Approach to a child with chronic diarrhea

Riccardo Troncone
Definitions

Diarrhea

>200 ml/m²/day
>150-200 g/m²/day

Chronic diarrhea

Decrease of consistency and/or increase of frequency and/or volume of stools lasting longer than two weeks, where the change in stool consistency is more important than stool frequency
Mechanisms
(more than one may be implicated)

*Osmotic diarrhea*
Non absorbed substances reaching the distal bowel increase osmotic charge thus pulling water along the intestinal lumen

*Secretory diarrhea*
Increased active secretion of water and electrolytes into the intestinal lumen surpassing the absorptive capability

*Inflammatory diarrhea*
Enterocyte injury with inflammatory response, impaired intestinal permeability

*Motility alterations*
Hypermotility or hypomotility
Main mechanisms for diarrhoea

**Figure 1**

<table>
<thead>
<tr>
<th></th>
<th>Osmotic diarrhea</th>
<th>Secretory diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to fasting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Daily fecal volume</td>
<td>Large</td>
<td>Very large</td>
</tr>
<tr>
<td>Stool osmolality</td>
<td>Normal-increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Fecal pH</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Reducing substances</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Fecal ion gap (mOsm/Kg)</td>
<td>&gt;125</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
History

• Age
• Modalities of beginning
• Family history
• Growth
• Associated symptoms
• Dietary history
• Stool characteristics
### Diseases characterized by chronic diarrhea according to the age at beginning

<table>
<thead>
<tr>
<th>0-30 days</th>
<th>2-24 months</th>
<th>2-18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>Chronic infections</td>
<td>Chronic infections</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>Post-infectious diarrhea</td>
<td>Post-infectious diarrhea</td>
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<tr>
<td>Congenital chloridorrhea</td>
<td>Coeliac disease</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Congenital sodiorrhea</td>
<td>Chronic non-specific diarrhea</td>
<td>Irritable bowel disease</td>
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<tr>
<td>Short bowel syndrome</td>
<td>Food allergy</td>
<td>Lactose intolerance</td>
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<td>Congenital lactase deficiency</td>
<td>Cystic fibrosis</td>
<td>Inflammatory bowel diseases</td>
</tr>
<tr>
<td>Disaccharidase deficiency</td>
<td>Autoimmune enteropathy</td>
<td>Tumours</td>
</tr>
<tr>
<td>Food allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose-galactose malabsorption</td>
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<td></td>
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<tr>
<td>Hirschsprung’s disease</td>
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<td>IPEX</td>
<td></td>
<td></td>
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<tr>
<td>Malrotation</td>
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<td>Congenital microvillous atrophy</td>
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<tr>
<td>Lymphangectasia</td>
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<td>Biliary acids defect</td>
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<td>Tufting enteropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic intestinal pseudoobstruction</td>
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<td></td>
</tr>
<tr>
<td>Chronic infections</td>
<td></td>
<td></td>
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<tr>
<td>Post-infectious diarrhea</td>
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<td>Coeliac disease</td>
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<td>Inflammatory bowel diseases</td>
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<td></td>
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<tr>
<td>Tumours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Modalities of beginning

Abrupt (e.g. infection)

Gradual
Family history

• Coeliac disease
• Cystic fibrosis
• Atopy
• IBD
• Autoimmunity/immunodeficiency
Growth

Very important the help from growth charts

**Toddler’s diarrhea (chronic non specific diarrhea)**

- No failure to thrive
- Most common cause between two and four years of age
- Intermittent and self limited
- 3-6 stool day
- Not formed
- Mucous and undigested food particles
- No pain, no distension, no vomiting
- No effect on weight and on nutritional status
Associated symptoms

- Vomiting
- Fever
- Abdominal pain
- Anorexia
- Recurrent infections
Dietary history

Age of introduction of:

• Cow’s milk proteins

• Gluten
Stool characteristics

- Undigested food particles
- Mucus
- Blood
- Steatorrhea
- Offensive smell
- Watery diarrhoea
Physical examination

• Weight and height for age

• BMI

• Wasting

• Abdominal distension

• Tenderness

• Abdominal mass

• Perianal area (erythema, fissures, fistulas)

