Pancreatic Diseases
Michael J. Lentze
ESPGHAN goes Africa Course
March 2015

Bonn

Tbilisi/Georgia
Bonn - Germany
Georgia
4 year old Girl: Isabell

- 2nd child of healthy parents, pregnancy and delivery normal. BW 3250 g BH 53 cm. Healthy up to the 3rd year of life
- October 2003 first episode of an acute pancreatitis with abdominal pain and vomiting. Lipase > 16.000. Fast improvement with decrease of lipase
- 3 weeks later first relapse (Lipase > 14.000)
Investigations

- Sono Abdomen normal: no bile stones
- Collagenosis: ANA, DNS-AB negative
- Vasculitis: p-ANCA, c-ANCA normal
- CF: sweat test neg. Genetics normal
- Trypsinogen Gene: normal
- SPINK1 Gene: normal
- Alpha-1-Antitrypsin: normal
- No Infections: EBV, and others
3rd Relaps Sept. 2004

- 4 year old girl in good general health
  height 102 (25-50P). Weight 16.7 kg (50-75P)
- Clinical examination unremarkable
- Lipase 833, Amylase 128, remaining lab data normal
- What next?
Fetal Development of Pancreas

1. Bud Formation
2. Beginning Rotation of Common Duct and of Ventral Pancreas
3. Rotation Completed but Fusion Has Not Yet Taken Place
4. Fusion of Ventral and Dorsal Pancreas and Union of Ducts
Pancreas divisum
Pancreas

B = body
H = head
N = neck
T = tail
Un = uncinate

Figure 16.13

The glandular portions of the pancreas are grossly exaggerated.
Digestion in the upper GI-Tract

Liver and gallbladder
- Bile secretion and ejection from gallbladder

Food in stomach
- Increased acid production and motility
- Gastrin release

Gastrin release

Chyme in duodenum
- Secretin and CCK release

Pancreas
- GIP release
- Enzymes and buffers secreted
- Endocrine pancreas
- Exocrine pancreas

Materials enter jejunum

Nutrients absorbed

Gastrointestinal system

Stimulation
- Red

Inhibition
- Blue

Nutrient utilization by all tissues
Structure of exocrine Pancreas

Functions of Pancreas Stellate Cells

Cellular Pathomechanisms of Pancreatitis

Bai HX et al. JPGN 52: 262-70, 2011
Activation of Pro-Enzymes

ENZYME ACTIVATION

Trypsinogen
Chymotrypsinogen
Proelastase
Procarboxypeptidase B
Procarboxypeptidase A
Enterokinase
Trypsin
Chymotrypsin
Elastase
Carboxypeptidase B
Carboxypeptidase A
Necrosis-Fibrosis Sequence

Episodes of acute pancreatitis

Degree of pancreatic damage

Time

Role of digestive Enzymes

**normal pancreas**

- trypsinogen
- SPINK1
- trypsin
- enzyme cascade
- autodigestion

**chronic pancreatitis**

- trypsinogen
- SPINK1
- trypsin
- enzyme cascade
- autodigestion → pancreatitis

Definitions of Pancreatitis

- **Acute pancreatitis**
  - Abdominal pain
  - Serum lipase 3x normal
  - Imaging findings compatible with

- **Acute recurrent pancreatitis**
  - Complete resolution of symptoms
  - Complete normalisation of lipase of at least 1 month between episodes

- **Chronic pancreatitis: one of the three**
  - Abdominal pain with pancreatic origin
  - Exocrine pancreatic insufficiency and imaging compatible with
  - Endocrine pancreatic insufficiency an imaging compatible with

Or

  surgical or pancreatic biopsy with the histopathology of chronic pancreatitis

Sensitivity and Specificity of Pancreatic Function Tests in chronic Pancreatitis

<table>
<thead>
<tr>
<th>Test</th>
<th>Mild exocrine insufficiency</th>
<th>Moderate exocrine insufficiency</th>
<th>Severe exocrine insufficiency</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-elastase-1 (stool elastase)</td>
<td>54%</td>
<td>75%</td>
<td>95%</td>
<td>1a/b</td>
</tr>
<tr>
<td>Qualitative stool fat determination</td>
<td>0%</td>
<td>0%</td>
<td>78%</td>
<td>*3</td>
</tr>
<tr>
<td>Chymotrypsin activity in stool</td>
<td>&lt;50%</td>
<td>ca. 60%</td>
<td>80–90%</td>
<td>1a/b</td>
</tr>
<tr>
<td>$^{13}$C breath tests (mixed triglycerides)</td>
<td>62–100%</td>
<td>90–100%</td>
<td>80–90%</td>
<td>1b/2b</td>
</tr>
</tbody>
</table>

