimize these limitations by comparing the epidemiological and major outcome distributions of the data analyzed and the whole cohort. We confirmed that the population under investigation represents a normal AP cohort.

III.4. Conclusion

Our results confirm that HTG dose-dependently increases the complications and severity of AP, and highlight the necessity of better awareness of an accurate determination of causative and influencing risk factors in AP regardless of the etiology. Our data suggest that lipid-lowering therapy may be important clinically at a much lower TG level than we previously thought.

IV. CHILDREN ARE NOT SMALL ADULTS

Since childhood onset pancreatitis is a different entity compared with pancreatitis in adults, there are remarkable differences in incidence, etiology, clinical course and severity between the two age groups. However, trials are limited and based on small cohorts or completely lacking in children. Therefore, most of the pediatric guidelines are adopted from the adult protocols.

IV.1. THE PINEAPPLE STUDY

IV.1.1. Methods

We initiated an international, multicenter observational clinical trial called PINEAPPLE. The study has been established and drafted by the HPSG. The trial consists of a retrospective and a prospective subtrial. PINEAPPLE-R is a retrospective review of electronic computerized records of children (under 18 years old) appearing at emergency units, centered around their clinical symptoms (abdominal pain, nausea, vomiting), serum pancreatic enzyme

measurement (sPEM), and abdominal imaging examinations. PINEAPPLE-P is the prospective part of the study and has a questionnaire-style data collection method. Each patient under 18 years old presenting at ER units with acute abdominal pain is enrolled to the study regardless of the etiology. Acute abdominal pain was defined as pain of less than one month duration. Detailed pediatric patients' data are collected via a questionnaire, sPEM and abdominal US are performed in all cases. Patients and parents must be informed accordingly, and the 'informed consent form' is required to be signed. The definition of APP is based on the fulfillment of '2 out of 3' of the following criteria: (i) abdominal pain compatible with AP; (ii) serum amylase and/or lipase ≥3x upper limit of normal; (iii) characteristic findings of AP by abdominal imaging.

We aim to analyze patient data in different age groups. Association between each collected parameter and AP will be determined. Statistical analysis will be carried out by data mining methods. The applied methods will be determined based on the main characteristics of the collected data, and the most suitable method – or method combination – will be chosen. The following data mining methods are being contemplated: logistic regression, discriminant analysis, random forest analysis, decision tree, and cluster analysis. ROC (receiver operating characteristic) analysis will be performed to evaluate the predictive power of the classification algorithm.

The study has been accepted by the scientific committee of the IAP, and is therefore running under the auspices of HPSG and IAP. The PINEAPPLE trial has been registered at the ISRCTN registry (ISRCTN35618458), a primary clinical trial registry recognized by the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) which accepts all clinical research studies, providing content validation and curation as well as the unique identification number necessary for publication. The study received the relevant ethical approval (No.: ad.52857-2/2014) issued by the National Hungarian Ethical Authority (ETT TUKEB) in 2014. Completion of the 'Letter of intent' form is mandatory for registering the participation of each institution. Study management strictly follows the Ethical Guidelines for Observational Studies.

IV.1.2. Expected results

The PINEAPPLE trial is ongoing and expected to be finished by December 2020. The PINEAPPLE-R study will aid understanding of our current clinical practice of APP in children with abdominal pain in different countries and centers. The PINEAPPLE-P study will provide

the real incidence of APP and help to establish a fast, simple, and authentic scoring system to evaluate the necessity of pancreatic enzyme tests and abdominal US when a child has abdominal pain. As of the preparation of the thesis, 48,170 patient records have been enrolled into PINEAPPLE-R, and 926 patients have been involved in PINEAPPLE-P.

IV.1.3. Discussion

The '2 out of 3' criterion is used to diagnose AP both in adults and children (abdominal pain, sPEM, and abdominal imaging). Therefore, without measuring serum pancreatic enzymes and/or performing transabdominal imaging, AP may remain undiagnosed.

