# Approach to a child with chronic diarrhea

Riccardo Troncone

# Definitions

## Diarrhea

>200 ml/$m^2$/day
>150-200 g/$m^2$/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*

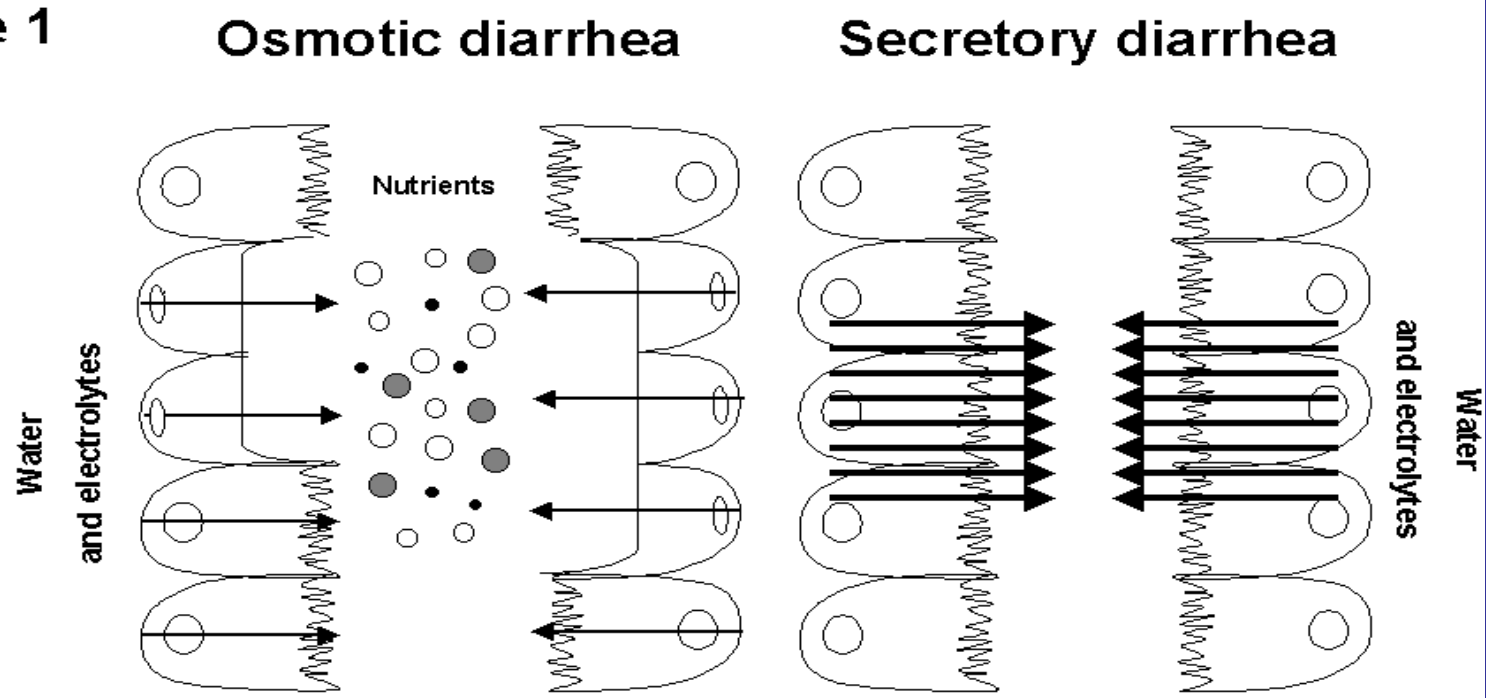
Enterocyte injury with inflammatory response, impaired intestinal permeability

*Motility alterations*

Hypermotility or hypomotility

# Main mechanisms for diarrhoea

Figure 1




| | | |
|---|---|---|
| **Response to fasting** | Yes | No |
| **Daily fecal volume** | Large | Very large |
| **Stool osmolality** | Normal-increased | Normal |
| **Fecal pH** | Low | Normal |
| **Reducing substances** | Positive | Negative |
| **Fecal ion gap (mOsm/Kg)** | >125 | <50 |

# 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

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

# 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

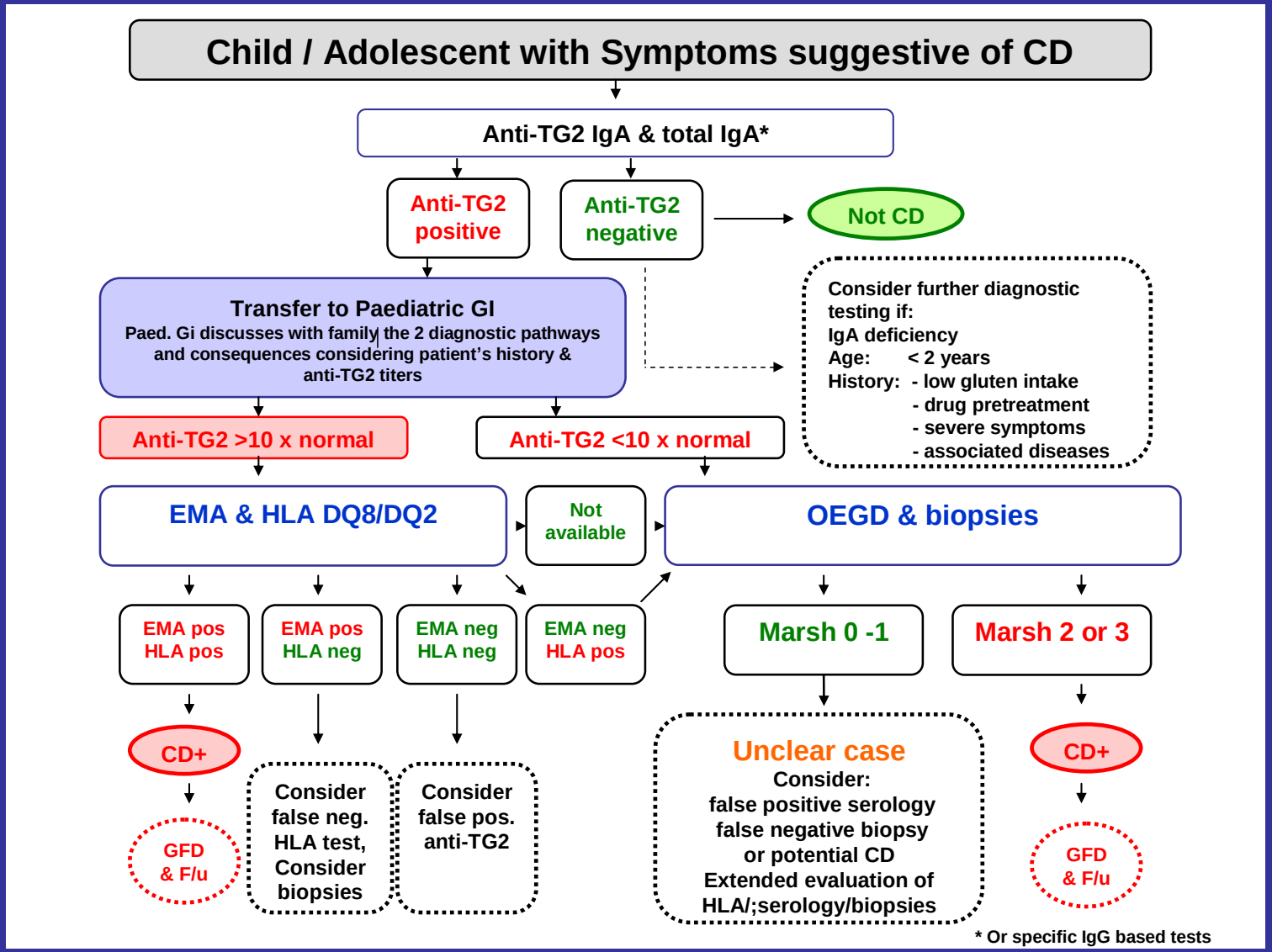
- Blood count
- Inflammatory parameters (ferritin, C protein, ESR)
- Nutritional status (iron, transferrin, folate,…)
- Coeliac disease serology