• Other organs affected (e.g. skin, respiratory…)
Investigations

• Feces
• Blood
• Imaging
• Endoscopy & Pathology
Blood tests

• Blood count

• Inflammatory parameters (ferritin, C protein, ESR)

• Nutritional status (iron, transferrin, folate, …)

• Coeliac disease serology
Serological test for celiac disease and new ESPGHAN guidelines

- Anti-gliadin and anti-deamidated gliadin antibodies
- Anti tissue transglutaminase antibodies
- Antiendomysium antibodies

*Biopsy may be avoided if:*
- High anti-TG2 titres (>10x)
- EMA positivity
- HLA DQ2/8
- Symptoms disappearing on GFD
Child / Adolescent with Symptoms suggestive of CD

Anti-TG2 IgA & total IgA*

Anti-TG2 positive → Transfer to Paediatric GI
Paed. Gi discusses with family the 2 diagnostic pathways and consequences considering patient’s history & anti-TG2 titers

Anti-TG2 negative → Not CD

Anti-TG2 >10 x normal → EMA & HLA DQ8/DQ2
EMA pos HLA pos → CD+
EMA pos HLA neg → Consider false neg. HLA test, Consider biopsies
EMA neg HLA neg → Consider false pos. anti-TG2
EMA neg HLA pos → GFD & F/u

Anti-TG2 <10 x normal → EMA & HLA DQ8/DQ2
EMA neg HLA neg → Consider further diagnostic testing if:
- IgA deficiency
- Age: < 2 years
- History: - low gluten intake
- - drug pretreatment
- - severe symptoms
- - associated diseases

EMA & HLA DQ8/DQ2 Not available → OEGD & biopsies
Marsh 0 -1 → Unclear case
- Consider: false positive serology
- false negative biopsy
- or potential CD
- Extended evaluation of HLA/serology/biopsies
Marsh 2 or 3 → CD+
GFD & F/u

* Or specific IgG based tests
Asymptomatic person at genetic risk for CD
explain implication of positive test result(s) and get consent for testing

HLA DQ2 / DQ8 (+/- TG2)

- HLA positive
  - DQ2 and/or DQ8

- HLA negative
  - DQ2 and DQ8

OEGD & Biopsies from Bulbus & 4 x pars descendens, proper histological work up

- Marsh 2 or 3
- Marsh 0 or 1

- TG2 & total IgA*
  - Titer > 3 x normal
  - Titer < 3 x normal
  - TG2 Negative

- EMA
  - EMA positive
  - EMA negative

No CD, no riks for CD

Consider retesting in intervals or if symptomatic

Not CD

Consider:
- False negative results, exclude IgA deficiency and history of low gluten intake or drugs

CD+

GFD & F/u

Unclear case

F/u on normal diet Consider:
- false pos serology, false neg biopsy or potential CD

Consider:
- Transient / false positive Anti-TG2
  F/u on normal diet with further serological testing

* Or specific IgG based tests
Investigations on feces

• Electrolytes and pH

• Reducing substances

• Fat (steatocrit)

• Elastase

• Alpha 1 antitripsin

• Calprotectin/lactoferrin

• Laxatives

• Microbiology

• Gut hormones
If feces are liquid

Na\(^+\) and K\(^+\) on the liquid part

Osmotic gap = 290 – 2 (Na\(^+\) + K\(^+\))

> 125 mOsm/Kg = osmotic
< 50 mOsm/Kg = secretive
Approach to secretory diarrhoea (watery diarrhea with no or minimum osmotic gap)

• Salmonella, Campylobacter, Shigella, E Coli toxins
• Rotavirus

More rare causes

• Microvillous atrophy (small intestinal biopsy)
• Rare tumors (gastrin, VIP, calcitonin)
Approach to osmotic diarrhoea and malabsorptive syndromes

- pH and reducing substances
- Breath test (lactose for lactose intolerance, lactulose for small bowel overgrowth)
- Sweat test (cystic fibrosis)
- Immunological tests (Ig, lymphocyte subsets)
- Small intestinal biopsy
**Imaging**

- Barium follow through
- TAC
- MRI
- Ultrasound
- Scintigraphy (leukocytes, albumin, RBC)
Approach to inflammatory diarrhea

• Inflammatory parameters
• Calprotectin
• ECP
• Intestinal permeability
• Upper tract and lower tract endoscopy & biopsies
Alimentary Tract

