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Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial

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What Is Known

- AP is an underdiagnosed disease in children.
- No evidence-based guidelines are available to give proper instruction concerning the necessity of pancreatic enzyme measurement during abdominal pain.
- No large worldwide prospective clinical trials exist for understanding the most common clinical characteristics of AP.

What Is New

- A multinational prospective clinical trial is registered and open for all centers.
- This is the first large worldwide study to explore the route from the first sign of abdominal pain to the diagnosis of AP (PINEAPPLE-P).
- This trial will help to diagnose AP in a reliable and cost-efficient way.

Key Words
Pediatric pancreatitis · Acute pancreatitis · Abdominal pain · Pancreatic enzyme · Evidence-based medicine

Abstract
Background: There are unexpectedly large differences between the incidences of acute pancreatitis (AP) as indicated by different hospitals. Retrospective studies suggest that the reason behind this is the large differences that exist between the local managements of abdominal pain at emergency units. Unfortunately, no evidence-based medicine (EBM) guidelines are available to give proper instruction concerning the necessity of serum pancreatic enzyme measurement during abdominal pain. ***Summary:*** Pain in Early Phase of Pediatric Pancreatitis (PINEAPPLE) is an observational, multinational observational clinical trial to explore the route from the first sign of abdominal pain to the diagnosis of pancre-

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atitis (PINEAPPLE trial). The PINEAPPLE-R subtrial is a retrospective review on the records of children (patients under 18) appearing at emergency units – a review of their clinical symptoms, results of imaging examinations and laboratory parameters. The PINEAPPLE-P subtrial is a prospective trial designed to develop a fast and simple EBM guideline that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme test and abdominal ultrasonography (or even computed tomography) when a child has abdominal pain. The trial has been registered at the ISRCTN registry and has received the relevant ethical approval. ***Key Message:*** The PINEAPPLE trial will help to recognize AP in children in a highly efficient manner.

Introduction

Several publications describe an increasing incidence of acute pancreatitis (AP) in both children and adults [1–3]. Importantly, AP became the most common reason of hospitalization in the United States in 2012 with over 270,000 discharges [4]. The reason behind the impressive incidence of AP could be either improved awareness of the disease and/or the elevated number of the new incidence [5–7].

Although two major studies have proved that the incidence of AP is not much less in children than in adults (3.6–13.2 per 100,000), the overall incidence is below 1 per 100,000 or even less worldwide [8, 9]. A retrospective trial in Pittsburgh suggested a close relationship between the number of serum amylase and lipase measurement and the rising incidence of the disease [7]. Their data showed that the increased pancreatic enzyme testing could account for 94% of the change in all AP admission, suggesting that pediatric pancreatitis is an underdiagnosed disease.

There are factors that make the diagnosis of AP challenging when it comes to ordering pancreatic enzymes: (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 [10], (ii) most of the hospitals cannot afford measuring serum amylase/lipase in every children having abdominal pain [10], however (iii) no evidence-based medicine (EBM) guidelines are available to give proper instruction concerning the necessity of pancreatic enzyme measurement during abdominal pain. Therefore, most of the pancreatic enzyme test ordering are based on individual experience of the clinicians. It is almost needless to say that international clinical observational trials are crucially needed to understand the most common clinical characteristics of AP.

The Hungarian Pancreatic Study Group (HPSG) was established in 2011 in order to improve patients' life suffering in pancreatic diseases. To achieve our aims, we (i) developed an electronic data registry and biobank for patients (www.pancreas.hu), (ii) published the currently available EBM guidelines [11–15], (iii) established specific study sessions including a pediatric session, and (iv) organized multicentre clinical trials [16, 17].

Here we propose a multicenter, clinical trial called PINEAPPLE (Pain in Early Phase of Pediatric Pancreatitis), which is open to all institutions to join in. The trial protocol aims at exploring the route from the first sign of abdominal pain to the diagnosis of pancreatitis in a retrospective (PINEAPPLE-R) and prospective (PINEAPPLE-P) way.

Methods

Preliminary Settings

The study has been initiated and drafted by the HPSG. The protocols have been introduced in our latest international meeting held in Szeged in November 2014 (http://pancreas.hu/sites/info/files/conferences/ALPD2014-Program.pdf), which was attended by some of the well-established pediatric pancreatologists. Around 100 clinicians – 60 Hungarians and 40 international (from 9 different countries) investigators attended. The trial has been discussed and the suggested modifications have been included. The study has been discussed and accepted by the scientific committee of the International Association of Pancreatology (IAP), and therefore, it is running under the auspices of HPSG and IAP.