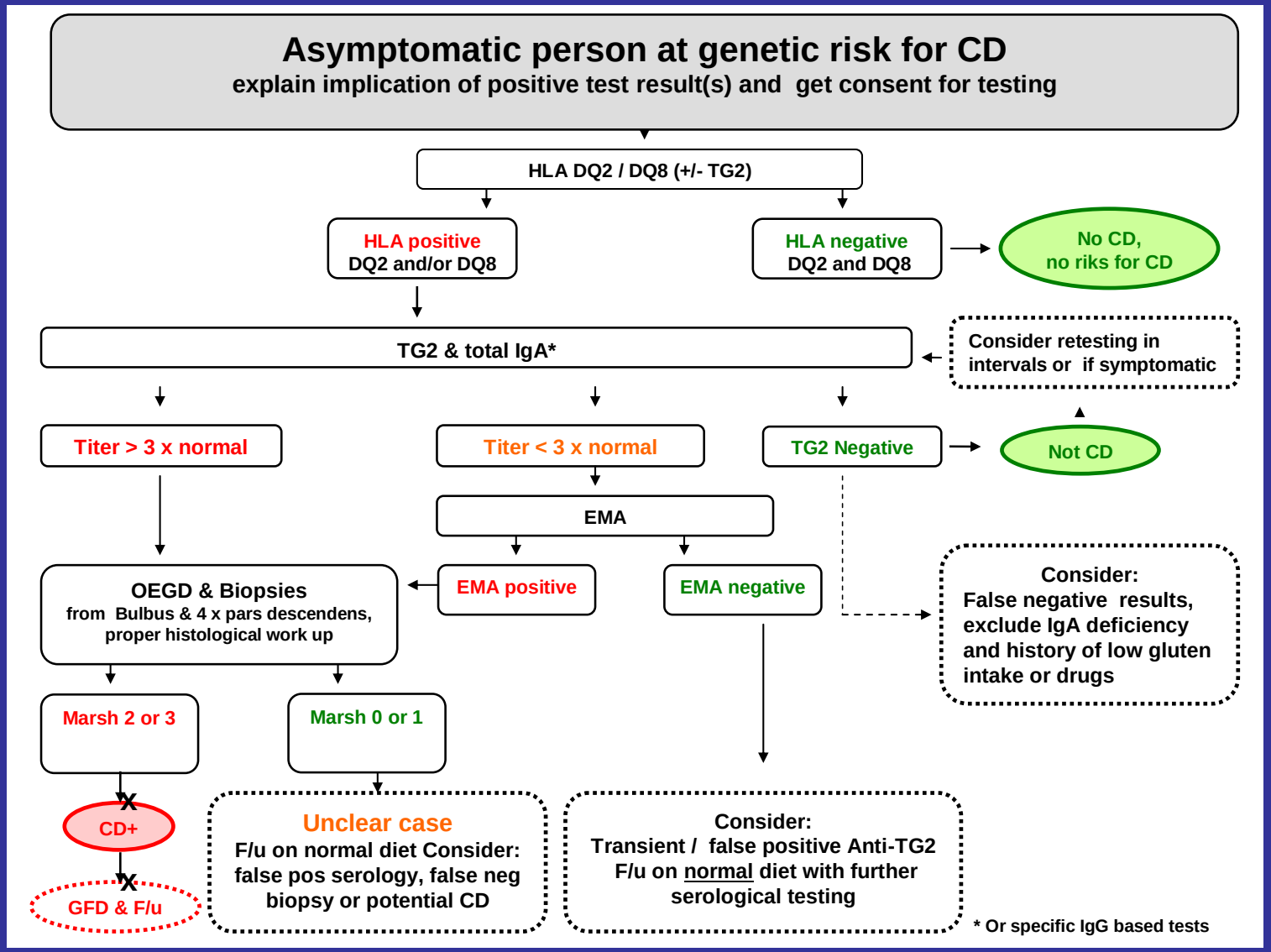
# Serological test for celiac disease and new ESPGHAN guidelines

- 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
Anti-TG2 negative
Not CD
Transfer to Paediatric GI
Paed. Gi discusses with family the 2 diagnostic pathways and consequences considering patient's history & anti-TG2 titers
Consider further diagnostic testing if:
IgA deficiency
Age: < 2 years
History: - low gluten intake
- drug pretreatment
- severe symptoms
- associated diseases
Anti-TG2 >10 x normal
Anti-TG2 <10 x normal
EMA & HLA DQ8/DQ2
Not available
OEGD & biopsies
EMA pos HLA pos
EMA pos HLA neg
EMA neg HLA neg
EMA neg HLA pos
Marsh 0 -1
Marsh 2 or 3
CD+
GFD & F/u
Consider false neg. HLA test, Consider biopsies
Consider false pos. anti-TG2
Unclear case
Consider:
false positive serology
false negative biopsy
or potential CD
Extended evaluation of HLA/;serology/biopsies
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
No CD,
no riks for CD
TG2 & total IgA*
Consider retesting in
intervals or if symptomatic
Titer > 3 x normal
Titer < 3 x normal
TG2 Negative
Not CD
EMA
EMA positive
EMA negative
OEGD & Biopsies
from Bulbus & 4 x pars descendens,
proper histological work up
Consider:
False negative results,
exclude IgA deficiency
and history of low gluten
intake or drugs
Marsh 2 or 3
Marsh 0 or 1
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*

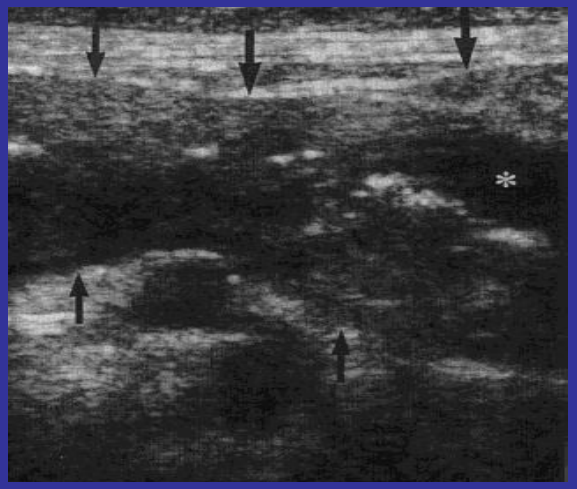
- Microvillous atrophy (small intestinal biopsy)
- Rare tumors (gastrin, VIP, calcitonin)

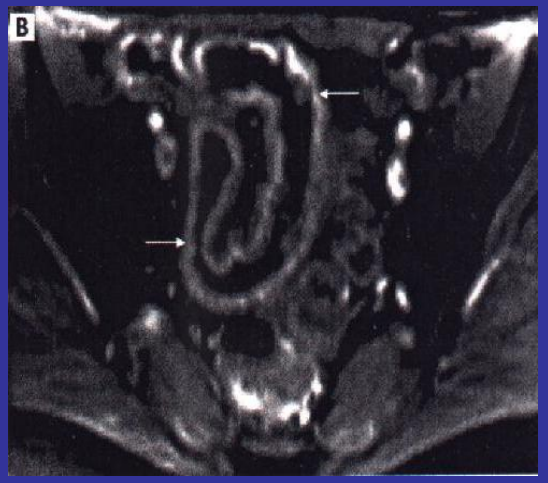
# Approach to osmotic diarrhoea and malabsorptive syndromes