Diagnostic value of faecal calprotectin in paediatric gastroenterology clinical practice

R. Berni Canani\textsuperscript{a, *}, L. Rapacciuolo\textsuperscript{a}, M.T. Romano\textsuperscript{a}, L. Tanturri de Horatio\textsuperscript{a}, G. Terrin\textsuperscript{a}, F. Manguso\textsuperscript{b}, P. Cirillo\textsuperscript{a}, F. Paparo\textsuperscript{a}, R. Troncone\textsuperscript{a}
Combined use of non-invasive tests

- Positive fecal calprotectin, ultrasound, and ASCA/pANCA antibodies
  - Probability of having IBD if all tests positive: 99.7%

- Negative fecal calprotectin, ultrasound, and ASCA/pANCA antibodies
  - Probability of not having IBD if all tests negative: 3.5%

Berni Canani R. et al. JPGN 2005
Protein losing enteropathy

• Lymphangectasia

• Infections

• Allergic gastroenteropathy

• IBD

• Congenital disorders of glicosylation

• Constrictive pericarditis & congestive heart failure
Protein losing enteropathy

- Diarrhoea
- Edema
- Pleural and pericardial effusions
- Serum levels of albumin, alpha 1 antirypsin, fibrinogen, transferrin
- Malabsorption of fat soluble vitamins
- Hypogammaglobulinemia
- Lymphopenia and altered CMI
Classification of congenital diarrhea

Defects of digestion, absorption and transport of nutrients and electrolytes

Defects of enterocyte differentiation and polarization

Defects of enteroendocrine cell differentiation

Defects of modulation of the intestinal immune response

Enterocyte
Nutrients or electrolytes
Enteroendocrine cell
Immune cell
Molecular basis of defects of digestion, absorption and transport of nutrients and electrolytes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Location</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disaccharidase deficiency</td>
<td>LCT</td>
<td>2q21</td>
<td>Lactase-phlorizin hydrolase activity</td>
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<tr>
<td>Congenital lactase deficiency</td>
<td>EC 3.2.1.48</td>
<td>3q25-q26</td>
<td>Isomaltase-sucrase</td>
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<tr>
<td>Sucrase-isomaltase deficiency</td>
<td>MGAM</td>
<td>7q34</td>
<td>Maltase-glucoamylase activity</td>
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<tr>
<td>Malate-glucoamylase deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ion and nutrient transport defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glucose-galactose malabsorption</td>
<td>SGLT1</td>
<td>22q13.1</td>
<td>Na⁺/glucose cotransporter</td>
<td>(10,11)</td>
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<tr>
<td>Fructose malabsorption</td>
<td>GLUT5</td>
<td>1p36</td>
<td>Fructose transporter</td>
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<tr>
<td>Fanconi-Bickel syndrome</td>
<td>GLUT2</td>
<td>3q26</td>
<td>Basolateral glucose transporter</td>
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<tr>
<td>Cystic fibrosis</td>
<td>CFTR</td>
<td>7q31.2</td>
<td>cAMP-dependent Cl⁻ channel</td>
<td>(14)</td>
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<td>Acrodermatitis enteropathica</td>
<td>SLC39A4</td>
<td>8q24.3</td>
<td>Zn²⁺ transporter</td>
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<td>Congenital chloride diarrhea</td>
<td>DRA</td>
<td>7q22-q31.1</td>
<td>Cl⁻/base exchanger</td>
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<td>Congenital sodium diarrhea</td>
<td>SPINT2*</td>
<td>19q13.1</td>
<td>Serine-protease inhibitor</td>
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<td>Lysinuric protein intolerance</td>
<td>SLC7A7</td>
<td>14q11</td>
<td>Hydrolyzes endo-/exoepitides</td>
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<td>Congenital bile acid intolerance</td>
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<td>13q3</td>
<td>Ileal Na⁺/bile salt transporter</td>
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<td>Pancreatic insufficiency</td>
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<td>Enterokinase deficiency</td>
<td>PRSS7</td>
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<td>Proenterokinase</td>
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<td>Trypsinogen deficiency</td>
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<td>7q35</td>
<td>Trypsinogen synthesis</td>
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<td>Pancreatic lipase deficiency</td>
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<td>10q26.1</td>
<td>Hydrolyzes triglycerides to fatty acids</td>
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<td>Lipid trafficking</td>
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<td>Abetalipoproteinemia</td>
<td>MTP</td>
<td>4q22</td>
<td>Transfer lipids to apolipoprotein B</td>
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<td>Hypobetalipoproteinemia</td>
<td>APOB</td>
<td>2p24</td>
<td>Apolipoprotein that forms chylomicrons</td>
<td>(22,23)</td>
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<td>Chylomicron retention disease</td>
<td>SAR1B</td>
<td>5q31.1</td>
<td>Intracellular chylomicron trafficking</td>
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</tr>
</tbody>
</table>