Sensitivity and Specificity of Imaging Studies for the Diagnosis of chronic Pancreatitis

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>n/a</td>
<td>n/a</td>
<td>2b</td>
</tr>
<tr>
<td>ERCP</td>
<td>70–80%</td>
<td>80–100%</td>
<td>2a</td>
</tr>
<tr>
<td>MRCP</td>
<td>88%</td>
<td>98%</td>
<td>2b</td>
</tr>
<tr>
<td>US</td>
<td>60–81%</td>
<td>70–97%</td>
<td>2a</td>
</tr>
<tr>
<td>EUS</td>
<td>80–100%</td>
<td>80–100%</td>
<td>2a</td>
</tr>
</tbody>
</table>

Pancreatitis in children

Causes

- Hemolytic uremic syndrome 21%
- Trauma 20%
- Pancreas divisum 11%
- Infections 11%
- Medication 10%
- Cystic Fibrosis 10%
- Hereditary Pancreatitis 5%
- Metabolic causes 5%
- Gallstones 3%
Pancreatitis in Children

Gallstones

- Hemolysis (sickle-cell anemia)
- Hypercholesterolemia
- Idiopathic
- Antibiotics (rocefin)
- Rapid weight loss
Choledochus Cyst
Pancreatitis in children

**Infections**

- Measles, Mumps, Rubella
- Rotavirus
- EBV, CMV, HIV
- Hepatitis A and B
- Toxoplasmosis, candida (immune compromised children)
- Ascariasis
Pancreatitis in children

**Drugs**
- Paracetamol
- L-Asparaginase
- Azathioprine
- Furosemide
- Corticosteroids
- Valproate
- 5-Aminosalicylic acid
- Sulfasalazine
- Glucantime (Leishmaniosis)
- Stavudine (HIV)
- Linezulid (Drug resistant TB)
Pancreatitis in children

**Hereditary Pancreatitis**

- Positive family history

- Genetic defect in trypsinogen activation (serine-protease inhibitor KAZAL type I (SPINK-1))
  - Early activation
  - Incomplete inactivation

- Onset before the second year in life

- Calcification of the pancreas
Influence of environmental and genetic Factors for chronic Pancreatitis

ACP alcohol. chronic Pancreatitis (CP)
TCP Tropical CP
ICP Idiopathic Pankreatitis
HP Hereditary Pancreatitis

# Chronic Pancreatitis

Frequency of *PRSS1* and *SPINK1* Mutations in pediatric Patients (n=140)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>yes (n=40)</th>
<th>no (n=100)</th>
<th>total (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PRSS1 (R122H,N29I)</em></td>
<td>7 (17.5%)</td>
<td>0</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>(A16V)</td>
<td>1 (2.5%)</td>
<td>6 (6%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td><em>SPINK1 (N34S</em>)*</td>
<td>3 (7.5%)</td>
<td>23 (9) (23%)</td>
<td>26 (18.6%)</td>
</tr>
<tr>
<td>(other)</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
<td>4 (2.9%)</td>
</tr>
</tbody>
</table>

No Mutation 27 (67.5%) 69 (69%) 96 (68.5%)

**CFTR - Mutation Frequency in CP (n=140) and CF**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>CP in %</th>
<th>CF in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>24 (9/37)</td>
<td>71</td>
</tr>
<tr>
<td>R117H</td>
<td>11 (4/37)</td>
<td>0.2</td>
</tr>
<tr>
<td>Other</td>
<td>65 (24/37)</td>
<td>(15)</td>
</tr>
</tbody>
</table>