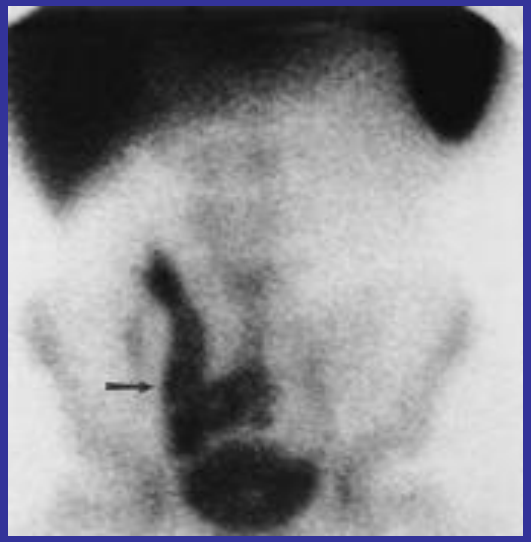
- pH and reducing substances
- Breath test (lactose for lactose intolerance, lactulose for small bowel overgrowth)
- Sweat test (cystic fibrosis)
- Immunological tests (Ig, lymphocyte subsets)
- Small intestinal biopsy

# Imaging

- Barium follow through
- TAC
- MRI
- Ultrasound
- Scintigraphy (leukocytes, albumin, RBC)





# Approach to inflammatory diarrhea

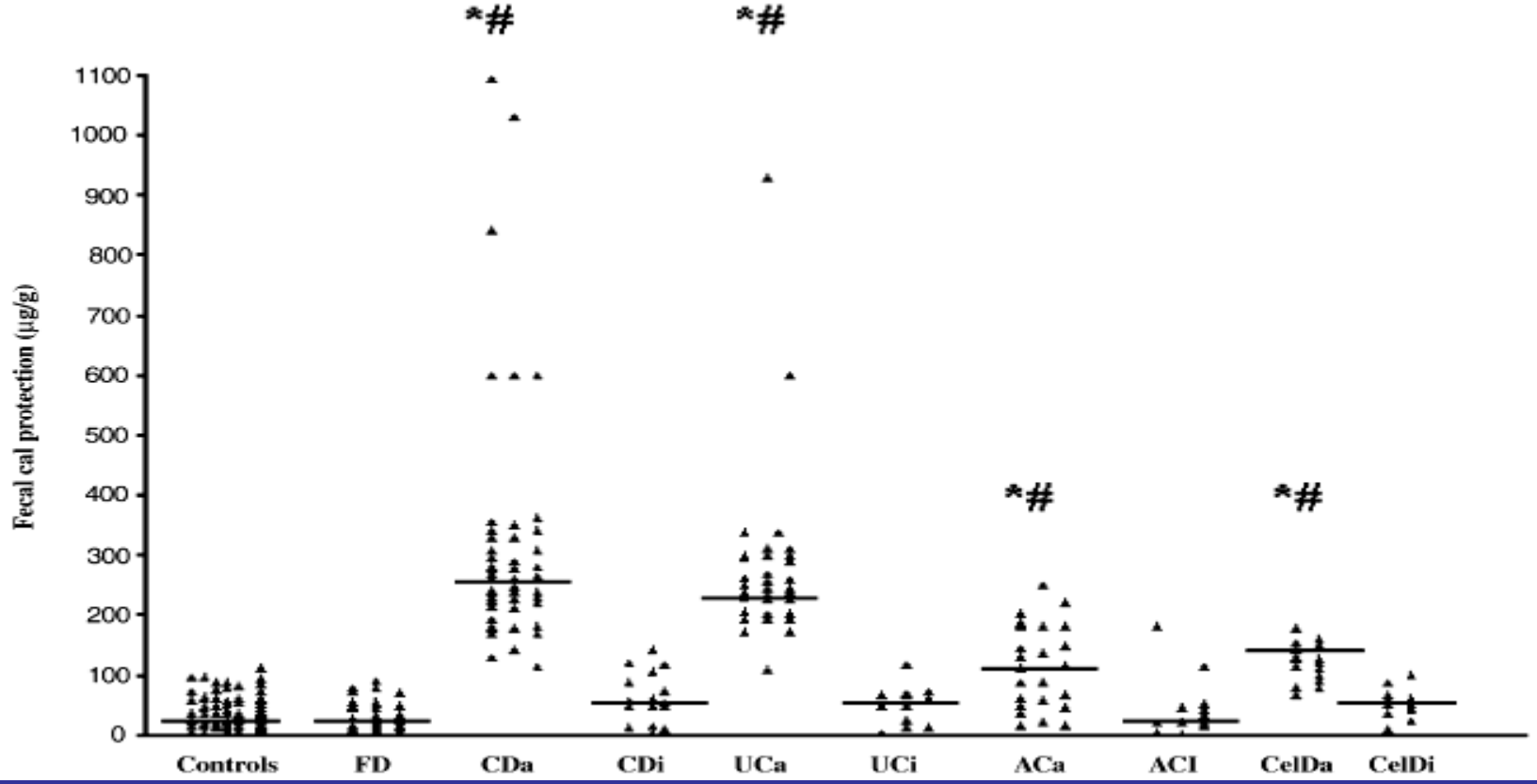
- Inflammatory parameters
- Calprotectin
- ECP
- Intestinal permeability
- Upper tract and lower tract endoscopy & biopsies

Digestive and Liver Disease 36 (2004) 467–470

Alimentary Tract

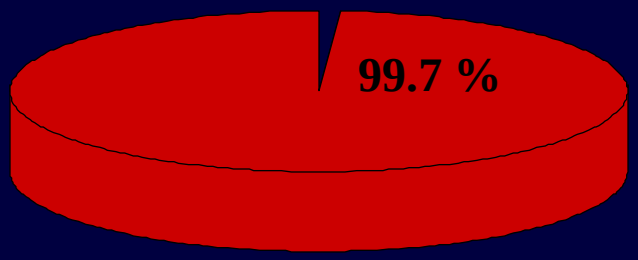
# Diagnostic value of faecal calprotectin in paediatric gastroenterology clinical practice

R. Berni Canani [a,*], L. Rapacciuolo [a], M.T. Romano [a], L. Tanturri de Horatio [a], G. Terrin [a], F. Manguso [b], P. Cirillo [a], F. Paparo [a], R. Troncone [a]