cAMP = cyclic adenosine monophosphate.

*This mutation has been associated with the syndromic form of congenital sodium diarrhea.

Berni Canani et al, JPGN 2010; 50: 360
CLD (CLD-OMIM 214700) is a congenital disorder characterised by a defect of intestinal chloride absorption due to mutations in the SLC26A3/DRA gene.

Complications
- Severe dehydration
- Intestinal pseudobstruction (surgical interventions)
- Mental retardation
- Renal impairment
- Scarce quality of life
About 50 mutation has been identified on the gene of CLD. All these mutations could be classified in 4 type:

a) Missence  
b) Del/Ins  
c) Splicing  
d) Nonsense
Butyrate reduces ion fecal losses

Data are expressed as mmol/L
Molecular basis of defects of enterocyte differentiation and polarization

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Microvillous inclusion disease</td>
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<td>2p21</td>
<td>Cell-cell interaction</td>
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EpCAM = epithelial cell adhesion molecule.

Berni Canani et al, JPGN 2010; 50: 360
Microvillous congenital atrophy

PAS staining
Microvillous congenital atrophy

Electron microscopy
Molecular basis of defects of enteroendocrine cells differentiation

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<tbody>
<tr>
<td>Enteric anendocrinosis</td>
<td><em>NEUROG3</em></td>
<td>10q21.3</td>
<td>Enteroendocrine cell fate determination</td>
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<td>Proprotein convertase 1 deficiency</td>
<td><em>PCSK1</em></td>
<td>5q15-q21</td>
<td>Prohormone processing</td>
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*NEUROG-3 = neurogenin-3.*
Molecular basis of defects of modulation of intestinal immune response

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<tr>
<td>IPEX</td>
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</tbody>
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APS-1 = autoimmune polyglandular syndrome-1; FOXP3 = forkhead box P3; GAGD = generalized autoimmune gut disorder; IPEX = immune dysregulation polyendocrinopathy, enteropathy, X-linked syndrome.

Berni Canani et al, JPGN 2010; 50: 360
Algorhythm for the differential diagnosis of severe diarrhea with neonatal onset

From Goulet, 2012
Microvillous Inclusion Disease

Tufting Enteropathy

Enteric Anendocrinosis

TOTAL PARENTERAL NUTRITION

• Recurrent sepsis
• PN associated liver disease
• Loss of central vascular access

INTESTINAL TRANSPLANTATION
<table>
<thead>
<tr>
<th>Option</th>
<th>Disease</th>
<th>1 y</th>
<th>4 y</th>
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<tbody>
<tr>
<td>TPN</td>
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<tr>
<td>Intestinal Tx</td>
<td>Intestine</td>
<td>70</td>
<td>47</td>
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<tr>
<td></td>
<td>Intestine+Liver</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Multivisceral</td>
<td>45</td>
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</table>
SUCCESSFUL USE OF THE NEW IMMUNE-SUPPRESSOR SIROLIMUS IN IPEX (IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME)

Lutz Bindl, MD, Troy Torgerson, MD, PhD, Lucia Perroni, MD, Nelly Youssif, MD, Hans D. Ochs, MD, Oliver Goulet, MD, and Frank M. Ruefmele, MD, PhD

Before treatment

4 years of follow-up

BONE MARROW ALLOGENIC TRANSPLANTATION IN IPEX SYNDROME

Conclusions

Chronic diarrhea may occur in many diseases including a variety of infectious and immunological conditions.

Great progress recently made in the understanding of disease mechanisms at molecular level.

Rare syndromes of intractable diarrhea have provided important insights into gut physiology and immunology.

All these new information have opened the way to more efficient treatment for both common and rare conditions.