*5T Allel: 18/562 (3.20%) - Controls: 26/668 (3.89%)*

Pancreatitis in children

Cystic Fibrosis

- Exocrine pancreatic dysfunction, pancreas insufficient, steatorrhoea
- No pancreatitis in exocrine pancreas insufficiency
- Combination severe and light mutation
  Compound heterozygotes
- Pancreatitis more often in heterozygotes?
- Onset variable: 2-20 year
Original Sweat Test
Original Instruments by Gibson & Cooke

Gibson & Cooke Pediatrics 24:545-49, 1959
Sweat-Test with Pilocarpine-Iontophoresis-Stimulation
Collection of Sweat in Glas Capillaries and Measurement of Chloride

Values over 70 mmol Cl\textsuperscript{-} /L are pathological
Diagnosis of Exocrine Pancreatic Insufficiency: Fecal Elastase 1

Sensitivity and Specificity of Fecal Elastase 1 in EPI

<table>
<thead>
<tr>
<th>Exocrine pancreatic insufficiency</th>
<th>Elastase cut off</th>
<th>Chymotrypsin cut off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;100 µg/g (%)</td>
<td>&lt;200 µg/g (%)</td>
</tr>
<tr>
<td>I</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>II</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>III</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>total</td>
<td>86</td>
<td>93</td>
</tr>
</tbody>
</table>

| Sensitivity                      |                  |                      |
|                                 | 98               | 93                   | 89                  |

| Specificity                      |                  |                      |
|                                 |                  |                      |

I=mild; II=moderate; III=severe; total=total exocrine pancreatic insufficiency as estimated by the secretin-caerulein test.

Advantages of fecal Elastase 1 Determinations for EPI

- FE1 is pancreas specific
- FE1 is stable during intestinal transit
- Correlates well with direct studies
- Intraindividual variation is low
- Monoclonal Ab do not interfere with elastase from animal origin (pancreatic enzymes)
- High stability of FE1 → convenient mailing

Pancreatitis in children

**Metabolic causes**

- Lipoprotein lipase deficiency
- Apoprotein C-2 activator-deficiency
- Hypertriglyceridemia
- Hypercholesterolemia
- Urea cycle defects
- Citrullinemia
- Methylmalonacidemia
- Maple syrup urine disease
- Homocystinuria
- Glycogen storage disease
Diagnostics of Pancreatitis

- Clinical signs:
  - abdominal pain (87%),
  - vomiting (64%),
  - abdominal tenderness (77%),
  - abdominal distension (18%)
- Lipase in serum: 3x over normal range
- Amylase: not specific!
- Sonography
- ERCP
- MRCP
Diseases with Lipase Elevation

- Acute pancreatitis
- Relapse of chronic pancreatitis
- Cystic fibrosis
- After ERCP (!)
- Renal insufficiency
- Acute abdomen (ileus, perforated ulcer, cholecystitis)
- Viral hepatitis
- Diabetic ketoacidosis
- Mumps
- Sarcoidosis
11 Year old Boy

- Rapid abdominal pain of 8 h duration
- Nausea and vomiting
- Abdominal tenderness
- Lipase 898 IU
- ALT 38, AST 34, Bili 1.2 mg/dl, Hb 12.4, AP 166, Sed. rate 40 mm
Sonography 2

Endoscopy: Ascaris in Duodenum and pancreatic Duct

ERCP in Acute Pancreatitis

Choledochal Cyst  Pancreas divisum  PSC

Enestvedt BK et al JPN 2013 epub DOI 10.1097MPG.0b013e.31829e0bb6
Congenital defects

Pancreas Annulare

Vomiting, Abdominal pain, Ulcer, Blood vomiting

Normal Pancreatic tissue

Ultrasound, ERCP

Surgery (duodenotomy)
Congenital Defects

Ectopic Pancreas

Usually asymptomatic
Normal pancreatic tissue
Pain, dyspepsia, bleeding
Histology, ultrasound
Surgery (extirpation)
Congenital defects

Pancreatic Hypoplasia with neonatal Diabetes mellitus:

– Failure to thrive, fat malabsorption, hyperglycemia
– MRI, CT scan
– Supplementation pancreatic enzymes, insuline
Genetic Diseases of the Pancreas (very rare)