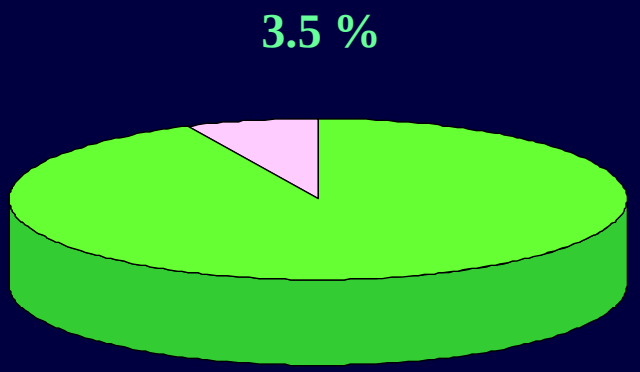
# Combined use of non-invasive tests

- Positive fecal calprotectin, ultrasound, and ASCA/pANCA antibodies




- Probability of having IBD if all tests positive

- Negative fecal calprotectin, ultrasound, and ASCA/pANCA antibodies




- Probability of not having IBD if all tests negative

*Berni Canani R. et al JPGN 2005*

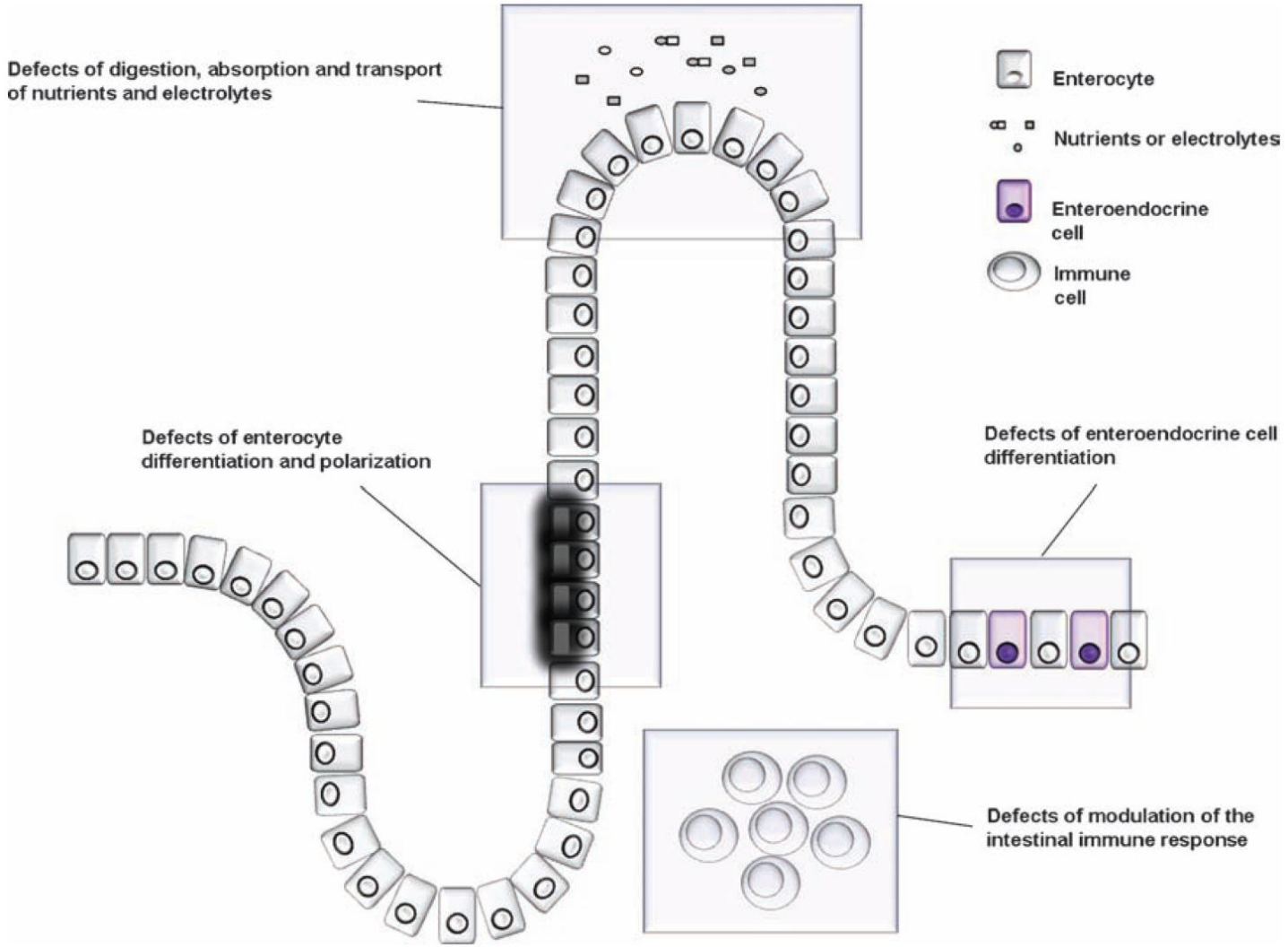
# Protein losing enteropathy

- 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




*Berni Canani R et al, J Pediatr Gastroenterol Nutr 2010; 50: 360-6*

# Molecular basis of defects of digestion, absorption and transport of nutrients and electrolytes

| Disease | Gene | Location | Function | References |
|---|---|---|---|---|
| Disaccharidase deficiency | | | | |
| Congenital lactase deficiency | *LCT* | 2q21 | Lactase-phlorizin hydrolase activity | (7) |
| Sucrase-isomaltase deficiency | *EC 3.2.1.48* | 3q25-q26 | Isomaltase-sucrase | (8) |
| Maltase-glucoamylase deficiency | *MGAM* | 7q34 | Maltase-glucoamylase activity | (7,9) |
| Ion and nutrient transport defects | | | | |
| Glucose-galactose malabsorption | *SGLT1* | 22q13.1 | $Na^+$/glucose cotransporter | (10,11) |
| Fructose malabsorption | *GLUT5* | 1p36 | Fructose transporter | (10,12) |
| Fanconi-Bickel syndrome | *GLUT2* | 3q26 | Basolateral glucose transporter | (13) |
| Cystic fibrosis | *CFTR* | 7q31.2 | cAMP-dependent $Cl^-$ channel | (14) |
| Acrodermatitis enteropathica | *SLC39A4* | 8q24.3 | $Zn^{2+}$ transporter | (15) |
| Congenital chloride diarrhea | *DRA* | 7q22-q31.1 | $Cl^-$/base exchanger | (16) |
| Congenital sodium diarrhea | *SPINT2** | 19q13.1 | Serine-protease inhibitor | (17,18) |
| Lysinuric protein intolerance | *SLC7A7* | 14q11 | Hydrolyzes endo-/exopeptidases<br>Amino acid basolateral transport | (18) |
| Congenital bile acid diarrhea | *ABAT* | 13q3 | Ileal $Na^+$/bile salt transporter | (19) |
| Pancreatic insufficiency | | | | |
| Enterokinase deficiency | *PRSS7* | 21q21 | Proenterokinase | (20,21) |
| Trypsinogen deficiency | *PRSS1* | 7q35 | Trypsinogen synthesis | (20,21) |
| Pancreatic lipase deficiency | *PNLIP* | 10q26.1 | Hydrolyzes triglycerides to fatty acids | (21) |
| Lipid trafficking | | | | |
| Abetalipoproteinemia | *MTP* | 4q22 | Transfer lipids to apolipoprotein B | (22,23) |
| Hypobetalipoproteinemia | *APOB* | 2p24 | Apolipoprotein that forms chylomicrons | (22,23) |
| Chylomicron retention disease | *SAR1B* | 5q31.1 | Intracellular chylomicron trafficking | (23) |

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*

# Congenital Chloride Losing Diarrhea

CLD (CLD-OMIM 214700) is a congenital disorder characterised by a defect of intestinal chloride absorption due to mutations in the **SLC26A3/DRA gene**.

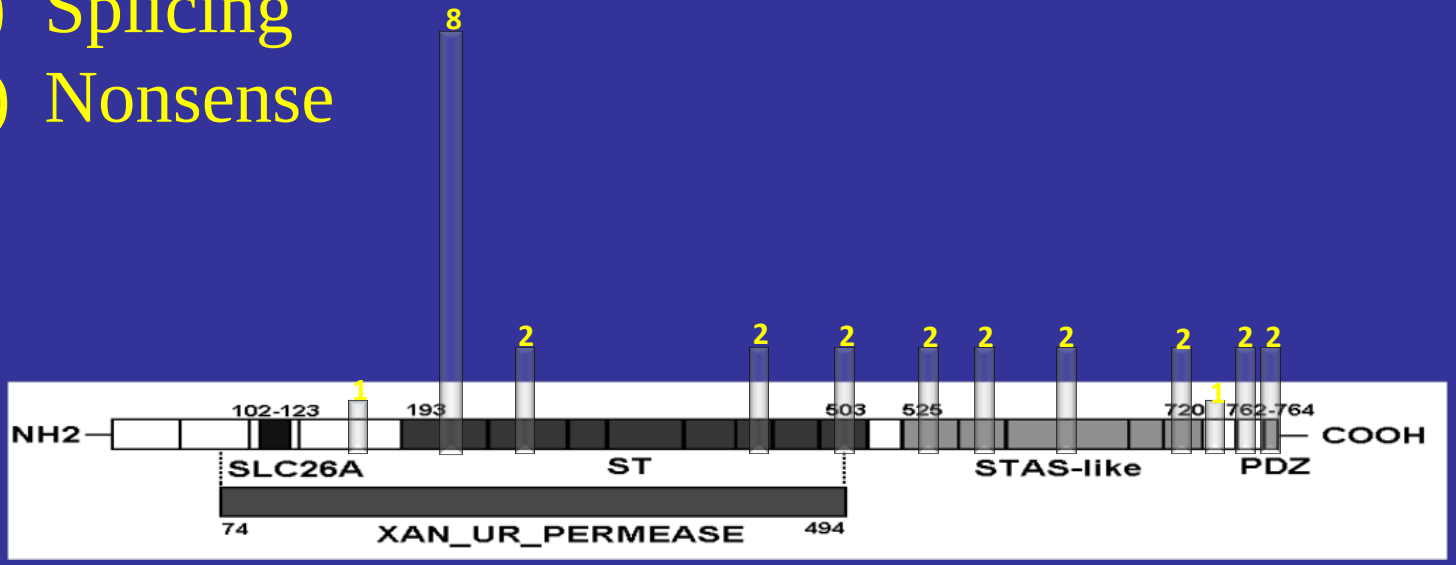
Complications
- Severe dehydration
- Intestinal pseudobstruction (surgical interventions)
- Mental retardation
- Renal impairment
- Scarce quality of life