According to previous pediatric studies in AP, abdominal pain is present in 66 to 95% of the children with AP; however, inconsistency and high variability exist between the studies. Most of the trials investigating the characteristics of abdominal pain have either low numbers or missing parameters causing inconsistencies between their data. Based on the review of Bai et al., abdominal pain was most commonly localized to the epigastric region (62–89% of cases). Radiation to the back was seen only in 1.6–5.6% of the cases. Diffuse abdominal pain was found in 12–20% of AP patients, guarding in 29–37%, whereas abdominal distension was reported in 21–46%. Nausea or vomiting was noted in 40–80% of the AP cases. Other symptoms might be fever, ascites, pleural effusion, and jaundice. Symptoms of infants and toddlers are much more unspecific: abdominal pain was found in 43%, epigastric tenderness in 57%, and nausea in 29%. In a study from Pittsburgh, 16% of the infants and toddlers had abdominal distension and 40% had fever.

In summary, a large, international prospective cohort is necessary to understand the complaints and symptoms of AP in children.

IV.2. EARLY ENTERAL NUTRITION IN ACUTE PEDIATRIC PANCREATITIS

IV.2.1. Methods

The preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) was followed. Our structured literature search was based on the participants, intervention, comparison and outcomes (PICO) format [P: patients under the age of twenty-one suffering from AP; I: EEN (per os/nasogastric- or nasojejunal tube feeding started within 24-48 hours); C: NPO therapy (per os/nasogastric- or enteral tube feeding started after 24-48

hours); O: LOH, need for ICU, complications, necessity of antibiotics, surgical/non-surgical interventions, and mortality].

In February 2016, a literature search was performed on the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (https://www.embase.com) databases using the following Medical Subject Headings and search terms: “pediatric” OR “paediatric” AND “pancreatitis”. The search was limited to human studies, full-text publications with abstracts in English with no time period, resulting in 632 articles altogether (PubMed: 131; EMBASE: 501). The articles were checked separately. Meta-analyses, reviews, case reports and articles on CP were excluded and duplicates were removed. Potentially eligible papers were selected, and finally five of them with relevant data on EEN or with NPO therapy in APP in patients under 21 years old were included. Details in the collected articles were checked, and only articles where both EEN and NPO therapy were presented separately were used. Two articles met this criterion which contained three separate data pairs, where EEN was compared to NPO therapy. The following parameters were collected: LOH, need for treatment at ICU, and development of SAP. Only one of the three investigated parameters (LOH) contained a minimum of three items, which were analyzed statistically.

The meta-analytic calculation was made with Comprehensive MetaAnalysis (V3) software using the random effects model (the DerSimonian-Laird method). We calculated a weighted standard difference in means and 95% CI. In the case of one study (Abu-El-Haija et al., 2016), we converted the median and range values to means and standard deviation using the modified Hozo’s formula. For a visual inspection, we used a forest plot.

IV.2.2. Results

It was only possible to perform forest plot analyses on LOH. EEN significantly decreased LOH (SD= 0.806, $p = 0.034$) compared to the standard NPO diet in case of APP.

IV.2.3. Discussion

Several therapeutic recommendations are available in the literature on nutrition in AP. The IAP/APA guideline suggests enteral tube feeding as the first-line therapy in patients with predicted SAP, and oral feeding in the case of predicted mild AP. According to the Japanese guideline, enteral nutrition can decrease the incidence of complications and elevate the survival rate in the early phase of SAP. Moreover, group analysis of 17 parameters including laboratory

parameters (such as CRP and WBC), presence of SIRS and symptoms (such as pain) suggested that EEN also has merits in mild AP.