Ethical Issues

The studies have received the relevant ethical approval (No.: ad.52857-2/2014) issued by the National Hungarian Ethical Authority (ETT TUKEB). Study management will strictly follow the Ethical Guidelines for Observational Studies.

Trial Registration

The PINEAPPLE trial has been registered at the ISRCTN registry (ISRCTN35618458), which is a primary clinical trial registry recognized by WHO and ICMJE, which accepts all clinical research studies, providing content validation and curation and the unique identification number necessary for publication.

Centers throughout the world are welcome to participate in the PINEAPPLE trial. 'Online Call for Centers' will be available at http://www.pancreas.hu/en/studies/pineapple. Completion of the 'LETTER OF INTENT' form will be mandatory for registering participation of each institution. HPSG will acknowledge receipt of the 'LETTER OF INTENT' form and will contact centers providing them with additional study information.

Patients and Centers Involved in the Trial

The PINEAPPLE trial is divided into 2 subtrials.

The aim of PINEAPPLE-R is a retrospective review on records of children (patients under 18) appearing at emergency units in one or two months depending on the size of the center; the review is centered around their clinical symptoms, results of imaging examinations and laboratory parameters.

The aim of PINEAPPLE-P is to provide a fast, simple and authentic system that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme test and abdominal ultrasonography (or even computed tomography) when a child has abdominal pain.

For the PINEAPPLE-R subtrial, we aim to collect around 1,000–2,000 cases (appearing in the ER unit with any kind of reasons/symptoms) from each center. Preliminary data suggested that around 5–10% of children admitted to the ER unit have abdominal pain. Therefore, per center, we expect around 100–200 cases with abdominal pain. Altogether, we wish to collect around 20,000 cases with abdominal pain within 3 years.

The PINEAPPLE-P is for patients under 18 years old appearing at ER unit with a leading symptom of abdominal pain. Our aim was to collect around 100 cases from each center. Altogether we wish to collect around 20,000 cases with abdominal pain within 3 years (http://www.pancreas.hu/en/studies/pineapple).

Protocol for Retrospective Data Collection for PINEAPPLE-R

This is a pure retrospective review of electronic computerized records of the relevant centers. Diagnosis and data concerning basic clinical symptoms (abdominal pain [yes/no], vomiting [yes/no], nausea [yes/no]) are required for all patients appearing on the ER unit. A diagnosis of abdominal pain is decided based on the doctor's opinion/record. If the patient has abdominal pain, information about the imaging examination of the pancreas (yes/no, if yes: positive/negative for pancreatitis) and laboratory parameters pancreatic enzyme measurements (either amylase or lipase, yes/no, if yes whether it is increased with 3×) are obligatory. Where data are available, information concerning the experience of the doctor in charge needs to be given (experienced doctor: at least 10 years experience with board certification, beginner: others). The information is collected into a uniform harmonized excel sheet that can be downloaded from the study website (http://pancreas.hu/en/studies/pineapple).

Inclusion Criteria for PINEAPPLE-R

- Under 18 years old
- Accurate electronic data mentioned in the protocol

Exclusion Criteria for PINEAPPLE-R

- Above 18 years old
- Inaccurate electronic data mentioned in the protocol

Protocol for Prospective Data Collection for PINEAPPLE-P

The PINEAPPLE-P subtrial has a questionnaire style data-collection method. The form is available on the web system http://www.pancreas.hu/en/studies/pineapple (table 1). The patients and parents have to be informed accordingly. The 'informed consent form' needs to be signed and the 'Questionnaire' needs to be filled out. Four quality control points are established. First, the local clinical research assistant must upload the data electronically and confirm that the data are the same as those in the hard copy. Second, the local institutional principal investigator (who has to have a medical doctoral degree) must recheck the uploaded data and confirm their validity and accuracy. Third, the central data administrator, who is based at the headquarters of HPSG, must control the accuracy and finally, the trial leader must go through the details. Patients with inadequate or insufficient data will be excluded.

Inclusion Criteria for PINEAPPLE-P

- Under 18 years old
- The leading symptom is acute abdominal pain

Exclusion Criteria for PINEAPPLE-P

- Above 18 years old
- No or chronic abdominal pain

Statistical Analyses

Patients data will be analyzed in 4 different age categories (0–6, 6–10, 10–16, 16–18 years). Association between each collected parameters (medical history, symptoms, etc.) 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, cluster analysis. ROC analysis and/or confusion matrix will be performed to evaluate the predictive power of the classification algorithm.