Shwachmann-Diamond Syndrome:
- Exocrine pancreatic Insufficiency, Bone-Disease, Neutropenia
Genetic Diseases of the Pancreas (very rare)

• Johanson-Blizzard-Syndrome:
  – Exocrine Pancreatic Insufficiency, anal Agenesis, Agenesis of Nose Cartilage
Treatment of acute Pancreatitis

• Adequate parenteral fluid replacement
• Pain management: i.v. paracetamol
• Early enteral nutrition: 1-2 days after beginning of symptoms by slow continuous nasogastric or duodenal tube feeding
• Parenteral nutrition not recommended
• PPI i.v. (?)
• In case of signs for necrotizing pancreatitis: antibiotics (ciprofloxacin, metronidazol)
• Pseudocysts: drainage by surgical intervention
# Early EN vs late EN or TPN on Infectious Complications

Bai HX et al. PLoS ONE 8: e64926, 2013

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Total</th>
<th>Late EN or TPN Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eckerwall G E 2006</td>
<td>3</td>
<td>23</td>
<td>0</td>
<td>25</td>
<td>3.3%</td>
<td>8.71 [0.43, 176.37]</td>
</tr>
<tr>
<td>Gupta R 2003</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>4.2%</td>
<td>0.50 [0.04, 6.86]</td>
</tr>
<tr>
<td>Kalfarentzos F 1997</td>
<td>5</td>
<td>18</td>
<td>10</td>
<td>20</td>
<td>10.6%</td>
<td>0.38 [0.10, 1.49]</td>
</tr>
<tr>
<td>McClave S A 1997</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>16</td>
<td>5.9%</td>
<td>1.00 [0.12, 8.13]</td>
</tr>
<tr>
<td>Olah A 1996</td>
<td>2</td>
<td>18</td>
<td>4</td>
<td>20</td>
<td>7.2%</td>
<td>0.50 [0.08, 3.13]</td>
</tr>
<tr>
<td>Olah A 2002</td>
<td>5</td>
<td>41</td>
<td>13</td>
<td>48</td>
<td>12.8%</td>
<td>0.37 [0.12, 1.18]</td>
</tr>
<tr>
<td>Petrov M S 2006</td>
<td>11</td>
<td>35</td>
<td>27</td>
<td>34</td>
<td>13.2%</td>
<td>0.12 [0.04, 0.36]</td>
</tr>
<tr>
<td>Qin H L 2008</td>
<td>8</td>
<td>36</td>
<td>21</td>
<td>38</td>
<td>14.1%</td>
<td>0.23 [0.08, 0.64]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>195</td>
<td>210</td>
<td>71.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>37</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.23; \chi^2 = 9.88, df = 7 (P = 0.20); I^2 = 29\%

Test for overall effect: \( Z = 3.26 (P = 0.001) \)

<table>
<thead>
<tr>
<th>Retrospective</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker O J 2009</td>
<td>49</td>
<td>184</td>
<td>38</td>
<td>112</td>
<td>20.5%</td>
<td>0.71 [0.42, 1.18]</td>
</tr>
<tr>
<td>Vieira J P 2010</td>
<td>3</td>
<td>15</td>
<td>11</td>
<td>16</td>
<td>8.3%</td>
<td>0.11 [0.02, 0.59]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>199</td>
<td>128</td>
<td>28.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 1.29; \chi^2 = 4.32, df = 1 (P = 0.04); I^2 = 77\%

Test for overall effect: \( Z = 1.21 (P = 0.23) \)

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>394</td>
<td>338</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>128</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.37; \chi^2 = 17.44, df = 9 (P = 0.04); I^2 = 48\%

Test for overall effect: \( Z = 3.25 (P = 0.001) \)