# Genetic aspects of CLD

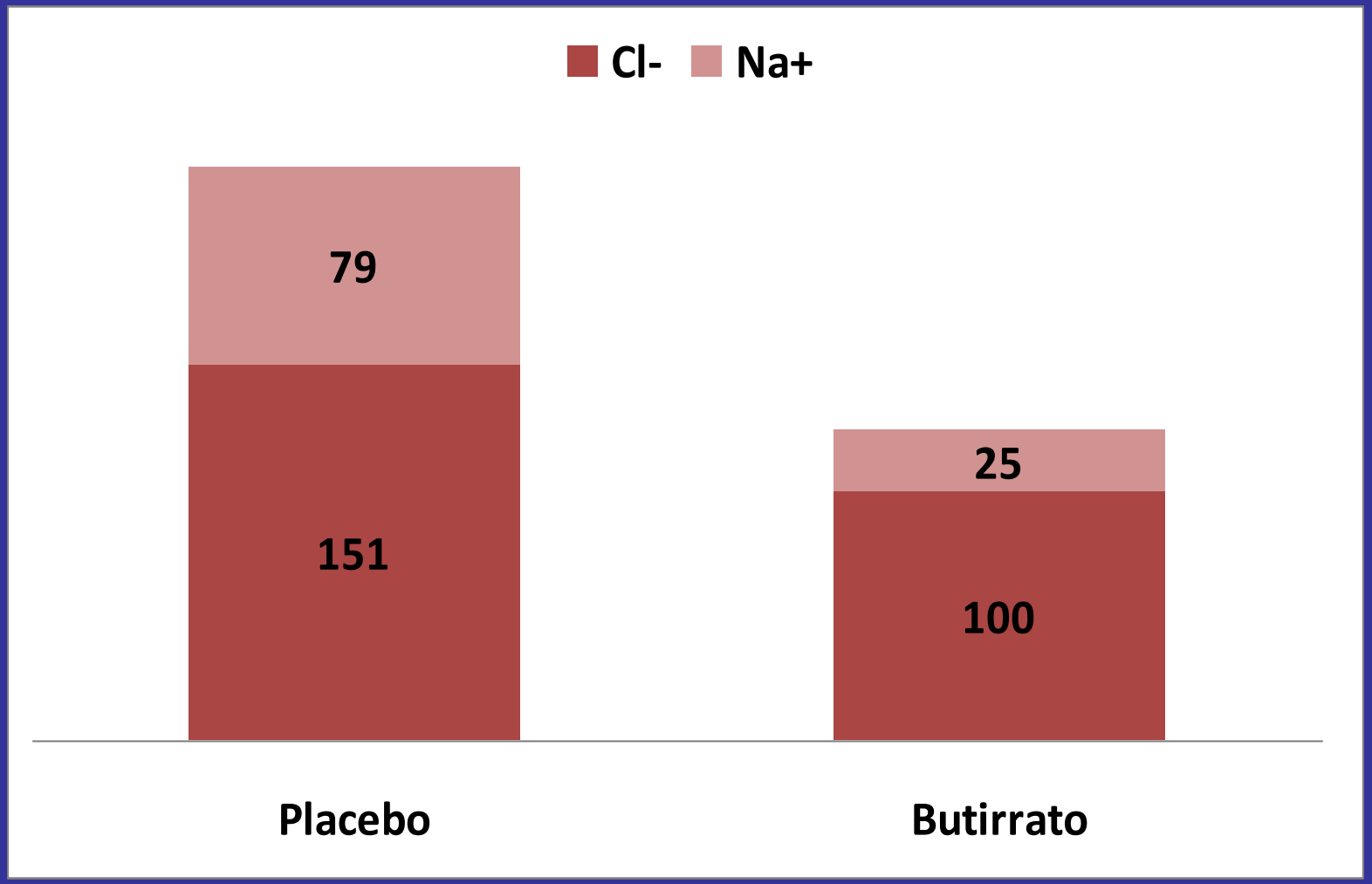
About **50 mutation** has been identified on the gene of CLD.

All these mutations could be **classified in 4 type**:

a) Missence
b) Del/Ins
c) Splicing
d) Nonsense



# Butyrrate reduces ion fecal losses




Data are expressed as mmol/L

# Molecular basis of defects of enterocyte differentiation and polarization

TABLE 2. Molecular basis of the main forms of congenital diarrheal diseases: defects of enterocyte differentiation and polarization

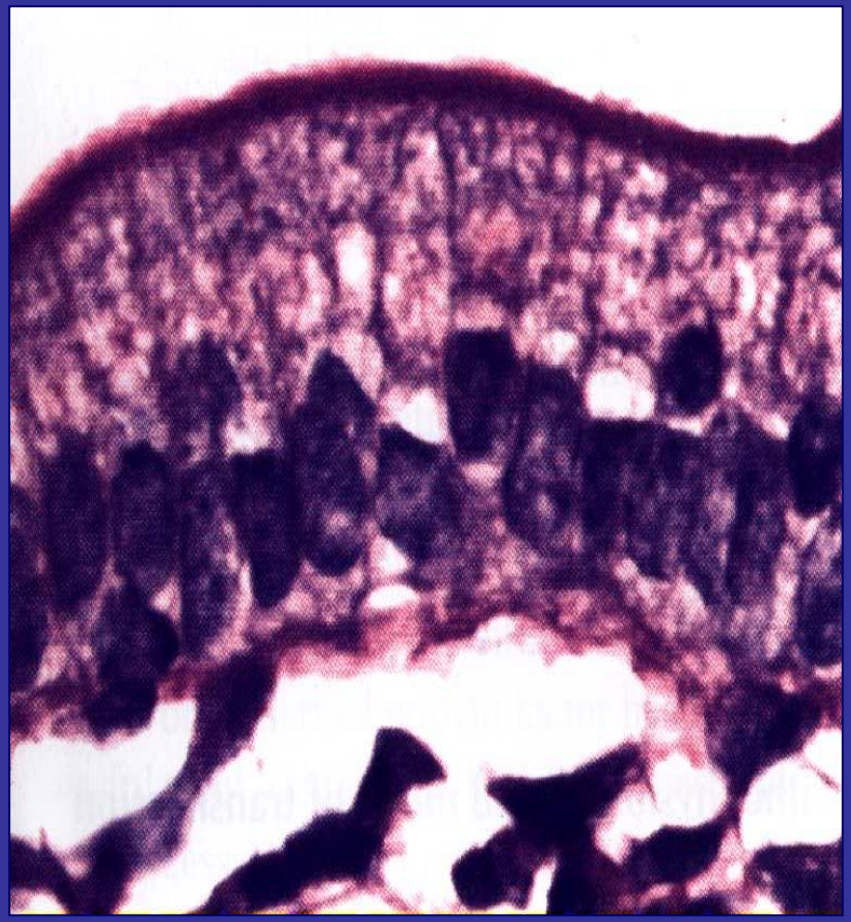
| Disease | Gene | Location | Function | References |
|---|---|---|---|---|
| Microvillous inclusion disease | *MY05B* | 18q21 | Intracellular protein trafficking | (55) |
| Congenital tufting enteropathy | *EpCAM* | 2p21 | Cell-cell interaction | (24) |
| Syndromic diarrhea | Unknown | Unknown | Unknown | (25) |