Since the incidence of APP has risen in the past twenty years, we systematically reviewed the literature to understand whether there is any beneficial effect of EEN versus NPO therapy in children. We faced several difficulties during our review: (i) APP is still underdiagnosed, thus decreasing the possibility of performing clinical trials; (ii) the number of studies on the management of these patients is very low, and there is still only a small number of studies focused on understanding the characteristics of the childhood onset disease ; (iii) studies have not focused on the early management of the patients, therefore the groups were not separated; and finally, (iv) the quality of the methods sections and data presentation in these articles is very low. Consequently, in many cases it was impossible to obtain quality analyzable data from the articles for proper broad-spectrum meta-analysis. By the end of the search, we identified five articles containing relevant data on nutritional management during the early phase of APP. Although three of these studies point out several disadvantages of the NPO diet, none of them could be enrolled in our meta-analysis. Finally, it was possible to collect three sets of analyzable data pairs where both NPO therapy and EEN were present. Abu-El-Haija et al. conducted a prospective study of 33 patients (38 admissions) suffering from mild AP, and retrospectively investigated the relationship of nutrition with abdominal pain and LOH. EEN, even with high fat intake, did not cause elevation in pain in children, suggesting that EEN is a well tolerable nutritional possibility in children. The fact that LOH was shorter in the EEN group versus the NPO group suggests that EEN is a better way of treating APP. The most advanced study was performed by Szabo et al., where several parameters were collected to understand the effect of EEN on the course of APP. A total of 201 patients suffering from mild AP on admission were enrolled retrospectively. They compared EEN versus NPO therapy both with and without aggressive fluid resuscitation. Fluid therapy was administered during the first 24 hours, and the type of nutrition was determined during the first 48 hours. Besides the beneficial effects of EEN on LOH, they also showed that EEN reduced the severity of the disease and the rate of ICU transfer.

Although our aim was to perform a meta-analysis on several parameters to understand the differences between EEN and NPO therapy in childhood onset AP, we were only able to perform the statistical analysis on LOH, which suggested that EEN is not only a safe method of nutrition but also substantially decreases LOH, resulting in a better and less expensive treatment of APP.

IV.3. CONCLUSION

Based on our current knowledge, there are remarkable differences between childhood and adult onset AP. However, the majority of the current pediatric guidelines are adopted from adult data. Therefore, prospective observational and interventional pediatric clinical trials would be necessary to understand the differences between childhood and adult onset AP and to be able to provide appropriate patient care to children suffering from AP. However, most of the pediatric cohorts are limited as a result of the low incidence of AP and small sample size, which is particularly due to missing evidence-based diagnostic guidelines and lower awareness of AP among pediatricians. The HPSG aimed to solve this unmet need and established the PINEAPPLE study to estimate the real incidence of AP in children, and to create an evidence-based diagnostic guideline for APP. Additionally, not only diagnostic, but also therapeutic guidelines for childhood onset AP are based on adult data. EEN was proven to be beneficial for treating AP in adults compared to NPO and TPN therapy. Therefore, we aimed to collect all the relevant data on EEN in APP from the literature to achieve a higher level of evidence in childhood as well. Our meta-analysis suggests that EEN should have priority in treating APP compared to NPO therapy, and confirmed the necessity of further clinical trials in children.

V. SUMMARY

Chapter III: Dose-dependent effect of hypertriglyceridemia on acute pancreatitis

1. Although we confirmed that biliary etiology is less common with HTG-AP, HTG-AP was associated with biliary etiology in 5.4%, but with alcoholic etiology in 38.2%.
2. HTG was significantly and dose-dependently linked to younger age, male gender, obesity and pre-existing DM in AP patients.
3. Amylase and lipase levels have shown a significant and dose-dependent reduction with the elevation of TG in AP.
4. Our analysis has shown that local complications and organ failure were significantly and dose-dependently increased by HTG in AP.
5. TG level above 11.3 mmol/l was associated with a significantly higher rate of moderately severe AP and longer hospital stay, whereas TG level above 22.6 mmol/l was significantly related to SAP as well.

6. Our data suggest that lipid-lowering therapy may be important clinically at a much lower TG level in HTG-AP patients than we previously thought.

Chapter IV: Children are not small adults

The PINEAPPLE study will help to estimate the real incidence of AP in children and create evidence-based diagnostic guidelines for APP.

Our meta-analysis: (i) proves that EEN shortens the LOH in the case of AP not only in adults, but also in children; (ii) suggests that EEN is safe and should have priority in treating APP compared to NPO therapy, and; (iii) confirms the necessity of further interventional clinical trials in children.

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