Expected Results

PINEAPPLE-R study will help to understand our current clinical practice on patients with abdominal pain in different countries and centers. The PINEAPPLE-P study will help to establish an EBM guideline, which will help to provide a fast, simple and authentic system to evaluate (in a reliable and cost-efficient way) the necessity of the pancreatic enzyme test and abdominal ultrasonography when a child has abdominal pain.

Authorship Policy

In order to give appropriate credit to each investigator/center, we will use standardized authorship policy. Concerning the PINEAPPLE-R subtrial: under 1,500 patients will generate 1, whereas above 1,500 patients will generate maximum of 2 co-authors from the center PINEAPPLE-P: every 100 patients will generate 1 co-author. All other investigators/contributors who do not meet the criteria for authorship will be listed in an 'Acknowledgements' section. For example, those who provide purely technical help or a department chair who provided only general support will appear in this section.

Discussion

The 2 out of 3 criteria rule is used to dianose AP both in adults and children [9, 11, 13]. Two of the following parameters are required: (1) abdominal pain, (2) serum amylase and/or lipase values ≥3 times upper limits of

Table 1. Summary of clinical data required for PINEAPPLE-P

1. Patient personal details	
Gender	Male/female
Ethnicity/race	White/Black/Asian-Indian/not known
2. Details from the medical history	
(a) Family medical history	
Pancreas disorders in family history: AP/CP/AIP/PC	Yes/no, if yes: relationship to patient
(b) Medical history of the child	
Known diseases	Yes/no, if yes: description of the disease
Abdominal surgery	Yes/no, if yes: description of the disease
New medications taken in the last 2 weeks	Yes/no, if yes: description of them
New symptoms in the last 2 weeks	Yes/no, if yes: description of them
New diet, change in diet in the last 2 weeks	Yes/no, if yes: description of it
Any event strongly affecting the child emotionally in the last 2 weeks	Yes/no, if yes: description of it
Any event strongly affecting the child emotionally in the last 2 weeks	Yes/no, if yes: description of it
Change in the environment of the child in the last 2 weeks	Yes/no, if yes: description of it
Was there any examination concerning abdominal pain?	Yes/no, if yes: description of it
Length of breast milk feeding	Number of months
3. Complaints, symptoms	
(a) Abdominal pain	
How many hours have passed since the pain started?	Number of hours
How long did it last?	Number of hours
Intensity on a 1–10 scale	Number
Intensity	Decreasing/intensifying/stagnating
Forced posture	Yes/no
Nature	Dull/sharp/cramping
Location	Diffuse/localized
(b) In case of abdominal pain longer than 48 h	
Was the everyday activity influenced?	Yes/no
Did the child wake up at night because of the pain?	Yes/no
Which part of the day the pain appeared mostly?	After waking up/in the morning/in the Afternoon/in the evening/at night
Was it connected to eating?	Yes/no
Subfebrility, fever	Before eating/while eating/after eating
(c) Other complains	
Nausea	Yes/no
Vomiting	Yes/no, if yes: how many times?, and content of cast
Subfebrility, fever	Yes/no, if yes: since when? Temperature
Appetite	Good/retained/bad
Weight loss	Yes/no, if yes: how much? (kg), how long did it take? (weeks)
Jaundice	Yes/no, if yes: since when?
Stool	Normal/diarrhea/constipation/fatty/putrid/undigested food/bloody/mucus
4. Admission details, status	
Blood pressure, mm Hg, heart rate, /min	Number
Body weight, kg, body height, m	Number
Respiratory rate, /min	Number
Body temperature, °C	Number
Abdominal tenderness	Yes/no, location of abdominal tenderness
Abdominal guarding	Yes/no
Jaundice	Yes/no
Bowel sounds	No/hypoactive/normal/hyperactive
5. Laboratory parameters	
Amylase and/or lipase, U/l	

Table 1. (continued)

6. Imaging examinations at admission	
Pancreas deviation suggesting AP	Yes/no
Pancreas deviation suggesting CP	Yes/no
7. Diagnosis	
8. Diagnosis – main group	Unknown, autoimmun, cardiology, dermatology, endocrinology, gastroenterology, etc.
9. What happened with the patient?	Admission to an inpatient department/went home/other