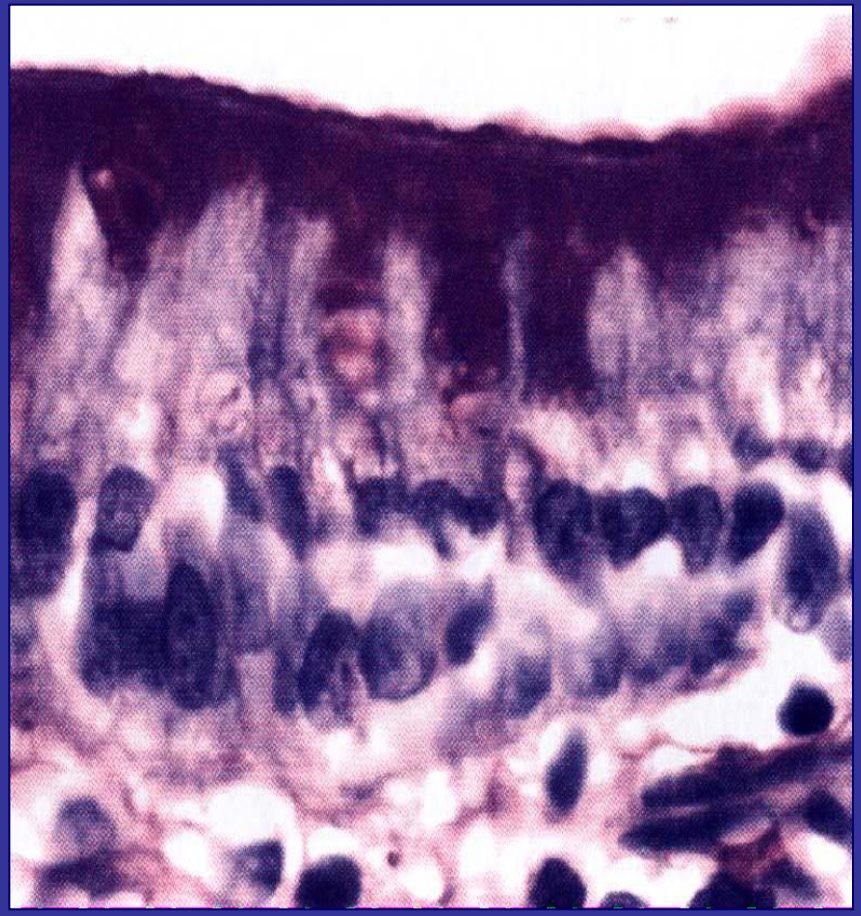
EpCAM = epithelial cell adhesion molecule.

*Berni Canani et al, JPGN 2010; 50: 360*

# Microvillous congenital atrophy

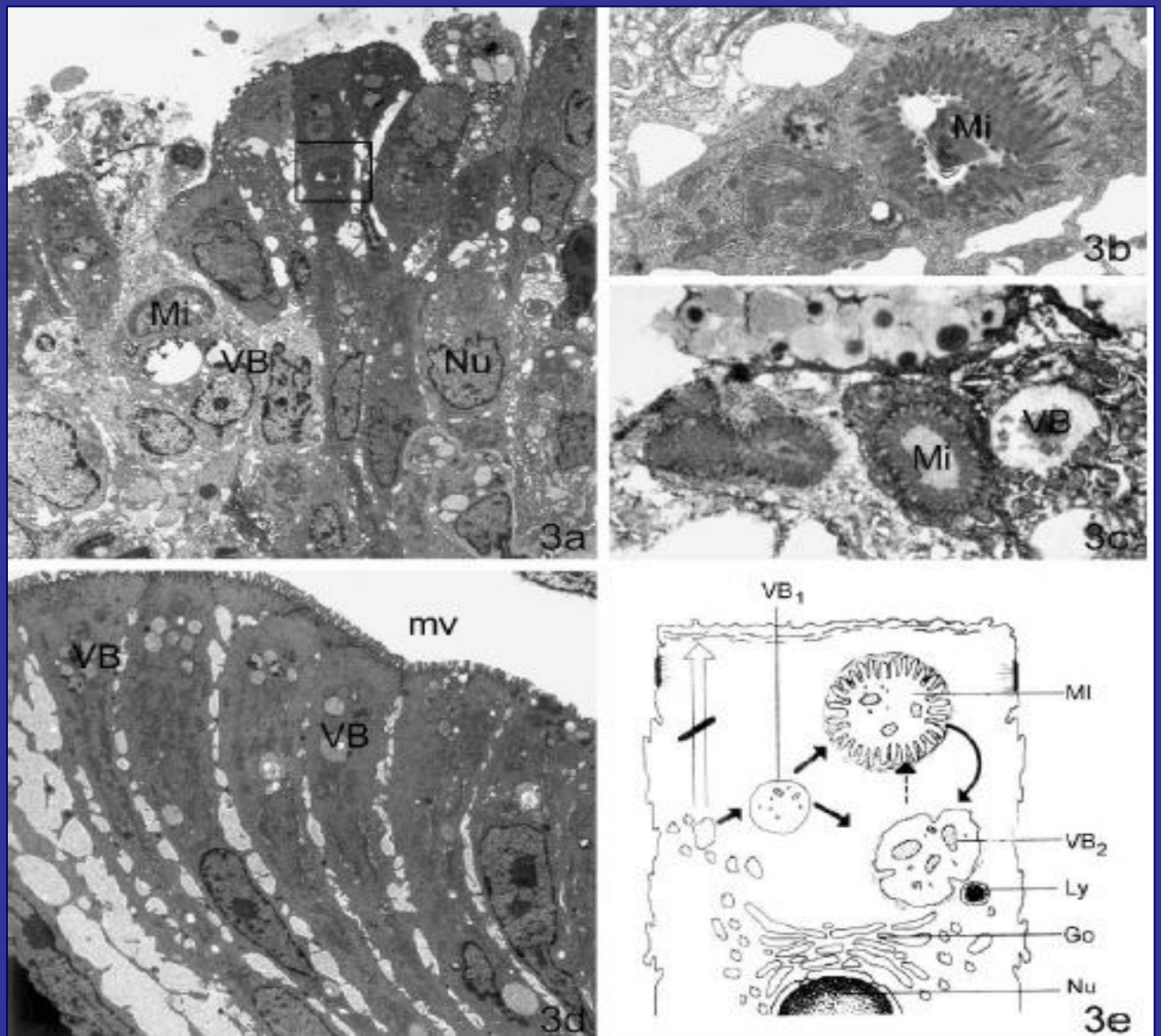
*PAS staining*





# Microvillous congenital atrophy

*Electron microscopy*



# Molecular basis of defects of enteroendocrine cells differentiation

TABLE 3. Molecular basis of the main forms of congenital diarrheal diseases: defects of enteroendocrine cells differentiation

| Disease | Gene | Location | Function | References |
|---|---|---|---|---|
| Enteric anendocrinosis | *NEUROG3* | 10q21.3 | Enteroendocrine cell fate determination | (26,27) |
| Enteric dysendocrinosis | Unknown | Unknown | Enteroendocrine cell function | (26,27) |
| Proprotein convertase 1 deficiency | *PCSK1* | 5q15-q21 | Prohormone processing | (28) |

NEUROG-3 = neurogenin-3.