Test for subgroup differences: \( \chi^2 = 0.00, df = 1 (P = 0.98), I^2 = 0\% \)
Early EN vs late EN or TPN on Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN</th>
<th>Late EN or TPN</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>RCT</td>
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<td></td>
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<tr>
<td>Eckerwall G E 2006</td>
<td>1</td>
<td>23</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Kalfarentzos F 1997</td>
<td>1</td>
<td>18</td>
<td>2</td>
<td>20</td>
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<td>20</td>
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<tr>
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<td>48</td>
</tr>
<tr>
<td>Petrov M S 2006</td>
<td>2</td>
<td>35</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>135</strong></td>
<td><strong>147</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2 = 4.37$, df = 4 (P = 0.35); $I^2 = 9%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.39$ (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Retrospective     |          |                |            |            |                      |                      |
| Vieira J P 2010   | 0        | 16             | 3          | 15         | 15.5%                 | 0.11 [0.01, 2.29]    |
| **Subtotal (95% CI)** | **16** | **15**        |            |            | **15.5%**             | **0.11 [0.01, 2.29]** |
| Total events      | 0        | 3              |            |            |                      |                      |
| Heterogeneity: Not applicable | 0        | 3              |            |            |                       |                      |
| Test for overall effect: $Z = 1.43$ (P = 0.15) | 0        | 3              |            |            |                       |                      |

**Total (95% CI)**  
| 151                | 162      | 100.0%         | 0.31 [0.14, 0.71] |
| 7                  | 23       |                |                      |

Heterogeneity: $\chi^2 = 4.94$, df = 5 (P = 0.42); $I^2 = 0\%$  
Test for overall effect: $Z = 2.77$ (P = 0.006)  
Test for subgroup differences: $\chi^2 = 0.53$, df = 1 (P = 0.47), $I^2 = 0\%$

Bai HX et al. PLoS ONE 8: e64926, 2013
EN vs. PN on Length of Hospital Stay


<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early EN N Mean (SD)</th>
<th>N</th>
<th>PN Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abou-Assi</td>
<td>26 14.20 (1.90)</td>
<td>27</td>
<td>18.40 (1.90)</td>
<td>—</td>
<td>43.32</td>
<td>-4.20 [-5.22, -3.18]</td>
<td>2002</td>
</tr>
<tr>
<td>Lotule</td>
<td>10 26.20 (17.40)</td>
<td>19</td>
<td>40.30 (42.40)</td>
<td>←</td>
<td>0.72</td>
<td>-14.10 [-36.46, 0.26]</td>
<td>2002</td>
</tr>
<tr>
<td>McClave</td>
<td>16 9.70 (1.30)</td>
<td>16</td>
<td>11.90 (2.60)</td>
<td>—</td>
<td>38.83</td>
<td>-2.20 [-3.62, -0.78]</td>
<td>1997</td>
</tr>
<tr>
<td>Clah</td>
<td>41 16.80 (7.80)</td>
<td>48</td>
<td>23.60 (10.20)</td>
<td>←</td>
<td>17.12</td>
<td>-6.80 [-10.55, -3.05]</td>
<td>2002</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>93 305.80 (72.80)</td>
<td>109</td>
<td>23.60 (10.20)</td>
<td>←</td>
<td>100.00</td>
<td>-3.94 [-5.66, -2.02]</td>
<td>2002</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi^2 = 8.84, df = 3 (P = 0.03), I^2 = 86.3%  
Test for overall effect: Z = 4.03 (P < 0.0001)
Pancreatic Lipase: Secretion and Steatorrhea

Enteral Nutrition in Pancreatitis

- In acute or relapsing chronic pancreatitis an enteral nutrition is possible with polymer liquids via intraduodenal application distal of the Papilla Vateri.
- Special tubes (Benmark®-Tube) guarantee the position.
Transpyloric Nutrition via Bengmark®-Tube
Benchmark®-Tube in situ as nasogastric, PEG or PEG-J-Tube
Bengmark®-Tube
Radiological Control
Indications for transpyloric Nutrition
(n= 48, 4 PEG-J)

- Chemotherapy-induced vomiting/mucositis: 19
- Pancreatitis: 14
- Cardiogenic dystrophy and vomiting: 4
- ARDS 2: 2
- HIV with „wasting syndrome“: 2
- Crohn‘s disease: 1
- Perinatal Asphyxia: 1
- Hypertrophic Pyloric stenosis: 1
- Duodenal drainage tube prior to a stenosis: 1

Probiotics in acute Pancreatitis?

Thank you for your Attention