normal, (3) characteristic imaging finding for AP. Therefore, without measuring serum pancreatic enzymes and/or performing either transabdominal ultrasonograpy or CT, AP cannot be diagnosed. According to previous pediatric studies in AP, abdominal pain is present in 66 to 95% of the children with AP [18–24]; 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. Abdominal pain was most commonly localized to the epigastric region (62–89% of cases) [18, 25, 26] and was rarely associated with back pain (<10%) [20, 24]. Radiation to the back was only in 1.6–5.6% [22, 23, 26] of the cases. Diffuse abdominal pain was reported in 12–20% of patients [18, 22, 23], guarding at 29–37% [18, 20], whereas nausea or vomiting was found in 40–80% of patients [21–29]. A clinical study from Mexico described ileus at just under 50% of the children [27]. Abdominal distension was reported in 21–46% of the patients [18–22]. Other symptoms might be fever, ascites, pleural effusion and jaundice. Palpable abdominal mass was reported in a quarter of the patients in a study from Taiwan [26]. Symptoms of infants and toddlers are much more unspecific: fever with abdominal pain is found in 43%, epigastric tenderness in 57%, nausea in 29% [25]. In a study from Pittsburgh, 16% of the infants and toddlers had abdominal distension and 40% had fever [30]. Therefore, it is almost needless to say that a large international prospective cohort is necessary to understand the complaints and symptoms of AP in children.

In summary, here we propose an international observational clinical trial (PINEAPPLE) to collect a critical mass of clinical data from children with abdominal pain in order to develop EBM guidelines concerning the necessity for obtaining serum pancreatic enzyme testing and pancreatic imaging in pediatric patients who present to the emergency room with abdominal pain.

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Disclosure Statement

All authors disclose any sponsorship or funding arrangements relating to their research and disclose any possible conflicts of interest.

Authors' Contributions

P.H. initiated, whereas F.Z. and P.H. drafted the study. All of the authors were involved in designing and conducting discussions on the study.

References

1 Satoh K, Shimosegawa T, Masamune A, Hirota M, Kikuta K, Kihara Y, Kuriyama S, Tsuji I, Satoh A, Hamada S; Research Committee of Intractable Diseases of the Pancreas: Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas 2011;40:503–507.

2 Yadav D, Lowenfels AB: Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 2006;33:323–330.

3 Joergensen M, Brusgaard K, Crüger DG, Gerdes AM, de Muckadell OB: Incidence, prevalence, etiology, and prognosis of first-time chronic pancreatitis in young patients: a nationwide cohort study. Dig Dis Sci 2010;55:2988–2998.

4 Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ: Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179–1187.

5 Bai HX, Lowe ME, Husain SZ: What have we learned about acute pancreatitis in children? J Pediatr Gastroenterol Nutr 2011;52:262–270.

6 Park A, Latif SU, Shah AU, Tian J, Werlin S, Hsiao A, Pashankar D, Bhandari V, Nagar A, Husain SZ: Changing referral trends of acute pancreatitis in children: a 12-year single-center analysis. J Pediatr Gastroenterol Nutr 2009;49:316–322.

7 Morinville VD, Barmada MM, Lowe ME: Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? Pancreas 2010;39:5–8.

8 Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crameri J, Oliver MR: Changing incidence of acute pancreatitis: 10-year experience at the royal children's hospital, Melbourne. J Gastroenterol Hepatol 2007;22:1313–1316.

9 Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, Freedman SD, Himes R, Lowe ME, Pohl J, Werlin S, Wilschanski M, Uc A; INSPPIRE Group: Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr 2012;55:261–265.

10 Dhroove G, Chogle A, Saps M: A million-dollar work-up for abdominal pain: is it worth it? J Pediatr Gastroenterol Nutr 2010;51:579–583.

11 Hritz I, Czakó L, Dubravcsik Z, Farkas G, Kelemen D, Lásztity N, Morvay Z, Oláh A, Pap Á, Párniczky A, Sahin-Tóth M, Szentkereszti Z, Szmola R, Szücs Á, Takács T, Tiszlavicz L, Hegyi P; Magyar Hasnyálmirigy Munkacsoport, Hungarian Pancreatic Study Group: [Acute pancreatitis. Evidence-based practice guidelines, prepared by the Hungarian Pancreatic Study Group]. Orv Hetil 2015;156:244–261.

12 Takács T, Czakó L, Dubravcsik Z, Farkas G, Hegyi P, Hritz I, Kelemen D, Lásztity N, Morvay Z, Oláh A, Pap Á, Párniczky A, Patai Á, Sahin-Tóth M, Szentkereszti Z, Szmola R, Tiszlavicz L, Szücs Á; Magyar Hasnyálmirigy Munkacsoport: [Chronic pancreatitis. Evidence based management guidelines of the Hungarian Pancreatic Study Group]. Orv Hetil 2015;156:262–288.