*Berni Canani et al, JPGN 2010; 50: 360*

# Molecular basis of defects of modulation of intestinal immune response

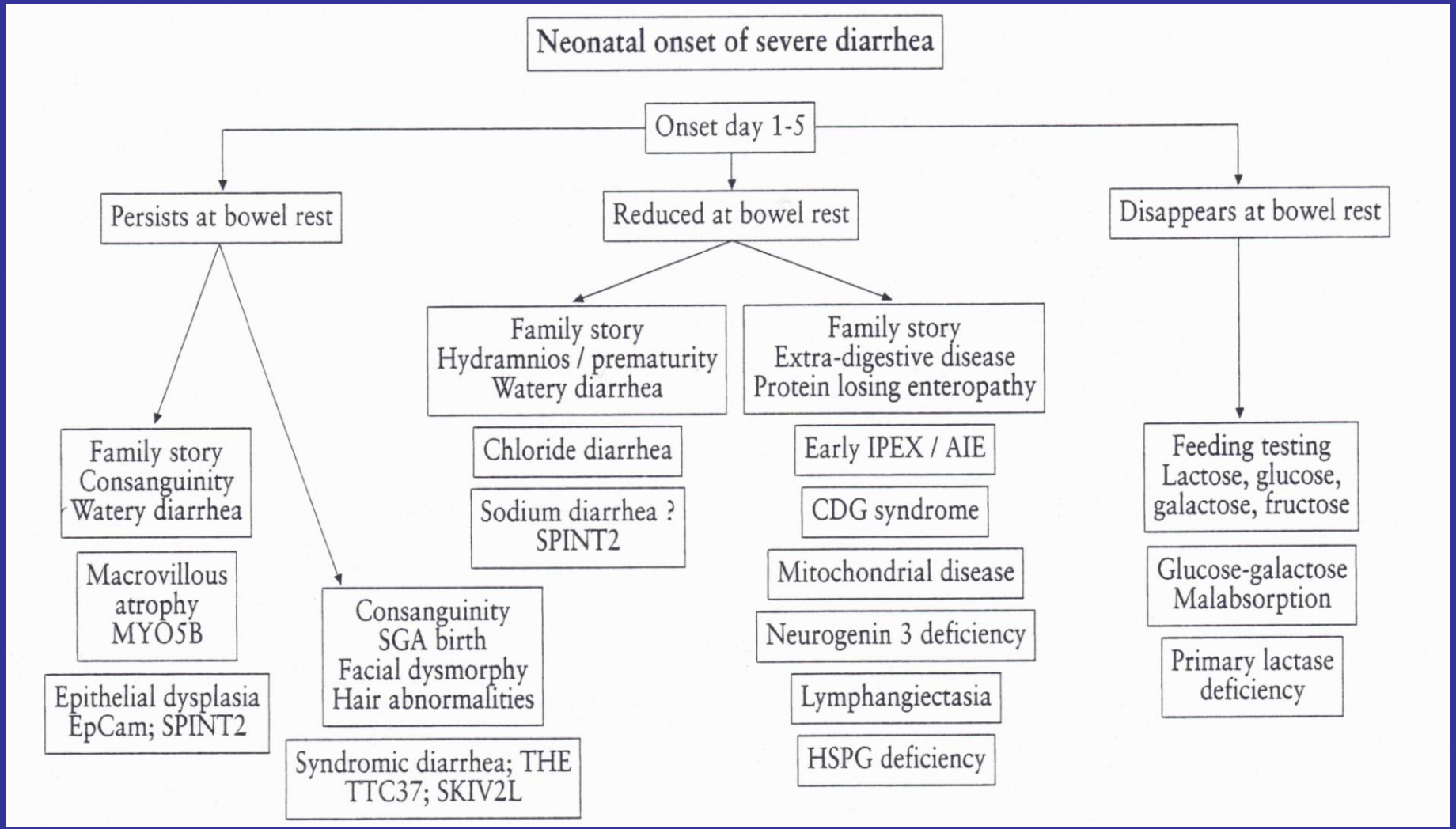
TABLE 4. Molecular basis of the main forms of congenital diarrheal diseases: defects of modulation of intestinal immune response

| Disease | Gene | Location | Function | References |
|---|---|---|---|---|
| IPEX | *FOXP3* | Xp11.23-q13.3 | Transcription factor | (29–32) |
| IPEX-like syndrome | Unknown | Unknown | Unknown | (29–32) |
| Immunodeficiency-associated autoimmune enteropathy | Unknown | Unknown | Unknown | (33) |
| APS-1 | *AIRE* | 21p22.3 | Regulation gene transcription | (34) |
| Autoimmune enteropathy with colitis-GAGD | Unknown | Unknown | Unknown | (35) |

APS-1 = autoimmune polyglandular syndrome-1; *FOXP3* = forkhead box P3; GAGD = generalized autoimmune gut disorder; IPEX = immune dysregulation polyendocrinopathy, enteropathy, X-linked syndrome.

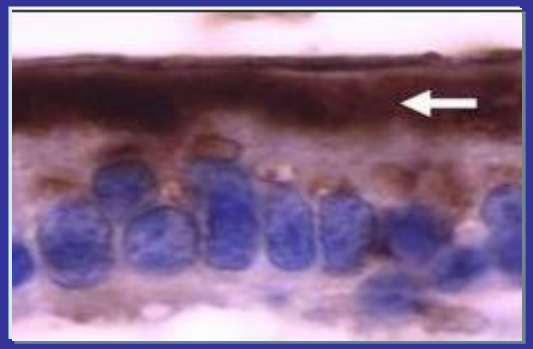
*Berni Canani et al, JPGN 2010; 50: 360*

# Algorhytm for the differential diagnosis of severe diarrhea with neonatal onset

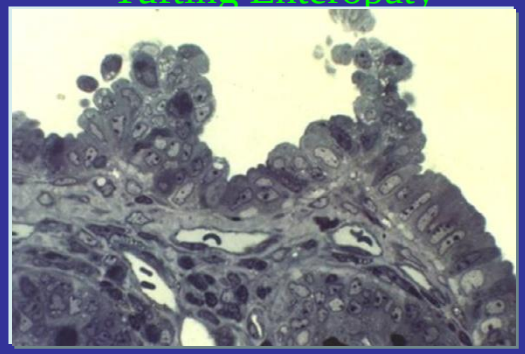



*From Goulet, 2012*

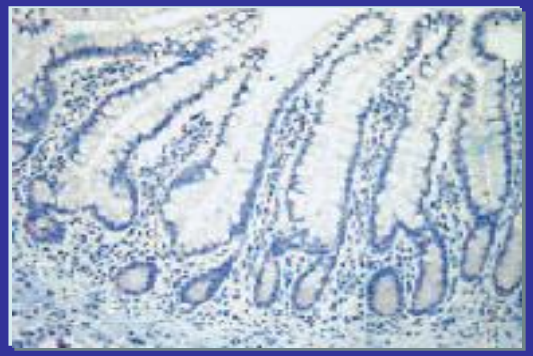
Microvillous Inclusion Disease



Tufting Enteropaty



Enteric Anendocrinosis



TOTAL PARENTERAL NUTRITION

- **Recurrent sepsis**
- **PN associated liver disease**
- **Loss of central vascular access**

INTESTINAL TRANSPLANTATION

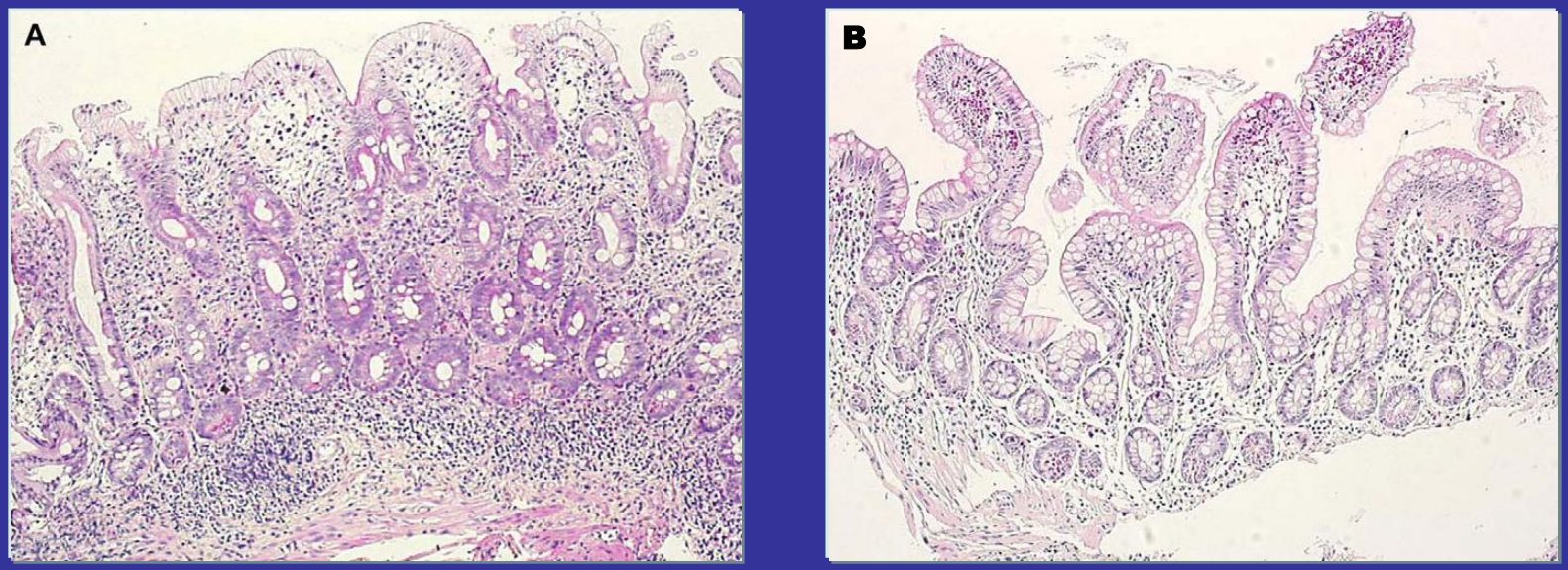
# TPN vs. INTESTINAL TRANSPLANTATION

| Option | Disease | Survival (%) | |
|---|---|---|---|
| | | 1 y | 4 y |
| TPN | | 94 | 80 |
| Intestinal Tx | | | |
| | Intestine | 70 | 47 |
| | Intestine+Liver | 62 | 40 |
| | Multivisceral | 45 | 40 |

Modified by SS Kaufman, JB Atkinson, A Bianchi, OJ Goulet. Pediatr Transplantation 2001; 5:80-87

# 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 YOUSSEF, MD, HANS D. OCHS, MD, OLIVIER GOULET, MD, AND FRANK M. RUEMMELE, MD, PHD

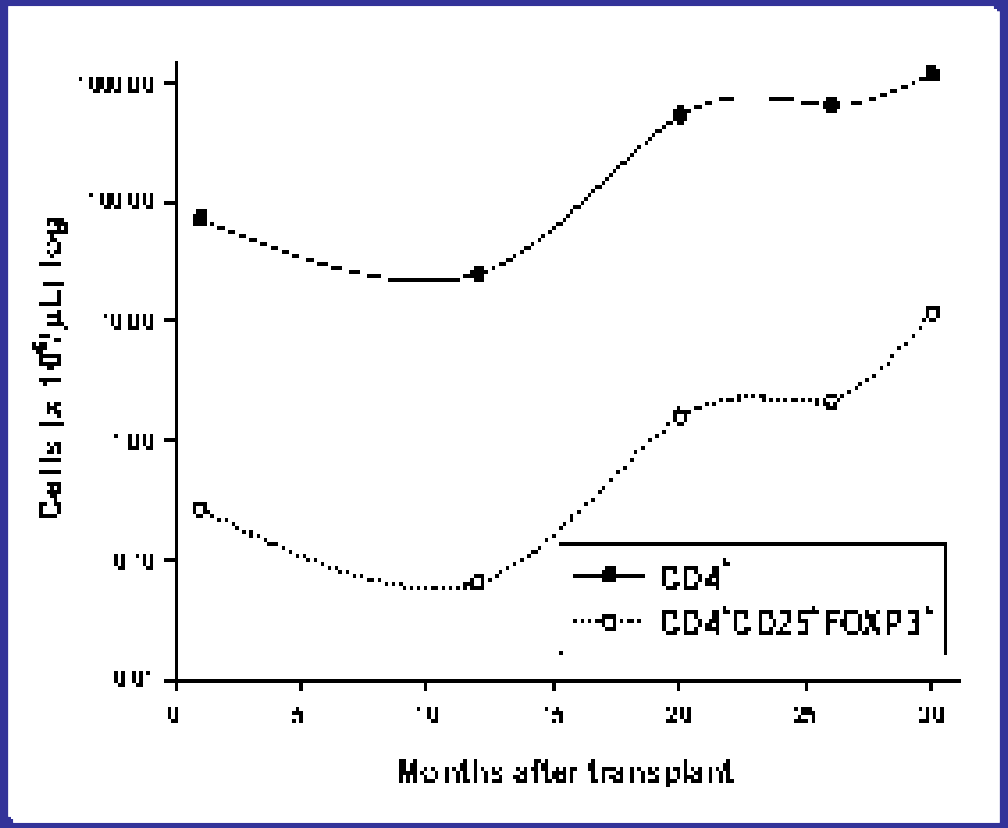


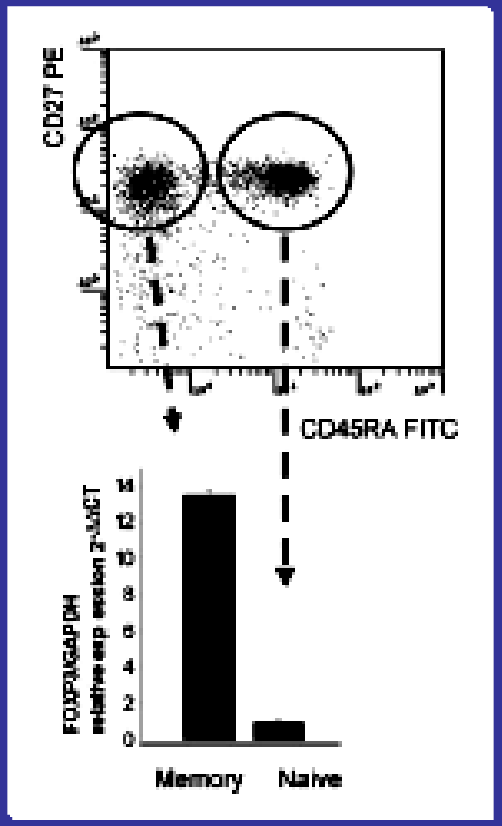

*Before treatment*

*4 years of follow-up*

*L Bndl, T Togerson, L Perroni et al. J Pediatr 2005: 147:256-59*

# BONE MARROW ALLOGENIC TRANSPLANTATION IN IPEX SYNDROME




*Aarati Rao, Naynesh Kamani, Alexandra Filipovich . Blood 2007;109:383-85*

# 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