13 Párniczky A, Czakó L, Dubravcsik Z, Farkas G, Hegyi P, Hritz I, Kelemen D, Morvay Z, Oláh A, Pap Á, Sahin-Tóth M, Szabó F, Szentkereszti Z, Szmola R, Takács T, Tiszlavicz L, Veres G, Szücs Á, Lásztity N; Magyar Hasnyálmirigy Munkacsoport Hungarian Pancreatic Study Group: [Pediatric pancreatitis. Evidence based management guidelines of the Hungarian Pancreatic Study Group]. Orv Hetil 2015;156:308–325.

14 Dubravcsik Z, Farkas G, Hegyi P, Hritz I, Kelemen D, Lásztity N, Morvay Z, Oláh A, Pap Á, Párniczky A, Sahin-Tóth M, Szentkereszti Z, Szmola R, Takács T, Tiszlavicz L, Szücs Á, Czakó L; Magyar Hasnyálmirigy Munkacsoport Hungarian Pancreatic Study Group: [Autoimmune pancreatitis. Evidence based management guidelines of the Hungarian Pancreatic Study Group]. Orv Hetil 2015;156:292–307.

15 Szmola R, Farkas G, Hegyi P, Czakó L, Dubravcsik Z, Hritz I, Kelemen D, Lásztity N, Morvay Z, Oláh A, Párniczky A, Rubovszky G, Sahin-Tóth M, Szentkereszti Z, Szücs Á, Takács T, Tiszlavicz L, Pap Á; Magyar Hasnyálmirigy Munkacsoport Hungarian Pancreatic Study Group: [Pancreatic cancer. Evidence based management guidelines of the Hungarian Pancreatic Study Group]. Orv Hetil 2015;156:326–339.

16 Hritz I, Hegyi P: Early achievable severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. J Gastrointestin Liver Dis 2015;24:177–182.

17 Dubravcsik Z, Madácsy L, Gyökeres T, Vincze Á, Szepes Z, Hegyi P, Hritz I, Szepes A; Hungarian Pancreatic Study Group: Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology 2015;15:115–123.

18 Berney T, Belli D, Bugmann P, Beghetti M, Morel P, LeCoultre C: Influence of severe underlying pathology and hypovolemic shock on the development of acute pancreatitis in children. J Pediatr Surg 1996;31:1256–1261.

19 Yeung CY, Lee HC, Huang FY, Ho MY, Kao HA, Liang DC, Hsu CH, Hung HY, Chang PY, Sheu JC: Pancreatitis in children – experience with 43 cases. Eur J Pediatr 1996;155:458–463.

20 Haddock G, Coupar G, Youngson GG, MacKinlay GA, Raine PA: Acute pancreatitis in children: a 15-year review. J Pediatr Surg 1994;29:719–722.

21 Weizman Z, Durie PR: Acute pancreatitis in childhood. J Pediatr 1988;113(1 pt 1):24–29.

22 Ziegler DW, Long JA, Philippart AI, Klein MD: Pancreatitis in childhood. Experience with 49 patients. Ann Surg 1988;207:257–261.

23 Jordan SC, Ament ME: Pancreatitis in children and adolescents. J Pediatr 1977;91:211–216.

24 Werlin SL, Kugathasan S, Frautschy BC: Pancreatitis in children. J Pediatr Gastroenterol Nutr 2003;37:591–595.

25 Park AJ, Latif SU, Ahmad MU, Bultron G, Orabi AI, Bhandari V, Husain SZ: A comparison of presentation and management trends in acute pancreatitis between infants/toddlers and older children. J Pediatr Gastroenterol Nutr 2010;51:167–170.

26 Tiao MM, Chuang JH, Ko SF, Kuo HW, Liang CD, Chen CL: Pancreatitis in children: clinical analysis of 61 cases in southern Taiwan. Chang Gung Med J 2002;25:162–168.

27 Sánchez-Ramírez CA, Larrosa-Haro A, Flores-Martínez S, Sánchez-Corona J, Villa-Gómez A, Macías-Rosales R: Acute and recurrent pancreatitis in children: etiological factors. Acta Paediatr 2007;96:534–537.

28 Chen CF, Kong MS, Lai MW, Wang CJ: Acute pancreatitis in children: 10-year experience in a medical center. Acta Paediatr Taiwan 2006;47:192–196.

29 Goh SK, Chui CH, Jacobsen AS: Childhood acute pancreatitis in a children's hospital. Singapore Med J 2003;44:453–456.

30 Kandula L, Lowe ME: Etiology and outcome of acute pancreatitis in infants and toddlers. J Pediatr 2008;152:106–110.